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Healthy Longevity and Immune System

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Healthy Ageing and Longevity

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Rapidly changing demographics worldwide towards increased proportion of the elderly in the population and increased life-expectancy have brought the issues, such as “why we grow old”, “how we grow old”, “how long can we live”, “how to maintain health”, “how to prevent and treat diseases in old age”, “what are the future perspectives for healthy ageing and longevity” and so on, in the centre stage of scientific, social, political, and economic arena. Although the descriptive aspects of ageing are now well established at the level of species, populations, individuals, and within an individual at the tissue, cell and molecular levels, the implications of such detailed understanding with respect to the aim of achieving healthy ageing and longevity are ever-changing and challenging issues. This continuing success of gerontology, and especially of biogerontology, is attracting the attention of both the well established academicians and the younger generation of students and researchers in biology, medicine, bioinformatics, bioeconomy, sports science, and nutritional sciences, along with sociologists, psychologists, politicians, public health experts, and health-care industry including cosmeceutical-, food-, and lifestyle-industry. Books in this series will cover the topics related to the issues of healthy ageing and longevity. This series will provide not only the exhaustive reviews of the established body of knowledge, but also will give a critical evaluation of the ongoing research and development with respect to theoretical and evidence-based practical and ethical aspects of interventions towards maintaining, recovering and enhancing health and longevity.

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Preface

The number of adults older than 65 years is crescent and individuals with 85 years and more (oldest old) are the fasting growing group. Unfortunately, the extension in life expectancy is not accompanied with a similar increase in disability-free life expectancy. In addition, older adults are a very heterogenic group and thus it is a challenge to identify markers of healthy ageing (maintenance of functional abilities).

Infections in older adults have been associated with high morbidity and mortality mainly in those with comorbidities. In the last two years, researchers confirmed this negative outcome in aged individuals infected with SARS-CoV-2. In this scenario, studies focused on the understanding of how changes occurring in the immune system during the ageing process contribute to morbidities (cardiovascular, pulmonary, neurologic, cancer) and impairment in the response against pathogens are crucial (Chap. 1).

The decline in percentage and function of immune system cells, termed immunosenescence, has been linked to the poor response to infections, vaccine, and cancer observed in older individuals. In addition, a chronic low grade of systemic inflammation identified in old individuals (inflammageing) has been associated with age-related diseases.

Immunosenescence has been linked to architectural changes in the lymphoid organs (Chap. 2) which affect directly or indirectly cells from the immune system (Chaps. 3 and 4). Therefore, responses to infectious agents (Chaps. 5 and 6) are inefficient leading to greater hospitalization and mortality. Vaccination also presents less efficacy in older adults compared to young counterparts (Chap. 7) and strategies (number of doses, site of injection, more potent adjuvants) to improve the immunity have been evaluated.

Cancer numbers are higher in old individuals and have been linked to a lifetime exposure to carcinogens, decline in immunosurveillance, capacity of the tumor cells to escape from the immune system, and less efficient immune response against tumor cells (Chap. 8). Myeloid-derived suppressor cells increased percentage in tumor microenvironment and peripheral blood contributes to tumor progression, thus these cells have been related to the lower efficacy of cancer therapies.

Immunosenescence and inflammageing have been considered the most important underlying age-related factor for Alzheimer's disease. However, in Chap. 9 it will be discussed that changes occurring in the immune system during the ageing process are both detrimental and adaptive and thus novel treatment approaches are needed.

The role played by healthy nutrition, supplement, and physical activity in reducing immunosenescence/inflammageing has been recognized recently and is an open road to improve immunity in older adults.

Our aim is to discuss not only how a compromised immune system impacts the health of older individuals but also how healthy habits can modulate, at least at some extent, immunosenescence and inflammageing. The further understanding of the complex dual ageing and immune system can lead to public health policies to ensure longevity with functionality.

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Chapter 1
Healthy Longevity and Immune System: A Brief Introduction

Alphonse Laya and Valquiria Bueno

Abstract Since 1990 it has been observed a significant increase of the global aged population with a perspective of 1.5 billion of older individuals by 2050 and 3 billion by 2100 due to increased longevity. To guarantee healthy longevity to this population, public policies focused in economic, social and health aspects are crucial. Healthy longevity is influenced by genetics, habits (i.e. healthy nutrition, physical activity, non-smoking) and environment. Several changes occur in organs and tissues during the ageing process, therefore the immune system also suffers alterations that could play a role in age-related conditions (cardiovascular, respiratory, neurologic, tumoral, and infectious). Recently we had a clear example of how an infectious disease (COVID-19) is exacerbated in aged patients with high morbidity and mortality (mainly in those with comorbidities). It was found an association between elevated morbidity/mortality after SARS-CoV-2 and increased expression of inflammageing and immunosenescence markers. To fight immunosenescence it has been proposed that healthy nutrition and supplements (vitamins B, D, C, or E, essential minerals, and amino acids) could be used. In addition, physical activity has been suggested for the maintenance of adequate function of respiratory and cardiovascular systems, memory, and immune system. Considering the complexity of healthy longevity, this introduction will briefly comment some alterations occurring in the innate and adaptive immunity during the ageing process and possible alternatives of intervention in order to reach old age with functionality. The complete discussion about these changes will be distributed in the Chaps. 2–9.

Keywords Healthy longevity · Ageing · Diet · Physical activity · Immunosenescence · Immune system

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Since 1990 it has been observed a significant increase of the aged population in the world. In percentage, individuals aged 65 years or more increased globally to 9% in 2019 (6% in 1990, United Nations 2019). In numbers, it corresponds to 703 million persons and is projected to double by 2050 (United Nations 2019). Bloom and Luca (2016) projected a rise to 3 billion of individuals >65 years in 2100. The improvement in medicine, nutrition, and public health policies has been associated with the observed increase in longevity. In agreement, the study by Li et al. (2019) showed that organism maintenance of homeostasis is associated with lifespan extension. To reach healthy longevity factors such as genetics, habits and environment have to be considered.

Several changes occur in tissues during the ageing process and thus the immune system is also remodeled and it is considered to underlie many age-related conditions such as cardiovascular, respiratory, neurologic, tumoral, and infectious. For infectious diseases, it has been shown an increased susceptibility of aged individuals to develop severe forms (i.e. pneumonia and influenza) in comparison with younger persons (Pawelec et al. 2020). Moreover, the immune response after vaccination is less efficient in old individuals (Chap. 7). Recently we had a clear example of how an infectious disease (COVID-19) is exacerbated in aged individuals with high morbidity and mortality. It has been shown that individuals aged 55–64 years and 65+ have respectively 8.1 and 62 times higher incident rate ratio of severe COVID-19 compared with those aged below 54 years. The increased severity of COVID19 in old individuals has been linked to comorbidities such as cardiovascular disease and diabetes type 2 in addition to increased expression of immunosenescence and inflammageing markers (Chap. 6).

Weyh et al. (2020) claims that changes occurring in the percentage and functions of the immune system; based on T cells evaluation, can be reversed by regular physical activity. Also, micro nutrients are required at adequate levels for effective function of the immune system (Reider et al. 2020). These findings suggest that it is possible to "modulate" the immune system via physical activity, healthy nutrition, and supplements such as vitamins (B, D, C, E), essential minerals, and amino acids. In reinforcement of this idea, it has been shown that the deficiency in essential micro-nutrients affects the efficacy of the immune system against pathogens (Reider et al. 2020). The innate immune system is considered the first line of defense against pathogens, and can be boosted by nutrition of good quality (Reider et al. 2020). For the adaptive immune system, it has been shown that vitamin E enhances lymphocyte proliferation, interleukin-2 (IL-2) production, and inhibits the production of prostaglandin E2 (PGE2) (Gombart et al. 2020).

Considering that the immune system can be "modulated" this book will discuss the changes in primary and secondary lymphoid organs, innate and adaptive immunity, and suppressive cells, in healthy older individuals. The same parameters will be described in conditions such as infections, and age-related conditions (cancer, neurodegenerative diseases, autoimmune diseases) and finally how the lifestyle/interventions can contribute for healthy longevity.

1.1 Changes in Primary and Secondary Lymphoid Organs (Bone Marrow, Thymus, Lymph Nodes, Spleen)

Lymphoid organs are classified as primary (thymus and bone marrow) or secondary (lymph nodes and spleen). Primary lymphoid organs are responsible for the generation and maturation of leukocytes whereas secondary lymphoid organs are associated with antigen presentation and activation of immune cells. During ageing, the production of leukocytes by bone marrow decreases, thymus suffers involution and thus the release of naive T cells is diminished. Secondary lymphoid organs also undergo architecture changes which impact the encounter of the immune cells and antigens, in addition to the reduced activation of the immune response (Chap. 2). These architectural changes in primary and secondary lymphoid organs and the consequences for the immune system explain, at least in part, the higher susceptibility to infection and reduced responses to vaccination observed in older individuals in comparison with young counterparts (Chap. 2). Moreover, the infections are the leading causes of morbidity and mortality in individuals >65 years which have been correlated with changes in the adaptive immune system such as the reduction of naive T cells and increase of effector/memory T cells subsets (Weng 2006; Pawelec and Larbi 2008). T cell responsiveness has also been associated with intrinsic defects such as altered cell membrane fluidity, changes in the cell surface expression of co-stimulatory molecules and cytokine receptors, molecular and transcriptional changes (Larbi et al. 2006; Chen et al. 2013). Also, the loss of T cell receptor (TCR) diversity has been reported which can lead to lower capacity to respond to new pathogens/antigens (Lerner et al. 1989; Kieper and Jameson 1999).

1.2 Innate Immunity (Neutrophils, Monocytes, Macrophages)

The first line protection represented by innate immunity is triggered for example in response to inflammatory distress with subsequent migration of neutrophils and mast cells to the damaged site. NK and NKT cells present in the gut epithelium can also be stimulated by cytokines produced locally (Cocteau 2014).

Neutrophils act both defending against infection and activating/regulating the innate and adaptive immune responses. Activated neutrophils are cited as the initial responder and facilitate the clearance of inflammation caused by pathogens, tissue injury, and cellular dysfunction due to stress as part of physiological host defense (Feng et al. 2019). Regarding to tumor, neutrophils have been associated with tumor resistance via direct cytotoxic activity and/or activation of T cell-dependent immunity. In addition, the expression of regulatory proteins such as SIRPα by neutrophils, monocytes and macrophages are crucial for the phagocytosis checkpoint (Feng et al. 2019; Jaillon et al. 2020). Innate immunity is affected by the ageing process resulting in lower ability of immediate response to pathogens and in reduced integration

with the adaptive immune response. Neutrophils' impaired function with poor regulation of cell receptors and downstream signaling pathways have been shown to interfere with immune response against pathogens and after vaccination. Reactive oxygen species produced by monocytes are reduced in addition to the dysregulation of cytokines release. Neutrophils present deficient migration and reduction in the capability to form neutrophil extracellular traps (NETs) (Chap. 3).

1.3 Adaptive Immunity (T and B Lymphocytes: Naïve, Effector and Memory Phenotypes and Functions)

The cells of the innate immune system, including phagocytes, neutrophils, dendritic cells and natural killer cells (NK), play critical roles in the body's defenses by neutralizing pathogens and facilitating the adaptive immune response. The adaptive immune system, formed by B and T cells along with their products, is not only responsible for a specific response to pathogens but also for the development of immunological memory for future immune challenge (Reider et al. 2020). Immunological memory is a unique characteristic of the adaptive immunity and it is essential for the organism protection against pathogens and after vaccination.

During the ageing process it has been observed reduction in the proportion of naive B cells, in addition to a less efficient antibody response by activated B cells. The collaboration between B cells and T cells is reduced, and the recognition of self and non-self is impaired. As consequence it has been reported the production of antibodies with low-specificity and decrease avidity, and hematological disorders in older individuals respectively (Cunha et al. 2020). In summary, changes observed in B cells lead to reduced protection and poor response to infections and vaccines (Chap. 7).

Considering T cells, it has been reported a decrease of the naive subtype both in circulation and lymphoid organs (spleen, lymph nodes). The lower diversity of T cell receptor (TCR) has been associated with thymus involution and impairs the recognition of new antigens. After activation, naive T cells are expected to differentiate into central memory T cells (TCM), which reside in the lymph nodes, and effector memory T cells (TEM), which reside in the peripheral tissues (Zuluaga et al. 2020). These cells are fundamental for the organism protection against infections and after vaccination. An important change in T cell profile is a relative increase of memory T cells (in particular terminally-differentiated T cells TEMRA). The decrease in peripheral naive CD8 + T cells and the increase in TEMRA cells have been associated with impaired immune response against virus infections. These findings have been linked to the reduced thymic output of naive cells and persistent cell activation due to a lifetime's exposure to pathogens (Pawelec et al. 2020). The function of T cells (proliferation, cytokines production) is also affected during the ageing process and contributes for the immunosenescent profile.

1.4 Suppressive Cells (MDSC)

Myeloid-derived suppressor cells (MDSCs) are suppressive cells that have been associated with decreased immune response in cancer, in some infections, and autoimmune diseases (Chap. 4). MDSCs act suppressing immune responses and there are few evidences that these cells increase in healthy old individuals (Verschoor et al. 2013; Alves et al. 2018). It has been reported that MDSCs impair the functions of T, NK, and dendritic cells. MDSCs execute their suppressive effects via arginase 1 (Arg-1), indoleamine dioxygenase (IDO), IL-10, inducible nitric oxide synthase (iNOS), nitric oxide (NO), heme oxygenase 1 (HO-1), carbon monoxide (CO), prostaglandin E2 (PGE2), ROS, and cysteine depletion (Gabrilovich and Nagaraj 2009; Zhao et al. 2016).

The accumulation of MDSCs due to accelerated myelopoiesis during chronic inflammation, such as in late sepsis, is not simply an expansion in their numbers or expression of phenotypes, but rather an enhanced suppressive function gained under pathological conditions (Dai et al. 2015). MDSCs have been reported to act in synergy with other cells for the inhibition of immune effector cell function. As an example, MDSCs alone or in synergy with T regulatory (T reg) cells can contribute to the progression or latency of HIV infection, and this may explain the lack of efficacy of some immune-based treatments and vaccinations (Macatangay et al. 2011; Vollbrecht et al. 2012; Garg and Spector 2014).

1.5 Infections: Influenza, Pneumonia, and COVID (Chaps. 5 and 6)

Infectious diseases are more common and severe in older individuals in comparison with younger counterparts, and the most frequent sites are respiratory and urinary tract probably due to the impaired barrier function of the mucosa and diminished adaptive immune response (Cunha et al. 2020). The ageing immune system presents a decreased ability to protect against infections and whereas for healthy adults seasonal influenza is rarely linked to severe infection, for the old individuals it is a serious health concern. According to Center for Disease Control and Prevention in US (CDC), the estimated influenza-associated deaths with underlying respiratory and circulatory conditions is significantly higher in individuals older than 65 years. The pneumonia requiring hospitalization overall can be 1 per 1,000 cases, but in individuals older than 75 years the rate reaches 12 per 1,000 cases. In addition, resistant pathogens are more common in older individuals with comorbidities that have been medicated with antibiotics or are hospitalized.

Regarding SARS-CoV-2, in old individuals the increased virus susceptibility has been linked to comorbidities that are common in the aged population (Cunha et al. 2020). The invasion of the airway epithelial by SARS-CoV-2 break the barrier integrity, triggering a vicious cycle of inflammation and tissue injury that is more

pronounced in old individuals. The uncontrolled systemic inflammation causes endothelial injury and activation of coagulation cascade leadind to an explosive process of disseminated intravascular coagulation and consumption of coagulation factors that culminate in organ damage and death (Cunha et al. 2020).

The worse outcome in aged individuals has been linked to changes in respiratory and immune system observed in this population. The lethality of COVID-19 has been related to immunosenescence and inflammageing that are main characteristics of the ageing process. Immunosenescence combines a lower efficacy of T cell response and decreased avidity/ specificity of antibodies and may explain the lethality amongst the old individuals with COVID-19. Inflammageing is linked to the collapse of homeostasis, leading to severe organ dysfunction (Cunha et al. 2020).

1.6 Vaccine Responses are Typically Impaired in Older Individuals

The protection induced by vaccine against influenza varies from 41 to 58% in individuals aged 60–74 years and among those aged more than 75 years, the vaccine protects in 29–46% of cases. The trivalent inactivated influenza vaccine (TIV- H1N1, H3N2, and influenza B) efficacy in old individuals, ranges from 30 to 70% in preventing pneumonia hospitalization. The increased susceptibility of old individuals to pneumonia has been associated with comorbidities and immunosenescence and thus vaccination is highly recommended. They include the 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent conjugated vaccine (PCV13). Even in presence of comorbidities, PCV13 is safe and immunogenic in old individuals whereas PPV23 results in a suboptimal protection (Chap. 7).

Regarding to COVID-19, several vaccines have been developed or are in development but it is not clear whether old individuals will present efficient and long-term immunogenicity. The age-related decline and dysregulation observed in the immune response (i.e., immunosenescence and inflammageing) in association with comorbidities contribute to the higher vulnerability to worse COVID-19 outcomes in older adults. To overcome the poor response to vaccines by the ageing immune response, strategies such increase in the vaccine antigen per dose, administration by intradermal route and formulation with different adjuvants have been proposed (Dong et al. 2020).

1.7 Cancer and Immunosenescence

Considering that the aged population presents decreased immunity and that the immune surveillance is also impaired, age is reported as the single most significant risk factor for malignancy. In developed countries the incidence of breast, lung,

prostate, and colorectal malignancy increases exponentially with age (*Mandurian & Bueno* 2016). A life history of accumulated cell mutations and the chronic inflammation characteristic of the inflammageing process have been pointed as potential risk for tumor development (Chap. 8).

Obesity is also considered a risk factor for the onset and progression of many cancers and it is accompanied by dysregulated metabolism and chronic low-grade inflammation of white adipose tissue. Inflammation is induced by adipose-associated macrophages that are polarized toward a proinflammatory M1-like phenotype and produce multiple tumor-promoting cytokines including TNFα, IL-6, and IL-1β (Ostrand-Rosenberg 2020).

Myeloid-derived suppressor cells (MDSCs) increased expression during inflammatory processes support the hypothesis that MDSC induced by inflammation accumulate in premalignant states and may facilitate malignancy by inhibiting immune surveillance (*Ostrand-Rosenberg and Sinha*, 2009). Accumulation of MDSCs over time in aged individuals has been shown to increase the incidence of tumour development as reported in many studies. For instance, it was reported that MDSCs promote age-related increase of lung cancer growth via inhibiting anti-tumour T cell responses through upregulating the expression of immune checkpoint protein, namely PD-1 (the so-called B7-H1) (Yaseen et al. 2020). MDSCs cause suppression of innate and adaptive cells contributing thus for cancer progression. In the setting of pathological conditions, especially those with chronic inflammatory responses such as cancer amongst others, MDSCs can be detected at very high levels in the bone marrow and peripheral tissues (e.g., spleen, liver, lymph nodes, and blood circulation), as well as within the inflammation sites, especially as the disease progress (Kusmartsev and Gabrilovich 2006; Ochoa et al. 2007; Ilkovitch and Lopez 2009).

Considering the immune-suppressive potency and virtually universal presence of MDSCs in cancer patients, it has become apparent that elimination or inactivation of MDSCs could contribute for the success of T cell–based immunotherapies and natural antitumor immunity (Ostrand-Rosenberg 2020). However, considering the lack of specific markers or signal transduction pathways specific for MDSCs, it is almost impossible to development therapies targeting specifically MDSCs with no impact in other cells (Ostrand-Rosenberg 2020). Another possibility is combining 'rejuvenation' immunotherapy with standard chemotherapy in order to improve the outcome of old patients with cancer (Jackaman and Nelson 2014).

1.8 Neurodegenerative Diseases

In ageing individuals, it has been proposed that the dual immunosenescence and inflammageing can cause a chronic low-grade inflammation in the central nervous system (CNS) by modulating neuronal immune cell activity and reactivity. Chronic inflammation has been associated with many age-related conditions such as insulin

resistance, cardiovascular disease, osteoarthritis, chronic obstructive pulmonary disease, emphysema, pulmonary arterial hypertension, Alzheimer's, Parkinson's, and macular degeneration, which are all characterized by the accumulation of senescent cells (Furman et al. 2019).

The inflammatory response against pathogens or dying cells becomes dysregulated, causing thus tissue damage (i.e. injury or death of neurons), and are commonly observed in Alzheimer's disease (AD) and Parkinson's disease (PD). Interventions such as caloric restriction, probiotic and prebiotic supplements, in addition to changes in unhealthy lifestyle (high sugar diets, alcohol and tobacco addiction or high fat diets) have been investigated in order to retard neurodegeneration and its consequences (brain ageing, cognitive deficit, memory loss) (Chap. 9).

It has been shown that regular exercise training and specific nutrition strategies can boost successful immune response and decrease the risk of maladaptive immune ageing (Weyh et al. 2020). For example there are several healthy dietary components such as polyunsaturated fatty acids and antioxidants such as polyphenols, vitamins E, D, C, carotenoids, minerals, caloric restriction, which may counteract ageing and associated neurodegenerative diseases via increased autophagy or increased neurogenesis in brain of older individuals. Monacelli et al. (2017) showed that the association between ascorbic acid and vitamin E supplementation presented synergy and had a preventive action on AD. Many other studies are highlighting iron homeostasis in mitochondria and the impact of inflammation on iron overload in neurodegenerative diseases (Popa-Wagner et al. 2020).

1.9 Lifestyle/Interventions (Physical Activity, Nutrition, Supplements)

The commonly observed decline in the immune system in ageing individuals can be influenced by physical activity, nutrition and pharmacological interventions. The physical inactivity, and its consequences, such as adipose tissue accumulation and muscle dysfunction, deleteriously can affect both innate and adaptive immunity. Sedentarism has been associated with increased systemic inflammation (increased TNF-α, IFN-γ, and CRP), impaired natural killer cell cytolytic activity and reduced T-cell proliferation and cytokine production, all of which can result in poor immune response against virus infections. It has been shown that physical activity during life reduces the risk of non-communicable diseases (cancer, cardiovascular, chronic inflammatory disorders) and improves the immunity (Sellami et al. 2018).

Studies in different species including primates have shown that restriction of food intake without malnutrition increases longevity and delays age-related diseases. In addition, chronic nutrient excess can cause local (adipocytes and hepatocytes) and systemic inflammation contributing thus for the age-related inflammageing process (Colman et al. 2014). On the other hand, the malnutrition risk increases with age is has been associated with decreased immune function and increased susceptibility to

infections in ageing individuals. The lack of essential nutrients such as amino acids, minerals, vitamins and fatty acids increases the susceptibility of aged individuals to infections and degenerative diseases. The adequacy of supplementation for older adults may act boosting their immune system or delaying the ageing process. Also probiotic consumption increases the number and function of immune cells and in old individuals was shown to improve vaccine responses (Kawakami et al. 1999).

The consumption of fruit and vegetables which are important components of a healthy diet, and represent rich sources of micronutrients, dietary fibers and antioxidants reduces the risk of cardiovascular diseases, diabetes type 2, several cancers, and cognitive function. Vitamins A, C, D, E, zinc, iron, and selenium are all involved in the innate and/or adaptive immune response (Reider et al. 2020). In addition, it has been shown that exercise and diet are the main protective mechanisms that may reduce the cognitive decline attributed to the normal ageing process and protect against changes related to neurodegenerative diseases such as Alzheimer's disease (Liparoti et al. 2020).

1.10 Conclusions

The healthy longevity seems to be a combination of factors such as genetics, habits and environment. During the ageing process changes occurring in organs and the alterations in the immune system are considered to underlie many age-related diseases such as cardiovascular, neurodegenerative, autoimmune diseases, cancer, and infections. Immunosenescence is the designation for all the age-associated changes in immune parameters and it has been linked to the impaired immune response after infection and vaccination in older adults. The malnutrition risk increases with age is has been associated with decreased immune function and increased susceptibility to infections in the aged population. In addition, healthy diet and supplements can help to obtain nutrient adequacy and boost the immune system. Physical activity has also been pointed as fundamental for the reduction of non-communicable diseases (cancer, cardiovascular, chronic inflammatory disorders) and improvement of the immunity.

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Compliance with Ethical Standards

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References

Adeegbe DO, Nishikawa H (2013) Natural and inducedT regulatory cells in cancer. Front Immunol 11(4):190. https://doi.org/10.3389/fimmu.2013.00190

Alves AS, Ishimura ME, Duarte YAO, Bueno V (2018) Parameters of the immune system and vitamin D levels in old individuals. Front Immunol 9:1122. https://doi.org/10.3389/fimmu.2018.01122

Bloom DE, Luca DL (2016) The global demography of aging: facts, explanations. Future https://ftp.iza.org/dp10163.pdf

Chen G, Lustig A, Weng N-P (2013) T cell aging: a review of the transcriptional changes determined from genome-wide analysis. Front Immunol 4:121

Cocteau J (2014) Mucosal and cutaneous immunity. 269–292. https://doi.org/10.1016/B978-0-12-385245-8.00012-1

Colman R, Beasley T, Kemnitz J et al. (2014) Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun 5:3557. https://doi.org/10.1038/ncomms4557.

Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV (2020) Remodeling of the Immune Response With Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. Front Immunol 11:1748. https://doi.org/10.3389/fimmu.2020.01748

Dai J, Gazzar ME, Li GY, Moorman JP, Yao ZQ (2015) Myeloid-derived suppressor cells: paradoxical roles in infection and immunity. J Innate Immun 7:116–126. https://doi.org/10.1159/000368233

Damiot A, Pinto AJ, Turner JE, Gualano B (2020) Immunological implications of physical inactivity among older adults during the COVID-19 pandemic,1–8. Gerontology. https://doi.org/10.1159/000509216

Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou FF (2020) A systematic review of SARS-CoV-2 vaccine candidates. Signal Trans Target Therapy 5:237. https://doi.org/10.1038/s41392-020-00352-y

Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF et al (1998) Changes in thymic function with age and during the treatment of HIV infection. Nature 396:690–695

Farage MA, Miller KW, Maibach HI (2017) Degenerative changes in aging skin 3. In Farage et al (eds) Textbook of aging skin. Springer, Berlin Heidelberg. https://doi.org/10.1007/978-3-662-47398-6_4

Feng M et al (2019) Phagocytosis checkpoints as new targets for cancer immunotherapy. Nat Rev Cancer 19:568–586

Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C et al (2019) Chronic inflammation in the etiology of disease across the life span. Nat Med 25(12):1822–1832

Gabrilovich DI (2017) Myeloid-derived suppressor cells. Cancer Immunol Res 5:3–8. https://doi.org/10.1158/2326-6066.CIR-16-0297

Gabrilovich DI, Nagaraj S (2009) Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 9:162–174. https://doi.org/10.1038/nri2506

Garg A, Spector SA (2014) HIV type 1 gp120-induced expansion of myeloid derived suppressor cells is dependent on interleukin 6 and suppresses immunity. J Infect Dis 209:441–451

Gombart AF, Pierre A, Maggini SA (2020) Review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients 12:236

Ilkovitch D, Lopez DM (2009) The liver is a site for tumor-induced myeloid-derived suppressor cell accumulation and immunosuppression. Can Res 69(13):5514–5521

Jackaman C, Nelson DJ (2014) Are macrophages, myeloid derived suppressor cells and neutrophils mediators of local suppression in healthy and cancerous tissues in aging hosts? Experim Gerontol 54:53–57. https://doi.org/10.1016/j.exger.2013.11.009

Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A (2020) Neutrophil diversity and plasticity in tumour progression and therapy. Nat Rev Cancer 20:503

Kauppinen A, Kaarniranta K, Salminen A (2020) Potential role of myeloid-derived suppressor cells (MDSCs) in age-related macular degeneration (AMD). Front Immunol 11:384. https://doi.org/10.3389/fimmu.2020.00384

Kawakami K, Kadota J, Iida K et al (1999) Reduced immune function and malnutrition in the elderly. Tohoku J Exp Med 187(2) : 157–71 (1999). https://doi.org/10.1620/tjem.187.157

Kieper WC, Jameson SC (1999) Homeostatic expansion and phenotypic conversion of naive T cells in response to self peptide/MHC ligands. Proc Natl Acad Sci USA 96:13306–13311

Kim SW, Mo JH, Kim JW, Kim DY, Rhee CS, Lee CH, Min YG (2007) Change of nasal function with aging in Korean. Acta Otolaryngol Suppl 558(1):90–94

Kinn PM, Holdren GO, Westermeyer BA, Abuissa M, Fischer CL, Fairley JA, Brogden KA, Brogden NK (2015) Age-dependent variation in cytokines, chemokines, and biologic analytes rinsed from the surface of healthy human skin. Sci Rep 5(1):10472

Kusmartsev S, Gabrilovich DI (2006) Role of immature myeloid cells in mechanisms of immune evasion in cancer. Cancer Immunol Immunother 55(3):237–245

Lang S et al (2018) Clinical relevance and suppressive capacity of human myeloid-derived suppressor cell subsets. Clinic Cancer Res 24:4834–4844. https://doi.org/10.1158/1078-0432.CCR-17-3726

Larbi A, Dupuis G, Khalil A, Douziech N, Fortin C, Fülöp T (2006) Differential role of lipid rafts in the functions of CD4+ and CD8+ human T lymphocytes with aging. Cell Signal 18:1017–1030

Lerner A, Yamada T, Miller RA (1989) Pgp-1hi T lymphocytes accumulate with age in mice and respond poorly to concanavalin A. Eur J Immunol 19:977–982

Li QQ, Huc C, Lina J, Yang Z, Zhou Q, Yang R, Yuan H, Zhu X, Lv Y, Liang Q, Lv Z, Sun L, Zhang Y (2019) Urinary ionomic analysis reveals new relationship between minerals and longevity in a Han Chinese population. J Trace Elem Med Biol 53:69–75

Linton PJ, Dorshkind K (2004) Age-related changes in lymphocyte development and function. Nat Immunol 2004(5):133–139

Liparoti M, Madonna G, Minino R (2020) The role of physical activity and diet in preventing cognitive decline. J Phys Educ Sport (JPES) 20(4). Art 316:2342–2348

Macatangay B, Roper J, Borowski L, Whiteside TL, Rinaldo CR (2011) Levels of cellular immune activation and myeloid-derived suppressor cells are elevated after administration of an HIV-dendritic cell therapeutic vaccine. Conference on Retroviruses and Opportunistic Infections, Boston, USA

Manoukian N, Bueno V (2016) Cancer, ageing and immunosenescence. In: Bueno V, Lord JM, Jackson TA (ed) The ageing immune system and health, vol 1 (Springer, Switzerland), pp 105–124

McGhee JR, Fujihashi K (2012) Inside the mucosal immune system. PLoS Biol 10:e1001397. https://doi.org/10.1371/journal.pbio.1001397

Monacelli F, Acquarone E, Giannotti C, Borghi R, Nencioni A (2017) Aging and Alzheimer's disease. Nutrients. https://doi.org/10.3390/nu9070670

Ochoa AC, Zea AH, Hernandez C, Rodriguez PC (2007) Arginase, prostaglandins, and myeloid-derived suppressor cells in renal cell carcinoma. Clinic Cancer Res 13(2):721s–726s

Ostrand-Rosenberg S (2020) Myeloid-derived suppressor cells: facilitators of cancer and obesity-induced cancer. Annual Rev Cancer Biol 11:48

Pawelec G, Larbi A (2008) Immunity and ageing in man: annual review 2006/2007. Exp Gerontol 43:34–38

Pawelec G, Bronikowski A, Cunnane SC, Ferrucci L, Franceschi C, Fül¨op T, Gaudreau P, Gladyshev VN, Gonos ES, Gorbunova V, Kennedy BK, Larbi A, Lemaître J-F, Liu G-H, Maier AB, et al (2020)The conundrum of human immune system "senescence". Mech Age Dev 192:111357

Popa-Wagner A, Dumitrascu DI, Capitanescu B, Petcu EB, Surugiu R, Fang WH, Dumbrava DA (2020) Dietary habits, lifestyle factors and neurodegenerative diseases. Neural Regen Res 15(3):394–400. https://doi.org/10.4103/1673-5374.266045

Reider CA, Chung R-Y, Devarshi PP, Grant RW, Mitmesser SH (2020) Inadequacy of immune health nutrients: intakes in US adults, the 2005–2016 NHANES. Nutrients 12:1735. https://doi.org/10.3390/nu12061735

Sellami M, Gasmi M, Denham J et al (2018) Effects of acute and chronic exercise on immunological parameters in the elderly aged : can physical activity counteract the effects of aging? Front Immunol 2018(9):2187. https://doi.org/10.3389/fimmu.2018.02187

Turvey SE, Broide DH (2010) Innate immunity. J Allergy Clin Immunol 2010(125):S24-32

United Nations (2019) World Population Ageing 2019. Highlights. Department of Economic and Social Affairs, Population Division ST/ESA/SER.A/430. New York

Verschoor CP, Johnstone J, Millar J et al (2013) Blood CD33(+)HLA-DR(-) myeloid-derived suppressor cells are increased with age and a history of cancer. J Leukoc Biol 93(4):633–637. https://doi.org/10.1189/jlb.0912461

Vollbrecht T, Stirner R, Tufman A, Roider J, Huber RM, Bogner JR, Lechner A, Bourquin C, Draenert R (2012) Chronic progressive HIV-1 infection is associated with elevated levels of myeloid-derived suppressor cells. AIDS 26:F31–F37

Weng N-P (2006) Aging of the immune system: how much can the adaptive immune system adapt? Immunity 2006(24):495–499

Weyh C, Krüger K, Strasser B (2020) Physical activity and diet shape the immune system during aging. Nutrients 12:622. https://doi.org/10.3390/nu12030622

Whiteside TL, Schilling SPB (2012) Induced and natural regulatory Tcells inhuman cancer. Expert Opin Biol Ther 12(10):1383–1397. https://doi.org/10.1517/14712598.2012.707184

Wilke CM, Wu K, Zhao E, Wang G, Zou W (2010) Prognos-tic significance of regulatory T cells in tumor. Int J Cancer 127(4):748–758. https://doi.org/10.1002/ijc.25464

Yaseen MM, Abuharfeil NM, Darmani H, Daoud A (2020) Mechanisms of immune suppression by myeloid-derived suppressor cells: the role of interleukin-10 as a key immunoregulatory cytokine. Open Biol 10:200111. https://doi.org/10.1098/rsob.200111

Zhao Y, Wu T, Shao S, Shi B, Zhao Y (2016) Phenotype, development, and biological function of myeloid-derived suppressor cells. Oncoimmunology. 5:e1004983. https://doi.org/10.1080/2162402X.2015.1004983

Zuluaga P, Sanvisens A, Teniente-Serra A, Ars OE, Fuster D, Quirant-Sánchez B, Martínez-Cáceres E, Muga R (2020) Loss of naive T lymphocytes is associated with advanced liver fibrosis in alcohol use disorder. Drug Alcohol Dependence 213:108046

Chapter 2
Age-Related Changes in Primary and Secondary Lymphoid Organs

Valquiria Bueno

Abstract Bone marrow is a primary lymphoid organ which gives rise to leukocytes and provides maturation of B cells whereas thymus is also a primary lymphoid organ and promotes T cells maturation. Spleen and lymph nodes are secondary lymphoid organs with a favorable microenvironment for immune cells response to pathogenic materials present in blood/lymph and development of long-term adaptive immunity. Therefore, changes in the architecture of primary and secondary lymphoid organs during the ageing process can contribute for the impaired immune response to infections, vaccines, and tumors observed in old individuals. The literature is scarce in aged human lymphoid organs and most of the data are from post mortem or individuals submitted to some type of clinical procedure. Thus, data about lymphoid organs are mostly results of rodent investigation. Conflicting results in architecture and physiology between rodents and human can explain the differences in cells proportions and functions reported in literature. Nevertheless, even considering the limitation of data disposable, in this chapter, the focus will be human lymphoid changes during the ageing process. Considering the importance of lymphoid organs in infections, this chapter also reports data obtained in recent literature about COVID-19 and lymphoid organs.

Keywords Lymphoid organs · Bone marrow · Thymus · Lymph nodes · Spleen

Abbreviations

AID	Activation-induced deaminase
Bcl6	B-cell lymphoma 6 protein
BM	Bone marrow
CT	Computed tomography
HEV	High endothelial vessels

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HPSC Hematopoietic progenitor stem cells
HSC Hematopoietic stem cells
MDSC Myeloid-derived suppressor cells
NKT Natural killer T cells
PD-1 Program cell death protein 1
TCR T-cell receptor
TEC Thymic epithelial cells
Tim-3 T cell immunoglobulin and mucin domain-containing protein 3
TREC T cell receptor excised circles

2.1 Bone Marrow and Hematopoiesis

Hematopoietic stem cells (HSC) give rise to leukocytes including myeloid and lymphoid subtypes that are responsible for innate and adaptive immunity. HSC develop at bone marrow (BM) niche, and it has been reported decreased numbers, increased numbers, or no changed numbers of HSC during the ageing process (Povsic et al. 2010; Kuranda et al. 2011; Ogawa et al. 2000). Povsic et al. (2010) observed opposite trends according to the tissue investigated, with an age-related decline in circulating hematopoietic progenitor stem cells (HPSC, $CD133^{+}CD34^{+}$) and no relationship between BM-resident progenitors and age.

Signals from BM niche components contribute for the complex process that regulates HSC production. Therefore, variations observed in BM architecture due to age and morbidities can contribute for the heterogeneity of HSC numbers in the aged population. Tuljapurkar et al. (2011) observed an age-related increase of fat content in the femoral BM in man which was associated with decrease in HSC. Aguilar-Navarro et al. (2020) observed a significant decrease in hematopoietic area and an increase in adipocyte content in older adult BM (65–92 years). In agreement, Justesen et al. (2001) found decrease in the hematopoietic tissue and increase in the adipocyte tissue, both age-related. Moreover, patients with osteoporosis (52–92 years) displayed an increase in the adipocyte tissue compared to healthy normal individuals (30–100 years). Another characteristic observed in aged individuals is the bias in leukocyte generation leading to increase of myeloid progenitor cells and decrease of lymphoid progenitor cells. Aguilar-Navarro et al. (2020) found that older adults (65–92 years) presented a higher percentage of maturing myeloid cells in the hematopoietic area of BM which correlated with a peripheral increase in total myeloid cells and decrease in lymphoid cells in these individuals. In agreement Pang et al. (2011) observed in old individuals (65–85 years) that human HSC exhibit myeloid-biased differentiation potential compared with young HSC.

Considering these findings, it has been suggested that aged individuals present a decrease in the number of leukocytes in circulating blood and an increase in the myeloid-derived suppressor cells (MDSC) in comparison with the young population. In addition, morbidities can act as enhancers of these alterations in blood components.

Regarding to mature leukocytes presence in BM due to migration from peripheral blood, it was observed by Herndler-Brandstetter et al. (2012) that the number of $CD4^+$ and $CD8^+$ T cells is maintained in BM of ageing individuals (66 ± 3.1 years) with a decline of naïve and increase in effector memory T cells. Ogawa et al. (2000) performed immunohistology in biopsies of BM (newborn—100 years) and observed that older individuals (80–100 years) presented low cellularity, decreased proliferative activity and increased apoptosis. T cells, B cells and macrophages were also diminished in BM of older individuals. In addition, committed $CD34^+CD19^+$ B-lymphoid progenitors were also found in reduced percentage in BM with age (>70 years) (Kuranda et al. 2011).

Pritz et al. (2015) found in BM biopsies mainly plasma B cells whereas a higher percentage of memory B cells was preferentially observed in peripheral blood. Frequencies of plasma and memory B cells either in bone marrow and blood decreased with age, while no effect was observed in immature and naïve B cells. BM plasma B cells specific for tetanus and diphtheria declined, whereas influenza A- and cytomegalovirus-specific BM plasma cells were not affected.

Naismith et al. (2019) found in BM an increase of total T cells and also of highly differentiated $CD8^+$ T cells with age (39–87 years old). Conversely, natural killer T cells (NKT), monocytes, B ($CD19^+$) cells and naïve $CD8^+$ T cells presented age-related decrease. Concentrations of diphtheria-specific antibodies in blood correlated negatively with highly differentiated $CD8^+$ T cells and $CD8^+$ and $CD4^+$ exhausted central memory in BM.

Changes observed in the studied cells should be considered as they probably impact the efficacy of immunity after vaccination in older individuals.

2.1.1 Thymus and Thymopoiesis

The migration of stem cells from BM to thymus (thymocytes) and subsequent steps lead to T cell development. This complex process denominated thymopoiesis comprises: (1) rearrangement of T-cell receptor (TCR) genes with unique specificities, (2) positive and negative selection that will lead to immunocompetent T cells capable to develop immune responses against non-self-antigens and absence of autoreactivity, (3) acquisition of maturation markers by T cells, and (4) migration of naïve T cells to peripheral blood.

Thymus is composed by cortex and medulla, with a network of epithelial and stromal cells. The perivascular space is outside of this network and contains thymus vessels. Thymus epithelium (thymic epithelial cells – TEC) decreases during the ageing process whereas thymic perivascular space becomes more prominent and presents infiltrates of peripheral lymphocytes and adipose tissue (reviewed in Hale 2004). Main causes of thymic involution during the ageing process include reduction in numbers and intrinsic defects in HSC, loss of thymic epithelial cells (TEC) and alterations in thymus stroma; effects of extrinsic factors such as hormones, growth factors, cytokines (reviewed in Dixit 2010). The evaluation of the perivascular space

has shown T cells expressing memory markers and B cells with somatic mutations in immunoglobulin genes suggesting that these cells have migrated from periphery to thymus (Flores et al. 1999, 2001).

Despite the prevailing findings of thymic involution and changes in the thymus architecture and composition, some authors have reported activity in thymic tissue in aged individuals (Flores et al. 1999; Jamieson et al. 1999; von Gaudecker 1978; Bertho et al. 1997). However, the total T cell pool in periphery seems to be maintained by homeostatic expansion of preexisting T cells instead of exporting cells from thymus (Goronzy and Weyand 2005; Yager et al. 2008).

To identify cells exported from thymus, an assay measures T cell receptor excised circles or TRECs that are episomes retained after DNA excised from the chromosome due to TCR rearrangement and has been validated as surrogate marker for thymopoiesis in aging individuals (Flores et al. 1999). TRECs cannot replicate and are lost when T cells expand after encountering an antigen in periphery, thus naïve T cells are measured in periphery as $CD3^{+}CD45RA^{+}TREC^{+}$. TCR diversity is another assay for the evaluation of thymic function can also be evaluated by the TCR diversity. During the ageing process it has been reported a decrease in the naïve T cells in periphery and a decline in TCR diversity (Kimmig et al. 2002; Kohler et al. 2005) that are possible causes for the progressive deficiency in response to vaccine and infection. T cell phenotype ($CD4^{+}$ and $CD8^{+}$) has been based on surface markers such as $CD45RA^{+}$ and $CD27^{+}$ present in naïve cells, in addition to $CCR7^{+}$, $CD31^{+}$, and TREC. After activation via antigens/mitogens, T cells acquire distinct phenotypes, based on CD45RA and CD27, as it follows (Alves et al. 2018):

$CD45RA^{neg}CD27^{+}$ Central Memory, $CD45RA^{neg}CD27^{neg}$ Effector Memory, $CD45RA^{+}CD27^{neg}$ Effector Memory RA.

2.1.2 Lymph Nodes

Human lymph nodes are composed by B cells follicles and T cells follicles in cortex, paracortex, and centrally the medulla region. T cells, B cells, dendritic cells, macrophages and stroma cells can be observed in all compartments of the lymph nodes (Willard-Mack 2006; Hoorweg and Cupedo 2008). In these secondary lymphoid organs, the lymphatic fluid encounter with macrophages and stromal cells that are initial responders (Junt et al. 2008). In addition, cell–cell interactions occur between components such as sinus macrophages and T lymphocytes, afferent veiled cells and T/B lymphocytes, and dendritic cells and afferent antigens. Therefore, lymph nodes present favorable microenvironment for immune cells rapid response to pathogens from blood and lymph and development of long-term adaptive immune responses. The number of lymph nodes, in addition to area and volume of cortex, paracortex and medulla have been reported to decrease during the ageing process (Luscieti et al. 1980; Ahmadi et al. 2013).

Hadamitzky et al. (2010), evaluated superficial inguinal lymph nodes from cadaveric donors and observed diffuse degeneration and a tendency to lymphocyte loss (T and B cells) in aged donors. Lymph nodes presented in majority of the individuals older than 46 years to death very few high endothelial vessels (HEV) suggesting a disconnection from the vascular system and decrease in the immune function. Fibrosis has highly prevalent in age groups 61–75 and 76 + years and lipomatosis was more prominent in donors older than 46 years to death. Taniguchi et al. (2004) found that donors from 72 to 95 years to death presented in lymph nodes very rare germinal centre and secondary follicles larger than the primary follicles or B lymphocyte clusters. Lazuardi et al. (2005) observed in old individuals (67–88 years) that lymph node architecture was maintained but the relative proportion germinal centre/mantle zone was negative correlated with age. Germinal centres were reduced whereas perifollicular B cells tended to be increased. Naïve T cells were diminished in lymph nodes which was probably thymus involution-related with a reduction in $CD8^+$ T cells and not altered numbers of $CD4^+$ T cells. In comparison with young donors, aged individuals presented lower numbers of IgM^+ cells and no difference in IgG^+ cells. Erofeeva et al. (2020) found in mesenteric lymph nodes from cadaveric donors' active fibrosis, lipomatosis, small lymphoid nodules (mainly without a germinal centre), and decrease in Ki-67^+ lymphocytes (proliferation) in both B- and T-dependent zones. Changes were more pronounced in senile age (88 ± 5 years) in comparison with old age (66 ± 3 years) cadaveric donors.

2.1.3 Spleen

Reconstructions of human spleens indicate that the marginal zone is highly-vascularized implying a role in the filtration of pathogens and antigens from the blood (Kusumi et al. 2015). In the red pulp, a large number of macrophages (phagocyte) remove mainly red blood cells, micro-organisms, and cellular debris. In the white pulp, B and T lymphocytes can be activated and proliferate.

Ageing-related changes in the microarchitecture of the human spleen have been described by Alex et al. (2015). They observed that thickness in splenic capsule was influenced by age, thickening post-adolescence and into middle age before thinning again in old age. Increased atrophy of splenic tissue was found in donors of advanced age (70 + years) and corroborated with the decrease in the number and size of B cell follicles with age. Cellularity and vascularity decreased in both red and white pulp and follicles were totally atrophied by the eighth decade. Conversely, Banerjee et al. (2000, 2002) showed that spleens either from post mortem or splenectomized donors (17–81 years) presented no age-related difference in B cells follicle content or in the size of individual follicles. In T cell zones but not in B cells follicles, $CD8^+$ proportion was significantly reduced in the older age group. Moreover, in B cell follicles there was a reduction in the proportion of $CD4^+$ T cells in the older group (Banerjee et al. 2000, 2002).

2.2 Lymphoid Organs and COVID-19

High affinity pathogen-specific antibodies and long-lasting memory B cells are essential against viral infections and after vaccination. The complex mechanisms evolved in this process are highly dependent on T and B cells (generation, maturity, and T-B cells interactions) and, consequently, lymphoid organs integrity is crucial for the adequate immune response. Thus, dysfunctional lymphoid organs may be a predisposing factor for severe COVID-19 disease. A brief report from data obtained in recent literature about COVID-19 and lymphoid organs is listed as it follows.

Bone marrow: post mortem studies conducted in COVID-19 by Falasca et al. (2020) showed that BM presented the hematopoietic tissue replaced by yellow adipocyte-riche marrow either in patients with (27–92 years) or without comorbidities (35–65 years), whereas Ihlow et al. (2021) observed mild fibrosis of BM medullar area (62–79 years). In patients with no comorbidity it was found megakaryocytes hyperplasia (Falasca et al. 2020). Another study, found immaturity of myelopoiesis, severe loss of $CD20^+$ B cells and normal $CD3^+$ T cells (Bao et al. 2020).

Thymus: computed tomography (CT) showed a significant correlation between increased thymus fat tissue and presence of lung involvement in COVID-19 patients (Çakmak et al. 2021). Cuvalier et al. (2021) found that 66% of patients ($n = 50$; 63.2 $\pm$ 16.5 years) with COVID-19 presented enlargement of the thymus which was associated with more extensive lung injury on CT scans but a lower mortality rate. Patients had a higher concentration of IL-7 in circulation and increased production on new lymphocytes (based on TREC levels). Authors suggested that increased thymus mass in COVID patients was a beneficial adaptation to virus-induced lymphopenia. Moreover, thymosin alpha 1 (Tα1), produced by thymic epithelial cells, was administered to patients (21–92 years) with severe COVID-19 and thymic output was measured in periphery by TREC expression and markers of cell exhaustion (PD-1 and Tim-3). The treatment reduced mortality, increased T-cell counts including older patients and in patients with chronic diseases. Cell exhaustion markers decreased in $CD8^+$ T cells and increased thymus output based on levels of TREC (Liu et al. 2020).

Lymph nodes: Kaneko et al. (2020) found in thoracic lymph nodes of severe ill patients that succumbed either before 8 days of admission (66.2 $\pm$ 11.2 years) or succumbed later (63.9 $\pm$ 9.3 years) lack of germinal centre and decrease of B and T cells. The same was reported in 11 patients (66 to 91 years) by Lax et al. (2020). Conversely, Elsoukkary et al. (2021) observed in 32 cases (30–100 years) lymph node architecture preservation, sinus dilatation and congestion. In perihilar and paratracheal lymph nodes, Menter et al. (2020) also found congestion and sinus dilation in lymph nodes in addition to increased number of reactive plasmablasts ($n = 21$; 53–96 years).

Spleen: it was observed atrophy of white pulp (Buja et al. 2020) and lymphocyte depletion (Lax et al. 2020). In agreement, Kaneko et al. (2020) found in severe ill patients, paucity of white pulp, B and T cell reduction. Germinal centre presented B cells with reduction in $Bcl6^+$ and preservation of AID^+ (activation-induced deaminase). Falasca et al. (2020) observed in autopsy of 22 patients (35–65 years) with

COVID-19, reduced volume and size in addition to congested red pulp and lymphoid hypoplasia. Ihlow et al. (2021) found in post mortem samples from patients with COVID-19 (62–79 years), spleen with atrophy of peri-arteriolar white pulp, loss of $CD20^+$ B cells and regular distribution of peri-arteriolar $CD3^+$ T cells. In patients COVID-19 with severe disease (41–79 years) there was more spleen shrinkage than mild patients (16–71 years) (Bao et al. 2020).

2.3 Conclusions

- there are age-related structural changes in primary lymphoid organs that have been associated with reduced cell numbers leaving BM and myeloid-biased generation.
- in periphery cell numbers are maintained by proliferative homeostasis.
- changes in thymus lead to a decreased percentage of naïve lymphocytes and reduced TCR repertoire.
- age-related changes in secondary lymphoid organs lead to impairment in the immunity against infections and/or after vaccination.
- in COVID-19, a higher percentage of aged patients presented more vigorous infection and exacerbation of inflammatory responses.
- structural changes were observed in primary and secondary lymphoid organs of patients with COVID-19.
- it is not possible to differentiate changes caused by age and those associated to COVID-19.
- the further knowledge about changes in lymphoid organs due age and infections could be used to improve the development of vaccines and other therapies.

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Compliance with Ethical Standards

Conflict of Interest: Author declare no conflict of interest.

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References

Aguilar-Navarro AG, Meza-León B, Gratzinger D et al (2020) Human aging alters the spatial organization between CD34+ hematopoietic cells and adipocytes in bone marrow. Stem Cell Reports 15(2):317–325. https://doi.org/10.1016/j.stemcr.2020.06.011

Ahmadi O, McCall JL, Stringer MD (2013) Does senescence affect lymph node and morphology? A Syst Rev ANZ J Surg 83(9):612–618. https://doi.org/10.1111/ans.12067)

Alex L, Rajan ML, Xavier B et al (2015) Microscopic study of human spleen in different age groups. Int J Res Med Sci 3(7):1701–1706. https://doi.org/10.18203/2320-6012.ijrms20150255

Alves AS, Ishimura ME, Duarte YAO et al (2018) Parameters of the immune system and vitamin D levels in old individuals. Front Immunol 9:1122. https://doi.org/10.3389/fimmu.2018.01122

Banerjee M, Sandersosn JD, Spencer J et al (2000) Immunohistochemical analysis of ageing human B and T cell populations reveals and age-related decline of CD8 T cells in spleen but not gut-associated lymphoid tissue (GALT). Mech Ageing Dev 115:85–99. https://doi.org/10.1016/s0047-6374(00)00106-8

Banerjee M, Mehr R, Belelovsky A et al (2002) Age- and tissue-specific differences in human germinal center B cell selection revealed by analysis of IgVH gene hypermutation and lineage trees. Eur J Immunol 32:1947–1957. https://doi.org/10.1002/1521-4141(200207)32)

Bao H, Li G, Fang Y et al (2020) Immunosuppression and cardiovascular dysfunction in patients with severe versus mild coronavirus disease 2019: a case series. Clin Transl Immunology 9(10):e1188. https://doi.org/10.1002/cti2.1188

Bertho J-M, Demarquay C, Moulian N et al (1997) Phenotypic and immunohistological analysis of the human adult thymus: evidence for an active thymus during adult life. Cell Immunol 179(1):30–40. https://doi.org/10.1006/cimm.1997.1148

Buja LM, Wolf DA, Zhao B et al (2020) The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc Pathol 48:107233. https://doi.org/10.1016/j.carpath.2020.107233

Çakmak V, Yilmaz A, Sari T et al (2021) An evaluation of chest computed tomography and hemogram data in patients with COVID-19: the importance of the thymus. Turk J Med Sci. https://doi.org/10.3906/sag-2007-306

Cuvalier P, Hèlène Roux, Couëdel-Courteille A et al. (2021) Protective reactive thymus hyperplasia in COVID-19 acute respiratory distress syndrome. Crit Care 25:4. (2021). https://doi.org/10.1186/s13054-020-03440-1

Dixit VD (2010) Thymic fatness and approaches to enhance thymopoietic fitness in aging. Curr Opin Immunol 22(4):521–528. https://doi.org/10.1016/j.coi.2010.06.010

Erofeeva LM, Mnikhovich MV (2020) Structural and functional changes in the mesenteric lymph nodes in humans during aging. Bull Exp Biol Med 168(5):694–698. https://doi.org/10.1007/s10517-020-04782-0

Elsoukkary SS, Mostyka M, Dillard A et al (2021) Autopsy findings in 32 patients with COVID-19: a single-institution experience. Pathobiology 88(1):56–68. https://doi.org/10.1159/000511325

Falasca L, Nardacci R, Colombo D et al. (2020) Postmortem findings in Italian patients with COVID-19: a descriptive full autopsy study of cases with and without comorbidities. J Infect Dis 9,222(11):1807–1815. doi:10.1093/ infdis/jiaa578.

Flores K, Li J, Sempowski GD et al (1999) Analysis of the thymic perivascular space during aging. J Clin Invest 104:1031–1039. https://doi.org/10.1172/JCI7558

Flores K, Li J, Hale LP (2001) B cells in epithelial and perivascular compartments of adult human thymus. Human Pathol 32:926–934. https://doi.org/10.1053/hupa.2001.27106

Goronzy JJ, Weyand CM (2005) T cell development and receptor diversity during aging. Curr Opin Immunol 17(5):468–475. https://doi.org/10.1016/j.coi.2005.07.020

Hadamitzky C, Spohr H, Debertin AS et al (2010) Age-dependent histoarchitectural changes in human lymph nodes: an underestimated process with clinical relevance? J Anat 216(5):556–562. https://doi.org/10.1111/j.1469-7580.2010.01213.x

Hale LP (2004) Histologic and molecular assessment of human thymus. Ann Diagn Pathol 8(1):50–60. https://doi.org/10.1016/j.anndiagpat.2003.11.006

Herndler-Brandstetter D, Landgraf K, Tzankov A et al (2012) The impact of aging on memory T cell phenotype and function in the human bone marrow. J Leukoc Biol 91(2):197–205. https://doi.org/10.1189/jlb.0611299

Hoorweg K, Cupedo T (2008) Development of human lymph nodes and Peyer's patches. Semin Immunol 20(3):164–170. https://doi.org/10.1016/j.smin.2008.02.003

Ihlow J, Michaelis E, Greuel S (2021) B cell depletion and signs of sepsis-acquired immunodeficiency in bone marrow and spleen of COVID-19 deceased. Int J Infect Dis 103:628–635. https://doi.org/10.1016/j.ijid.2020.12.078

Jamieson BD, Douek DC, Killian S et al (1999) Generation of functional thymocytes in the human adult. Immunity 10(5):569–575. https://doi.org/10.1016/s1074-7613(00)80056-4

Junt T, Scandella E, Ludewig B (2008) Form follows function: lymphoid tissue microarchitecture in antimicrobial immune defense. Nat Rev Immunol 8(10):764–775. https://doi.org/10.1038/nri2414

Justesen J, Stenderup K, Ebbesen EN et al (2001) Adipocyte tissue volume in bone marrow is increased in patient with osteoporosis. Biogerontology 2(3):165–171. https://doi.org/10.1023/a:1011513223894

Kaneko N, Kuo HH, Boucau J et al (2020) Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. Cell 183(1):143-157.e13. https://doi.org/10.1016/j.cell.2020.08.025

Kimmig S, Przybylski G, Schmidt CA et al (2002) Two subsets of naïve T helper cells with distinct T cell receptor excision circle content in human adult peripheral blood. J Exp Med 195(6):789–794. https://doi.org/10.1084/jem.20011756

Kohler S, Wagner U, Pierer M et al (2005) Post-thymic in vivo proliferation of naïve CD4+ T cells constrains the TCR repertoire in healthy human adults. Eur J Immunol 35(6):1987–1994. https://doi.org/10.1002/eji.200526181

Kuranda K, Vargaftig J, de la Rochere P et al (2011) Age-related changes in human hematopietic stem/progenitor cells. Aging Cell 10(3):542–546. https://doi.org/10.1111/j.1474-9726,2011.00675.x

Kusumi S, Koga D, Kanda T et al (2015) Three-dimensional reconstruction of serial sections for analysis of the microvasculature of the white pulp and the marginal zone in the human spleen. Biomed Res 36:195–203. https://doi.org/10.2220/biomedres.36.195

Lax SF, Skok K, Zechner P et al (2020) Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med 173(5):350–361. https://doi.org/10.7326/M20-2566

Lazuardi L, Jenewein B, Wolf AM et al (2005) Age-related loss of naïve T cells and dysregulation of T-cell/B-cell interactions in human lymph nodes. Immunology 114(1):37–43. https://doi.org/10.1111/j.1365-2567.2004.02006.x

Liu Y, Pan Y, Hu Z et al (2020) Thymosin alpha 1 reduces the mortality of severe coronavirus disease 2019 by restoration of lymphocytopenia and reversion of exhausted T cells. Clin Infec Dis 71(16):2150–2157. https://doi.org/10.1093/cid/ciaa630.)

Luscieti P, Hubschmidt T, Cottier H et al (1980) Human lymph node morphology as a function of age and site. J Clin Pathol 33:454–461. https://doi.org/10.1136/jcp.33.5.454

Menter T, Haslbauer JD, Nienhold R et al (2020) Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 77(2):198–209. https://doi.org/10.1111/his.14134

Naismith E, Pangrazzi L, Grasse M et al (2019) Peripheral antibody concentrations are associated with highly differentiated T cells and inflammatory processes in the human bone marrow. Immun Ageing 16:21. https://doi.org/10.1186/s12979-019-0161-z

Ogawa T, Kitagawa M, Hirokawa K (2000) Age-related changes of human bone marrow: a histometric estimation of proliferative cells, apoptotic cells, T cells, B cells and macrophages. Mech Ageing Dev 117(1–3):57–68. https://doi.org/10.1016/s0047-6374(00)00137-8)

Pang WW, Price EA, Sahoo D et al (2011) Human bone marrow hematopoietic stem cells are increased in frequency and myeloid-biased with age. Proc Natl Acad Sci USA 108(50): 20012–20017. https://doi.org/10.1073/pnas.1116110108

Povsic TJ, Zhou J, Adams SD et al (2010) Aging is not associated with bone marrow- resident progenitor cell depletion. J Gerontol A Biol Sci Med Sci 65(10):1042–1050. https://doi.org/10.1093/gerona/glq110

Pritz T, Lair J, Ban M et al (2015) Plasma cell numbers decrease in bone marrow of old patients. Eur J Immunol 45(3):738–746. https://doi.org/10.1002/eji.201444878

Taniguchi I, Sakurada A, Murakami G et al (2004) Comparative histology of lymph nodes from aged animals and humans with special reference to the proportional areas of the nodal cortex and sinus. Ann Anat 186(4):337–347. https://doi.org/10.1016/S0940-9602(04)80053-0

Tuljapurkar SR, McGuire TR, Brusnahan SK et al (2011) Changes in bone marrow fat content associated with changes in hematopoietic stem cell numbers and cytokine levels with aging. J Anat 219(5):574–581. 10.1111/j. 1469–7580.2011. 01423.x

von Gaudecker B (1978) Ultrastructure of the age-involuted adult human thymus. Cell Tiss Res 186:507–525. https://doi.org/10.1007/BF00224939

Yager EJ, Ahmed M, Lanzer K et al (2008) Age-associated decline in T cell repertoire diversity leads to holes in the repertoire and impaired immunity to influenza virus. J Exp Med 205(3):711–723. https://doi.org/10.1084/jem.20071140

Willard-Mack CL (2006) Normal structure, function, and histology of lymph nodes. Toxicol Pathol 34(5):409–424. https://doi.org/10.1080/01926230600867727

Chapter 3
Immunesenescence and Compromised Removal of Senescent Cells: Implications for Health in Old Age

Jon Hazeldine and Janet M. Lord

Abstract Cellular senescence is a state of stable cell cycle arrest triggered by internal and external stressors. A major hallmark of senescent cells is the senescent associated secretory phenotype (SASP), an inflammatory secretome consisting of cytokines, chemokines, growth factors and proteases. When transient in nature, senescent cells are beneficial, aiding in such physiological processes as tissue repair and regeneration. However, when senescent cells persist, SASP-driven inflammation promotes tissue and organ dysfunction. Through direct cytotoxicity, the immune system regulates an individuals senescent cell load. Compared to younger subjects, older adults exhibit an increased senescent cell burden that has been suggested to drive the development of age-related pathologies. The accumulation of senescent cells that occurs with age is accompanied by remodelling of the immune system. Termed immunesenescence, ageing results in marked alterations in the innate and adaptive arms of the immune system. Here, we discuss immunosurveillance of senescent cells in the context of an ageing immune system, suggesting that immunesenescence underpins the increased senescent cell load of older adults. Moreover, we propose the idea of a vicious cycle, whereby, via the SASP, senescent cells exacerbate immunesenescence by promoting dysregulation in aspects of the immune response that are otherwise unaffected by the ageing process.

Keywords Ageing · Cellular senescence · Immunesenescence · Senescence associated secretory phenotype · Senescent cells

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3.1 Introduction

Triggered in response to a range of stressors, which include DNA damage, protein aggregation and chronic mitogen stimulation, cellular senescence describes a state of stable cell cycle arrest (Hernandez-Segura et al. 2018; Robbins et al. 2021; Song et al. 2020). Depending upon the type of stressor that causes cells to enter a senescent state, the process of cellular senescence can be broadly defined as replicative-induced, stress-induced or oncogene-induced (Song et al. 2020). Whilst a diverse array of stimuli can promote cellular senescence, it is the activation of two signalling pathways that is primarily responsible for establishing and maintaining the state of cell cycle arrest. By inhibiting the cyclin-dependent kinases (CDK)-2, CDK-4 and CDK-6, activation of p53 and $p16^{INK4a}$ signalling pathways triggers growth arrest by preventing inactivation of the tumour suppressor protein, retinoblastoma (RB) (Ohtani et al. 2004, 2009).

Currently, whilst we await the discovery of a single, universal and highly specific biomarker of cellular senescence, senescent cells are identified using a combination of morphological, phenotypic and inflammatory markers (Burton and Stolzing 2018; Hernandez-Segura et al. 2018; Di Micco et al. 2021; Robbins et al. 2021). Visually, senescent cells are characterised by an enlarged flattened morphology, nuclear expansion and an increased lysosomal content, the latter coinciding with an up-regulation in the activity of the lysosomal hydrolase beta–galactosidase (Hernandez-Segura et al. 2018; Song et al. 2020). A consequence of reduced mitophagy, an accumulation of aged and dysfunctional mitochondria is another morphological hallmark of senescent cells (Hernandez-Segura et al. 2018; Korolchuk et al. 2017; Song et al. 2020). Due to decreased membrane potential, these mitochondria generate increased amounts of reactive oxygen species (ROS), which are also important for maintaining growth arrest during the early stages of senescence induction (Hernandez-Segura et al. 2018; Passos et al. 2007; Ziegler et al. 2015). Other features of senescent cells include a resistance to apoptosis, increased metabolic activity and an inflammatory secretome termed the senescence-associated secretory phenotype (SASP) (Hernandez-Segura et al. 2018; Song et al. 2020). Considered one of the major hallmarks of cellular senescence, the SASP encompasses a broad range of inflammatory molecules that are actively secreted by senescent cells and includes pro-inflammatory cytokines, chemokines, growth factors, proteases, microRNAs and bioactive lipids (Coppé et al. 2008, 2010; Hernandez-Segura et al. 2018; Narzt et al. 2021; Robbins et al. 2021). Analysis of cell culture supernatants has shown that many of these components, including microRNAs and cytokines, reside in extracellular vesicles (EVs) (Terlecki-Zaniewicz et al. 2018; Wallis et al. 2020). Lipid encapsulated membranous structures, EVs facilitate the transport of SASP-associated factors between cells. Consequently, it is via EVs and their cargo that senescent cells communicate with their environment, and influence the phenotype and function of neighbouring cells (Acosta et al. 2013; Nelson et al. 2012, 2018; da Silva et al. 2019; Terlecki-Zaniewicz et al. 2018; Wallis et al. 2020).

Beyond its well established role as a potent mechanism of tumour suppression, cellular senescence is implicated in a range of physiological processes such as tissue repair and regeneration, wound healing and embryonic development (Demaria et al. 2014; Jun and Lau 2010; Krizhanovsky et al. 2008; Muñoz-Espín et al. 2013; Sarig et al. 2019). In these settings, the beneficial effects of senescent cells are attributed to their transient nature. Indeed, when senescent cells persist, tissue regeneration is dysregulated and a return to homeostasis is delayed (Krizhanovsky et al. 2008). Involving both the innate and adaptive arms of the immune system, immunosurveillance is one mechanism that regulates an individuals senescent cell burden. Through recognition of SASP-associated chemokines, natural killer (NK) cells, neutrophils, monocytes and both $CD4^+$ and $CD8^+$ T cells are attracted towards senescent cells (Egashira et al. 2017; Eggert et al. 2016; Kang et al. 2011; Krizhanovsky et al. 2008; Xue et al. 2007). Activated by the presence of stress-inducible ligands on the surface of senescent cells, including MICA and ULBP2, immune cells contribute to the elimination of senescent cells through direct and indirect cytotoxicity (Burton and Stolzing 2018; Kale et al. 2020; Sagiv and Krizhanovsky 2013). It has been proposed that in situations where immunosurveillance is impaired, and senescent cells persist, that a SASP-induced chronic inflammatory state would ensue (Davan-Wetton et al. 2021). Suggested to promote tissue and organ dysfunction, this increased senescent cell burden would be reinforced by bystander senescence, a term used to describe the ability of senescent cells to induce a senescent phenotype in neighbouring proliferation-competent cells (Acosta et al. 2013; Nelson et al. 2012, 2018; da Silva et al. 2019). Thus, taken together, these data indicate that whilst beneficial in the short-term, persistent cell senescence may have detrimental consequences for the host.

Senescent cell accumulation is a hallmark of ageing, with senescent cell loads correlating positively with chronological age (Dimri et al. 1995; Martin and Buckwalter 2001; Ressler et al. 2006). It has been suggested that by promoting changes in tissue architecture, interfering with tissue homeostasis and stimulating chronic inflammatory responses that life-long accumulation of senescent cells contributes to the ageing process and the development of age-related diseases (Davan-Wetton et al. 2021; van Deursen 2014; Ovadya and Krizhanovsky 2014). Supporting this idea, senescent cells have been detected in the affected tissues of patients with such age-associated conditions as osteoarthritis (OA) and idiopathic pulmonary fibrosis (IPF) (Jeon et al. 2017; Waters et al. 2018), whilst in murine studies, selective elimination of senescent cells prolongs healthy lifespan by reversing or delaying age-related deterioration (Baker et al. 2011, 2016; Xu et al. 2018). Increased production and/or reduced clearance are two possible explanations for the increased senescent cell burden of older adults. Focussing on the latter, ageing is accompanied by marked alterations in the function, phenotype and composition of the immune system. This age-related remodelling, termed immunesenescence, spans both innate and adaptive immunity, and results in reduced activity of immune cells that are crucial for the recognition and elimination of senescent cells (Agarwal and Busse 2010; Hazeldine and Lord 2015). Thus, two defining features of the ageing process, immunesenescence and cellular senescence appear to be intimately linked.

Focussing on the older adult, the purpose of this chapter is to summarise our current understanding of senescent cell immunosurveillance and consider how this process may be altered as a consequence of immunesenescence. Moreover, with recent studies showing that senescent cells can evade detection by the immune system by modulating their surface phenotype, and also suppress immune activation via their SASP, we propose that cellular senescence exacerbates immunesenescence by promoting dysregulation in aspects of the immune response that are otherwise unaffected by the ageing process. We conclude our review by discussing whether strategies aimed at delaying or circumventing immunesenescence represent viable therapeutic approaches by which to reduce the increased senescent cell burden of older adults and thus delay the onset of age-related pathologies.

3.1.1 The Role of Cellular Senescence in Ageing and Age-Related Disease

Based on their discovery that human fibroblasts underwent a finite number of divisions in vitro before entering an irreversible state of cell cycle arrest, Hayflick and Moorhead were the first to propose a role for cellular senescence in the ageing process (Hayflick and Moorhead 1961). For many years, support for this theory was restricted to associative data, with both murine and human-based studies reporting an age-related increase in senescent cell numbers across multiple tissues (Dimri et al. 1995; Iske et al. 2020; Martin and Buckwalter 2001; Ressler et al. 2006; Waaijer et al. 2012). However, over the past decade, methodological advancements, combined with a greater understanding of cellular senescence at the molecular level, have provided researchers with the tools and insight to directly investigate whether senescent cells drive physiological ageing and the development of age-associated disorders.

Using a combined transgenic and pharmacological approach to directly eliminate $p16^{INK4a+}$ senescent cells in a murine model of accelerated ageing, Baker and colleagues were the first to demonstrate a role for cellular senescence in both the onset and progression of age-related phenotypes (Baker et al. 2011). Compared to littermate controls, mice subjected to life-long or late-life clearance of senescent cells exhibited delayed onset of kyphosis, cataracts and sarcopenia, with the retention in muscle mass and fibre size coinciding with enhanced functional performance (Baker et al. 2011). Employing similar genetic and pharmacological techniques to those of Baker et al., subsequent studies have shown that removal of senescent cells can extend healthy lifespan (Baker et al. 2016), attenuate age-related deterioration in organ function (Baker et al. 2016), prevent age-associated bone loss (Farr et al. 2017), preserve cognitive function (Bussian et al. 2018), alleviate physical dysfunction (Xu et al. 2018) and reduce the risk of mortality without extending late-life morbidity (Xu et al. 2018). Conversely, transplanting senescent cells into young mice directly induces physical dysfunction and frailty (Xu et al. 2018). Interestingly, in a murine model of accelerated T cell senescence, Desdin-Mico and colleagues recently

showed that by creating a systemic pro-inflammatory environment, dysfunctional T cells promoted widespread organ dysfunction that culminated in multi-morbidity and premature death (Desdín-Micó et al. 2020). Demonstrating that T cells regulate organismal fitness and lifespan, these results suggest that the effects of immunesenescence may extend beyond compromising the immune response of older adults. Based in part on the findings of these studies, a revised model for how cellular senescence may contribute to organismal ageing has recently been proposed. Expanding upon the theory of Hayflick and Moorhead (Hayflick and Moorhead 1961), this model hypothesises that by (i) interfering with tissue homeostasis and regeneration, (ii) stimulating chronic inflammatory responses and/or (iii) promoting changes in tissue architecture, senescent cells promote physiological ageing by driving both tissue and organ dysfunction (van Deursen 2014; Naylor et al. 2013).

Identified by their flattened morphology, heightened β–galactosidase activity and increased expression of $p16^{INK4a}$, p21 or telomere-associated foci, senescent cells have been detected in the affected tissues of patients with such age-related diseases as OA (Jeon et al. 2017), IPF (Álvarez et al. 2017; Minagawa et al. 2011; Schafer et al. 2017), atherosclerosis (Gorenne et al. 2006; Minamino et al. 2002) and Alzheimer's disease (Baker and Petersen 2018; Martínez-Cué and Rueda 2020). Suggesting that their presence may contribute to the development of these conditions, retention of senescent cells in mice has been shown to promote age-related cartilage degeneration (Jeon et al. 2017) and atheroma formation (Childs et al. 2016), whilst clearance of senescent cells prevented neurodegeneration and alleviated fibrotic lung disease (Bussian et al. 2018; Schafer et al. 2017). Akin to the beneficial effects reported in murine models, statistically significant and clinically meaningful improvements in physical function were recently reported for fourteen patients with mild to severe IPF who participated in the first clinical trial of short-term dasatinib and quercetin therapy (Justice et al. 2019). As a combined treatment, dasatinib, a protein tyrosine kinase inhibitor, and quercetin, a flavonoid that interferes with anti-apoptotic signalling, significantly reduces senescent cell tissue burden by selectively inducing apoptosis of senescent cells (Hickson et al. 2019; Xu et al. 2018). Thus, although requiring validation in larger randomised clinical trials, these preliminary results suggest that senescent cell clearance may be of potential clinical benefit for patients with established age-associated chronic diseases. On this note, a clinical trial examining the effect of senescent cell clearance on physical ability and frailty in individuals with diabetic chronic kidney disease is currently underway (ClinicalTrials.gov Identifier: NCT02848131).

3.1.2 *Immunesenescence: A Contributory Factor in the Age-Associated Accumulation of Senescent Cells?*

Having established that cellular senescence is causally implicated in ageing, gerontologists are now focussing upon understanding the mechanisms by which senescent cells accumulate with age. A product of mathematical modelling, Karin et al. recently devised the saturating removal (SR) model, which posits that the increased senescent cell burden within tissues of older adults is a consequence of two interacting factors: (i) a linear increase in senescent cell production rate with age and (ii) a reduced rate of immune-mediated clearance that is directly dependent upon senescent cell load rather than donor age (Karin et al. 2019). If correct, then one would predict that the capacity for senescent cell removal would be inversely associated with senescent cell burden. Recently, using the experimental approach of parabiosis, Yousefzadeh and colleagues demonstrated that, when compared to isochronic pairings of old mice, markers of cellular senescence (e.g. $p16^{INK4a}$, $p21^{Cip1}$, IL-6) were significantly lower in tissues obtained from old mice that had undergone heterochronic parabiosis with young mice (Yousefzadeh et al. 2020). In the context of the SR model, this result can potentially be explained by the fact that the shared immune system of parabiotic mice would be exposed to, and thus inhibited by, the average senescent cell concentration of the two mice (Karin and Alon 2020). Hence, the overall lower senescent cell burden of a young-old heterochronic pairing would result in a greater rate of senescent cell removal in the old heterochronic parabiont due to the partial alleviation of senescent cell-mediated inhibition of immune function (Karin and Alon 2020). Mechanistically, it has yet to be determined exactly how senescent cells inhibit their own removal, though it appears likely that more than one process is involved. Saturation of immune cells, disruption of tissue architecture and/or the production of inhibitory factors are some of the hypotheses proposed to date (Karin et al. 2019; Karin and Alon 2020).

Via their secretion of pro-inflammatory cytokines and chemokines, senescent cells are highly immunogenic, with in vivo studies demonstrating the presence of both innate and adaptive immune cells at sites of senescent cell accumulation (Egashira et al. 2017; Eggert et al. 2016; Kang et al. 2011; Krizhanovsky et al. 2008; Xue et al. 2007). In this section, as well as discussing our current understanding of how immune cells recognise and eliminate senescent cells, we consider the impact that immunesenescence may have on this process. Specifically, we posit that, independent of senescent cell load, ageing results in impaired immunosurveillance of senescent cells (Fig. 3.1). Creating a vicious cycle, the ensuing senescent cell burden would further dampen the immune response of older adults, resulting in the expansion of a senescent cell pool that would subsequently drive tissue and organ dysfunction.

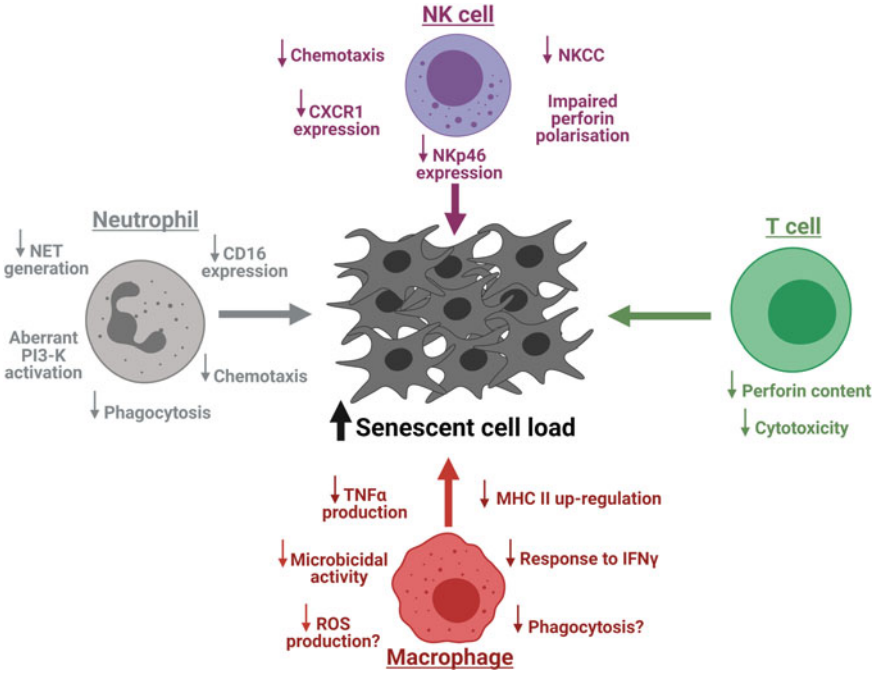

Fig. 3.1 Immunesenescence: a driver of senescent cell accumulation in the older adult? Summary of the age-associated changes in innate and adaptive immunity that we propose would result in impaired clearance of senescent cells. IFN-γ, Interferon-gamma; MHC II, Major histocompatibility complex class II; NKCC, Natural killer cell cytotoxicity; NET, Neutrophil extracellular trap; PI3K, phosphatidylinositol-3-kinase; ROS, Reactive oxygen species; TNFα, Tumour necrosis factor-alpha. Figure created with BioRender.com.

3.1.3 NK Cells

Renowned for their role in the early detection and elimination of virus-infected, cancerous and stressed cells, NK cells are large granular lymphocytes of the innate immune system. Over the past decade, it has become increasingly evident that senescent cells are also subject to NK cell-mediated immunosurveillance (Brighton et al. 2017; Krizhanovsky et al. 2008; Sagiv et al. 2013, 2016; Soriani et al. 2009; Xue et al. 2007). For example, results of in vitro cytotoxicity assays have shown senescent fibroblasts and senescent hepatic stellate cells (HSCs) are NK cell targets (Krizhanovsky et al. 2008; Sagiv et al. 2013, 2016), whilst in an in vivo model of liver fibrosis, an increased senescent cell burden was detected in NK cell depleted mice when compared to littermate controls (Krizhanovsky et al. 2008).

Characterised by the secretion of the pore-forming protein perforin and a collection of serine proteases termed granzymes, the granule exocytosis pathway is one of two contact-dependent mechanisms utilised by NK cells to directly eliminate their

targets (Smyth et al. 2005). Demonstrating the importance of this pathway in NK cell-mediated clearance of senescent cells, pre-treating NK cells in vitro with the perforin inhibitor concanamycin A or the granzyme B inhibitor 3,4-Dichloroisocoumarin significantly reduces their cytotoxic activity towards senescent cells in co-culture experiments (Brighton et al. 2017; Sagiv et al. 2013).

The induction of NK cell cytotoxicity (NKCC) is governed by the balance of signals transmitted through an array of surface expressed activatory and inhibitory receptors (Paul and Lal 2017). Phenotypic comparisons of proliferating and senescent cells have shown cellular senescence coincides with an up-regulation in the surface expression of ligands recognised by a number of NK cell activating receptors. These ligands include MHC class I polypeptide-related sequence A (MICA), the UL16 binding proteins (ULBP) 1 and 2 and the type III intermediate filament protein vimentin, which are detected by the receptors NKG2D or NKp46 (Frescas et al. 2017; Iannello et al. 2013; Krizhanovsky et al. 2008; Pereira et al. 2019; Sagiv et al. 2016). Highlighting a central role for NKG2D signalling in NK cell immunosurveillance of senescent cells, the addition of NKG2D blocking antibodies to NK cell-senescent cell co-cultures significantly reduces NKCC (Brighton et al. 2017; Sagiv et al. 2016).

Physiological ageing is associated with significant changes in NK cell biology. Dominated by mature cytotoxic $CD56^{DIM}$ and terminally differentiated $CD56^{+}57^{+}$ NK cells, the circulating NK cell pool of older adults is significantly larger than that of younger subjects, with this expansion suggested to be the result of an age-associated accumulation of long-lived NK cells (Almeida-Oliveira et al. 2011; Le Garff- Tavernier et al. 2010; Hazeldine et al. 2012; Di Lorenzo et al. 1999; Lutz et al. 2005; Lutz et al. 2011; Simpson et al. 2008; Zhang et al. 2007). Phenotypically, whilst the expression of NKG2D is comparable between NK cells of young and older adults (Le Garff-Tavernier et al. 2010; Hazeldine et al. 2012), a significant age-related reduction in the frequency of $NKp46^{+}$ NK cells and the surface density of the chemokine receptor CXCR1 has been described (Almeida-Oliveira et al. 2011; Hazeldine et al. 2012; Mariani et al. 2002).

Functionally, age-associated impairments in both NK cell migration and cytotoxicity at the single cell level have been reported across a number of studies (Beli et al. 2011; Fang et al. 2010; Hazeldine et al. 2012; Mariani et al. 1990; Miyaji et al. 1997). With regards to NKCC, whilst it is currently unclear as to whether perforin expression is reduced with age (Hazeldine et al. 2012; Mariani et al. 1996; Rukavina et al. 1998), we have shown that upon the recognition of leukaemic target cells K562, NK cells from older adults release significantly less perforin into the immunological synapse (Hazeldine et al. 2012).

In terms of how NK cell immunesenescence may impact on senescent cell immunosurveillance, we suggest that reduced surface expression of CXCR1, a receptor for the SASP-associated chemokine IL-8, coupled to the age-related decline in the frequency of $NKp46^{+}$ NK cells and reduced perforin release upon target cell binding would result in NK cells of older adults exhibiting impaired migration towards and cytotoxicity against senescent cells. Providing some support for this theory, an increased senescent cell burden was recently detected in aged perforin

knockout mice, who when compared to littermate controls, exhibited an accelerated ageing phenotype and shortened life-span (Ovadya et al. 2018). However, in a perforin knockout mouse, the cytolytic activity of both NK cells and $CD8^+$ T cells would be disrupted meaning that it is not possible to assign the increased senescent load solely to defective NKCC. Moreover, a total deficiency of perforin is not representative of the remodelled immune system of older adults, which is characterised by a significant impairment in, but not a total absence of, perforin-mediated NKCC.

3.1.4 Macrophages

Coinciding with increased expression of the chemoattractants macrophage colony-stimulating factor and monocyte chemoattractant protein-1 (MCP-1), macrophages infiltrate tissues that contain senescent cells (Egashira et al. 2017; Eggert et al. 2016; Hall et al. 2016; Kang et al. 2011; Krizhanovsky et al. 2008; Xue et al. 2007). The importance of macrophages in senescent cell clearance is demonstrated by the increased senescent cell loads of mice selectively depleted of these phagocytes (Egashira et al. 2017; Kang et al. 2011).

Macrophages can be broadly divided into one of two distinct subsets, both of which are potentially involved in senescent cell immunosurveillance. Characterised by increased production of pro-inflammatory cytokines and ROS, "classically activated" M1 macrophages exhibit strong microbicidal activity. Treating macrophages in vitro with conditioned media from cultures of senescent HSCs promotes polarisation of macrophages towards an M1 phenotype (Lujambio et al. 2013). In accordance with their cytotoxic nature, M1 macrophages directly eliminate senescent HSCs upon in vitro co-culture (Lujambio et al. 2013). Although renowned for their angiogenic, tissue remodelling and resolution properties, "alternatively activated" M2 macrophages exhibit enhanced phagocytic activity when compared to M1 macrophages (Schaper et al. 2016; Schulz et al. 2019). Suggesting a potential role for this macrophage subset in the removal of senescent cells, Hall et al. demonstrated that macrophages with an M2-like phenotype surrounded senescent cells that were implanted into the peritoneal cavity of mice (Hall et al. 2016, 2017).

Mechanistically, macrophages directly eliminate senescent cells via a two-step process. First, via the secretion of tumour necrosis factor-alpha (TNF-α), macrophages induce apoptosis of the senescent cell before engulfing it via phagocytosis (Ogata et al. 2021). Exactly how macrophages recognise senescent cells is an area of research that has received little attention to date. However, some potential receptor-ligand pairings have been proposed (Burton and Stolzing 2018). For instance, oxidized phospholipids present on the surface of senescent cells could be detected by the scavenger receptors CD36 and receptor for advanced glycation end products (RAGE) (Burton and Stolzing 2018), whilst the C-type lectin receptor macrophage galactose-type lectin may bind to the modified surface glycans that decorate the surface of senescent cells (Burton and Stolzing 2018).

How physiological ageing impacts upon macrophage function is currently unclear. For example, whilst on the one hand, significant age-associated impairments in macrophage polarisation, TNF-α secretion and microbicidal activity have been reported (Boehmer et al. 2004; Mahbub et al. 2012; Thevaranjan et al. 2017), the phagocytic capacity of these cells and their ability to generate ROS has been reported to be either increased, decreased or unchanged with age (Albright et al. 2016; Gomez et al. 2008; Plowden et al. 2004). Thus, in order to investigate whether impaired immune surveillance by macrophages may contribute to the age-associated accumulation of senescent cells, a greater understanding of precisely how macrophages eliminate these cells and how these functions are influenced by the ageing process is required.

3.1.5 Neutrophils

Attracted by the SASP residing chemokines CXCL-8 and CXCL-1, neutrophils infiltrate tissues that contain senescent cells (Kang et al. 2011; Krizhanovsky et al. 2008; Xue et al. 2007). As frontline effector cells of the innate immune system, neutrophils are equipped with a range of defence mechanisms, which include the generation of neutrophil extracellular traps (NETs). NETs are DNA lattices decorated in granule-derived peptides and enzymes that are released by neutrophils into the extracellular space in order to capture and neutralise invading pathogens (Brinkmann et al. 2004). Triggered in response to IL-1β and CXCL-1, neutrophils were recently shown to generate NETs when cultured in vitro with senescent endothelial cells, a response that resulted in the induction of senescent cell apoptosis (Binet et al. 2020). Demonstrating the physiological relevance of this response, NETs were detected adjacent to senescent vascular endothelial cells in a murine model of oxygen-induced retinopathy, with NET-induced removal of senescent cells promoting vascular remodelling (Binet et al. 2020).

In an attempt to identify novel biomarkers of cellular senescence, Frescas et al. screened plasma samples obtained from mice immunised with senescent cells and discovered a germ-line-encoded monoclonal IgM antibody that recognised vimentin, an intermediate filament protein expressed on the surface of senescent cells (Frescas et al. 2017). Suggesting a potential role for humoral innate immunity in the clearance of senescent cells, these naturally occurring antibodies would, via the process of opsonisation, coat senescent cells in "eat me" signals that would be detected by Fc receptors expressed on the surface of phagocytic cells. Thus, alongside NET formation, neutrophils may eliminate senescent cells through the process of phagocytosis.

When treated with CXCL-8 or CXCL-1, neutrophils isolated from older adults exhibit reduced NET production and chemotaxis, with this latter impairment associated with aberrant activation of the lipid kinase phosphatidylinositol-3-kinase (Hazeldine et al. 2014; Sapey et al. 2014). Furthermore, attributed to reduced surface expression of the Fc receptor CD16, we have previously demonstrated an age-associated

reduction in neutrophil phagocytosis of opsonised pathogens (Butcher et al. 2001). Thus, as three key immune surveillance mechanisms of neutrophils are impaired with age, neutrophil-mediated clearance of senescent cells may be reduced in older adults.

3.1.6 T Cells

In vitro co-culture experiments have shown cytotoxic $CD8^+$ T cells induce apoptosis of senescent human dermal fibroblasts (Pereira et al. 2019). Considered a marker of degranulation, the presence of the lysosomal membrane protein CD107a on the surface of $CD8^+$ T cells following exposure to senescent fibroblasts suggests that granule exocytosis is the pathway through which $CD8^+$ T cells eliminate senescent cells (Pereira et al. 2019). As reported for NK cells (Brighton et al. 2017; Sagiv et al. 2016), pre-incubation of $CD8^+$ T cells with NKG2D blocking antibodies significantly reduces their cytotoxicity towards senescent fibroblasts (Pereira et al. 2019).

Compared to $CD8^+$ T cells isolated from younger adults, those obtained from older subjects exhibit significantly reduced perforin content and impaired cytotoxicity against target cells expressing MICA, a ligand of NKG2D (Rukavina et al. 1998). Thus, although further studies are required, we hypothesise that physiological ageing would coincide with a marked decline in $CD8^+$ T cell-mediated cytotoxicity towards senescent cells.

Both $CD4^+$ and $CD8^+$ T cells are recruited to tissues that contain senescent cells (Kang et al. 2011). In contrast to the above mentioned in vitro study, results of an in vivo model of oncogene-induced senescence found that it was antigen-specific $CD4^+$, and not $CD8^+$, T cells that were responsible for the removal of precancerous senescent hepatocytes (Kang et al. 2011). Indeed, whereas mice genetically or pharmacologically depleted of $CD8^+$ T cells exhibited a level of senescent cell clearance that was comparable to that of wild type mice, an increased senescent cell burden was detected in the livers of mice lacking $CD4^+$ T cells (Kang et al. 2011). However, rather than eliciting a direct cytotoxic effect, the role of $CD4^+$ T cells was immunomodulatory, with these lymphocytes requiring the anti-microbial functions of monocytes/macrophages to eliminate the senescent hepatocytes (Kang et al. 2011). Although not investigated by the authors, it is conceivable that this co-operation between monocytes/macrophages and $CD4^+$ T cells involved a T cell-derived IFN-γ driven activation of monocyte/macrophage function. For instance, in response to this pro-inflammatory cytokine, macrophages exhibit an enhanced oxidative burst response and up-regulate their transcription of major histocompatibility complex II (MHC II) genes (Khan et al. 2016; Nathan et al. 1983; Wu et al. 2019). In the context of ageing, increased production and secretion of IFN-γ has been reported for $CD4^+$ T cells isolated from older adults when compared to younger subjects (Sakata-Kaneko et al. 2000; Yen et al. 2000). However, the responsiveness of macrophages to IFN-γ stimulation is significantly impaired. For example, reduced surface expression of

MHC II molecules, decreased ROS production and impaired activation of intracellular signalling pathways are all features of macrophages isolated from aged rodents following IFN-γ treatment (Davila et al. 1990; Ding et al. 1994; Herrero et al. 2001; Yoon et al. 2004). Thus, as a consequence of an altered innate immune response, the efficiency by which $CD4^+$T cells mediate the removal of senescent cells is likely to be diminished with age.

3.1.7 Does the SASP Contribute to Senescent Cell Accumulation in Older Adults by Exacerbating Age-Related Defects in Innate and Adaptive Immunity?

In an attempt to avoid detection and removal by the immune system, senescent cells are equipped with a range of immune evasion strategies, which include (i) the upregulation of ligands for inhibitory receptors expressed by cytotoxic lymphocytes, (ii) inhibition of innate immune cell function and (iii) the shedding of activatory ligands detected by NK and $CD8^+$ T cells (Muñoz et al. 2019; Narzt et al. 2021; Pereira et al. 2019). Appearing integral to all of these strategies is the SASP. In this section, we discuss the SASP-mediated immune evasion mechanisms of senescent cells and propose that they further dampen the weakened immune response of older adults.

3.1.8 Shedding of Activatory Ligands, Expression of Inhibitory Ligands and Modulation of NK Cell Phenotype

Treating NK cells with supernatants of senescent cell cultures results in a significant reduction in their expression of the activatory receptor NKG2D (Muñoz et al. 2019). In the older adult, this SASP-driven modulation of NK cell phenotype would be accompanied by the age-related decrease that occurs in the surface expression of NKp46, the receptor that detects the senescent cell associated protein vimentin (Frescas et al. 2017; Garg et al. 2006; Hazeldine et al. 2012). Thus, we suggest that, via a combination of age and the SASP, NK cells of older adults would express fewer receptors capable of detecting senescent cells. Exacerbating this situation further would be the recently described ability of senescent cells to reduce their expression of stress-inducible ligands that activate NK cells. Through the secretion of matrix metalloproteinases, senescent cells can downregulate their expression of the NKG2D ligand MICA (Muñoz et al. 2019). As would be predicted, this shedding of MICA results in increased senescent cell survival in in vitro cytotoxicity assays (Muñoz et al. 2019).

Exposing non-senescent cells to either the conditioned media of senescent cell cultures or the SASP-associated cytokine IL-6 triggers a significant up-regulation in the surface expression of HLA-E (Pereira et al. 2019). A non-classical MHC class I molecule, HLA-E is a ligand of the inhibitory receptor CD94/NKG2A that is expressed by NK and $CD8^+$ T cells (Lee et al. 1998; Pereira et al. 2019). An important immune evasion strategy, inhibition of NKG2A/HLA-E signalling has been shown to enhance both NK and $CD8^+$ T cell-mediated cytotoxicity towards senescent cells (Pereira et al. 2019). Whilst studies have reported either no change or a significant decrease in the frequency of $NKG2A^+$ NK cells with age (Le Garff-Tavernier et al. 2010; Lutz et al. 2005), older adults present with an increased proportion of highly differentiated $CD28^-$ $CD27^-$ $CD8^+$ T cells, whose expression of NKG2A is significantly higher than other $CD8^+$ T cell subsets (Pereira et al. 2019). Thus, the combination of a SASP-induced increase in HLA-E expression on the surface of senescent cells and an age-associated expansion of $NKG2A^+$ $CD8^+$ T cells may contribute to impaired elimination of senescent cells in older adults (Pereira et al. 2019). When combined with the abovementioned SASP-mediated shedding of NKG2D activatory ligands (Muñoz et al. 2019), it may be that the immunological synapse that forms between senescent cells and cytotoxic lymphocytes of older adults is dominated by the ligation of inhibitory receptors. If correct, then this would negatively impact upon NK cell activation, a consequence of which would be the suppression of granule exocytosis and reduced senescent cell clearance.

3.1.9 Secretion of EVs Containing Immunomodulatory MicroRNAs

Alongside pro-inflammatory cytokines, EVs are a prominent component of the SASP (Misawa et al. 2020). EVs are lipid encapsulated membranous structures that transport proteins, lipids and nucleic acids between cells. As a mode of intercellular communication, EVs act both locally and systemically to influence a range of physiological processes.

Replicative senescence in endothelial cells results in a significant up-regulation in the expression of the microRNA miR-146a (Olivieri et al. 2013). Detected in the circulation of older adults (Liu et al. 2021), the EV-associated miR-146a is a negative regulator of NK cell function, with in vitro studies demonstrating that overexpression of this microRNA significantly inhibits NKCC and reduces the expression of perforin (Xu et al. 2017). Conversely, inhibition of miR-146a in NK cells promotes the secretion of the pro-inflammatory cytokines IFN-γ and TNF-α (Xu et al. 2017). Thus, a senescent EV-induced impairment in NK cell function could contribute to the age-related accumulation of senescent cells. Mechanistically, we suggest that this would result from inhibition of NKCC and/or a reduction in the generation of immunomodulatory cytokines, with the latter impairment reducing the ability of NK cells to augment the cytolytic activity of neighbouring immune cells (e.g. macrophages).

3.1.10 Inhibition of Macrophage Function

It has been suggested that via the secretion of pro-inflammatory cytokines and oxidised phospholipids, senescent cells protect themselves from macrophage-mediated cytotoxicity and clearance (Narzt et al. 2021; Ogata et al. 2021). Indeed, pre-treating macrophages with supernatants collected from senescent cell cultures reduces their ability to induce apoptosis of senescent fibroblasts in co-culture experiments (Ogata et al. 2021). This impairment in macrophage cytotoxicity was suggested to result from a SASP-induced reduction in the expression of TNF-α, the cytokine through which these phagocytes trigger apoptosis in senescent cells (Ogata et al. 2021). Expressed on the surface of apoptotic senescent cells is phosphatidylserine, a ligand for the macrophage expressed receptor STAB1. Exposing macrophages in vitro to either senescent cell conditioned media or the SASP associated inflammatory cytokines GM-CSF or IL-1α downregulates expression of STAB1 (Ogata et al. 2021). Interestingly, when compared to samples from younger adults, significantly reduced frequencies of STAB1 positive macrophages and an increased abundance of senescent fibroblasts have been reported in skin samples from older adults (Ogata et al. 2021). Thus, we suggest that a combination of age (Mahbub et al. 2012) and SASP (Narzt et al. 2021; Ogata et al. 2021) induced changes in macrophage phenotype and function would contribute, via reduced cytotoxicity and clearance, to the persistence of senescent cells in older adults.

3.1.11 Recruitment of Immature Myeloid-Derived Suppressor Cells (MDSCs)

In a murine model of oncogene-induced hepatocyte senescence, Eggert et al. reported that via the secretion of the chemokine MCP-1, senescent cells promoted the intrahepatic accumulation of $CCR2^+$ immature myeloid cells (Eggert et al. 2016). Identified as granulocytic and monocytic MDSCs, these immunosuppressive subsets were shown in vitro and in vivo to inhibit $CD8^+$ T cell proliferation, NK cell activation and NKCC mediated by the granule exocytosis pathway (Eggert et al. 2016). Suggested to be the result of an age-related enhancement in myelopoiesis (Bueno et al. 2014), significantly increased frequencies/numbers of MDSCs have been detected in the bone marrow, spleen and lymph nodes of aged mice (Enioutina et al. 2011) as well as in the circulation of older adults (Verschoor et al. 2013; Alves et al. 2018). It is conceivable therefore to think that the recruitment of MDSCs to sites of senescent cell accumulation would be greater in older adults, which would be further intensified by the fact that many components of the SASP (e.g. IL-6, GM-CSF, IL-13) promote MDSC expansion and activation (Gabrilovich and Nagaraj 2009). By creating an immunosuppressive environment, MDSCs would inhibit the cytotoxic activity of NK cells, $CD8^+$ T cells and macrophages, resulting in reduced clearance of senescent cells.

Taken together, these data suggest that via the SASP, senescent cells create a suppressive microenvironment in order to evade detection and elimination by the immune system. We propose that whilst this can be overcome in younger subjects, due to their robust immune response and lower senescent cell burden, the SASP suppresses the immune response of older adults by promoting dysregulation in aspects of immunity that are otherwise unaffected by the ageing process. When these alterations are combined with those that occur as a consequence of immunesenescence, the immunosurveillance of senescent cells in the older adult would be significantly impaired.

3.1.12 Could Immunesenescence Reduce the Efficacy of Strategies Targeting Senescent Cells for the Treatment of Age-Related Diseases?

With a growing body of evidence implicating cellular senescence in the ageing process, senescent cells have been suggested as potential therapeutic targets for the treatment and/or prevention of age-associated diseases. In the past decade, a greater understanding of the signalling pathways that underpin the survival of senescent cells and the mechanisms through which they promote tissue dysfunction has led to the development of senolytics and senomorphics. Two classes of drug with distinct modes of action, senolytics directly eliminate senescent cells whilst senomorphics alleviate the detrimental effects of the SASP (Di Micco et al. 2021; Ovadya and Krizhanovsky 2018; Robbins et al. 2021).

Attributed in part to increased expression of the anti-apoptotic proteins BCL-2, BCL-XL and BCL-W, senescent cells demonstrate resistance to intrinsic and extrinsic apoptosis-inducing signals (Yosef et al. 2016). Drugs that target these proteins are therefore emerging as potential senolytic agents. ABT-263 and ABT-737, two broad acting drugs that inhibit the activity of BCL-2, BCL-XL and BCL-W, as well as the BCL-XL specific inhibitor A1331582, have been shown in animal models of aging to rejuvenate stem cell activity, delay physical decline and extend lifespan (Chang et al. 2016; Moncsek et al. 2018; Oltersdorf et al. 2005; Ovadya et al. 2018). However, senescent cells within certain tissue types (e.g. adipose) are resistant to the actions of these drugs (Zhu et al. 2016), which also induce apoptosis in non-senescent cells such as platelets and neutrophils, resulting in thrombocytopenia and neutropenia respectively (Cang et al. 2015). Thus, with concerns over their safety profile and inability to eliminate all types of senescent cell, inhibitors of BCL-2 family proteins are unlikely to reach the clinical setting as a therapy for senescence associated diseases (Ovadya and Krizhanovsky 2018; Song et al. 2020). In contrast, the efficacy of a combined senolytic therapy of dasatinib, a pan tyrosine kinase inhibitor, and quercetin, a dietary flavonoid that inhibits the PI3K-AKT pathway, has been investigated in clinical trials of patients with chronic age-related conditions. Benefits of this treatment regimen that have been reported to date include: (i) a reduction in senescent cell load, (ii)

reduced systemic inflammation and (iii) improved physical function (Hickson et al. 2019; Justice et al. 2019). However, despite such promising data, concerns have been raised about the lack of understanding of the mechanisms by which these senolytics induce apoptosis of senescent cells as well as the potential side-effects that may arise from long-term treatment (Ovadya and Krizhanovsky 2018; Song et al. 2020). That said, with a recent study suggesting that a senescent cell load equivalent to that of an individual 12 years younger could theoretically be obtained with senolytic therapy every 1–2 months (Karin and Alon 2020), then the benefits of dasatinib and quercetin therapy may be attainable with intermittent "hit and run" treatment regimens.

With many of the detrimental effects associated with cellular senescence assigned to the SASP, suppressing the pro-inflammatory nature of senescent cells may have therapeutic potential. Treating senescent cells in vitro with inhibitors of mitogen activated protein kinases (e.g. P38 and JNK1/2), the mammalian target of rapamycin (mTOR) or modulators of NF-κB activity (e.g. apigenin, kaempferol or metformin) has been shown to significantly decrease their generation of pro-inflammatory cytokines, chemokines and/or growth factors (Alimbetov et al. 2016; Freund et al. 2011; Laberge et al. 2015; Lim et al. 2015; Moiseeva et al. 2013; Xu et al. 2015). Collectively termed senomorphics, one theory for why these compounds may help treat age-related diseases is that by suppressing the SASP, you would reduce senescent cell load by decreasing the rate of bystander senescence (Nelson et al. 2018). Highlighting the potential clinical benefit of this approach, senomorphic treatment of aged mice has been shown to enhance their metabolic and physical function, and prevent age-related bone and fat loss (Farr et al. 2017; Xu et al. 2015a, b). When compared to senolytics, a potential advantage of senomorphics is the retention of senescent cells. Whilst this may seem counterintuitive, it should be remembered that the induction of cellular senescence is important for tissue repair and regeneration and wound healing (Demaria et al. 2014; Jun and Lau 2010; Krizhanovsky et al. 2008). Thus, via the retention of viable senescent cells, senomorphics would be predicted to have less impact upon these physiological processes.

By reducing senescent cell load and alleviating SASP-induced inflammation, it has been suggested that an additional benefit of senolytic or senomorphic therapies would be rejuvenation of the immune system (Prata et al. 2018). Whilst this may be true for younger subjects, we propose that this benefit would not extend to older adults due to the effects of immunesenescence. For example, dampening the suppressive microenvironment created by the SASP would not overcome the inherent age-related defects in the cytotoxic capacity of NK or $CD8^+$ T cells nor the impaired effector functions of neutrophils. Thus, whilst in the short-term, senolytics or senomorphics may reduce the senescent cell load in older adults, their re-emergence would be inevitable due to defective immunosurveillance. We also suggest that immunesenescence would negatively impact upon the efficacy of the immunotherapies that are currently under consideration for increasing the rate of senescent cell clearance in the older adult. These strategies include senescence vaccines and chimeric antigen receptor T cell (CAR-T) therapy (Burton and Stolzing 2018; Kale et al. 2020). Owing to an age-related decline in adaptive immunity, vaccine responses and vaccine longevity are significantly reduced in older adults (Lord 2013), whilst

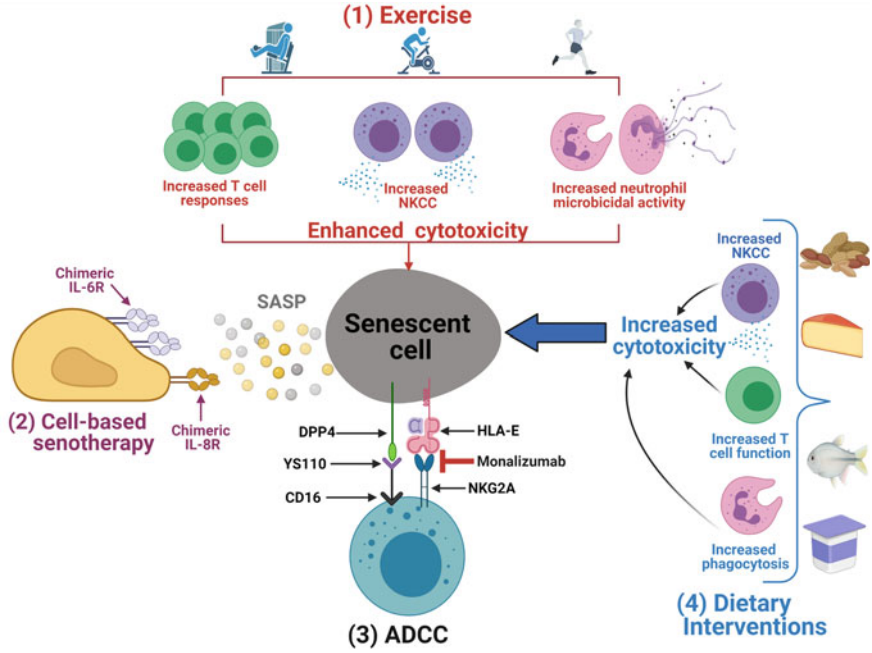

Fig. 3.2 Strategies to increase senescent cell clearance in the older adult. Examples of potential approaches that could enhance immunosurveillance of senescent cells in the older adult by delaying the onset of immunesenescence or bypassing the age-associated defects in immune cell function. ADCC, Antibody dependent cell cytotoxicity; DPP4, Dipeptidyl peptidase 4; HLA-E, Human leukocyte antigen-E; IL-6R, Interleukin-6 receptor; IL-8R, Interleukin-8 receptor; SASP, Senescence associated secretory phenotype. Figure created with BioRender.com

the blunted proliferative capacity of aged T cells (Haynes et al. 1999) would be predicted to result in impaired ex vivo expansion, thereby comprising CAR-T based therapies. Our proposed solution to this dilemma is to focus on the mechanisms of senescent cell immunosurveillance that are not impacted by the ageing process and to consider strategies that can boost the immune response of older adults (Fig. 3.2). Our suggested therapeutic approaches include.

3.1.13 Antibody Dependent Cell Cytotoxicity (ADCC)

Unlike natural cytotoxicity, the efficiency by which NK cells from older adults eliminate antibody-coated target cells is comparable to that of NK cells from younger subjects (Lutz et al. 2005). This retention in ADCC may be explained by the maintained activation of signalling pathways downstream of the Fc receptor CD16 (Mariani et al. 1998) and the age-related expansion in $CD57^{+}$ NK cells, a subset

that is highly proficient in ADCC (Lopez-Vergès et al. 2010). Recently, dipeptidyl peptidase 4 (DPP4) was identified as a membrane specific marker of senescent fibroblasts, with the addition of anti-DPP4 antibodies to fibroblast-NK cell co-cultures resulting in the elimination of senescent but not proliferating fibroblasts (Kim et al. 2017). Interestingly, YS110, a humanised IgG1 monoclonal antibody with high affinity towards DPP4 recently underwent testing in a phase I clinical trial of patients with solid tumours where it was well-tolerated and showed potential clinical benefit (Angevin et al. 2017). In the context of senescent cell immunosurveillance, a combined immunotherapy of YS110 and Monalizumab, a humanised anti-NKG2A antibody, could be particularly beneficial. Mechanistically, YS110 would drive NK cells of older adults towards ADCC, whilst Monalizumab would enhance NK cell activation by blocking the inhibitory signals delivered to NK cells by HLA-E, a ligand of NKG2A whose expression is up-regulated on the surface of senescent cells (Pereira et al. 2019). Indeed, in in vitro cytotoxicity assays, the presence of Monalizumab enhances ADCC towards HLA-E expressing target cells (André et al. 2018). A promising area of research that warrants further investigation, this field would benefit greatly from the discovery of additional senescent cell specific surface antigens against which antibodies could be developed.

3.1.14 Exercise

Physical activity is a potent modulator of immune function. Compared to sedentary individuals, the onset of immunesenescence is delayed in older adults who exercise. Culminating in enhanced immune responses upon antigenic challenge, regular habitual exercise has been associated with increased NKCC, enhanced T cell proliferation, reduced frequencies of functionally exhausted $CD4^+$ and $CD8^+$ T cells and increased neutrophil microbicidal activity (Duggal et al. 2019; Simpson et al. 2012). Suggesting a potential relationship between exercise and immunosurveillance of senescent cells, two independent cross-sectional studies of adults aged 18–80 years found exercise duration negatively correlated with the expression levels of circulating biomarkers of DNA damage and/or the level of $p16^{INK4a}$ mRNA in T cells (Liu et al. 2009; Song et al. 2010). Moreover, acute and chronic exercise training has been shown to be associated with reduced expression of the senescent markers $p16^{INK4a}$ and $p21^{Cip1}$ in a range of cell types that includes mononuclear cells, vascular endothelial cells, adipocytes and endothelial progenitor cells (Justice et al. 2018; Rossman et al. 2017; Werner et al. 2009; Yang et al. 2018). Thus, *is exercise a natural senolytic medicine?* This question was posed and addressed in a recent systematic review and meta-analysis whose examination of human-based studies found both habitual physical activity and exercise training significantly reduced markers of cellular senescence (Chen et al. 2021). Future studies that define the optimal length and type of exercise that yields maximal benefits in respect of senescent cell clearance will move this field of research forward (Chen et al. 2021). Moreover, it is conceivable that exercise in

combination with senolytic or senomorphic therapies may prove to be more effective in eliminating senescent cells in older adults than either practice alone, a theory that could be tested in preclinical and clinical studies.

3.1.15 Nutritional Intervention

Using an in vitro co-culture system, Li et al. recently demonstrated that macrophages pre-treated with carnosine, an endogenous dipeptide comprised of the amino acids β–alanine and L-histidine, exhibited significantly increased cytotoxicity towards senescent keratinocytes and fibroblasts (Li et al. 2020). This enhancement in senescent cell clearance was attributed to increased phagocytic activity, secondary to an up-regulation in the expression of the scavenger receptors CD36 and RAGE (Li et al. 2020). The authors suggested that by augmenting immunosurveillance of senescent cells, carnosine could possibly be used to reverse skin ageing (Li et al. 2020). Along these lines, both human and animal-based studies have shown that through supplementation with micronutrients such as zinc and vitamin B, as well as probiotics, certain features of immunesenescence can be reversed (Pae et al. 2012). Importantly, in the context of immunosurveillance of senescent cells, these treatments enhance NKCC, T cell function and neutrophil anti-microbial responses (Pae et al. 2012). Thus, by restoring innate and adaptive immune responses, nutritional interventions are a feasible strategy that could in theory enhance the rate of senescent cell clearance in older adults. However, it should be noted that many of the beneficial effects of nutritional supplementation are lost when the practice stops (Pae et al. 2012), meaning that this approach would need to be a life-long intervention.

3.1.16 Cell-Based Senotherapy

Engineering cells that actively seek sites of senescent cell accumulation to deliver targeted therapeutics is a potential approach by which to overcome the inherent age-associated defects in immune cell migration and the potential off-target effects of senolytics. By transfecting HEK293 cells with a chimeric IL-6 receptor and calcium activated RhoA protein, Qudrat et al. showed that it was possible to generate cells that directly migrated towards sources of IL-6, a key component of the SASP (Qudrat et al. 2017). In response to low pH, these engineered cells, which also expressed herpes simplex virus type 1 thymidine kinase, underwent membrane fusion with target cells, forming multinucleated bodies that were subsequently eliminated with ganciclovir treatment (Qudrat et al. 2017). Engineering cells that recognise additional components of the SASP (e.g. IL-8) may help in the specificity and efficacy of this approach, which could also be applied to immune cells ex vivo (Qudrat et al. 2017). In terms of its clinical application, it is likely that this technique would be a standalone

therapy as a combined approach with senolytics or senomorphics would, by reducing production of the SASP, potentially impede the ability of the engineered cells to migrate towards senescent cells.

3.1.17 Conclusions

Confirming a hypothesis that was first proposed 60 years ago (Hayflick and Moorhead 1961), the last decade has seen data accumulate that causally implicates cellular senescence in the ageing process and the development of age-associated pathologies. By detecting and eliminating senescent cells, the immune system is responsible in part for regulating the size of an individuals senescent cell burden. Thus, the changes that occur in the composition, phenotype and function of the immune system with age are considered major underlying factors for the increased senescent cell load of older adults. However, as no study to date has investigated whether immune cells from aged mice or humans exhibit decreased cytotoxicity towards senescent cells, this hypothesis remains to be tested. If proven correct, then therapies aimed at rejuvenating the immune response of older adults could enhance the immunosurveillance of senescent cells. Given that a recent study showed that senescent cells impair immune responses to pathogenic challenge (Chambers et al. 2021), then the benefits of increasing the rate of senescent cell clearance in older adults may extend beyond the prevention and/or treatment of age-associated pathologies.

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Compliance with Ethical Standards

Conflict of Interest All authors declare they have no conflict of interest.

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References

Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, Athineos D, Kang TW, Lasitschka F, Andrulis M, Pascual G, Morris KJ, Khan S, Jin H, Dharmalingam G, Snijders AP, Carroll T, Capper D, Pritchard C, Inman GJ, Longerich T, Sansom OJ, Benitah SA, Zender L, Gil J (2013) A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat Cell Biol 15:978–990

Agarwal S, Busse PJ (2010) Innate and adaptive immunosenescence. Ann Allergy, Asthma Immunol 104:183–190

Albright JM, Dunn RC, Shults JA, Boe DM, Afshar M, Kovacs EJ (2016) Advanced age alters monocyte and macrophage responses. Antioxidants Redox Signal 25:805–815

Alimbetov D, Davis T, Brook AJC, Cox LS, Faragher RGA, Nurgozhin T, Zhumadilov Z, Kipling D (2016) Suppression of the senescence-associated secretory phenotype (SASP) in human fibroblasts using small molecule inhibitors of p38 MAP kinase and MK2. Biogerontology 17:305–315

Almeida-Oliveira A, Smith-Carvalho M, Porto LC, Cardoso-Oliveira J, dos Ribeiro A, S, Falcão RR, Abdelhay E, Bouzas LF, Thuler LCS, Ornellas MH, Diamond HR (2011) Age-related changes in natural killer cell receptors from childhood through old age. Hum Immunol 72:319–329

Álvarez D, Cárdenes N, Sellarés J, Bueno M, Corey C, Hanumanthu VS, Peng Y, D'Cunha H, Sembrat J, Nouraie M, Shanker S, Caufield C, Shiva S, Armanios M, Mora AL, Rojas M (2017) IPF lung fibroblasts have a senescent phenotype. Am J Physiol Lung Cell Mol Physiol 313:L1164–L1173

Alves AS, Ishimura ME, Duarte YAO, Bueno V (2018) Parameters of the immune system and Vitamin D levels in old individuals. Front Immunol 9:1122. https://doi.org/10.3389/fimmu.2018.01122

André P, Denis C, Soulas C, Bourbon-Caillet C, Lopez J, Arnoux T, Bléry M, Bonnafous C, Gauthier L, Morel A, Rossi B, Remark R, Breso V, Bonnet E, Habif G, Guia S, Lalanne AI, Hoffmann C, Lantz O, Fayette J, Boyer-Chammard A, Zerbib R, Dodion P, Ghadially H, Jure-Kunkel M, Morel Y, Herbst R, Narni-Mancinelli E, Cohen RB, Vivier E (2018) Anti-NKG2A mAb Is a Checkpoint Inhibitor that Promotes Anti-tumor Immunity by Unleashing Both T and NK Cells. Cell 175:1731-1743.e13

Angevin E, Isambert N, Trillet-Lenoir V, You B, Alexandre J, Zalcman G, Vielh P, Farace F, Valleix F, Podoll T, Kuramochi Y, Miyashita I, Hosono O, Dang NH, Ohnuma K, Yamada T, Kaneko Y, Morimoto C (2017) First-in-human phase 1 of YS110, a monoclonal antibody directed against CD26 in advanced CD26-expressing cancers. Br J Cancer 116:1126–1134

Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, A. Saltness R, Jeganathan KB, Verzosa GC, Pezeshki A, Khazaie K, Miller JD, Van Deursen JM (2016) Naturally occurring p16 Ink4a-positive cells shorten healthy lifespan. Nature 530:184–189

Baker DJ, Petersen RC (2018) Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. J Clin Invest 128:1208–1216

Baker DJ, Wijshake T, Tchkonia T, Lebrasseur NK, Childs BG, Van De Sluis B, Kirkland JL, Van Deursen JM (2011) Clearance of p16 Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479:232–236

Beli E, Clinthorne JF, Duriancik DM, Ii H, Kim S, Gardner EM (2011) Natural killer cell function is altered during the primary response of aged mice to influenza infection. Mech Ageing Dev 132:503–510

Binet F, Cagnone G, Crespo-Garcia S, Hata M, Neault M, Dejda A, Wilson AM, Buscarlet M, Mawambo GT, Howard JP, Diaz-Marin R, Parinot C, Guber V, Pilon F, Juneau R, Laflamme R, Sawchyn C, Boulay K, Leclerc S, Abu-Thuraia A, Côté JF, Andelfinger G, Rezende FA, Sennlaub F, Joyal JS, Mallette FA & Sapieha P (2020) Neutrophil extracellular traps target senescent vasculature for tissue remodeling in retinopathy. Science 369:eaay5356. https://doi.org/10.1126/science.aay5356

Boehmer ED, Goral J, Faunce DE, Kovacs EJ (2004) Age-dependent decrease in Toll-like receptor 4-mediated proinflammatory cytokine production and mitogen-activated protein kinase expression. J Leukoc Biol 75:342–349

Brighton PJ, Maruyama Y, Fishwick K, Vrljicak P, Tewary S, Fujihara R, Muter J, Lucas ES, Yamada T, Woods L, Lucciola R, Hou Lee Y, Takeda S, Ott S, Hemberger M, Quenby S, Brosens JJ (2017) Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium. Elife 6:e31274. https://doi.org/10.7554/eLife.31274

Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A (2004) Neutrophil extracellular traps kill bacteria. Science 303:1532–1535

Bueno V, Sant'Anna OA, Lord JM (2014) Ageing and myeloid-derived suppressor cells: possible involvement in immunosenescence and age-related disease. Age 36:9729. https://doi.org/10.1007/s11357-014-9729-x

Burton DGA, Stolzing A (2018) Cellular senescence: immunosurveillance and future immunotherapy. Ageing Res Rev 43:17–25

Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ (2018) Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature 562:578–582

Butcher SK, Chahal H, Nayak L, Sinclair A, Henriquez NV, Sapey E, O'Mahony D, Lord JM (2001) Senescence in innate immune responses: reduced neutrophil phagocytic capacity and CD16 expression in elderly humans. J Leukoc Biol 70:881–886

Cang S, Iragavarapu C, Savooji J, Song Y, Liu D (2015) ABT-199 (venetoclax) and BCL-2 inhibitors in clinical development. J Hematol Oncol 8:129. https://doi.org/10.1186/s13045-015-0224-3

Chambers ES, Vukmanovic-Stejic M, Shih BB, Trahair H, Subramanian P, Devine OP, Glanville J, Gilroy D, Rustin MHA, Freeman TC, Mabbott NA, Akbar AN (2021) Recruitment of inflammatory monocytes by senescent fibroblasts inhibits antigen-specific tissue immunity during human aging. Nat Aging 1:101–113

Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, Janakiraman K, Sharpless NE, Ding S, Feng W, Luo Y, Wang X, Aykin-Burns N, Krager K, Ponnappan U, Hauer-Jensen M, Meng A, Zhou D (2016) Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat Med 22:78–83

Chen XK, Yi ZN, Wong GTC, Hasan KMM, Kwan JSK, Ma ACH, Chang RCC (2021) Is exercise a senolytic medicine? A Syst Rev Aging Cell. 2:e13294. https://doi.org/10.1111/acel.13294

Childs BG, Baker DJ, Wijshake T, Conover CA, Campisi J, Van Deursen JM (2016) Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science 354:472–477

Coppé JP, Desprez PY, Krtolica A, Campisi J (2010) The senescence-associated secretory phenotype: The dark side of tumor suppression. Annu Rev Pathol Mech Dis 5:99–118

Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6:2853–2868

Davan-Wetton CSA, Pessolano E, Perretti M, Montero-Melendez T (2021) Senescence under appraisal: hopes and challenges revisited. Cell Mol Life Sci. https://doi.org/10.1007/s00018-020-03746-x

Davila DR, Edwards CK, Arkins S, Simon J, Kelley KW (1990) Interferon-γ-induced priming for secretion of superoxide anion and tumor necrosis factor-α declines in macrophages from aged rats. FASEB J 4:2906–2911

Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, Laberge RM, Vijg J, VanSteeg H, Dollé MET, Hoeijmakers JHJ, deBruin A, Hara E, Campisi J (2014) An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell 31:722–733

Desdín-Micó G, Soto-Heredero G, Aranda JF, Oller J, Carrasco E, Gabandé-Rodríguez E, Blanco EM, Alfranca A, Cussó L, Desco M, Ibañez B, Gortazar AR, Fernández-Marcos P, Navarro MN, Hernaez B, Alcamí A, Baixauli F, Mittelbrunn M (2020) T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. Science 368:1371–1376

van Deursen JM (2014) The role of senescent cells in ageing. Nature 509:439–446

Di Lorenzo G, Balistreri CR, Candore G, Cigna D, Colombo A, Romano GC, Colucci AT, Gervasi F, Listì F, Potestio M, Caruso C (1999) Granulocyte and natural killer activity in the elderly. Mech Ageing Dev 108:25–38

Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, Peacocke M, Campisi J (1995) A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc Natl Acad Sci USA 92:9363–9367

Ding A, Hwang S, Schwab R (1994) Effect of aging on murine macrophages. Diminished response to IFN-gamma for enhanced oxidative metabolism. J Immunol 153:2146–2152

Duggal NA, Niemiro G, Harridge SDR, Simpson RJ, Lord JM (2019) Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? Nat Rev Immunol 19:563–572

Egashira M, Hirota Y, Shimizu-Hirota R, Saito-Fujita T, Haraguchi H, Matsumoto L, Matsuo M, Hiraoka T, Tanaka T, Akaeda S, Takehisa C, Saito-Kanatani M, Maeda KI, Fujii T, Osuga Y (2017) F4/80+ macrophages contribute to clearance of senescent cells in the mouse postpartum uterus. Endocrinology 158:2344–2353

Eggert T, Wolter K, Ji J, Ma C, Yevsa T, Klotz S, Medina-Echeverz J, Longerich T, Forgues M, Reisinger F, Heikenwalder M, Wang XW, Zender L, Greten TF (2016) Distinct functions of senescence-associated immune responses in liver tumor surveillance and tumor progression. Cancer Cell 30:533–547

Enioutina EY, Bareyan D, Daynes RA (2011) A role for immature myeloid cells in immune senescence. J Immunol 186:697–707

Fang M, Roscoe F, Sigal LJ (2010) Age-dependent susceptibility to a viral disease due to decreased natural killer cell numbers and trafficking. J Exp Med 207:2369–2381

Farr JN, Xu M, Weivoda MM, Monroe DG, Fraser DG, Onken JL, Negley BA, Sfeir JG, Ogrodnik MB, Hachfeld CM, LeBrasseur NK, Drake MT, Pignolo RJ, Pirtskhalava T, Tchkonia T, Oursler MJ, Kirkland JL, Khosla S (2017) Targeting cellular senescence prevents age-related bone loss in mice. Nat Med 23:1072–1079

Frescas D, Roux CM, Aygun-Sunar S, Gleiberman AS, Krasnov P, Kurnasov OV, Strom E, Virtuoso LP, Wrobel M, Osterman AL, Antoch MP, Mett V, Chernov OB, Gudkov AV (2017) Senescent cells expose and secrete an oxidized form of membrane-bound vimentin as revealed by a natural polyreactive antibody. Proc Natl Acad Sci USA 114:E1668–E1677

Freund A, Patil CK, Campisi J (2011) P38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. EMBO J 30:1536–1548

Gabrilovich DI, Nagaraj S (2009) Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 9:162–174

Garg A, Barnes PF, Porgador A, Roy S, Wu S, Nanda JS, Griffith DE, Girard WM, Rawal N, Shetty S, Vankayalapati R (2006) Vimentin expressed on mycobacterium tuberculosis-infected human monocytes is involved in binding to the NKp46 receptor. J Immunol 177:6192–6198

Gomez CR, Nomellini V, Faunce DE, Kovacs EJ (2008) Innate immunity and aging. Exp Gerontol 43:718–728

Gorenne I, Kavurma M, Scott S, Bennett M (2006) Vascular smooth muscle cell senescence in atherosclerosis. Cardiovasc Res 72:9–17

Hall BM, Balan V, Gleiberman AS, Strom E, Krasnov P, Virtuoso LP, Rydkina E, Vujcic S, Balan K, Gitlin I, Leonova K, Polinsky A, Chernova OB & Gudkov A V. (2016) Aging of mice is associated with p16(Ink4a)- and β-galactosidasepositive macrophage accumulation that can be induced in young mice by senescent cells. Aging (Albany. NY) 8:1294–1315

Hall BM, Balan V, Gleiberman AS, Strom E, Krasnov P, Virtuoso LP, Rydkina E, Vujcic S, Balan K, Gitlin II, Leonova KI, Consiglio CR, Gollnick SO, Chernova OB, Gudkov AV (2017) p16(Ink4a) and senescence-associated β-galactosidase can be induced in macrophages as part of a reversible response to physiological stimuli. Aging (Albany. NY) 9:1867–1884

Hayflick L, Moorhead PS (1961) The serial cultivation of human diploid cell strains. Exp Cell Res 25:585–621

Haynes L, Linton PJ, Eaton SM, Tonkonogy SL, Swain SL (1999) Interleukin 2, but not other common γ chain-binding cytokines, can reverse the defect in generation of CD4 effector T cells from naive T cells of aged mice. J Exp Med 190:1013–1023

Hazeldine J, Hampson P, Lord JM (2012) Reduced release and binding of perforin at the immunological synapse underlies the age-related decline in natural killer cell cytotoxicity. Aging Cell 11:751–759

Hazeldine J, Harris P, Chapple IL, Grant M, Greenwood H, Livesey A, Sapey E, Lord JM (2014) Impaired neutrophil extracellular trap formation: a novel defect in the innate immune system of aged individuals. Aging Cell 13:690–698

Hazeldine J, Lord JM (2015) Innate immunesenescence: underlying mechanisms and clinical relevance. Biogerontology 16:187–201

Hernandez-Segura A, Nehme J, Demaria M (2018) Hallmarks of cellular senescence. Trends Cell Biol 28:436–453

Herrero C, Marqués L, Lloberas J, Celada A (2001) IFN-γ-dependent transcription of MHC class II IA is impaired in macrophages from aged mice. J Clin Invest 107:485–493

Hickson LTJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, Herrmann SM, Jensen MD, Jia Q, Jordan KL, Kellogg TA, Khosla S, Koerber DM, Lagnado AB, Lawson DK, LeBrasseur NK, Lerman LO, McDonald KM, McKenzie TJ, Passos JF, Pignolo RJ, Pirtskhalava T, Saadiq IM, Schaefer KK, Textor SC, Victorelli SG, Volkman TL, Xue A, Wentworth MA, Wissler Gerdes EO, Zhu Y, Tchkonia T, Kirkland JL (2019) Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine 47:446–456

Iannello A, Thompson TW, Ardolino M, Lowe SW, Raulet DH (2013) p53-dependent chemokine production by senescent tumor cells supports NKG2D-dependent tumor elimination by natural killer cells. J Exp Med 210:2057–2069

Iske J, Seyda M, Heinbokel T, Maenosono R, Minami K, Nian Y, Quante M, Falk CS, Azuma H, Martin F, Passos JF, Niemann CU, Tchkonia T, Kirkland JL, Elkhal A, Tullius SG (2020) Senolytics prevent mt-DNA-induced inflammation and promote the survival of aged organs following transplantation. Nat Commun 11:4289. https://doi.org/10.1038/s41467-020-18039-x

Jeon OH, Kim C, Laberge RM, Demaria M, Rathod S, Vasserot AP, Chung JW, Kim DH, Poon Y, David N, Baker DJ, Van Deursen JM, Campisi J, Elisseeff JH (2017) Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med 23:775–781

Jun J Il, Lau LF (2010) The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. Nat Cell Biol 12:676–685

Justice JN, Gregory H, Tchkonia T, Lebrasseur NK, Kirkland JL, Kritchevsky SB, Nicklas BJ (2018) Cellular Senescence Biomarker p16 INK4a + Cell Burden in Thigh Adipose is Associated with Poor Physical Function in Older Women. J Gerontol Ser A Biol Sci Med Sci 73:939–945

Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, Prata L, Masternak MM, Kritchevsky SB, Musi N, Kirkland JL (2019) Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine 40:554–563

Kale A, Sharma A, Stolzing A, Stolzing A, Desprez PY, Desprez PY, Campisi J, Campisi J (2020) Role of immune cells in the removal of deleterious senescent cells. Immun Ageing 17:16. https://doi.org/10.1186/s12979-020-00187-9

Kang TW, Yevsa T, Woller N, Hoenicke L, Wuestefeld T, Dauch D, Hohmeyer A, Gereke M, Rudalska R, Potapova A, Iken M, Vucur M, Weiss S, Heikenwalder M, Khan S, Gil J, Bruder D, Manns M, Schirmacher P, Tacke F, Ott M, Luedde T, Longerich T, Kubicka S, Zender L (2011) Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. Nature 479:547–551

Karin O, Agrawal A, Porat Z, Krizhanovsky V, Alon U (2019) Senescent cell turnover slows with age providing an explanation for the Gompertz law. Nat Commun 10:5495. https://doi.org/10.1038/s41467-019-13192-4

Karin O, Alon U (2020) Senescent cell accumulation mechanisms inferred from parabiosis. GeroScience. https://doi.org/10.1007/s11357-020-00286-x

Khan TA, Mazhar H, Saleha S, Tipu HN, Muhammad N, Abbas MN (2016) Interferon-gamma improves macrophages function against M. tuberculosis in multidrug-resistant tuberculosis patients. Chemother Res Pract 2016:1–6

Kim KM, Noh JH, Bodogai M, Martindale JL, Yang X, Indig FE, Basu SK, Ohnuma K, Morimoto C, Johnson PF, Biragyn A, Abdelmohsen K, Gorospe M (2017) Identification of senescent cell surface targetable protein DPP4. Genes Dev 31:1529–1534

Korolchuk VI, Miwa S, Carroll B, von Zglinicki T (2017) Mitochondria in cell senescence: is mitophagy the weakest link? EBioMedicine 21:7–13

Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, Yee H, Zender L, Lowe SW (2008) Senescence of activated stellate cells limits liver fibrosis. Cell 134:657–667

Laberge RM, Sun Y, Orjalo AV, Patil CK, Freund A, Zhou L, Curran SC, Davalos AR, Wilson-Edell KA, Liu S, Limbad C, Demaria M, Li P, Hubbard GB, Ikeno Y, Javors M, Desprez PY, Benz CC, Kapahi P, Nelson PS, Campisi J (2015) MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. Nat Cell Biol 17:1049–1061

Le Garff-Tavernier M, Béziat V, Decocq J, Siguret V, Gandjbakhch F, Pautas E, Debré P, Merle-Beral H, Vieillard V (2010) Human NK cells display major phenotypic and functional changes over the life span. Aging Cell 9:527–535

Lee N, Llano M, Carretero M, Akiko-Ishitani NF, López-Botet M, Geraghty DE (1998) HLA-E is a major ligand for the natural killer inhibitory receptor CD94/NKG2A. Proc Natl Acad Sci USA 95:5199–5204

Li X, Yang K, Gao S, Zhao J, Liu G, Chen Y, Lin H, Zhao W, Hu Z, Xu N (2020) Carnosine stimulates macrophage-mediated clearance of senescent skin cells through activation of the AKT2 signaling pathway by CD36 and RAGE. Front Pharmacol 11:593832. https://doi.org/10.3389/fphar.2020.593832

Lim H, Park H, Kim HP (2015) Effects of flavonoids on senescence-associated secretory phenotype formation from bleomycin-induced senescence in BJ fibroblasts. Biochem Pharmacol 96:337–348

Liu HC, Han DS, Hsu CC, Wang JS (2021) Circulating MicroRNA-486 and MicroRNA-146a serve as potential biomarkers of sarcopenia in the older adults. BMC Geriatr 21:86. https://doi.org/10.1186/s12877-021-02040-0

Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Ibrahim JG, Thomas NE, Sharpless NE (2009) Expression of p16INK4a in peripheral blood T-cells is a biomarker of human aging. Aging Cell 8:439–448

Lopez-Vergès S, Milush JM, Pandey S, York VA, Arakawa-Hoyt J, Pircher H, Norris PJ, Nixon DF, Lanier LL (2010) CD57 defines a functionally distinct population of mature NK cells in the human CD56dimCD16+ NK-cell subset. Blood 116:3865–3874

Lord JM (2013) The effect of aging of the immune system on vaccination responses. Hum Vaccines Immunother 9:1364–1367

Lujambio A, Akkari L, Simon J, Grace D, Tschaharganeh DF, Bolden JE, Zhao Z, Thapar V, Joyce JA, Krizhanovsky V, Lowe SW (2013) Non-cell-autonomous tumor suppression by p53. Cell 153:449–460

Lutz CT, Karapetyan A, Al-Attar A, Shelton BJ, Holt KJ, Tucker JH, Presnell SR (2011) Human NK cells proliferate and die in Vivo more rapidly than T cells in healthy young and elderly adults. J Immunol 186:4590–4598

Lutz CT, Moore MB, Bradley S, Shelton BJ, Lutgendorf SK (2005) Reciprocal age related change in natural killer cell receptors for MHC class I. Mech Ageing Dev 126:722–731

Mahbub S, Deburghgraeve CR, Kovacs EJ (2012) Advanced age impairs macrophage polarization. J Interf Cytokine Res 32:18–26

Mariani E, Mariani AR, Meneghetti A, Tarozzi A, Cocco L, Facchini A (1998) Age-dependent decreases of NK cell phosphoinositide turnover during spontaneous but not Fc-mediated cytolytic activity. Int Immunol 10:981–989

Mariani E, Meneghetti A, Neri S, Ravaglia G, Forti P, Cattini L, Facchini A (2002) Chemokine production by natural killer cells from nonagenarians. Eur J Immunol 32:1524–1529

Mariani E, Roda P, Mariani AR, Vitale M, Degrassi A, Papa S, Facchini A (1990) Age-associated changes in CD8+ and CD16+ cell reactivity: clonal analysis. Clin Exp Immunol 81:479–484

Mariani E, Sgobbi S, Meneghetti A, Tadolini M, Tarozzi A, Sinoppi M, Cattini L, Facchini A (1996) Perforins in human cytolytic cells: the effect of age. Mech Ageing Dev 92:195–209

Martin JA, Buckwalter JA (2001) Telomere erosion and senescence in human articular cartilage chondrocytes. J Gerontol Ser A Biol Sci Med Sci 56:B172–B179

Martínez-Cué C, Rueda N (2020) Cellular Senescence in neurodegenerative diseases. Front Cell Neurosci 14:16. https://doi.org/10.3389/fncel.2020.00016

Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F (2021) Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol 22:75–95

Minagawa S, Araya J, Numata T, Nojiri S, Hara H, Yumino Y, Kawaishi M, Odaka M, Morikawa T, Nishimura SL, Nakayama K, Kuwano K (2011) Accelerated epithelial cell senescence in IPF and the inhibitory role of SIRT6 in TGF-β-induced senescence of human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol 300:L391–L401. https://doi.org/10.1152/ajplung.00097.2010

Minamino T, Miyauchi H, Yoshida T, Ishida Y, Yoshida H, Komuro I (2002) Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction. Circulation 105:1541–1544

Misawa T, Tanaka Y, Okada R, Takahashi A (2020) Biology of extracellular vesicles secreted from senescent cells as senescence-associated secretory phenotype factors. Geriatr Gerontol Int 20:539–546

Miyaji C, Watanabe H, Minagawa M, Toma H, Kawamura T, Nohara Y, Nozaki H, Sato Y, Abo T (1997) Numerical and functional characteristics of lymphocyte subsets in centenarians. J Clin Immunol 17:420–429

Moiseeva O, Deschênes-Simard X, St-Germain E, Igelmann S, Huot G, Cadar AE, Bourdeau V, Pollak MN, Ferbeyre G (2013) Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation. Aging Cell 12:489–498

Moncsek A, Al-Suraih MS, Trussoni CE, O'Hara SP, Splinter PL, Zuber C, Patsenker E, Valli PV, Fingas CD, Weber A, Zhu Y, Tchkonia T, Kirkland JL, Gores GJ, Müllhaupt B, LaRusso NF, Mertens JC (2018) Targeting senescent cholangiocytes and activated fibroblasts with B-cell lymphoma-extra large inhibitors ameliorates fibrosis in multidrug resistance 2 gene knockout (Mdr2−/−) mice. Hepatology 67:247–259

Muñoz-Espín D, Cañamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, Rodríguez-Baeza A, Varela-Nieto I, Ruberte J, Collado M, Serrano M (2013) Programmed cell senescence during mammalian embryonic development. Cell 155:1104–1118

Muñoz DP, Yannone SM, Daemen A, Sun Y, Vakar-Lopez F, Kawahara M, Freund AM, Rodier F, Wu JD, Desprez PY, Raulet DH, Nelson PS, van't Veer LJ, Campisi J, Coppé JP (2019) Targetable mechanisms driving immunoevasion of persistent senescent cells link chemotherapy-resistant cancer to aging. JCI Insight 5:e124716. https://doi.org/10.1172/jci.insight.124716

Narzt MS, Pils V, Kremslehner C, Nagelreiter IM, Schosserer M, Bessonova E, Bayer A, Reifschneider R, Terlecki-Zaniewicz L, Waidhofer-Söllner P, Mildner M, Tschachler E, Cavinato M, Wedel S, Jansen-Dürr P, Nanic L, Rubelj I, El-Ghalbzouri A, Zoratto S, Marchetti-Deschmann M, Grillari J, Gruber F, Lämmermann I (2021) Epilipidomics of senescent dermal fibroblasts identify lysophosphatidylcholines as pleiotropic senescence-associated secretory phenotype (SASP) factors. J Invest Dermatol 141:993-1006.e15. https://doi.org/10.1016/j.jid.2020.11.020

Nathan CF, Murray HW, Wlebe IE, Rubin BY (1983) Identification of interferon-γ, as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. J Exp Med 158:670–689

Naylor RM, Baker DJ, Van Deursen JM (2013) Senescent cells: a novel therapeutic target for aging and age-related diseases. Clin Pharmacol Ther 93:105–116

Nelson G, Kucheryavenko O, Wordsworth J, von Zglinicki T (2018) The senescent bystander effect is caused by ROS-activated NF-κB signalling. Mech Ageing Dev 170:30–36

Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin-Ruiz C, von Zglinicki T (2012) A senescent cell bystander effect: senescence-induced senescence. Aging Cell 11:345–349

Ogata Y, Yamada T, Hasegawa S, Sanada A, Iwata Y, Arima M, Nakata S, Sugiura K, Akamatsu H (2021) SASP-induced macrophage dysfunction may contribute to accelerated senescent fibroblast accumulation in the dermis. Exp Dermatol 30:84–91

Ohtani N, Mann DJ, Hara E (2009) Cellular senescence: its role in tumor suppression and aging. Cancer Sci 100:792–797

Ohtani N, Yamakoshi K, Takahashi A, Hara E (2004) The p16INK4a-RB pathway: molecular link between cellular senescence and tumor suppression. J Med Investig 51:146–153

Olivieri F, Lazzarini R, Recchioni R, Marcheselli F, Rippo MR, Di Nuzzo S, Albertini MC, Graciotti L, Babini L, Mariotti S, Spada G, Abbatecola AM, Antonicelli R, Franceschi C, Procopio AD (2013) MiR-146a as marker of senescence-Associated pro-inflammatory status in cells involved in vascular remodelling. Age (omaha) 35:1157–1172

Oltersdorf T, Elmore SW, Shoemaker AR, Armstrong RC, Augeri DJ, Belli BA, Bruncko M, Deckwerth TL, Dinges J, Hajduk PJ, Joseph MK, Kitada S, Korsmeyer SJ, Kunzer AR, Letai A, Li C, Mitten MJ, Nettesheim DG, Ng SC, Nimmer PM, O'Connor JM, Oleksijew A, Petros AM, Reed JC, Shen W, Tahir SK, Thompson CB, Tomaselli KJ, Wang B, Wendt MD, Zhang H, Fesik SW, Rosenberg SH (2005) An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature 435:677–681

Ovadya Y, Krizhanovsky V (2014) Senescent cells: SASPected drivers of age-related pathologies. Biogerontology 15:627–642

Ovadya Y, Krizhanovsky V (2018) Strategies targeting cellular senescence. J Clin Invest 128:1247–1254

Ovadya Y, Landsberger T, Leins H, Vadai E, Gal H, Biran A, Yosef R, Sagiv A, Agrawal A, Shapira A, Windheim J, Tsoory M, Schirmbeck R, Amit I, Geiger H, Krizhanovsky V (2018) Impaired immune surveillance accelerates accumulation of senescent cells and aging. Nat Commun 9:5435. https://doi.org/10.1038/s41467-018-07825-3

Pae M, Meydani SN, Wu D (2012) The role of nutrition in enhancing immunity in aging. Aging Dis 3:91–129

Passos JF, Saretzki G, Ahmed S, Nelson G, Richter T, Peters H, Wappler I, Birket MJ, Harold G, Schaeuble K, Birch-Machin MA, Kirkwood TBL, Von Zglinicki T (2007) Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence. PLoS Biol 5:1138–1151

Paul S, Lal G (2017) The molecular mechanism of natural killer cells function and its importance in cancer immunotherapy. Front Immunol 8:1124. https://doi.org/10.3389/fimmu.2017.01124

Pereira BI, Devine OP, Vukmanovic-Stejic M, Chambers ES, Subramanian P, Patel N, Virasami A, Sebire NJ, Kinsler V, Valdovinos A, LeSaux CJ, Passos JF, Antoniou A, Rustin MHA, Campisi J, Akbar AN (2019) Senescent cells evade immune clearance via HLA-E-mediated NK and CD8+ T cell inhibition. Nat Commun 10:2387. https://doi.org/10.1038/s41467-019-10335-5

Plowden J, Renshaw-Hoelscher M, Engleman C, Katz J, Sambhara S (2004) Innate immunity in aging: impact on macrophage function. Aging Cell 3:161–167

Prata LGPL, Ovsyannikova IG, Tchkonia T, Kirkland JL (2018) Senescent cell clearance by the immune system: emerging therapeutic opportunities. Semin Immunol 40:101275. https://doi.org/10.1016/j.smim.2019.04.003

Qudrat A, Wong J, Truong K (2017) Engineering mammalian cells to seek senescence-associated secretory phenotypes. J Cell Sci 130:3116–3123

Ressler S, Bartkova J, Niederegger H, Bartek J, Scharffetter-Kochanek K, Jansen-Dürr P, Wlaschek M (2006) p16INK4A is a robust in vivo biomarker of cellular aging in human skin. Aging Cell 5:379–389

Robbins PD, Jurk D, Khosla S, Kirkland JL, Lebrasseur NK, Miller JD, Passos JF, Pignolo RJ, Tchkonia T, Niedernhofer LJ (2021) Senolytic drugs: reducing senescent cell viability to extend health span. Annu Rev Pharmacol Toxicol 61:779–803

Rossman MJ, Kaplon RE, Hill SD, McNamara MN, Santos-Parker JR, Pierce GL, Seals DR, Donato AJ (2017) Endothelial cell senescence with aging in healthy humans: Prevention by habitual exercise and relation to vascular endothelial function. Am J Physiol Hear Circ Physiol 313:H890–H895

Rukavina D, Laskarin G, Rubesa G, Strbo N, Bedenicki I, Manestar D, Glavas M, Christmas SE, Podack ER (1998) Age-related decline of perforin expression in human cytotoxic T lymphocytes and natural killer cells. Blood 92:2410–2420

Sagiv A, Biran A, Yon M, Simon J, Lowe SW, Krizhanovsky V (2013) Granule exocytosis mediates immune surveillance of senescent cells. Oncogene 32:1971–1977

Sagiv A, Burton DGA, Moshayev Z, Vadai E, Wensveen F, Ben-Dor S, Golani O, Polic B & Krizhanovsky V (2016) NKG2D ligands mediate immunosurveillance of senescent cells. Aging (Albany. NY). 8:328–344

Sagiv A, Krizhanovsky V (2013) Immunosurveillance of senescent cells: the bright side of the senescence program. Biogerontology 14:617–628

Sakata-Kaneko S, Wakatsuki Y, Matsunaga Y, Usui T, Kita T (2000) Altered Th1/Th2 commitment in human CD4+ T cells with ageing. Clin Exp Immunol 120:267–273

Sapey E, Greenwood H, Walton G, Mann E, Love A, Aaronson N, Insall RH, Stockley RA, Lord JM (2014) Phosphoinositide 3-kinase inhibition restores neutrophil accuracy in the elderly: toward targeted treatments for immunosenescence. Blood 123:239–248

Sarig R, Rimmer R, Bassat E, Zhang L, Umansky KB, Lendengolts D, Perlmoter G, Yaniv K, Tzahor E (2019) Transient p53-mediated regenerative senescence in the injured heart. Circulation 139:2491–2494

Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, Oberg AL, Birch J, Salmonowicz H, Zhu Y, Mazula DL, Brooks RW, Fuhrmann-Stroissnigg H, Pirtskhalava T, Prakash YS, Tchkonia T, Robbins PD, Aubry MC, Passos JF, Kirkland JL, Tschumperlin DJ, Kita H, LeBrasseur NK (2017) Cellular senescence mediates fibrotic pulmonary disease. Nat Commun 8:14532. https://doi.org/10.1038/ncomms14532

Schaper F, de Leeuw K, Horst G, Bootsma H, Limburg PC, Heeringa P, Bijl M, Westra J (2016) High mobility group box 1 skews macrophage polarization and negatively influences phagocytosis of apoptotic cells. Rheumatol 55:2260–2270

Schulz D, Severin Y, Zanotelli VRT, Bodenmiller B (2019) In-depth characterization of monocyte-derived macrophages using a mass cytometry-based phagocytosis assay. Sci Rep 9:1925. https://doi.org/10.1038/s41598-018-38127-9

da Silva PFL, Ogrodnik M, Kucheryavenko O, Glibert J, Miwa S, Cameron K, Ishaq A, Saretzki G, Nagaraja-Grellscheid S, Nelson G, von Zglinicki T (2019) The bystander effect contributes to the accumulation of senescent cells in vivo. Aging Cell 18:e12848. https://doi.org/10.1111/acel.12848

Simpson RJ, Cosgrove C, Ingram LA, Florida-James GD, Whyte GP, Pircher H, Guy K (2008) Senescent T-lymphocytes are mobilised into the peripheral blood compartment in young and older humans after exhaustive exercise. Brain Behav Immun 22:544–551

Simpson RJ, Lowder TW, Spielmann G, Bigley AB, LaVoy EC, Kunz H (2012) Exercise and the aging immune system. Ageing Res Rev 11:404–420

Smyth MJ, Cretney E, Kelly JM, Westwood JA, Street SEA, Yagita H, Takeda K, Dommelen SLHV, Degli-Esposti MA, Hayakawa Y (2005) Activation of NK cell cytotoxicity. Mol Immunol 42:501–510

Song S, Lam EWF, Tchkonia T, Kirkland JL, Sun Y (2020a) Senescent cells: emerging targets for human aging and age-related diseases. Trends Biochem Sci 45:578–592

Song S, Tchkonia T, Jiang J, Kirkland JL, Sun Y (2020b) Targeting senescent cells for a healthier aging: challenges and opportunities. Adv Sci 7:2002611. https://doi.org/10.1002/advs.202002611

Song Z, von Figura G, Liu Y, Kraus JM, Torrice C, Dillon P, Rudolph-Watabe M, Ju Z, Kestler HA, Sanoff H, Rudolph KL (2010) Lifestyle impacts on the aging-associated expression of biomarkers of DNA damage and telomere dysfunction in human blood. Aging Cell 9:607–615

Soriani A, Zingoni A, Cerboni C, Lannitto ML, Ricciardi MR, Di GV, Cippitelli M, Fionda C, Petrucci MT, Guarini A, Foà R, Santoni A (2009) ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood 113:3503–3511

Terlecki-Zaniewicz L, Lämmermann I, Latreille J, Bobbili MR, Pils V, Schosserer M, Weinmüllner R, Dellago H, Skalicky S, Pum D, Almaraz JCH, Scheideler M, Morizot F, Hackl M, Gruber F, Grillari J (2018) Small extracellular vesicles and their miRNA cargo are anti-apoptotic members of the senescence-associated secretory phenotype. Aging (Albany. NY). 10: 1103–1132

Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, Loukov D, Schenck LP, Jury J, Foley KP, Schertzer JD, Larché MJ, Davidson DJ, Verdú EF, Surette MG, Bowdish DME (2017) Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe 21:455-466.e4

Verschoor CP, Johnstone J, Millar J, Dorrington MG, Habibagahi M, Lelic A, Loeb M, Bramson JL, Bowdish DME (2013) Blood CD33(+)HLA-DR(−) myeloid-derived suppressor cells are increased with age and a history of cancer. J Leukoc Biol 93:633–637

Waaijer MEC, Parish WE, Strongitharm BH, van Heemst D, Slagboom PE, de Craen AJM, Sedivy JM, Westendorp RGJ, Gunn DA, Maier AB (2012) The number of p16INK4a positive cells in human skin reflects biological age. Aging Cell 11:722–725

Wallis R, Mizen H, Bishop CL (2020) The bright and dark side of extracellular vesicles in the senescence-associated secretory phenotype. Mech Age Dev 189:111263. https://doi.org/10.1016/j.mad.2020.111263

Waters DW, Blokland KEC, Pathinayake PS, Burgess JK, Mutsaers SE, Prele CM, Schuliga M, Grainge CL, Knight DA (2018) Fibroblast senescence in the pathology of idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 315:L162–L172

Werner C, Fürster T, Widmann T, Pöss J, Roggia C, Hanhoun M, Scharhag J, Büchner N, Meyer T, Kindermann W, Haendeler J, Böhm M, Laufs U (2009) Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. Circulation 120:2438–2447

Wu X, Fan Z, Chen M, Chen Y, Rong D, Cui Z, Yuan Y, Zhuo L, Xu Y (2019) Forkhead transcription factor FOXO3a mediates interferon-γ-induced MHC II transcription in macrophages. Immunology 158:304–313

Xu D, Han Q, Hou Z, Zhang C, Zhang J (2017) MIR-146a negatively regulates NK cell functions via STAT1 signaling. Cell Mol Immunol 14:712–720

Xu M, Palmer AK, Ding H, Weivoda MM, Pirtskhalava T, White TA, Sepe A, Johnson KO, Stout MB, Giorgadze N, Jensen MD, LeBrasseur NK, Tchkonia T, Kirkland JL (2015a) Targeting senescent cells enhances adipogenesis and metabolic function in old age. Elife 4:e12997. https://doi.org/10.7754/eLife.12997

Xu M, Tchkonia T, Ding H, Ogrodnik M, Lubbers ER, Pirtskhalava T, White TA, Johnson KO, Stout MB, Mezera V, Giorgadze N, Jensen MD, LeBrasseur NK, Kirkland JL (2015b) JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. Proc Natl Acad Sci USA 112:E6301–E6310

Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, Inman CL, Ogrodnik MB, Hachfeld CM, Fraser DG, Onken JL, Johnson KO, Verzosa GC, Langhi LGP, Weigl M, Giorgadze N, LeBrasseur NK, Miller JD, Jurk D, Singh RJ, Allison DB, Ejima K, Hubbard GB, Ikeno Y, Cubro H, Garovic VD, Hou X, Weroha SJ, Robbins PD, Niedernhofer LJ, Khosla S, Tchkonia T, Kirkland JL (2018) Senolytics improve physical function and increase lifespan in old age. Nat Med 24:1246–1256

Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, Cordon-Cardo C, Lowe SW (2007) Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature 445:656–660

Yang C, Jiao Y, Wei B, Yang Z, Wu JF, Jensen J, Jean WH, Huang CY & Kuo CH (2018) Aged cells in human skeletal muscle after resistance exercise. Aging (Albany. NY). 10:1356–1365

Yen CJ, Lin SL, Huang KT, Lin RH (2000) Age-associated changes in interferon-γ and interleukin-4 secretion by purified human CD4+ and CD8+ T cells. J Biomed Sci 7:317–321

Yoon P, Keylock KT, Hartman ME, Freund GG & Woods JA (2004) Macrophage hyporesponsiveness to interferon-γ in aged mice is associated with impaired signaling through Jak-STAT. In: Mechanisms of ageing and development. Elsevier, Ireland, pp137–143

Yosef R, Pilpel N, Tokarsky-Amiel R, Biran A, Ovadya Y, Cohen S, Vadai E, Dassa L, Shahar E, Condiotti R, Ben-Porath I, Krizhanovsky V (2016) Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. Nat Commun 7:11190. https://doi.org/10.1038/ncomms11190

Yousefzadeh MJ, Wilkinson JE, Hughes B, Gadela N, Ladiges WC, Vo N, Niedernhofer LJ, Huffman DM, Robbins PD (2020) Heterochronic parabiosis regulates the extent of cellular senescence in multiple tissues. GeroScience 42:951–961

Zhang Y, Wallace DL, De Lara CM, Ghattas H, Asquith B, Worth A, Griffin GE, Taylor GP, Tough DF, Beverley PCL, Macallan DC (2007) In vivo kinetics of human natural killer cells: The effects of ageing and acute and chronic viral infection. Immunology 121:258–265

Zhu Y, Tchkonia T, Fuhrmann-Stroissnigg H, Dai HM, Ling YY, Stout MB, Pirtskhalava T, Giorgadze N, Johnson KO, Giles CB, Wren JD, Niedernhofer LJ, Robbins PD, Kirkland JL (2016) Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. Aging Cell 15:428–435

Ziegler DV, Wiley CD, Velarde MC (2015) Mitochondrial effectors of cellular senescence: beyond the free radical theory of aging. Aging Cell 14:1–7

Chapter 4
Myeloid-Derived Suppressive Cells in Ageing and Age-Related Diseases

Valquiria Bueno and Graham Pawelec

Abstract Myeloid-derived suppressor cells (MDSC) act regulating/suppressing immune responses and there are few evidences that these cells increase in healthy old individuals. MDSCs impair the functions of T cells, NK cells, and dendritic cells through several pathways that include expression of arginase I, inducible nitric oxide synthase, release of reactive oxygen species and peroxynitrite. The role played by MDSCs in immune modulation may be beneficial or detrimental to the health of aging individuals depending on their development, phenotype, functions, and the pathological conditions. MDSCs have been extensively studied in cancer and more recently these cells were correlated with other pathological conditions such as sepsis, tuberculosis, COVID-19, autoimmune diseases, obesity, diabetes and neurodegenerative diseases. In patients with COVID-19 it has been reported that the increase of MDSC correlated with disease severity and fatal cases. Considering that COVID-19 has caused morbidity and mortality with a higher incidence in ageing individuals and especially in those with chronic diseases, the projection of how the frequency and suppressive function of MDSC could be increased in ageing can lead to the development of more appropriate therapies for the aged population.

Keywords Ageing · Myeloid-derived suppressor cells · Cancer · Infections · Autoimmune diseases · Degenerative diseases

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Abbreviations

AD	Alzheimer's disease
ANA	Antinuclear antibody
ARG-1	Arginase-1
ASC	Antibody secreting B-cells
COVID-19	Corona virus disease
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
G-MDSC	Granulocytic Myeloid-derived suppressor cells
GVAX	Tumor vaccines composed of autologous tumor cells genetically modified to secrete granulocyte–macrophage colony-stimulating factor
HBC	Hepatitis C virus
HBV	Hepatitis B virus
HDL-c	High-density lipoprotein cholesterol
IDO	Indolamine-2,3-dioxygenase
IFN-γ	Interferon-gama
IL-10	Interleukin-10
iNOS	Inducible nitric oxide synthase
LOX1	Lectin-type oxidized low-density lipoprotein receptor-1
MDSC	Myeloid-derived suppressor cells
MUC1	Mucine-1
MS	Multiple sclerosis
NO	Nitric oxide
PD1	Programmed cell death protein 1
PD-L1	Programmed cell death protein ligand 1
PD-L2	Programmed cell death protein ligand 2
PMN-MDSC	Polymorphonuclear Myeloid-derived suppressor cells
PPLNs	Positive pelvic lymph nodes
PSA	Prostate-specific antigen
RA	Rheumatoid arthritis
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
STAT3	Signal transducer and activator of transcription 3
TB	Mycobacterium tuberculosis
TCR	T-cell receptor
TGF-β	Transforming growth factor-beta
TME	Tumor microenvironment
T1D	Type 1 diabetes
T2D	Type 2 diabetes

4.1 Myeloid-Derived Suppressor Cells (MDSC)

MDSC can be described as a group of heterogeneous myeloid cells with potent immune suppressive activity. Membrane surface, intracellular markers, secreted products, and cell functions have been used in an attempt to define a phenotype for human MDSC (Pawelec et al. 2021). In order to simplify the reading of this chapter, MDSC will be classified as granulocytic or polymorphonuclear (G-MDSC or PMN-MDSC; $CD11b^{+}CD14^{-}CD15^{+}$), monocytic (M-MDSC; $CD14^{+}CD15^{-}HLA\text{-}DR^{-/low}$) and early-stage (MDSC; $CD3^{-}CD14^{-}CD15^{-}CD19^{-}CD56^{-}HLA\text{-}DR^{-}CD33^{+}$) (Bueno et al. 2014). MDSCs have been extensively studied in cancer and more recently these cells were correlated with other pathological conditions such as sepsis, tuberculosis, COVID-19, autoimmune diseases, obesity, diabetes and neurodegenerative diseases (Pawelec et al. 2021).

In healthy young adults, MDSCs have been observed at very low frequency in blood whereas there is an increase in the percentage of these cells in ageing individuals (Verschoor et al. 2013; Alves et al. 2018). Some factors associated with the ageing process favor MDSC increased frequency. In older individuals, it has been suggested that the imbalance in hematopoiesis causing biased myelopoiesis could be a driving force for the rise in MDSC. Moreover, from cancer studies, it has been observed that the inflammatory microenvironment is an enhancer for MDSC generation. Thus, another possible contributor for MDSC elevation in older individuals is the low-grade inflammatory process (inflammageing) observed in this population (Veglia et al. 2018; Ostrand-Rosenberg 2010).

A significant amount of information about the suppressive function of MDSC in humans comes from cancer studies and it has been observed the increase of these cells both in tumor microenvironment and in peripheral blood. Isolated MDSC from patients exhibited in vitro the capacity to suppress T cells proliferation and IFN-γ secretion (Mao et al. 2013; Dubinski et al. 2016; Lang et al. 2018). In addition, arginase-1 (ARG-1) expressed mainly by PMN-MDSC from patients with cancer have been associated with suppression of the effector immune response (Dubinski et al. 2016; Lang et al. 2018; Romano et al. 2018).

Indolamine-2,3-dioxygenase- (IDO), nitric oxide (NO), IL-10, TGF-β, and LOX1 (lectin-type oxidized LDL receptor 1) also have been identified as factors linked mechanistically to the suppressive actions of MDSC (Chai et al. 2019; Condamine et al. 2016).

In literature, most of articles evaluate in the same study adults and older individuals with cancer (lung, colorectal, prostate, and breast), multiple sclerosis, type 1 diabetes, and COVID-19, presenting in common a higher percentage of MDSC in comparison with healthy controls. In addition, some studies in individuals older than 60 years with cancer (lung, colorectal cancer and metastatic prostate), reumathoid arthritis and osteoarthritis, Parkinson's disease, and Alzheimer's disease also show increased percentage of MDSC. Therefore, it hasn't been possible to distinguish between the age effect and the pathology effect on the increase of MDSC. Based on already reported results, we will extrapolate for a possible correlation between age

and accumulation of MDSC and their contribution to the development and evolution of age-related diseases.

4.2 Cancer

Considering that ageing has been associated with higher incidence of cancer and that old individuals present an increased frequency of MDSC, it is reasonable to hypothesize that the suppressive effect of MDSC negatively affect the immune system, and therefore facilitates tumor development. However, as tumor induces emergency myelopoiesis, and in turn MDSC, it is difficult to isolate the role played by age and by tumor in the increased frequency and suppressive action of MDSC. In fact, studies show that MDSC contributes for tumor progression through suppression of tumor-specific T cell responses, stimulation of tumor angiogenesis, or facilitating tumor cell metastasis. Considering all available cancer therapies, their impaired efficacy has been related, at least in part, to the accumulation of MDSC, which generates an immunosuppressive microenvironment (Gabrilovich and Nagaraj 2009; Marvel and Gabrilovich, 2015). The most prevalent types of cancer in ageing individuals are lung cancer, colorectal cancer, prostate cancer, and breast cancer. Therefore, the reports in cancer and MDSC will be focused in lung, colorectal, prostate and breast.

In non-small cell lung cancer, patients presented abundance of MDSC and the treatment with radiotherapy (Navarro-Martin et al. 2018), checkpoint inhibitors (PD1/PD-L1) plus chemotherapy (Bertelli et al. 2019), and chemotherapy plus immunotherapy (Bonomi et al. 2019) reduced the frequency of MDSC and promoted increased disease-free survival.

In patients from 30 to 96 years old with colorectal cancer, the tumor microenvironment (TME) presented high expression of PMN-MDSC and MDSC. In blood, increased frequency of MDSC (Choi et al. 2018) and high levels of PMN-MDSC expressing ARG-1 (blood and TME) have been reported and correlated with tumor stage and histological grade (Toor et al. 2016). A MUC1 (glycoprotein highly expressed in neoplastic cells) peptide vaccine for individuals (43.5–70.8 years) with advanced adenoma of colon showed high immunogenicity in 43.6% of cases and induced memory response. Non-responder patients presented at baseline higher frequency of MDSC in opposition to responders that had previously to vaccination low frequency of MDSC (Kimura et al. 2013).

In cases of castration-resistant prostate cancer (CRPC), tumor tissues were enriched by PMN-MDSC compared to patients with castration-sensitive prostate cancer (CSPC) (Calcinotto et al. 2018). In cases of radical prostatectomy, patients (53–72 years) presented PMN-MDSC accumulated in positive pelvic lymph nodes (PPLNs) and strongly expressed STAT3 and PD-L1/PD-L2 (Sharma et al. 2018). CRPC metastatic patients (57–85 years) had increased frequency of M-MDSC and these cells inhibited $CD4^+$ and $CD8^+$ T-cell proliferation in vitro in addition to high expression of iNOS. Increased levels of M-MDSC correlated with negative prognostic markers, plasma PSA and decreased overall survival (Idorn et al. 2014).

A dendritic cell-based cancer vaccine plus chemotherapy for CRPC patients (60–84 years) with metastasis had no effect on $CD4^+$ and $CD8^+$ T cells subsets but caused a significant decrease in MDSC during therapy in association with improved survival (Kongsted et al. 2017). In another study, CRPC patients with low frequency of M-MDSC and treated with anti-CTLA-4 (Ipilimumab) plus vaccine (GVAX) had prolonged survival in opposition to those with high frequency of M-MDSC pre-treatment that presented shorter overall survival (Santegoests et al. 2014).

Breast cancer patients (27–75 years) presented high frequency of MDSC that correlated with cancer stage, metastatic tumor burden stage IV. Increased levels of MDSC was observed even in the presence of therapy (doxorubicin plus cyclophosphamide and paclitaxel) (Diaz-Montero et al. 2009). Another study found high frequency of MDSC IDO^+ in tumor tissue and blood of patients with breast cancer that correlated with advanced clinical stages and lymph node metastasis. Proliferation of T cell/cytokines production were inhibited in vitro by MDSC (Yu et al. 2013). Wesolowski et al (2017) observed that the increase of PMN-MDSC after treatment with doxorubicin plus cyclophosphamide along with peg-filgrastim (metastatic breast cancer, 32–69 years) was replaced after 12 months by decreased levels of PMN-MDSC that correlated with absence of residual invasive carcinoma in breast and lymph nodes.

4.3 Infections

In oId individuals, high incidence and severity of infectious diseases have been reported. In this scenario, the suppressive capacity of MDSC could play a role inhibiting the effector responses of T cells. Reports from cases of tuberculosis (*Mycobacterium tuberculosis*, TB) have been associated with high levels of MDSC in peripheral blood, pleura, and bronco-alveolar lavage blood (du Plessis et al. 2013; El Daker et al. 2015). These increased percentages of MDSC returned to normal levels after successful treatment. In addition, MDSC from TB patients suppressed in vitro the proliferation and production of cytokines by T cells (du Plessis et al. 2013; El Daker et al. 2015).

In chronic hepatitis B virus (HBV), it was observed high percentage of MDSC (Lv et al. 2018) and M-MDSC (Fang et al. 2015). Moreover, in chronic hepatitis C virus (HCV), higher levels of MDSC and increase of NOS and IDO levels were observed (Salem et al. 2017). In another study, the frequency of MDSC decreased in patients with HCV treated with pegylated-interferon-α/ ribavirin (Zeng et al. 2014).

Sepsis occurs in 30 million patients/year and causes deaths worldwide in five-to-six million cases. It is characterized by a still not clear dysregulated host response and delay return to homeostasis (Schrijver et al. 2019) but some studies have shown the correlation between MDSC levels and patient outcome. MDSC and mainly the G-MDSC subset were significantly higher in patients (mean age 60 years) with severe sepsis/septic shock than in healthy control. The early mortality was correlated with high initial percentage of MDSC compared to patients surviving longer than 14 days.

Inadequate functional status and subsequent nosocomial infection were observed in patients with sustained MDSC frequency (Mathias et al. 2017). In another study, M-MDSC and G-MDSC were increased in patients with sepsis (41–75 years). In non-septic intensive care unit patients (62–76 years), M-MDSC were significantly increased whereas G-MDSC was more specific for sepsis and subsequent nosocomial infections (Uhel et al. 2017). Janols et al. (2014) also found that M-MDSC and PMN-MDSC were present in higher percentages in sepsis patients (20–94 years) in comparison to healthy controls. In all the studies the common finding was the inhibition of T cells in vitro by MDSC from sepsis patients.

Recently, data from patients with SARS-Cov-2 and MDSC were published. Increased frequencies of M-MDSCs were observed in the blood of patients with COVID-19 which were proportional to disease severity. COVID-19 patients with more severe disease and having high M-MDSC frequency were also significantly older than those with less severe disease. In addition, M-MDSC isolated from patients with COVID-19 had a suppressive effect on T cells, markedly reducing CD4 + and CD8 + T cell proliferation ex vivo (Falck-Jones et al. 2020). Similar findings have been reported regarding PMN-MDSC, which highly expanded in severe COVID-19 disease, and gradually decline with recovery (Agrati et al. 2020).

4.4 Autoimmune Diseases

Hurme et al. (2007) found in a cohort of 284 nonagerians a significantly higher level of autoantibodies (antinuclear ANA) than in the middle-age control. In addition, ageing has been considered an important risk for autoimmunity (Goronzy and Weyand 2012). MDSC increased expression has been observed in autoimmune diseases but the role played by these cells still has to be elucidated.

Patients with rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis presented higher frequency of MDSC, M-MDSC, and G-MDSC in comparison with healthy controls. MDSC and M-MDSC increase was correlated with disease activity and joint inflammation (Zhu et al. 2018). In another study, the higher percentage of MDSC was observed in patients with high activity of rheumatoid arthritis (RA) compared to patients with low disease activity and healthy control (Guo et al. 2016). In RA patients, Kurkó et al. (2014) observed in synovial fluid G-MDSC as the majority of cells and a small population of M-MDSC.

In cerebrospinal fluid of patients (18–60 years) with first clinical episode or established multiple sclerosis (MS) it was found the expression of antibody secreting B-cells (ASC). The frequency of ASC was negatively correlated with the percentage of PMN-MDSC $LOX1^{+}$. The culture of B cells with cytokines directing towards ASC showed that PMN-MDSC could suppress the proliferation of B cells in a dose-dependent manner (Knier et al. 2018). In another study, increased levels of G-MDSCs was observed in active MS patients compared with patients in remission or healthy control. In culture, MDSC from active multiple sclerosis patients inhibited T cell proliferation and reduced IL-2 secretion (Ioannou et al. 2012).

In Type 1 diabetes (T1D), it was found that patients (20–60 years) had increased frequency of MDSC compared to healthy control (Hassan et al. 2018). In addition, Whitfield-Larry et al. (2014) observed that patients with T1D (11–46 years) exhibited a main subset of M-MDSC.

Patients with systemic lupus erithematosus (17–65 years) presented higher frequency of M-MDSC than healthy control whereas only half showed increase of G-MDSC. The increase in both subsets of MDSC was correlated with the disease activity, serum level of Arg-1 activity, and increase in MDSC Arg-1^{+} mainly from the G-MDSC subset (Wu et al. 2016).

4.5 Obesity/Type 2 Diabetes

In obese individuals, the presence of chronic inflammation and the expression of the same factors (IL-6, IL-1β, TNF-α, and PGE2) (Chen et al. 2015) associated with tumor-induced MDSC could explain the increase of these cells in obesity. In comparison with lean individuals, Bao et al. (2015) observed higher percentage of M-MDSC in obese individuals. In addition, it was also observed impaired liver metabolism and a reduced expression of TCRζ on the surface of $CD8^{+}$ cells in obese individuals that could be associated with the immunosuppressives features of MDSC (Bao et al. 2015).

A study with studied lean individuals (mean age 43.4 years), overweight individuals (mean age 46.0 years), and obese individuals (mean age 46.4 years) showed that M-MDSC was highly expressed in obese individuals compared to the other groups. There was strong association between M-MDSC and body mass index, fat mass, waist circumference, triglycerides, HDL-c (decrease), glycosylated haemoglobin, and C reactive protein. In addition, M-MDSC was higher in obese individuals with type 2 diabetes (T2D) than in obese and non-diabetic individuals (Friedrich et al. 2019). T2D patients (35–62 years) evaluated by Fernández-Ruiz et al. (2019) exhibited increased percentage of MDSC. In addition, diabetic and non-diabetic individuals with systemic arterial hypertension showed an increase in the frequency of MDSC suggesting an inflammatory process leading to cardiovascular changes. Authors also suggest that MDSC may play a role in the development of infections in patients with T2D due to the suppression caused to T-cell immune responses.

4.6 Ageing Neurodegenerative Diseases

Neurodegenerative diseases have been associated with neuroinflammation and thus MDSC expression could be evolved in the progression of nervous system degeneration. In Alzheimer's disease (AD, patients older than 60 years) it was observed increased expression and suppressive function of MDSC in prodromal AD and decreased expression in moderate/severe AD dementia (Thome et al. 2018). In

Parkinson's disease, patients (61–79 years old) exhibited higher levels of MDSC than healthy controls (Chen et al. 2017).

4.7 Conclusions

MDSC are heterogeneous myeloid cells with potent immune suppressive activity and in healthy young individuals these cells are expressed in very low percentage. There are few studies focused in aged individuals and MDSC frequency/function. Since the ageing process has been associated with a low level of chronic inflammation and MDSC frequency increases during inflammatory conditions, it has been difficult to isolate the influence of chronological age in these cells. In addition, the evaluation of MDSC displays disparate results, probably due to the lack of exclusive human phenotype markers for MDSC, different cell preservation techniques and suppression assays.

In cancer MDSC are increased and suppressive suppressive function of these cells that correlate with advanced disease stage, resistance to treatment, and poor prognosis. Regarding infections, increased frequencies of MDSC have been shown and in sepsis, high levels of G-MDSC correlated with inadequate functional status, nosocomial infections, and early mortality. In autoimmune diseases, the suppressive capacity of MDSC was expected to modulate the disease-related inflammatory process and prevent tissue destruction. During disease activity, raised levels of MDSC have been reported in comparison with disease remission and healthy controls. In obesity, MDSC are increased and M-MDSC are higher in obese individuals with type 2 diabetes compared to non-diabetic individuals. Other studies showed that diabetes increases the frequency of MDSC and that diabetic and non-diabetic individuals with hypertension present higher levels of these cells. Considering that a new virus, COVID-19, is causing morbidity and mortality with a higher incidence in ageing individuals and especially in those with chronic diseases, the projection of how the frequency and suppressive function of MDSC could be increased in ageing can lead to the development of more appropriate therapies for the aged population.

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References

Agrati C (2020) Expansion of myeloid-derived suppressor cells in patients with severe coronavirus disease (COVID-19). Cell Death Differ 27:3196–3207. https://doi.org/10.1038/s41418-020-0572-6

Alves AS, Ishimura ME, Duarte YAO, Bueno V (2018) Parameters of the immune system and vitamin d levels in old individuals. Front Immunol 9:1122. https://doi.org/10.3389/fimmu.2018.01122

Bao Y, Mo J, Ruan L, Li G (2015) Increased monocytic CD14+HLADRlow/- myeloid-derived suppressor cells in obesity. Mol Med Rep 11(3):2322–2328. https://doi.org/10.3892/mmr.2014.2927

Bertelli G, Trovato R, Ugel S et al (2019) Characterization of myeloid-derived suppressor cells in a patient with lung adenocarcinoma undergoing Durvalumab treatment: a case report. Clin Lung Cancer 20(4):e514–e516. https://doi.org/10.1016/j.cllc.2019.04.013

Bonomi M, Ahmed T, Addo S et al (2019) Circulating immune biomarkers as predictors of the response to pembrolizumab and weekly low dose carboplatin and paclitaxel in NSCLC and poor PS: An interim analysis. Oncol Lett 17(1):1349–1356. https://doi.org/10.3892/ol.2018.9724

Bueno V, Sant'Anna OA, Lord JM (2014) Ageing and myeloid-derived suppressor cells: possible involvement in immunosenescence and age-related disease. Age (Dordr) 36(6):9729. https://doi.org/10.1007/s11357-014-9729-x.

Calcinotto A, Spataro C, Zagato E et al (2018) IL-23 secreted by myeloid cells drives castration-resistant prostate cancer. Nature 559(7714):363–369. https://doi.org/10.1038/s41586-018-0266-0

Chai E, Zhang L, Li C (2019) LOX-1+ PMN-MDSC enhances immune suppression which promotes glioblastoma multiforme progression. Cancer Manag Res 11:7307–7315. https://doi.org/10.2147/CMAR.S210545

Chen S, Akbar SM, Miyake T et al (2015) Diminished immune response to vaccinations in obesity: role of myeloid-derived suppressor and other myeloid cells. Obes Res Clin Pract 9(1):35–44. https://doi.org/10.1016/j.orcp.2013.12.006

Chen S et al (2017) Increased abundance of myeloid-derived suppressor cells and Th17 cells in peripheral blood of newly-diagnosed Parkinson's disease patients. Neurosci Lett 648:21–25. https://doi.org/10.1016/j.neulet.2017.03.045

Choi J, Maeng HG, Lee SJ et al (2018) Diagnostic value of peripheral blood immune profiling in colorectal cancer. Ann Surg Treat Res 94(6):312–321. https://doi.org/10.4174/astr.2018.94.6.312

Condamine T, Dominguez GA, Youn JI, et al (2016) Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. Sci Immunol 1: aaf8943. https://doi.org/10.1126/sciimmunol.aaf8943

El Daker S, Sacchi A, Tempestilli M, et al (2015) Granulocytic myeloid derived suppressor cells expansion during active pulmonary tuberculosis is associated with high nitric oxide plasma level. PLoS One 10(4):e0123772. https://doi.org/10.1371/journal.pone.0123772

Diaz-Montero CM, Salem ML, Nishimura MI et al (2009) Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclosphosphamide chemotherapy. Cancer Immunol Immunother 58(1):49–59. https://doi.org/10.1007/s.00262-008-0523-4

du Plessis N, Loebenberg L, Kriel M et al (2013) Increased frequency of myeloid-derived suppressor cells during active tuberculosis and after recent mycobacterium tuberculosis infection suppresses T-cell function. Am J Respir Crit Care Med 188(6):724–732. https://doi.org/10.1164/rccm.201302-0249OC

Dubinski D, Wölfer J, Hasselblatt M et al (2016) CD4+ T effector memory cell dysfunction is associated with the accumulation of granulocytic myeloid- derived suppressor cells in glioblastoma patients. Neuro Oncol 18(6):807–818. https://doi.org/10.1093/neuonc/nov280

Falck-Jones S (2020) Functional myeloid-derived suppressor cells expand in blood but not airways of COVID-19 patients and predict disease severity. medRxiv, 2020.2009.2008.20190272. https://doi.org/10.1101/2020.09.08.20190 272

Fang Z, Li J, Yu X et al (2015) Polarization of monocytic myeloid-derived suppressor cells by Hepatitis B surface antigen is mediated via ERK/IL-6/STAT3 signaling feedback and restrains the activation of T cells in Chronic Hepatitis B virus infection. J Immunol 195(10):4873–4883. https://doi.org/10.4049/jimmunol.1501362

Fernández-Ruiz JC, Galindo De Ávila JC et al (2019) Myeloid-derived suppressor cells show different frequencies in diabetics and subjects with arterial hypertension. J Diabetes Res 2019:1568457. 10.1155/ 2019/1568457

Friedrich K, Sommer M, Strobel S et al (2019) Perturbation of the monocyte compartment in human obesity. Front Immunol 10:1874. https://doi.org/10.3389/fimmu.2019.01874

Gabrilovich DI, Nagaraj S (2009) Myeloid-derived-suppressor cells as regulators of the immune system. Nat Rev Immunol 9(3):162–174. https://doi.org/10.1038/nri2506

Goronzy JJ, Weyand CM (2012) Immune aging and autoimmunity. Cell Mol Life Sci 9(10):1615–1623. https://doi.org/10.1007/s00018-012-0970-0

Guo C, Hu F, Yi H et al (2016) Myeloid-derived suppressor cells have a proinflammatory role in the pathogenesis of autoimmune arthritis. Ann Rheum Dis 75(1):278–285. https://doi.org/10.1136/annrheumdis-2014-205508

Hassan M, Raslan HM, Eldin HG et al (2018) CD33+HLA-DR- myeloid-derived suppressor cells are increased in frequency in the peripheral blood of type1 diabetes patients with predominance of CD14+ subset. Open Access Maced J Med Sci 6(2):303–309. https://doi.org/10.3889/oamjms.2018.080

Hurme M, Korkki S, Lehtimäki T et al (2007) Autoimmunity and longevity: presence of antinuclear antibodies is not associated with the rate of inflammation or mortality in nonagerians. Mech Ageing Dev 128(5–6):407–408. https://doi.org/10.1016/j.mad.2007.03.001

Iannou M, Alissafi T, Lazaridis I, et al (2012) Crucial role of granulocytic myeloid-derived suppressor cells in the regulation of central nervous system autoimmune disease. J Immunol 188(3):1136–1146. https://doi.org/10.4049/jimmunol.1101816

Idorn M, Køllgaard T, Kongsted P et al (2014) Correlation between frequencies of blood monocytic myeloid-derived suppressor cells, regulatory T cells and negative prognostic markers in patients with castration-resistant metastatic prostate cancer. Cancer Immunol Immunother 63(11):1177–1187. https://doi.org/10.1007/s00262-014-1591-2

Janols H, Bergenfelz C, Allaoui R et al (2014) A high frequency of MDSCs in sepsis patients with the granulocytic subtype dominating in gram-positive cases. J Leukoc Biol 96(5):685–693. https://doi.org/10.1189/jlb.5HI0214-074R

Kimura T, McKolanis JR, Dzubinski LA et al (2013) MUC1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. Cancer Prev Res (Phila) 6(1):18–26. https://doi.org/10.1158/1940-6207.CAPR-12-0275

Knier B, Hiltensperger M, Sie C et al (2018) Myeloid-derived suppressor cells control B cell accumulation in the central nervous system during autoimmunity. Nat Immunol 19(12):1341–1351. https://doi.org/10.1038/s41590-018-0237-5

Kongsted P, Borch TH, Ellebaek E et al (2017) Dendritic cell vaccination in combination with docetaxel for patients with metastatic castration- resistant prostate cancer: A randomized phase II study. Cytotherapy 19(4):500–513. https://doi.org/10.1016/j.jcyt.2017.01.007

Kurkó J, Vida A, Glant TT et al (2014) Identification of myeloid-derived suppressor cells in the synovial fluid of patients with rheumatoid arthritis: a pilot study. BMC Musculoskelet Disord 15:281. https://doi.org/10.1186/1471-2474-15-281

Lang S, Bruderek K, Kaspar C et al (2018) Clinical relevance and suppressive capacity of human myeloid-derived suppressor cells subsets. Clin Cancer Res 24(19):4834–4844. https://doi.org/10.1158/1078-0432.CCR-17-3726

Lv Y, Cui M, Lv Z et al (2018) Expression and significance of peripheral myeloid-derived suppressor cells in chronic hepatitis B patients. Clin Res Hepatol Gastroenterol 42(5):462–469. https://doi.org/10.1016/j.clinre.2018.04.002

Mao Y, Poschke I, Wennerberg E et al (2013) Melanoma-educated CD14+ cells acquire a myeloid-derived suppressor cell phenotype through COX-2- dependent mechanisms. Cancer Res 73(13):3877–3887. https://doi.org/10.1158/0008-5472.CAN-12-4115

Marvel D, Gabrilovich DI (2015) Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. J Clin Invest 125(9):3356–3364. https://doi.org/10.1172/JCI80005

Mathias B, Delmas AL, Ozrazgat-Baslanti T et al (2017) The Sepsis, Critical Illness Research Center Investigators. Myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/septic shock. Ann Surg 265(4):827–834. https://doi.org/10.1097/SLA.00000000 00001783.

Navarro-Martín A, Galiana IL, Berenguer Frances MA et al (2018) Preliminary study of the effect of stereotactic body radiotherapy (SBRT) on the immune system in lung cancer patients unfit for surgery: immunophenotyping analysis. Int J Mol Sci 19(12): pii: E3963. https://doi.org/10.3390/ijms19123963.

Ostrand-Rosenberg S (2010) Myeloid-derived suppressor cells: more mechanisms for inhibiting antitumor immunity. Cancer Immunol Immunother 59:1593–1600. 10.1007/ s00262-010-0855-8

Pawelec G, Picard E, Bueno V et al (2021) MDSCs, ageing and inflammageing. Cell Immunol 362:104297. https://doi.org/10.1016/j.cellimm.2021.104297

Romano A, Parrinello NL, La Cava P et al (2018) PMN-MDSC and arginase are increased in myeloma and may contribute to resistance to therapy. Expert Rev Mol Diagn 18(7):675–683. https://doi.org/10.1080/14737159.2018.1470929

Salem ML, Zidan AA, Attia M et al (2017) IFN-α-based treatment of patients with chronic HCV show increased levels of cells with myeloid-derived suppressor cell phenotype and of IDO and NOS. Immunopharmacol Immunotoxicol 39(4):188–198. https://doi.org/10.1080/08923973.2017.1320670

Santegoests SJ, Stam AG, Lougheed SM et al (2014) Myeloid derived suppressor and dendritic cell subsets are related to clinical outcome in prostate cancer patients treated with prostate GVAX and Ipilimumab. J Immunother Cancer 2:31. https://doi.org/10.1186/s40425-019-0663-4

Schrijver IT, Théroude C, Roger T (2019) Myeloid-derived suppressor cells in sepsis. Front Immunol 10:327. https://doi.org/10.3389/fimmu.2019.00327

Sharma V, Dong H, Kwon E, Karnes RJ (2018) Positive pelvic lymph nodes in prostate cancer harbor immune suppressor cells to impair tumor-reactive T cells. Eur Urol Focus 4(1):75–79. https://doi.org/10.1016/j.euf.2016.09.003

Thome AD et al (2018) Functional alterations of myeloid cells during the course of Alzheimer's disease. Mol Neurodegener 13:61. https://doi.org/10.1186/s13024-018-0293-1

Toor SM, Syed Khaja AS, El Salhat H et al (2016) Increased levels of circulating and tumor-infiltrating granulocytic myeloid cells in colorectal cancer patients. Front Immunol 7:560. https://doi.org/10.3389/fimmu.2016. 00560

Uhel F, Azzaoui I, Grégoire M et al (2017) Early expansion of circulating granulocytic myeloid-derived suppressor cells predicts development of nosocomial infections in patients with sepsis. Am J Respir Crit Care Med 196(3):315–327. https://doi.org/10.1164/rccm.201606-1143OC

Veglia F, Perego M, Gabrilovich D (2018) Myeloid-derived suppressor cells coming of age. Nat Immunol 19(2):108–119. https://doi.org/10.1038/s41590-017-0022-x

Verschoor CP, Johnstone J, Millar J et al (2013) Blood CD33(+)HLA-DR(-) myeloid-derived suppressor cells are increased with age and a history of cancer. J Leukoc Biol 93(4):633–637. https://doi.org/10.1189/jlb.0912461

Wesolowski R, Duggan MC, Stiff A et al (2017) Circulating myeloid-derived suppressor cells increase in patients undergoing neo-adjuvant chemotherapy for breast cancer. Cancer Immunol Immunother 66:1437–1447. https://doi.org/10.1007/s00262-017-2038-3

Whitfield-Larry F, Felton J, Buse J, Su MA (2014) Myeloid-derived suppressor cells are increased in frequency but not maximally suppressive in peripheral blood of Type 1 Diabetes Mellitus patients. Clin Immunol 153(1):156–164. https://doi.org/10.1016/j.clim.2014.04.006

Wu H, Zhen Y, Ma Z, et al (2016) Arginase-1-dependent promotion of TH17 differentiation and disease progression by MDSCs in systemic lupus erythematosus. Sci Transl Med 8(331):331ra40. 10.1126/ scItranslmed.aae0482.

Yu J, Du W, Yan F et al (2013) Myeloid-derived suppressor cells suppress antitumor immune response through IDO expression and correlate with lymph node metastasis in patients with breast cancer. J Immunol 190(7):3783–3797. https://doi.org/10.4049/jimmunol.1201449

Zeng QL, Yang B, Sun HQ et al (2014) Myeloid-derived suppressor cells are associated with viral persistence and down regulation of TCRζ chain expression on CD8(+) T cells in chronic hepatitis C patients. Mol Cells 37(1):66–73. https://doi.org/10.14348/molcells.2014.2282

Zhu J, Chen S, Wu L et al (2018) The expansion of myeloid-derived suppressor cells is associated with joint inflammation in rheumatic patients with arthritis. Biomed Res Int 2018:5474828. https://doi.org/10.1155/2018/5474828

Chapter 5
Effects of Aging and Associated Conditions on Humoral Responses to Respiratory Tract Infections

Daniela Frasca

Abstract Aging is associated with increased respiratory tract infections (RTIs) to which immunosenescence and inflammaging, the chronic low-grade systemic inflammation, significantly contribute. Immunological and structural changes occur in the lungs with advancing age and contribute to reduced lung function. In this chapter we summarize published results on the effects of aging on RTIs due to three different pathogens: Influenza, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) and *Streptococcus pneumoniae* ("pneumococcus"). We also summarize age-related changes in humoral immunity against these pathogens and potential mechanisms involved. We finally cover the importance of vaccination in reducing the probability of older adults to get infected and to succumb to complications that can lead them to long-term illness, hospitalization, and ultimately death.

Keywords Aging · B cells · Antibodies · Influenza infection · SARS-CoV-2 infection · *Streptococcus pneumoniae* infection · Vaccines

Abbreviations

CDC	Centers for Disease Control and Prevention
EMR	Excess mortality rates
HAI	HemAgglutination Inhibition
ICU	Intensive Care Units
PspA	Pneumococcal surface protein A
RTIs	Respiratory tract infections
TNF	Tumor Necrosis Factor

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TNFR Tumor Necrosis Factor Receptor
URT Upper respiratory tract
WHO Worls Health organization

5.1 Inflammaging and Immunosenescence

Aging is characterized by a progressive decline in immune function, called immunosenescence. Innate and adaptive immune responses are both decreased by aging, leading to increased frequency and severity of infectious diseases and reduced responses to vaccination (Ferrucci et al. 1997; McElhaney and Effros 2009). Hospitalization following infection is more common in the elderly than in younger individuals and is a major contributor to the development of disability (Ferrucci et al. 1997).

Aging is also characterized by increased chronic low-grade systemic inflammation, known as inflammaging (Franceschi et al. 2000), which is a significant risk factor for morbidity and mortality of elderly individuals as it is implicated in the pathogenesis of several debilitating chronic diseases of older adults including Type-2 Diabetes Mellitus (Prattichizzo et al. 2018), osteoporosis (Lencel and Magne 2011), Alzheimer's disease (Askarova et al. 2020; Costantini et al. 2018; Giunta et al. 2008), rheumatoid arthritis (Rezus et al. 2019; Zuo et al. 2019), and coronary heart disease (de Almeida et al. 2020; Ferrucci 2018; Zuo et al. 2019). Inflammaging is also associated with metabolic dysfunction and development of insulin resistance (IR).

Pro-inflammatory cytokines and chemokines, acute phase proteins and mannose- or manna-binding lectin are among the most common markers of inflammaging, associated with the development of age-associated conditions and diseases. However, significant person-to-person variations in inflammatory measures have been observed in different studies, suggesting the need for longitudinal studies to better evaluate age-dependent changes in the immune system of each individual. Recently, a multi-omics approach has been used to link inflammaging to disease risk. The study has performed high-throughput molecular profiling of adult individuals followed longitudinally, and has measured whole-blood gene expression (the transcriptome), immune cytokines and chemokines (the immunome), and frequencies of several immune cell subsets (CD4 and CD8 T cells, B cells, NK cells). Results have allowed the construction of a high-dimensional trajectory of immune aging, called IMM-AGE, that describes the immune status of the individual better than his/her chronological age, and also accurately predicts all-cause mortality (Alpert et al. 2019).

Various factors contribute to inflammaging. These factors include polymorphisms in the promoter regions of pro- and anti-inflammatory genes, chronic stimulation of immune cells with viruses such as cytomegalovirus, cellular senescence, increased deposition of fat in internal organs, increased permeability of the gut, changes in the composition of the gut microbiome, increased production of altered molecules generated by damaged or dead cells and organelles (Frasca et al. 2020). All these factors,

alone but especially in combination, induce defects in cells of the innate and adaptive immune system leading to increased frequency and severity of infectious diseases in the elderly. It has been proposed that the balance between inflammaging and anti-inflammaging determines the rate of aging, the onset of age-associated diseases and their severity, as well as the individual's ability to reach extreme longevity (Franceschi et al. 2007). Therefore the identification of pathways inducing inflammaging and anti-inflammaging across multiple systems is needed to design strategic therapeutic interventions aimed to increase healthspan of elderly individuals.

Inflammaging induces intrinsic inflammation in immune cells leading to decreased protective responses against infections and decreased responses to vaccines (Bryl et al. 2001; Frasca et al. 2014; Parish et al. 2009). Higher levels of inflammaging can be measured for example by serum TNF-α. Higher serum TNF-α induces higher intrinsic TNF-α in B cells from old mice (Frasca et al. 2012) and humans (Frasca et al. 2014). This higher inflammatory phenotype makes B cells from old mice and humans refractory to subsequent stimulation and reduces their capacity to make protective antibodies in response to infections or vaccination (Frasca et al. 2014, 2012). Mechanistically, serum TNF-α up-regulates the expression of its receptors (TNFRI and TNFRII) on B cells, leading to NF-kB activation and secretion of TNF-α as well as of other pro-inflammatory cytokines and chemokines (Miscia et al. 2002). Importantly, blocking TNF-α with specific antibodies has been shown to increase B cell function, at least in vitro, in mice (Frasca et al. 2014) and humans (Frasca et al. 2012).

Elevated serum TNF-α also negatively correlate with T cell function, as they are linked to the down-regulation of CD28 gene transcription and of CD28 membrane expression (Bryl et al. 2001). In particular, these studies have shown that incubation of T cell lines and clones with TNF-α induces a reduction in surface expression of CD28, an effect that disappeares after removal of the cytokine. However, prolonged exposure of CD4 + CD28 + T cell clones to TNF-α leads to the appearance of $CD28^{null}$ clones. Mechanistically, TNF-α has been shown to directly inhibit the activity of the CD28 minimal promoter, with the inactivation of the promoter being accompanied by a marked reduction in DNA–protein complex formation by two DNA sequence motifs corresponding to the transcriptional initiator of the CD28 gene. These results have demonstrated that TNF-α directly influences CD28 gene transcription.

The elevated circulating levels of TNF-α due to inflammaging also affect monocytes, leading to their premature egress from the bone marrow. These immature monocytes, when stimulated with bacterial products in vivo, secrete high levels of TNF-α, thus contributing to inflammaging. At the same time, however, similar to what has been shown for B and T cells, TNF-α induces dysfunctional tissue-associated monocytes leading to reduced bacterial clearance (Puchta et al. 2016).

5.2 Changes in the Lungs with Age

Aging is a major risk factor for developing non-communicable chronic lung diseases, including chronic obstructive pulmonary disease, lung cancer, and interstitial lung disease (Meiners et al. 2015).

The complex structure of the lungs enables the exchange of inhaled air with circulating blood. The lung is the organ with the largest surface area in humans, and for this reason is constantly exposed to the outside environment, to pollen, to bacterial or viral pathogens, to active or passive cigarette smoke, and to indoor occupational or home pollutants. A large number of protection mechanisms are in place. These include responses from resident innate and adaptive immune cells, such as alveolar macrophages, neutrophils and dendritic cells, that fight infections and counteract and clear environmental stressors (Meiners et al. 2015), as well as progenitor cells that provide the lung with a remarkable regenerative capacity if injury occurs (Hogan et al. 2014). These ways of protection, however, deteriorate with age and several immunological mechanisms have been proposed (Lowery et al. 2013). Among these, the age-associated increase in the secretion of superoxide anion by alveolar macrophages in response to stimuli from environmental exposure, as well as decreased responses to antigenic exposure, activate inflammatory pathways and consequent decreased function. Inflammaging in the lower respiratory tract can cause proteolytic and oxidant-mediated injury to the lung matrix resulting in loss of alveolar unit and impaired gas exchange across the alveolar membrane (Meyer et al. 1996). Both splenic and peritoneal macrophages from old mice secrete lower amounts of inducible nitric oxide synthase, an enzyme that regulates production of reactive oxygen species (Ding et al. 1994; Kissin et al. 1997), and have reduced cytotoxicity. Similarly, neutrophils from older adults ($\geq$85 years) produce less superoxide (Polignano et al. 1994), suggesting compromized host defense processes with age in humans as well. Aging increases susceptibility to cigarette smoke-induced inflammation through increased expression and activation of NF-kB in neutrophils and macrophages (Moriyama et al. 2010). Aging also induces delayed clearance of environmental toxins (i.e. diesel exhaust), due to the increased pulmonary neutrophilia in lung parenchyma (Sunil et al. 2009), suggesting a chronic, aberrant pulmonary immune response, which may translate into increased tissue damage. After pulmonary infection with *Francisella tularensis*, a delayed neutrophil recruitment was also observed (Mares et al. 2010).

In addition to the immunological changes that occur with advancing age, contributing to decreased lung function, other changes have been reported and include: (1) a reduction in the volume of the thoracic cavity and of the lungs, as well as in muscle function that supports respiration (Sharma and Goodwin 2006); (2) a decrease in intervertebral disk spaces and consequent curvature of the spine (Bartynski et al. 2005); (3) a decline in the strength of the diaphram, which is the most important respiratory muscle and plays an essential role during inspiration, leading to diaphragmatic fatigue and ventilatory failure during increased ventilatory load on the respiratory system (Enright et al. 1994; McClaran et al. 1995); (4) a decrease in the space between ribs, causing a decrease in the length of the intercostal

muscles (Culham et al. 1994); (5) an increased airway resistance causing increased work of breathing (Sharma and Goodwin 2006); (6) increased osteoporosis leading to decreased height of the thoracic vertebrae and ability of the thoracic cage to expand during inspiration, placing the diaphragm at a mechanical disadvantage to effectively contract; (7) a decrease in the capacity of the lungs to clear mucus, due to both reduced cough strength and reduced capacity to clear particles coming from the outside environment (McCool 2006).

5.3 Aging and Respiratory Tract Infections (RTI)

Respiratory tract infections (RTIs) are the major cause of death due to infectious diseases in older adults (Meyer 2004). Immunosenescence and the onset of age-associated organ dysfunction likely account for the significant increase in susceptibility to RTIs, as well as in morbidity and mortality rates. The presence of underlying conditions and diseases further increases the likelihood of developing severe RTIs in the elderly population, particularly in long-term residents of care facilities, are at high risk for developing severe and recurrent infections.

This chapter will show the experimental evidence that aging is linked to higher severity of RTIs. Potential mechanisms responsible for these effects will be discussed. We will focus on influenza, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) and *Streptococcus pneumoniae* ("pneumococcus") infections.

5.3.1 Influenza Virus RTI

Infection with influenza viruses represents a significant health concern worldwide, because infection causes high numbers of hospitalizations and deaths reported each year as a consequence of seasonal epidemics. In addition, viruses from the animal reservoir, such as the avian influenza viruses H5N1 and H7N9, that cause significant numbers of zoonotic infections, can sometimes cross the species barrier, and after they combine to create new subtypes with surface antigens of both the original strains, a process called antigenic shift, cause pandemics (Kramer et al. 2019). The morbidity and mortality associated with pandemics in general is higher than those due to seasonal influenza virus epidemics (Taubenberger and Morens 2010). Pandemics are usually caused by viruses that feature the surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), to which the human immune system is relatively naïve, as shown by the examples of the 1918 and 1957 pandemics, for HA and NA respectively (Palese, 2004). Antibodies against surface glycoproteins are not only protective against infection, but they have been identified as correlates of protection (Hobson 1972).

Influenza infection causes common cold, sinusitis, tonsillitis, pharyngitis and laryngitis in the upper RT, whereas causes pneumonia, bronchitis and tuberculosis

in the lower RT (Haq and McElhaney 2014). Following infection, several changes occur and these affect the proper function of the RT (Herold et al. 2015). It has been suggested that elderly individuals, who have already a dysfunctional RT, may be infected by multiple RT pathogens. Moreover, it has been shown that the alveolar macrophages of mice infected with influenza respond less to TLR-mediated stimuli, and secrete significantly lower amounts of chemokines with a consequent reduced recruitment of neutrophils and higher bacterial load during secondary RT infections (Didierlaurent et al. 2008).

A viral surveillance network has been created not only in the majority of high-income countries, but also in several developing countries, with the purpose to collect, analyze, and report local infection data, create influenza mortality estimates and improve influenza surveillance. These estimates are in general higher than those calculated by the World Health Organization (WHO), suggesting underestimated global mortality rates as a consequence of influenza infection. It has been shown that country-specific influenza-associated excess mortality rates (EMR), calculated in 33 low- and high-income countries around the world in the years 1999–2015, ranged from 0.1 to 6.4/100,000 individuals for people < 65 years of age, 2.9 to 44/100,000 individuals for people 65–74 years of age, and 17.9 to 223.5/100,000 for people > 75 years of age (Iuliano et al. 2018).

Influenza-associated deaths have increased from 20,000 deaths/season in the years 1976–1990 to 36,000 deaths/season in the early 2000s in the U.S. (Thompson et al. 2003), with > 40% of influenza deaths occurring in individuals ≥ 75 years of age and > 15% in individuals 65–74 year old (Iuliano et al. 2018). More specifically, influenza illness has been shown to be linked to all the six leading causes of catastrophic disability of older adults. These include stroke, congestive heart failure, pneumonia, ischemic heart disease, cancer and hip fracture (McElhaney et al. 2020).

The Influenza Hospitalization Surveillance Network (FluSurv-NET) (https://www.cdc.gov/mmwr/volumes/68/wr/mm6824a3.htm) of the Centers for Disease Control and Prevention (CDC) monitors laboratory-confirmed influenza infections and associated hospitalizations in the U.S. Data collected in the 2018–2019 season have confirmed data from previous years and have shown that hospitalization rates were significantly higher in individuals ≥ 65 years of age as compared to younger controls. The majority of the hospitalizations (95%) were due to the influenza A virus, 50% of which due to A/H3N2, a strain associated with heavy seasonal epidemics (Allen and Ross 2018), and especially in elderly individuals, leading to the highest numbers of hospitalization and deaths (Thompson et al. 2003). Only 4% of the hospitalizations were due to influenza B virus and 1% to influenza A and B virus co-infection. Similarly, data collected in Europe in the same season season (https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-annual-epidemiological-report-2018-2019) have shown that the majority of influenza cases were due to infections with both type A subtypes (A/H1N1pdm09 and A/H3N2), although different distributions of A subtypes were reported in different European countries. Only low numbers of type B viruses (B/Yamagata and B/Victoria) were detected. Hospitalizations in Intensive Care Units (ICU) were

mainly in individuals ≥ 65 years of age as compared to younger controls, and due to influenza A infections.

The burden of influenza infection in older adults is associated with immunosenescence and its complex interaction with multiple chronic conditions, among which chronic diseases, obesity, metabolic diseases, and neuromuscular disorders play a relevant role (Louie et al. 2009). Frailty represents another risk factor for influenza infection. Frailty is a measure of health, physical function and physiologic reserve, and a strong predictor of health outcomes (Clegg et al. 2013). Elderly individuals infected with influenza are not only at increased risk of serious complications of influenza and respond less to vaccination (Andrew et al. 2017), but they are also at increased risk to get additional infections with viruses that cause severe RTI, including the recent coronavirus SARS-CoV-2 of COVID-19. With improvements in health care and advances in medical treatments, older adults are now living longer with multiple (≥2) chronic conditions. Thus, new influenza vaccines are needed to prevent or mitigate the consequences of influenza in the aging population.

5.3.1.1 Age-Associated Decrease in Influenza-Specific Humoral Responses

Humoral immune responses play key roles in the clearance of the virus and in protection as they initially control the infection through the secretion of specific antibodies which gives time for cytotoxic T cell responses to develop. Antibodies bind to HA surface glycoprotein, that allows infection of the host cell, and neutralize the virus. Antibody titers are measured by the HemAgglutination Inhibition (HAI) assay, which represents the gold standard correlate of protection from infection and represent the only measure of vaccine efficacy. HAI titers, however, do not provide clinical protection against complications from influenza infection (Hobson et al. 1972). Antibodies specific for NA, are also induced by natural infection, although typically at lower levels than antibodies specific for HA, as NA has been described to be immunosubdominant and with lower immunogenicity as compared to HA (Johansson et al. 1987).

High baseline (pre-exposure) titers in general indicate a reduced probability to get infected. The 2009 H1N1 pandemic (H1N1pdm09) was characterized by lower morbidity and mortality in older as compared to younger people, likely because of pre-exposure of older people to the 1918 pandemic A/H1N1 virus that originated periodic seasonal strains that decreased in frequency only in the late 1950s. This occurred because the A/H1N1 viruses circulating in the 1918 and the 2009 pandemics shared similar cross-neutralization and protection (Wei et al. 2010). In a study conducted in 130 individuals 0–89 years of age, infected with the H1N1pdm09, an in-depth evaluation of antibody responses was performed and showed that not only HAI titers were higher in older adults as compared to younger controls (Verma et al. 2012). It was shown that the infection of elderly individuals (≥70 years old) with the H1N1pdm09 induced antibodies with broader epitope recognition, higher avidity

and lower antibody dissociation rates measured by surface plasmon resonance for the HA1 globular domain, but not for the conserved HA2 stalk, than those induced in younger individuals. This study was the first to show a better quality of the antibody response in the elderly, suggesting a recall of long-term memory B cells or long-lived plasma cells (Verma et al. 2012).

Similar to HA-specific antibodies, also NA-specific antibodies induced by natural infection were found to be present for many decades in the human population (Rajendran et al. 2017). A study comparing the antibody response to the neuraminidases of influenza A (N1, N2), and B viruses in young and elderly individuals has shown that antibody levels increase with age and are high against strains that circulated during the childhood of the individuals, providing evidence for "original antigenic sin", with the magnitude of the response being higher and cross-reactive for N2 and influenza B virus NA, as compared to N1 (Rajendran et al. 2017). Children are in general nonreactive, likely because they have not been exposed to influenza B virus.

5.3.2 Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) RTI

Since the last months of 2019, SARS-CoV-2 infection had caused > 180 million cases of Coronavirus Disease 2019 (COVID-19) and > 3,900,000 deaths worldwide (as reported by the WHO as of June 30th, 2021, https://covid19.who.int). The infection is known to be responsible for different clinical manifestations ranging from mild disease to severe respiratory tract infections, multiorgan failure and death. The severe manifestations of the disease are associated with an exuberant inflammatory response, and the initiation of cytokine storms that cause severe disease, including pneumonia and acute respiratory distress syndrome. However, several extrapulmonary manifestations of COVID-19 have also been observed, with consequences affecting the hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, ophthalmologic, and dermatologic systems (Gupta et al. 2020). These results have suggested extrapulmonary dissemination and replication of the virus, similar to what has been previously observed with infections with other coronaviruses, as well as widespread immunopathological sequelae of the disease (Holmes et al. 2003).

The mechanism responsible for a severe respiratory pathology only in some individuals are still not fully understood. However, it has been shown that patients requiring hospitalization are mainly older adults also affected by multimorbidity, including hypertension, diabetes, and/or obesity (Zhou et al. 2020). Data published earlier last year have indicated that inflammaging is a major cause of the cellular and molecular changes induced by SARS-CoV-2 and is responsible for the highest mortality rates (Mueller et al. 2020). Inflammaging has been shown to be exacerbated in elderly COVID-19 patients. It has also been postulated that SARS-CoV-2 infection per se predisposes to inflammaging even when the acute clinical syndrome

is mild and clinically resolved in a few days with no apparent immediate consequences (Bektas et al. 2020). Acute SARS-Cov-2 infection has been suggested to induce accumulation of subclinical damage in the organism, leading to the establishment of a chronic pro-inflammatory condition associated with immune activation and consequent immune dysfunction. This hypothesis, however, has not been corfirmed experimentally yet.

A study evaluating the effects of aging on susceptibility to SARS-Cov-2 infection in individuals of different ages has applied an age-structured mathematical model to pandemic data from different countries around the world: China, Italy, Japan, Singapore, Canada and South Korea. Results have shown that susceptibility in individuals < 20 years of age was approximately half than that in individuals > 20 years, with clinical symptoms of infections appearing in 21% of the individuals > 20 year old, and rising to 69% in individuals > 70 year old (Davies et al. 2020).

Although it has been clear since the beginning of the pandemic that infection severity significantly increases with age, the consistency of mortality patterns across countries has only been shown very recently (O'Driscoll et al. 2021). In general, the majority of deaths have occurred in patients ≥ 65 years of age, with patients ≥ 85 years of age suffering for more severe outcomes. Older adults living in facilities for seniors are at the highest risk due to the burden of chronic conditions and diseases and the impact of congregate housing. Using population age structures and age-specific death data, it has been shown a very consistent pattern in the relative risk of death by age for individuals > 65 years of age across countries and continents, with a strong log-linear relationship between age and risk of death for individuals who are 30–65 years old. The same study also showed that the risk of death was significantly higher for men than for women, particularly among older individuals.

As to the frequency of co-infection with other RT viruses, early reports from China have indicated that the frequency of co-infections was low in the whole population (Chen et al. 2020; Ding et al. 2020). Conversely, a study conducted in Stanford has showed higher rates of co-infection in the whole population, as compared to the initial report from China, with 20.7% of SARS-CoV-2 positive samples also positive for at least one RT virus. The most common co-infections were with rhinovirus/enterovirus (6.9%), Respiratory Syncytial Virus (5.2%) and non-SARS-CoV-2 Coronaviruses (4.3%). However, when the analysis was performed in young/adults versus elderly individuals, the frequency of elderly individuals co-infected with SARS-CoV-2 and another RT virus (influenza A virus) was only 1% (Kim et al. 2020). There are still conflicting reports as to whether the infection with SARS-CoV-2 increases the rates of co-infection with other RT viruses in older adults.

Co-infections with bacteria such as *Streptococcus pneumoniae* have also been reported as a significant cause of morbidity and mortality especially in the elderly. One of the reasons is that viral infections alter the structure of the lungs and favor the adherence, invasion and induction of disease by the bacterium. Interestingly, vaccination against seasonal influenza and pneumococcal polysaccharide significantly decreases rates of infection and COVID-19 mortality in older adults (Thindwa et al. 2020).

5.3.2.1 Age Effects on SARS-CoV-2-Specific Humoral Responses

There is insufficient knowledge about humoral responses to SARS-CoV-2, and the host factors responsible are largely unknown. The significance of studying humoral immunity in COVID-19 patients has recently been supported by promising data showing that production of antibodies to SARS-CoV-2 can be critical to limit disease progression, and it has been shown that critically ill patients were able to rapidly leave the ICU after receiving passive immunotherapy with antibodies derived from convalescent patients of any age (AminJafari and Ghasemi 2020; Duan et al. 2020). Current information on the role of antibodies in SARS-CoV-2 clearance and modulation of disease severity, as well as the durability of these responses following primary infection, is controversial. While some studies have found a rapid decay of virus-specific IgG antibodies by approximately 3 months after infection (Ibarrondo et al. 2020; Long et al. 2020), others have shown stable virus-specific IgG antibodies over several months (Gudbjartsson et al. 2020; Isho et al. 2020; Roltgen et al. 2020; Wang et al. 2020).

Studies evaluating the effects of aging on the secretion of SARS-CoV-2-specific antibodies in patients < 65 years or > 65 years of age have also shown controversial results, with publications showing either decreased antibodies in elderly patients (Wang et al. 2020), or no effects of aging (Lau et al. 2021; Ripperger et al. 2020). The only study so far published on decreased anti-SARS-CoV-2 antibody responses with age (Wang et al. 2020) evaluated the three different arms of the SARS-CoV-2-specific adaptive immune response (neutralizing antibodies, CD4 + and CD8 + T cell responses). Results have demonstrated that these responses were uncoordinated in patients > 65 years of age as compared to younger patients, potentially due to scarcity of naive T cells in older adults. Coordinated responses were better than partial responses, with prominent roles for SARS-CoV-2-specific CD4 + T cells associated with less COVID-19 disease severity, while minimal adaptive immunity was associated with more severe COVID-19 disease.

Moreover, while it is expected that SARS-CoV-2-specific antibody responses are higher in COVID-19 patients that are asymptomatic or with mild symptoms of disease as compared to those with severe symptoms, this was shown not to be the case in several studies (Long et al. 2020; Ma et al. 2020; Roltgen et al. 2020; Wang et al. 2020), raising concerns about the effectiveness of antibody responses to SARS-CoV-2 infection, and suggesting that the quality rather than the quantity of antibodies is crucial in predicting the outcome of infection and must be tested. Of great concern is the finding that the serum of adult COVID-19 patients contains antibodies that target the tissues of infected patients instead of targeting the disease-causing virus. Anti-type-I interferon antibodies are among several autoimmune antibodies found in COVID-19 patients with severe symptoms of the disease, and it has been postulated that these pathogenic antibodies may inactivate critical components of the anti-viral response (Woodruff et al. 2020). These findings altogether have suggested that SARS-CoV-2 infection may induce self-tolerance breakdown to a variety of autoantigens,

and more in older individuals. Another possibility is that the virus dissemination through the blood induces tissue damage, cell death and release of intracellular self antigens not known as autoantigens. This could also be increased in those of greater age.

5.3.3 Streptococcus Pneumoniae *(Pneumococcus) RTI*

The gram-positive bacterium *Streptococcus pneumoniae* ("pneumococcus") is spread through airborne droplets and invades the host by colonizing the nasopharynx asymptomatically, becoming part of the upper respiratory tract (URT) commensal microbiota (Bogaert et al. 2004). After colonization, if not effectively cleared by the immune system, the bacterium is spread and disseminates into the lower airways as well as into other organs and tissues, becoming pathogenic (van der Poll and Opal 2009). *Streptococcus pneumoniae* is shielded by an immunogenic polysaccharide capsule that determines the specific serotype based on unique chemical structures. Serotypes differ in their ability to cause invasive disease and in prevalence of nasopharyngeal colonization. In general, low invasive serotypes act as opportunistic bacteria and are associated with higher fatality rates and disease in immunocompromised patients, whereas highly invasive serotypes act as primary pathogens infecting predominantly healthy, immunocompetent individuals (Littorin et al. 2018).

Infection, most commonly associated with pneumonia, represents a major cause of morbidity and mortality, with the risk of infection being higher in older adults ($\geq$65 years of age) who experience up to fivefold increase in the incidence of death due to pneumococcal community-acquired pneumonia as compared to younger controls (Jain et al. 2015). Before antimicrobial treatments were available, $\geq$ 70% of patients hospitalized died of bacterial pneumococcal pneumonia and mortality rates were higher in older adults (Austrian and Gold, 164). By the end of the twentieth century, mortality rates significantly dropped to 20% in individuals $\geq$ 65 years of age and to 40% in those $\geq$ 85 years of age (Bennett et al. 1992; Breiman et al. 1990; Plouffe et al. 1996).

Inflammaging is associated with increased susceptibility to *Streptococcus pneumoniae* infection, with higher disease severity and decreased survival in older adults versus younger controls (Antunes et al. 2002; Yende et al. 2005). Inflammaging induces the expression of host proteins that enhance pneumococcus adhesion, and is often accompanied by other co-morbidities that increase risk of *S. pneumoniae* infections (Shea et al. 2014). Moreover, age-related changes in the URT microbiota have been suggested to contribute to *Streptococcus pneumoniae* colonization and its inefficient clearance, as shown by studies conducted in both mice (Thevaranjan et al. 2016) and humans (Whelan et al. 2014). The URT is colonized by different species of pathogens and is continuously exposed to bacteria present in the environment, which survive in the nasal and oral cavities of older individuals, due to loss of resistance to colonization and altered immunity.

5.3.3.1 Age Effects on *Streptococcus Pneumoniae*-Specific Humoral Responses

The protective role of antibody responses to pneumococcal infection is well known. IgM antibodies represent the first class of antibodies to be secreted and although they bind antigens with low affinity they are characterized by broad specificities (Boes 2000). Experiments conducted in mice have shown that adoptive transfer of IgM antibodies specific for pneumococcal polysaccharides can improve survival following a lethal pneumococcal challenge, suggesting that IgM antibody may be sufficient to confer protection against pneumococcal disease (Baxendale et al. 2008). Other experiments in mice have shown that the subset of B-1a B cells provides immediate protection from *Streptococcus pneumoniae* infection through the secretion of natural IgM antibodies. In particular, when *Streptococcus pneumoniae*-infected SCID mice were injected with IgG-depleted serum from young and old mice, they were protected only if they received IgG-depleted serum from young mice, suggesting an age-dependent decrease in protective IgM antibodies (Holodick et al. 2016). Sequence analysis of IgM antibodies secreted by B-1a B cells showed significant differences between young and old mice in nucleotide sequences in the V region of the antibody responsible for binding of B-1a cells to phosphorylcholine, the main antigen in the cell wall of *Streptococcus pneumoniae,* in the length and charge of the CDR-H3 loop region, and in V_H, D_H, and J_H usage (Holodick et al. 2016).

Experiments in humans have also indicated that the amount of antibodies specific for pneumococcal polysaccharides declines with aging, with the decrease in IgM levels being more pronounced than the decrease in IgG levels (Araujo et al. 2021; Leggat et al. 2013; Shi et al. 2005; Simell et al. 2008). However, IgM production in response to the pneumococcal surface protein A (PspA) has also been reported to be unchanged in some studies (German et al. 2018). PspA is a major virulence factor of *Streptococcus pneumoniae*, expressed in the majority of clinically important pneumococcal serotypes (Crain et al. 1990) and clade 4 in particular exhibits broad cross-reactivity (Darrieux et al. 2008).

Both the quantity and the quality (ability of antibodies to enhance phagocytosis of encapsulated *Streptococcus pneumoniae*) of naturally-acquired anti-pneumococcal capsular polysaccharide IgG antibodies were found to be reduced in elderly individuals as compared to younger controls (Balmer et al. 2007; Simell et al. 2008, 2011), thus contributing to the increased susceptibility of the elderly to pneumococcal diseases.

5.4 Importance of Vaccination

According to the CDC, vaccinations are among the top 10 public health accomplishments of the twentieth century, being able to significantly reduce the incidence of many serious infectious diseases. Vaccinations are needed throughout life, as immunity from childhood vaccinations wears off over time, and adults may also be at risk

for additional vaccine-preventable diseases. Vaccines are especially important for older adults, as their immune system weakens and becomes less effective in fighting off infections, with increased probability to get infected and to have complications that can lead to long-term illness, hospitalization, and even death. Potential strategies to improve vaccine immunogenicity have been developed and include higher antigen dose, alternative routes of administration, and the use of adjuvants. All these strategies, implemented for influenza vaccines, have shown moderately higher production of specific antibodies. Research on universal vaccines against influenza and *Streptococcus pneumoniae* is ongoing in order to overcome the limitations of the current strain-specific vaccines. Universal vaccines have the advantage to abolish the need for annual reformulation and vaccination with a seasonal vaccine. Their availability would markedly increase pandemic preparedness.

The next three paragraphs summarize published results on the effects of aging on vaccines specific for influenza, SARS-CoV-2 and *Streptococcus pneumoniae.*

5.4.1 Effects of Aging on Influenza Vaccine-Specific Antibody Responses

Although numbers of people that receive the influenza vaccine have significantly increased over the years, influenza is still a serious health concern for older adults. In the U.S., 2/3 of the 200,000 influenza-related hospitalizations occur in individuals $\geq$ 65 years of age, independently of associated conditions. Moreover, the length of hospital stay for elderly individuals is almost 3- and sixfold higher than middle age (50–64 year old) and younger individuals, respectively (McElhaney et al. 2020). These data suggest the need of vaccines with increased immunogenicity to improve the response of older adults (Finco et al. 2014; Weinberger et al. 2018).

Different types of influenza vaccines have been used throughout the years, with many of these still being in use, including whole inactivated virus vaccines, split virus and subunit vaccines, live-attenuated influenza virus vaccines and recombinant HA-based vaccines. Influenza vaccines induce virus-specific humoral and cellular immunity (Murasko et al. 2020). The antibody response is the first line of protection from subsequent infection with the secretion of IgM antibodies first and later with secondary switched antibodies (IgA and IgG) with neutralizing activity (Burlington et al. 1983). Although for a long time it has been believed that there is no pre-existing immunity to newly emerging influenza variants in humans (McMurry et al. 2008; Wrammert et al. 2008), it has been demonstrated that seasonal influenza vaccination induces polyclonal heterosubtypic neutralizing antibodies, and these antibodies have been shown to be cross-reactive with viruses of swine and avian origin, such as the H1N1pdm09 and the H5N1, respectively (Corti et al. 2010).

Both the production and the duration of high affinity protective antibodies generated in response to the influenza vaccine decline with age (Saurwein-Teissl et al.

2002). Young individuals respond better than elderly individuals to the first vaccination, but after repeated vaccinations with the same vaccine differences between young and elderly individuals are decreasing, suggesting the importance of pre-existing immunity (Mosterin Hopping et al. 2016). Influenza vaccine-specific antibodies do not persist year-round in older adults, suggesting the need for better strategies that provide improved clinical benefits (Young et al. 2017), and vaccinated elderly individuals can still be infected and can also get severe secondary complications such as hospitalization, catastrophic disability, exacerbation of underlying medical conditions and death (Gross et al. 1995; Simonsen et al. 2007; Vu et al. 2002), due to their compromised immunity. In addition to age, other causes are responsible for the reduced responses to vaccination among elderly adults. These include preexisting immunity, genetic polymorphisms, and the presence of chronic underlying conditions which may compromise the influenza vaccine response (Castrucci 2018; Dhakal and Klein 2019).

Systems vaccinology approaches have been successfully used in recent years to evaluate and characterize innate and adaptive immune responses to the influenza vaccine. Systems vaccinology has made possible the identification of molecular signatures pre-vaccination and at early and late post-vaccination time points, providing a global picture of the immune response to the influenza vaccine. Results from the numerous studies conducted in recent years have highlighted the importance of identifying signatures of influenza vaccine-specific antibody responses that can be shared across multiple seasons and can help to develop next-generation vaccines that can be highly protective. In one of these studies conducted on 212 individuals of different ages recruited from 2007 to 2011 in Atlanta and Miami, we found that the antibody response to the vaccine was negatively associated with age, but not with gender or race (Nakaia et al. 2015). Using a gene set enrichment analysis of genes correlated with the antibody response in each season, we found that early (3 days) post-vaccination signatures of inflammatory pathways in lymphocytes were positively associated (whereas those in monocytes were negatively associated) with serum antibodies. Baseline transcriptional signatures significantly associated with vaccine-specific antibody responses were also found in a multicenter study in which different cohorts recruited through the Human Immunology Project Consortium and the Center for Human Immunology were evaluated. Some of these signatures revealed the involvement of genes involved in autophagy, anti-viral innate immunity, antigen presentation, B cell receptor signaling (Team H-CSP Consortium H-I, 2017). In another study, it was found that the baseline transcripts found to be significantly correlated with antibody responses were enriched for pattern recognition and interferon signaling (Tsang et al. 2014), for age- and apoptosis-related gene module (Furman et al. 2013) or for lipid biosynthesis, also associated with sex and testosterone-dependent differences in the antibody response (Furman et al. 2014). Age-related changes in the expression of markers of immunosenescence associated with gene expression and regulation, cytokine secretion, telomerase expression and phenotype were good predictors of the decreased response of older adults to seasonal influenza A/H1N1 vaccination (Kennedy et al. 2016). These age-differences in gene expression patterns associated with vaccine-specific antibody responses were confirmed

in another study in which post-vaccination levels of KLRB1 (killer cell lectin-like receptor B1) and vaccine-specific antibody responses were positively associated only in young and not in older adults (Avey et al. 2020). When vaccine-specific antibody responses were corrected by disease factor, significant disease-age associations were found for genes involved in innate immune response, viral processes, defense response to virus, and NF-kB signaling pathway (Rogers et al. 2019). Young influenza vaccine responders are also characterized by higher levels of expression of genes and proteins controlling mitochondrial biogenesis and pathways of oxidative phosphorylation (Thakar et al. 2015). This study has provided the first genome-wide transcriptional analysis of metabolic measures performed before and after influenza vaccination in young and elderly individuals, showing the crucial role of mitochondrial pathways in influenza vaccine responses.

5.4.2 *Effects of Aging on COVID-19 Vaccine-Specific Antibody Responses*

The current SARS-CoV-2 pandemic has pushed the development of vaccines to protect the population from COVID-19. The U.S. Food and Drug Administration has granted emergency use authorization for the Pfizer/BioNTech and the Moderna COVID-19 mRNA vaccines. In December 2020, the first vaccines were approved worldwide and the vaccination campaign started. Both vaccines were shown to provide immunity against SARS-CoV-2 infection in the general population (Meo et al. 2021). However, although many Phase III trials have made efforts to recruit older adults, those with co-morbidities and frailty have been largely excluded. Only a few studies on the effects of aging on antibodies generated in response to COVID-19 vaccines have been published so far. One of these studies has evaluated the antibody response to the Pfizer/Biontech BNT162b2 vaccine in a cohort of young (<60 years) and elderly (>80 years) individuals in Germany (n = 179 individuals total) (Muller et al. 2021). The study has shown that the majority of participants in both age groups made specific IgG antibody titers against the SARS-CoV-2 spike protein. However, titers were significantly lower in elderly as compared to young participants. Although the increase in antibody levels after the second immunization was higher in elderly participants, mean titers remained lower than those in young participants. Importantly, after the second vaccination, only 70% of elderly and > 95% of young individuals had detectable neutralizing antibodies.

Another study involving older adults vaccinated with the mRNA-1273 Moderna vaccine (n = 20 individuals total) has shown high binding- and neutralizing-antibody titers in 56–70 years old participants, even higher in participants > 71 years of age (Anderson et al. 2020).

While we wait for better results on larger cohorts vaccinated in different countries with vaccines different from Pfizer/BioNTech and Moderna, we need to focus on effective strategies to enhance immunogenicity (adjuvants, increased amounts

or multiple doses of the same vaccine) not only in the general population, but in populations at risk. These strategies may also consider the combination of different vaccines for heterologous prime/boost protocols.

5.4.3 *Effects of Aging on* Streptococcus Pneumoniae *Vaccination*

Two vaccines are available for adults ≥ 65 years for protection from pneumococcus infection. The PPV23, a 23-valent pneumococcal polysaccharide vaccine, that induces T-cell independent antibody responses that are short-lived and poorly immunogenic in elderly individuals, with decreased IgM opsonic activity and potency (Park and Nahm 2011); and the PCV13, a 13-valent pneumococcal conjugate vaccine, in which bacterial polysaccharides are covalently conjugated to an immunogenic carrier protein, which induces T-cell dependent antibody responses and B-cell memory. As to vaccination schedule, PCV13 is given first, PPV23 is given at least 1 year later.

Data on efficacy of PPV23 against community-acquired pneumonia have been reported to be highly heterogeneous, going from no effect to around 50% in many studies. These differences depend on differences in cohorts, inclusion criteria and parameters measured (Van Buynder and Booy 2018).

PCV13 is common in pediatric immunizations programs, and also licensed for older persons, as shown by data from the CAPiTA study (Bonten et al. 2015). PCV13 has a well-established immunogenicity and safety profile, but data are lacking on efficacy and effectiveness in adults (Marra and Vadlamudi 2019). Since few countries have recently adopted PCV13 for routine adult immunization, future studies will soon be available with better data to evaluate the effectiveness of PCV13. Nevertheless, vaccines with a broader coverage and duration of protection are needed. Novel strategies should aim at improving the functionality of vaccine-induced antibodies in older people, or targeting alternative molecules such as surface proteins or non-capsular antigens (Adler et al. 2017). A mucosal vaccine, with an appropriate adjuvant, would be an attractive strategy that is currently under investigation (Adler et al. 2017; Kataoka et al. 2017).

5.5 Conclusions

Aging is associated with increased RTIs, that represent the major cause of death due to infectious diseases in older adults. Both immunological (through immunosenescence, inflammaging and dysfunctional immunity) and structural changes occur in the lungs with aging and contribute to reduced lung function and increased frequencies of RTIs. Humoral immune responses play a crucial role in the clearance of infectious

agents and in the initial protection of the individual by controlling the infection through the secretion of specific antibodies which gives time for cytotoxic T cell-mediated immune responses to develop. However, antibody responses to viruses and bacteria responsible for RTIs significantly decline with age. This has been shown for influenza viruses and for the pneumococcus. It is still too early to know if SARS-CoV-2 is also inducing a reduced antibody response in elderly individuals, but this is what we expect. Vaccination is the most effective way to prevent RTIs and vaccines developed with different technologies, but all based on the activation of B and T cell-based immune responses, are saving countless lives. Unfortunately, aging also decreases antibody response to vaccines, and vaccination recommendations in most countries include specific guidelines for older adults. While novel vaccines with higher immunogenicity and efficacy are needed for this vulnerable population, it is also crucial to increase awareness for the importance of vaccination, as vaccination coverage is still far from being optimal among older adults.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has not conflict of interest.

References

Adler H, Ferreira DM, Gordon SB, Rylance J (2017) Pneumococcal capsular polysaccharide immunity in the elderly. Clin Vaccine Immunol 24(6). https://doi.org/10.1128/CVI.00004-17

Allen JD, Ross TM (2018) H3N2 influenza viruses in humans: Viral mechanisms, evolution, and evaluation. Hum Vaccin Immunother 14(8):1840–1847. https://doi.org/10.1080/21645515.2018.1462639

Alpert A, Pickman Y, Leipold M, Rosenberg-Hasson Y, Ji X, Gaujoux R, Rabani H, Starosvetsky E, Kveler K, Schaffert S, Furman D, Caspi O, Rosenschein U, Khatri P, Dekker CL, Maecker HT, Davis MM, Shen-Orr SS (2019) A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. Nat Med 25(3):487–495. https://doi.org/10.1038/s41591-019-0381-y

AminJafari A, Ghasemi S (2020) The possible of immunotherapy for COVID-19: a systematic review. Int Immunopharmacol 83:106455. https://doi.org/10.1016/j.intimp.2020.106455

Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott AB, Flach B, Lin BC, Doria-Rose NA, O'Dell S, Schmidt SD, Corbett KS, Swanson PA 2nd, Padilla M, Neuzil KM, Bennett H, Leav B, Makowski M, Albert J, Cross K, Edara VV, Floyd K, Suthar MS, Martinez DR, Baric R, Buchanan W, Luke CJ, Phadke VK, Rostad CA, Ledgerwood JE, Graham BS, Beigel JH, m RNASG, (2020) Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 383(25):2427–2438. https://doi.org/10.1056/NEJMoa2028436

Andrew MK, Shinde V, Ye L, Hatchette T, Haguinet F, Dos Santos G, McElhaney JE, Ambrose A, Boivin G, Bowie W, al. e, (2017) The importance of frailty in the assessment of trivalent inactivated influenza vaccine effectiveness against influenza-related hospitalization in elderly people. J Infect Dis 216(4):405–414

Antunes G, Evans SA, Lordan JL, Frew AJ (2002) Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. Eur Respir J 20(4):990–995

Araujo AP, Colichio GBC, Oliveira MLS, German E, Nikolaou E, Chen T, Adler H, Ferreira DM, Miyaji EN (2021) Serum levels of anti-PspA and anti-PspC IgG decrease with age and do not correlate with susceptibility to experimental human pneumococcal colonization. PLoS One 16(2):e0247056. https://doi.org/10.1371/journal.pone.0247056

Askarova S, Umbayev B, Masoud AR, Kaiyrlykyzy A, Safarova Y, Tsoy A, Olzhayev F, Kushugulova A (2020) The links between the gut microbiome, aging, modern lifestyle and Alzheimer's disease. Front Cell Infect Microbiol 10:104. https://doi.org/10.3389/fcimb.2020.00104

Austrian R, Gold J (1964) Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med 60:759–776

Avey S, Mohanty S, Chawla DG, Meng H, Bandaranayake T, Ueda I, Zapata HJ, Park K, Blevins TP, Tsang S, Belshe RB, Kaech SM, Shaw AC, Kleinstein SH (2020) Seasonal variability and shared molecular signatures of inactivated influenza vaccination in young and older adults. J Immunol 204(6):1661–1673. https://doi.org/10.4049/jimmunol.1900922

Balmer P, Borrow R, Findlow J, Warrington R, Frankland S, Waight P, George R, Andrews N, Miller E (2007) Age-stratified prevalences of pneumococcal-serotype-specific immunoglobulin G in England and their relationship to the serotype-specific incidence of invasive pneumococcal disease prior to the introduction of the pneumococcal 7-valent conjugate vaccine. Clin Vaccine Immunol 14(11):1442–1450. https://doi.org/10.1128/CVI.00264-07

Bartynski WS, Heller MT, Grahovac SZ, Rothfus WE, Kurs-Lasky M (2005) Severe thoracic kyphosis in the older patient in the absence of vertebral fracture: association of extreme curve with age. AJNR Am J Neuroradiol 26(8):2077–2085

Baxendale HE, Johnson M, Stephens RC, Yuste J, Klein N, Brown JS, Goldblatt D (2008) Natural human antibodies to pneumococcus have distinctive molecular characteristics and protect against pneumococcal disease. Clin Exp Immunol 151(1):51–60. https://doi.org/10.1111/j.1365-2249.2007.03535.x

Bektas A, Schurman SH, Franceschi C, Ferrucci L (2020) A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging? Immun Ageing 17:23. https://doi.org/10.1186/s12979-020-00196-8

Bennett NM, Buffington J, LaForce FM (1992) Pneumococcal bacteremia in Monroe County. New York. Am J Public Health 82(11):1513–1516

Boes M (2000) Role of natural and immune IgM antibodies in immune responses. Mol Immunol 37(18):1141–1149. https://doi.org/10.1016/s0161-5890(01)00025-6

Bogaert D, De Groot R, Hermans PW (2004) Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis 4(3):144–154. https://doi.org/10.1016/S1473-3099(04)00938-7

Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, van Werkhoven CH, van Deursen AM, Sanders EA, Verheij TJ, Patton M, McDonough A, Moradoghli-Haftvani A, Smith H, Mellelieu T, Pride MW, Crowther G, Schmoele-Thoma B, Scott DA, Jansen KU, Lobatto R, Oosterman B, Visser N, Caspers E, Smorenburg A, Emini EA, Gruber WC, Grobbee DE (2015) Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 372(12):1114–1125. https://doi.org/10.1056/NEJMoa1408544

Breiman RF, Spika JS, Navarro VJ, Darden PM, Darby CP (1990) Pneumococcal bacteremia in Charleston County, South Carolina. A decade later. Arch Int Med 150(7):1401–1405

Bryl E, Vallejo AN, Weyand CM, Goronzy JJ (2001) Down-regulation of CD28 expression by TNF-alpha. J Immunol 167(6):3231–3238. https://doi.org/10.4049/jimmunol.167.6.3231

Burlington DB, Clements ML, Meiklejohn G, Phelan M, Murphy BR (1983) Hemagglutinin-specific antibody responses in immunoglobulin G, A, and M isotypes as measured by enzyme-linked immunosorbent assay after primary or secondary infection of humans with influenza A virus. Infect Immun 41(2):540–545

Castrucci MR (2018) Factors affecting immune responses to the influenza vaccine. Hum Vaccin Immunother 14(3):637–646. https://doi.org/10.1080/21645515.2017.1338547

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395(10223):507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Corti D, Suguitan AL, Jr., Pinna D, Silacci C, Fernandez-Rodriguez BM, Vanzetta F, Santos C, Luke CJ, Torres-Velez FJ, Temperton NJ, Weiss RA, Sallusto F, Subbarao K, Lanzavecchia A (2010) Heterosubtypic neutralizing antibodies are produced by individuals immunized with a seasonal influenza vaccine. J Clin Invest 120(5):1663–1673. https://doi.org/10.1172/JCI41902

Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K (2013) Frailty in elderly people. Lancet 381(9868):752–762. https://doi.org/10.1016/S0140-6736(12)62167-9

Costantini E, D'Angelo C, Reale M (2018) The role of immunosenescence in neurodegenerative diseases. Mediators Inflamm 2018:6039171. https://doi.org/10.1155/2018/6039171

Crain MJ, Waltman WD 2nd, Turner JS, Yother J, Talkington DF, McDaniel LS, Gray BM, Briles DE (1990) Pneumococcal surface protein A (PspA) is serologically highly variable and is expressed by all clinically important capsular serotypes of Streptococcus pneumoniae. Infect Immun 58(10):3293–3299. https://doi.org/10.1128/IAI.58.10.3293-3299.1990

Culham EG, Jimenez HA, King CE (1994) Thoracic kyphosis, rib mobility, and lung volumes in normal women and women with osteoporosis. Spine (Phila Pa 1976) 19(11):1250–1255. https://doi.org/10.1097/00007632-199405310-00010

Darrieux M, Moreno AT, Ferreira DM, Pimenta FC, de Andrade A, Lopes APY, Leite LCC, Miyaji EN (2008) Recognition of pneumococcal isolates by antisera raised against PspA fragments from different clades. J Med Microbiol 57(Pt 3):273–278. https://doi.org/10.1099/jmm.0.47661-0

Davies NG, Klepac P, Liu Y, Prem K, Jit M, group CC-w, Eggo RM, (2020) Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 26(8):1205–1211. https://doi.org/10.1038/s41591-020-0962-9

de Almeida A, de Almeida Rezende MS, Dantas SH, de Lima SS, de Oliveira J, de Lourdes Assuncao Araujo de Azevedo F, Alves R, de Menezes GMS, Dos Santos PF, Goncalves TAF, Schini-Kerth VB, de Medeiros IA, (2020) Unveiling the role of inflammation and oxidative stress on age-related cardiovascular diseases. Oxid Med Cell Longev 2020:1954398. https://doi.org/10.1155/2020/1954398

Dempsey JA (1995) Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. J Appl Physiol 78(5):1957–1968. https://doi.org/10.1152/jappl.1995.78.5.1957

Dhakal S, Klein SL (2019) Host factors impact vaccine efficacy: implications for seasonal and universal influenza vaccine programs. J Virol 93(21). https://doi.org/10.1128/JVI.00797-19

Didierlaurent A, Goulding J, Patel S, Snelgrove R, Low L, Bebien M, Lawrence T, van Rijt LS, Lambrecht BN, Sirard JC, Hussell T (2008) Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. J Exp Med 205(2):323–329. https://doi.org/10.1084/jem.20070891

Ding A, Hwang S, Schwab R (1994) Effect of aging on murine macrophages. Diminished response to IFN-gamma for enhanced oxidative metabolism. J Immunol 153 (5):2146–2152

Ding Q, Lu P, Fan Y, Xia Y, Liu M (2020) The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. doi:https://doi.org/10.1002/jmv.25781

Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X (2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 117(17):9490–9496. https://doi.org/10.1073/pnas.2004168117

Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE (1994) Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. Am J Respir Crit Care Med 149(2 Pt 1):430–438. doi:https://doi.org/10.1164/ajrccm.149.2.8306041

Ferrucci L, Fabbri E (2018) Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 15(9):505–522. https://doi.org/10.1038/s41569-018-0064-2

Ferrucci L, Guralnik JM, Pahor M, Corti MC, Havlik RJ (1997) Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. JAMA 277(9):728–734

Finco O, Rappuoli R (2014) Designing vaccines for the twenty-first century society. Front Immunol 5:12. https://doi.org/10.3389/fimmu.2014.00012

Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 908:244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x

Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S (2007) Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 128(1):92–105. https://doi.org/10.1016/j.mad.2006.11.016

Frasca D, Romero M, Diaz A, Alter-Wolf S, Ratliff M, Landin AM, Riley RL, Blomberg BB (2012) A Molecular mechanism for TNF-alpha-mediated downregulation of B cell responses. J Immunol 188(1):279–286. https://doi.org/jimmunol.1003964[pii]10.4049/jimmunol.1003964

Frasca D, Diaz A, Romero M, Landin AM, Blomberg BB (2014) High TNF-alpha levels in resting B cells negatively correlate with their response. Exp Gerontol 54:116–122. https://doi.org/10.1016/j.exger.2014.01.004

Furman D, Jojic V, Kidd B, Shen-Orr S, Price J, Jarrell J, Tse T, Huang H, Lund P, Maecker HT, Utz PJ (2013) Apoptosis and other immune biomarkers predict influenza vaccine responsiveness. Mol Syst Biol 9:659. https://doi.org/10.1038/msb.2013.15

Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, Thiebaut R, Tibshirani RJ, Davis MM (2014) Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc Natl Acad Sci U S A 111(2):869–874. https://doi.org/10.1073/pnas.1321060111

Frasca D, Diaz A, Romero M, Garcia D, Blomberg BB (2020) B cell immunosenescence. Annu Rev Cell Dev Biol 36:551–574. https://doi.org/10.1146/annurev-cellbio-011620-034148

German EL, Al-Hakim B, Mitsi E, Pennington SH, Gritzfeld JF, Hyder-Wright AD, Banyard A, Gordon SB, Collins AM, Ferreira DM (2018) Anti-protein immunoglobulin M responses to pneumococcus are not associated with aging. Pneumonia (nathan) 10:5. https://doi.org/10.1186/s41479-018-0048-3

Giunta B, Fernandez F, Nikolic WV, Obregon D, Rrapo E, Town T, Tan J (2008) Inflammaging as a prodrome to Alzheimer's disease. J Neuroinflammation 5:51. https://doi.org/10.1186/1742-2094-5-51

Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA (1995) The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med 123(7):518–527. https://doi.org/10.7326/0003-4819-123-7-199510010-00008

Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, Arnthorsson AO, Helgason D, Bjarnadottir K, Ingvarsson RF, Thorsteinsdottir B, Kristjansdottir S, Birgisdottir K, Kristinsdottir AM, Sigurdsson MI, Arnadottir GA, Ivarsdottir EV, Andresdottir M, Jonsson F, Agustsdottir AB, Berglund J, Eiriksdottir B, Fridriksdottir R, Gardarsdottir EE, Gottfredsson M, Gretarsdottir OS, Gudmundsdottir S, Gudmundsson KR, Gunnarsdottir TR, Gylfason A, Helgason A, Jensson BO, Jonasdottir A, Jonsson H, Kristjansson T, Kristinsson KG, Magnusdottir DN, Magnusson OT, Olafsdottir LB, Rognvaldsson S, le Roux L, Sigmundsdottir G, Sigurdsson A, Sveinbjornsson G, Sveinsdottir KE, Sveinsdottir M, Thorarensen EA, Thorbjornsson B, Thordardottir M, Saemundsdottir J, Kristjansson SH, Josefsdottir KS, Masson G, Georgsson G, Kristjansson M, Moller A, Palsson R, Gudnason T, Thorsteinsdottir U, Jonsdottir I, Sulem P, Stefansson K (2020) Humoral immune response to SARS-CoV-2 in Iceland. N Engl J Med 383(18):1724–1734. https://doi.org/10.1056/NEJMoa2026116

Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW (2020) Extrapulmonary manifestations of COVID-19. Nat Med 26(7):1017–1032. https://doi.org/10.1038/s41591-020-0968-3

Haq K, McElhaney JE (2014) Ageing and respiratory infections: the airway of ageing. Immunol Lett 162(1 Pt B):323–328. https://doi.org/10.1016/j.imlet.2014.06.009

Herold S, Becker C, Ridge KM, Budinger GR (2015) Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J 45(5):1463–1478. https://doi.org/10.1183/09031936.00186214

Hobson D, Curry RL, Beare AS, Ward-Gardner A (1972) The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg (lond) 70(4):767–777. https://doi.org/10.1017/s0022172400022610

Hogan BL, Barkauskas CE, Chapman HA, Epstein JA, Jain R, Hsia CC, Niklason L, Calle E, Le A, Randell SH, Rock J, Snitow M, Krummel M, Stripp BR, Vu T, White ES, Whitsett JA, Morrisey EE (2014) Repair and regeneration of the respiratory system: complexity, plasticity, and mechanisms of lung stem cell function. Cell Stem Cell 15(2):123–138. https://doi.org/10.1016/j.stem.2014.07.012

Holodick NE, Vizconde T, Hopkins TJ, Rothstein TL (2016) Age-related decline in natural IgM function: diversification and selection of the B-1a cell pool with age. J Immunol 196(10):4348–4357. https://doi.org/10.4049/jimmunol.1600073

Ibarrondo FJ, Fulcher JA, Goodman-Meza D, Elliott J, Hofmann C, Hausner MA, Ferbas KG, Tobin NH, Aldrovandi GM, Yang OO (2020) Rapid decay of Anti-SARS-CoV-2 antibodies in persons with mild Covid-19. N Engl J Med 383(11):1085–1087. https://doi.org/10.1056/NEJMc2025179

Isho B, Abe KT, Zuo M, Jamal AJ, Rathod B, Wang JH, Li Z, Chao G, Rojas OL, Bang YM, Pu A, Christie-Holmes N, Gervais C, Ceccarelli D, Samavarchi-Tehrani P, Guvenc F, Budylowski P, Li A, Paterson A, Yue FY, Marin LM, Caldwell L, Wrana JL, Colwill K, Sicheri F, Mubareka S, Gray-Owen SD, Drews SJ, Siqueira WL, Barrios-Rodiles M, Ostrowski M, Rini JM, Durocher Y, McGeer AJ, Gommerman JL, Gingras AC (2020) Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients. Sci Immunol 5(52). https://doi.org/10.1126/sciimmunol.abe5511

Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, Cohen C, Gran JM, Schanzer D, Cowling BJ, Wu P, Kyncl J, Ang LW, Park M, Redlberger-Fritz M, Yu H, Espenhain L, Krishnan A, Emukule G, van Asten L, Pereira da Silva S, Aungkulanon S, Buchholz U, Widdowson MA, Bresee JS, Collaborator G-A, N, (2018) Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 391(10127):1285–1300. https://doi.org/10.1016/S0140-6736(17)33293-2

Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM, Chappell JD, Qi C, Hart EM, Carroll F, Trabue C, Donnelly HK, Williams DJ, Zhu Y, Arnold SR, Ampofo K, Waterer GW, Levine M, Lindstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, McCullers JA, Pavia AT, Edwards KM, Finelli L, Team CES (2015) Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med 373(5):415–427. https://doi.org/10.1056/NEJMoa1500245

Johansson BE, Moran TM, Kilbourne ED (1987) Antigen-presenting B cells and helper T cells cooperatively mediate intravirionic antigenic competition between influenza A virus surface glycoproteins. Proc Natl Acad Sci U S A 84(19):6869–6873. https://doi.org/10.1073/pnas.84.19.6869

Kataoka K, Fukuyama Y, Briles DE, Miyake T, Fujihashi K (2017) Dendritic cell-targeting DNA-based nasal adjuvants for protective mucosal immunity to Streptococcus pneumoniae. Microbiol Immunol 61(6):195–205. https://doi.org/10.1111/1348-0421.12487

Kennedy RB, Ovsyannikova IG, Haralambieva IH, Oberg AL, Zimmermann MT, Grill DE, Poland GA (2016) Immunosenescence-related transcriptomic and immunologic changes in older individuals following influenza vaccination. Front Immunol 7:450. https://doi.org/10.3389/fimmu.2016.00450

Kim D, Quinn J, Pinsky B, Shah NH, Brown I (2020) Rates of Co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA. https://doi.org/10.1001/jama.2020.6266

Kissin E, Tomasi M, McCartney-Francis N, Gibbs CL, Smith PD (1997) Age-related decline in murine macrophage production of nitric oxide. J Infect Dis 175(4):1004–1007. https://doi.org/10.1086/513959

Lau EHY, Tsang OTY, Hui DSC, Kwan MYW, Chan WH, Chiu SS, Ko RLW, Chan KH, Cheng SMS, Perera R, Cowling BJ, Poon LLM, Peiris M (2021) Neutralizing antibody titres in SARS-CoV-2 infections. Nat Commun 12(1):63. https://doi.org/10.1038/s41467-020-20247-4

Leggat DJ, Thompson RS, Khaskhely NM, Iyer AS, Westerink MA (2013) The immune response to pneumococcal polysaccharides 14 and 23F among elderly individuals consists predominantly of switched memory B cells. J Infect Dis 208(1):101–108. https://doi.org/10.1093/infdis/jit139

Lencel P, Magne D (2011) Inflammaging: the driving force in osteoporosis? Med Hypotheses 76(3):317–321. https://doi.org/10.1016/j.mehy.2010.09.023

Littorin N, Udden F, Ahl J, Resman F, Slotved HC, Athlin S, Riesbeck K (2018) Serotypes with low invasive potential are associated with an impaired antibody response in invasive pneumococcal disease. Front Microbiol 9:2746. https://doi.org/10.3389/fmicb.2018.02746

Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, Hu JL, Xu W, Zhang Y, Lv FJ, Su K, Zhang F, Gong J, Wu B, Liu XM, Li JJ, Qiu JF, Chen J, Huang AL (2020) Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 26(8):1200–1204. https://doi.org/10.1038/s41591-020-0965-6

Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, Vugia D, Harriman K, Matyas B, Glaser CA, Samuel MC, Rosenberg J, Talarico J, Hatch D, California Pandemic Working G (2009) Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 302(17):1896–1902. https://doi.org/10.1001/jama.2009.1583

Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ (2013) The aging lung. Clin Interv Aging 8:1489–1496. https://doi.org/10.2147/CIA.S51152

Ma H, Zeng W, He H, Zhao D, Jiang D, Zhou P, Cheng L, Li Y, Ma X, Jin T (2020) Serum IgA, IgM, and IgG responses in COVID-19. Cell Mol Immunol 17(7):773–775. https://doi.org/10.1038/s41423-020-0474-z

Mares CA, Sharma J, Ojeda SS, Li Q, Campos JA, Morris EG, Coalson JJ, Teale JM (2010) Attenuated response of aged mice to respiratory Francisella novicida is characterized by reduced cell death and absence of subsequent hypercytokinemia. PLoS One 5(11):e14088. https://doi.org/10.1371/journal.pone.0014088

Marra F, Vadlamudi NK (2019) Efficacy and safety of the pneumococcal Conjugate-13 valent vaccine in adults. Aging Dis 10(2):404–418. https://doi.org/10.14336/AD.2018.0512

McClaran SR, Babcock MA, Pegelow DF, Reddan WG (1995) Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. J Appl Physiol 78:1957. https://doi.org/10.1152/jappl.1995.78.5.1957

McCool FD (2006) Global physiology and pathophysiology of cough: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl):48S-53S. https://doi.org/10.1378/chest.129.1_suppl.48S

McElhaney JE, Effros RB (2009) Immunosenescence: what does it mean to health outcomes in older adults? Curr Opin Immunol 21(4):418–424. https://doi.org/10.1016/j.coi.2009.05.023

McElhaney JE, Verschoor CP, Andrew MK, Haynes L, Kuchel GA, Pawelec G (2020) The immune response to influenza in older humans: beyond immune senescence. Immun Ageing 17:10. https://doi.org/10.1186/s12979-020-00181-1

McMurry JA, Johansson BE, De Groot AS (2008) A call to cellular and humoral arms: enlisting cognate T cell help to develop broad-spectrum vaccines against influenza A. Hum Vaccin 4(2):148–157. https://doi.org/5169[pii]

Meiners S, Eickelberg O, Konigshoff M (2015) Hallmarks of the ageing lung. Eur Respir J 45(3):807–827. https://doi.org/10.1183/09031936.00186914

Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC (2021) COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci 25(3):1663–1669. https://doi.org/10.26355/eurrev_202102_24877

Meyer KC (2004) Lung infections and aging. Ageing Res Rev 3(1):55–67. https://doi.org/10.1016/j.arr.2003.07.002

Meyer KC, Ershler W, Rosenthal NS, Lu XG, Peterson K (1996) Immune dysregulation in the aging human lung. Am J Respir Crit Care Med 153(3):1072–1079. https://doi.org/10.1164/ajrccm.153.3.8630547

Miscia S, Marchisio M, Grilli A, Di Valerio V, Centurione L, Sabatino G, Garaci F, Zauli G, Bonvini E, Di Baldassarre A (2002) Tumor necrosis factor alpha (TNF-alpha) activates Jak1/Stat3-Stat5B signaling through TNFR-1 in human B cells. Cell Growth Differ 13(1):13–18

Moriyama C, Betsuyaku T, Ito Y, Hamamura I, Hata J, Takahashi H, Nasuhara Y, Nishimura M (2010) Aging enhances susceptibility to cigarette smoke-induced inflammation through bronchiolar chemokines. Am J Respir Cell Mol Biol 42(3):304–311. https://doi.org/10.1165/rcmb.2009-0025OC

Mosterin Hopping A, McElhaney J, Fonville JM, Powers DC, Beyer WEP, Smith DJ (2016) The confounded effects of age and exposure history in response to influenza vaccination. Vaccine 34(4):540–546. https://doi.org/10.1016/j.vaccine.2015.11.058

Mueller AL, McNamara MS, Sinclair DA (2020) Why does COVID-19 disproportionately affect older people? Aging (albany NY) 12(10):9959–9981. https://doi.org/10.18632/aging.103344

Muller L, Andrée M, Moskorz W, Drexler I et al (2021) Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. medRxiv preprint. https://doi.org/10.1101/2021.03.03.21251066

O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, Fontanet A, Cauchemez S, Salje H (2021) Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 590(7844):140–145. https://doi.org/10.1038/s41586-020-2918-0

Palese P (2004) Influenza: old and new threats. Nat Med 10(12 Suppl):S82-87. https://doi.org/10.1038/nm1141

Parish ST, Wu JE, Effros RB (2009) Modulation of T lymphocyte replicative senescence via TNF-{alpha} inhibition: role of caspase-3. J Immunol 182(7):4237–4243. https://doi.org/10.4049/jimmunol.0803449

Park S, Nahm MH (2011) Older adults have a low capacity to opsonize pneumococci due to low IgM antibody response to pneumococcal vaccinations. Infect Immun 79(1):314–320. https://doi.org/10.1128/IAI.00768-10

Plouffe JF, Breiman RF, Facklam RR (1996) Bacteremia with Streptococcus pneumoniae. Implications for therapy and prevention. Franklin County Pneumonia Study Group. Jama 275(3):194–198

Polignano A, Tortorella C, Venezia A, Jirillo E, Antonaci S (1994) Age-associated changes of neutrophil responsiveness in a human healthy elderly population. Cytobios 80(322):145–153

Prattichizzo F, De Nigris V, Spiga R, Mancuso E, La Sala L, Antonicelli R, Testa R, Procopio AD, Olivieri F, Ceriello A (2018) Inflammageing and metaflammation: The yin and yang of type 2 diabetes. Ageing Res Rev 41:1–17. https://doi.org/10.1016/j.arr.2017.10.003

Puchta A, Naidoo A, Verschoor CP, Loukov D, Thevaranjan N, Mandur TS, Nguyen PS, Jordana M, Loeb M, Xing Z, Kobzik L, Larche MJ, Bowdish DM (2016) TNF drives monocyte dysfunction with age and results in impaired anti-pneumococcal immunity. PLoS Pathog 12 (1):e1005368. doi:https://doi.org/10.1371/journal.ppat.1005368

Rajendran M, Nachbagauer R, Ermler ME, Bunduc P, Amanat F, Izikson R, Cox M, Palese P, Eichelberger M, Krammer F (2017) Analysis of anti-influenza virus neuraminidase antibodies in children, adults, and the elderly by ELISA and enzyme inhibition: evidence for original antigenic Sin. mBio 8(2). https://doi.org/10.1128/mBio.02281-16

Rezus E, Cardoneanu A, Burlui A, Luca A, Codreanu C, Tamba BI, Stanciu GD, Dima N, Badescu C, Rezus C (2019) The link between inflammaging and degenerative joint diseases. Int J Mol Sci 20(3). https://doi.org/10.3390/ijms20030614

Ripperger TJ, Uhrlaub JL, Watanabe M, Wong R, Castaneda Y, Pizzato HA, Thompson MR, Bradshaw C, Weinkauf CC, Bime C, Erickson HL, Knox K, Bixby B, Parthasarathy S, Chaudhary S, Natt B, Cristan E, El Aini T, Rischard F, Campion J, Chopra M, Insel M, Sam A, Knepler JL, Capaldi AP, Spier CM, Dake MD, Edwards T, Kaplan ME, Scott SJ, Hypes C, Mosier J, Harris DT, LaFleur BJ, Sprissler R, Nikolich-Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, Liao P, Qiu JF, Lin Y, Cai XF, Wang DQ, Hu Y, Ren JH, Tang N, Xu YY, Yu LH, Mo Z, Gong F, Zhang XL, Tian WG, Hu L, Zhang XX, Xiang JL, Du HX, Liu HW, Lang CH, Luo XH, Wu SB, Cui XP, Zhou Z, Zhu MM, Wang J, Xue CJ, Li XF, Wang L, Li ZJ, Wang K, Niu CC, Yang QJ, Tang XJ, Zhang Y, Liu XM, Li JJ, Zhang DC, Zhang F, Liu P, Yuan J, Li Q, Hu JL, Chen J, Huang AL (2020) Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 26(6):845–848. https://doi.org/10.1038/s41591-020-0897-1

Rogers LRK, de Los CG, Mias GI (2019) Microarray gene expression dataset re-analysis reveals variability in influenza infection and vaccination. Front Immunol 10:2616. https://doi.org/10.3389/fimmu.2019.02616

Roltgen K, Powell AE, Wirz OF, Stevens BA, Hogan CA, Najeeb J, Hunter M, Wang H, Sahoo MK, Huang C, Yamamoto F, Manohar M, Manalac J, Otrelo-Cardoso AR, Pham TD, Rustagi A, Rogers AJ, Shah NH, Blish CA, Cochran JR, Jardetzky TS, Zehnder JL, Wang TT, Narasimhan B, Gombar S, Tibshirani R, Nadeau KC, Kim PS, Pinsky BA, Boyd SD (2020) Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. Sci Immunol 5(54). https://doi.org/10.1126/sciimmunol.abe0240

Saurwein-Teissl M, Lung TL, Marx F, Gschosser C, Asch E, Blasko I, Parson W, Bock G, Schonitzer D, Trannoy E, Grubeck-Loebenstein B (2002) Lack of antibody production following immunization in old age: association with CD8(+)CD28(-) T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines. J Immunol 168(11):5893–5899. https://doi.org/10.4049/jimmunol.168.11.5893

Sharma G, Goodwin J (2006) Effect of aging on respiratory system physiology and immunology. Clin Interv Aging 1(3):253–260. https://doi.org/10.2147/ciia.2006.1.3.253

Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI (2014) Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis 1 (1):ofu024. doi:https://doi.org/10.1093/ofid/ofu024

Shi Y, Yamazaki T, Okubo Y, Uehara Y, Sugane K, Agematsu K (2005) Regulation of aged humoral immune defense against pneumococcal bacteria by IgM memory B cell. J Immunol 175(5):3262–3267. https://doi.org/10.4049/jimmunol.175.5.3262

Simell B, Lahdenkari M, Reunanen A, Kayhty H, Vakevainen M (2008) Effects of ageing and gender on naturally acquired antibodies to pneumococcal capsular polysaccharides and virulence-associated proteins. Clin Vaccine Immunol 15(9):1391–1397. https://doi.org/10.1128/CVI.00110-08

Simell B, Vuorela A, Ekstrom N, Palmu A, Reunanen A, Meri S, Kayhty H, Vakevainen M (2011) Aging reduces the functionality of anti-pneumococcal antibodies and the killing of Streptococcus pneumoniae by neutrophil phagocytosis. Vaccine 29(10):1929–1934. https://doi.org/10.1016/j.vaccine.2010.12.121

Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA (2007) Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis 7(10):658–666. https://doi.org/10.1016/S1473-3099(07)70236-0

Sunil VR, Patel KJ, Mainelis G, Turpin BJ, Ridgely S, Laumbach RJ, Kipen HM, Nazarenko Y, Veleeparambil M, Gow AJ, Laskin JD, Laskin DL (2009) Pulmonary effects of inhaled diesel exhaust in aged mice. Toxicol Appl Pharmacol 241(3):283–293. https://doi.org/10.1016/j.taap.2009.08.025

Taubenberger JK, Morens DM (2010) Influenza: the once and future pandemic. Public Health Rep 125(Suppl 3):16–26

Thakar J, Mohanty S, West AP, Joshi SR, Ueda I, Wilson J, Meng H, Blevins TP, Tsang S, Trentalange M, Siconolfi B, Park K, Gill TM, Belshe RB, Kaech SM, Shadel GS, Kleinstein SH, Shaw AC (2015) Aging-dependent alterations in gene expression and a mitochondrial signature of responsiveness to human influenza vaccination. Aging (albany NY) 7(1):38–52. https://doi.org/10.18632/aging.100720

Thevaranjan N, Whelan FJ, Puchta A, Ashu E, Rossi L, Surette MG, Bowdish DM (2016) Streptococcus pneumoniae colonization disrupts the microbial community within the upper respiratory tract of aging mice. Infect Immun 84(4):906–916. https://doi.org/10.1128/IAI.01275-15

Thindwa D, Garcia Quesada M, Liu Y, Bennett J, Cohen C, Knoll MD, von Gottberg A, Hayford K, Flasche S (2020) Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality. Vaccine 38(34):5398–5401. https://doi.org/10.1016/j.vaccine.2020.06.047

Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289(2):179–186. https://doi.org/10.1001/jama.289.2.179

Van Buynder P, Booy R (2018) Pneumococcal vaccination in older persons: where are we today? Pneumonia (nathan) 10:1. https://doi.org/10.1186/s41479-017-0045-y

van der Poll T, Opal SM (2009) Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet 374(9700):1543–1556. https://doi.org/10.1016/S0140-6736(09)61114-4

Verma N, Dimitrova M, Carter DM, Crevar CJ, Ross TM, Golding H, Khurana S (2012) Influenza virus H1N1pdm09 infections in the young and old: evidence of greater antibody diversity and affinity for the hemagglutinin globular head domain (HA1 Domain) in the elderly than in young adults and children. J Virol 86(10):5515–5522. https://doi.org/10.1128/JVI.07085-11

Vu T, Farish S, Jenkins M, Kelly H (2002) A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. Vaccine 20(13–14):1831–1836. https://doi.org/10.1016/s0264-410x(02)00041-5

Wang Y, Zhang L, Sang L, Ye F, Ruan S, Zhong B, Song T, Alshukairi AN, Chen R, Zhang Z, Gan M, Zhu A, Huang Y, Luo L, Mok CKP, Al Gethamy MM, Tan H, Li Z, Huang X, Li F, Sun J, Zhang Y, Wen L, Li Y, Chen Z, Zhuang Z, Zhuo J, Chen C, Kuang L, Wang J, Lv H, Jiang Y, Li M, Lin Y, Deng Y, Tang L, Liang J, Huang J, Perlman S, Zhong N, Zhao J, Malik Peiris JS, Li Y, Zhao J (2020) Kinetics of viral load and antibody response in relation to COVID-19 severity. J Clin Invest 130(10):5235–5244. https://doi.org/10.1172/JCI138759

Wei CJ, Boyington JC, Dai K, Houser KV, Pearce MB, Kong WP, Yang ZY, Tumpey TM, Nabel GJ (2010) Cross-neutralization of 1918 and 2009 influenza viruses: role of glycans in viral evolution and vaccine design. Sci Transl Med 2(24):24ra21. https://doi.org/10.1126/scitranslmed.3000799

Weinberger B (2018) Vaccines for the elderly: current use and future challenges. Immun Ageing 15:3. https://doi.org/10.1186/s12979-017-0107-2

Whelan FJ, Verschoor CP, Stearns JC, Rossi L, Luinstra K, Loeb M, Smieja M, Johnstone J, Surette MG, Bowdish DM (2014) The loss of topography in the microbial communities of the upper respiratory tract in the elderly. Ann Am Thorac Soc 11(4):513–521. https://doi.org/10.1513/AnnalsATS.201310-351OC

Woodruff MC, Ramonell RP, Lee FE, Sanz I (2020) Clinically identifiable autoreactivity is common in severe SARS-CoV-2 Infection. https://www.medrxivorg/content/101101/2020102120216192v2. doi:https://doi.org/10.1101/2020.10.21.20216192

Wrammert J, Smith K, Miller J, Langley WA, Kokko K, Larsen C, Zheng NY, Mays I, Garman L, Helms C, James J, Air GM, Capra JD, Ahmed R, Wilson PC (2008) Rapid cloning of high-affinity human monoclonal antibodies against influenza virus. Nature 453(7195):667–671. https://doi.org/10.1038/nature06890nature06890 [pii]

Yende S, Tuomanen EI, Wunderink R, Kanaya A, Newman AB, Harris T, de Rekeneire N, Kritchevsky SB (2005) Preinfection systemic inflammatory markers and risk of hospitalization due to pneumonia. Am J Respir Crit Care Med 172(11):1440–1446. https://doi.org/10.1164/rccm.200506-888OC

Young B, Zhao X, Cook AR, Parry CM, Wilder-Smith A, MC IC (2017) Do antibody responses to the influenza vaccine persist year-round in the elderly? A systematic review and meta-analysis. Vaccine 35 (2):212-221. https://doi.org/10.1016/j.vaccine.2016.11.013

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zuo L, Prather ER, Stetskiv M, Garrison DE, Meade JR, Peace TI, Zhou T (2019) Inflammaging and oxidative stresss in human diseases: from molecular mechanisms to novel treatments. Int J Mol Sci 20 (18). doi:https://doi.org/10.3390/ijms20184472

Chapter 6
Ageing Mucosal Immunity and Its Consequences for Infectious Diseases in the Aged; A First Glance

Marieke van der Heiden and Debbie van Baarle

Abstract While our understanding on systemic immunological ageing has increased in the past years, knowledge on ageing of the mucosal immune system is lacking behind. Since the mucosa provides the first barrier for invading pathogens and harbors major part of the immune cells of the human body, this knowledge gap hampers our understanding on infectious disease vulnerability in the elderly. We here summarize the current limited knowledge as well as pinpoint major knowledge gaps of mucosal immunity at old age. Moreover, we outline the potential relations between mucosal immunity and the large burden of acute respiratory infections as well as reactivation of chronic herpes viruses in the elderly. In light of the rapidly ageing population and the increased spread of emerging infections, it is essential to enhance our understanding on immunological ageing at mucosal sites and investigate its consequences for protection against infectious disease. This enhanced knowledge will allow us to develop effective preventive measures, such as mucosal vaccines, for todays' and future populations.

Keywords Ageing · Infections · Mucosa · Immune system

6.1 Introduction

As a result of the increased life expectancy, the number of persons above 60 years of age is expected to double by 2050, with the highest growth predicted in the number of persons above 80 years of age (United Nations 2019; Chang et al. 2019). With age, important immune functions deteriorate, a process called *immunosenescence*, which enhances the susceptibility towards disease (Pawelec and Solana 1997; Fulop 2018). Consequently, ageing results in increased numbers of persons susceptible to

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disease and disability, causing a strong rise in health care costs in the population. In addition, the infection pressure of elderly is further enhanced by the increased globalization and spread of antibiotic resistance (Yoshikawa 2002). Therefore, the prevention of infectious diseases in older age groups is a prerequisite to establish healthy ageing and lower health care costs in todays' and future populations. This requires profound understanding of immunological ageing, its consequences for infectious disease vulnerability, as well as effective prevention measures such as vaccination programs.

As comprehensively reviewed elsewhere, immunological ageing is a complex process already starting at the hematopoietic stem cells and is largely affected by fat deposition in the bone marrow and thymus, along with thymic shrinkage (Boraschi et al. 2013; den Braber et al. 2012; Mitchell et al. 2010; Pritz et al. 2014). Albeit clear changes are observed in all branches of the immune system with age, the T-cell compartment is most profoundly affected. Of importance, the pace of immunological ageing largely deviates between individuals, indicating not only the importance of age, but also genetic predisposition and even more important non-hereditable factors (Brodin et al. 2015).

Current knowledge does however not allow us to distinguish between adaptive and detrimental changes in the ageing immune system and subsequently our understanding of associations between the ageing immune system and infectious disease vulnerability at older age is limited. A major reason for this limited understanding relates to the fact that immunological ageing is largely investigated in peripheral blood, that contains only 1–2% of the body's total immune cells (Ganusov and Boer 2007; Pawelec 2020). In contrast, the mucosa, the surfaces in contact with the external world, harbors a major part of immune cells and provides a crucial first line of defense against invading pathogens. This knowledge gap on ageing mucosal immunity and its relation to infectious disease protection with advancing age greatly affects our abilities to develop preventive measures against infectious diseases for the aged. Here we summarize the current knowledge in mucosal immune ageing (as schematically depicted in Fig. 6.1), its relation with systemic immune ageing, and its potential consequences for infectious diseases susceptibility in the aged.

6.2 Ageing Mucosal Immunity

The mucosa-associated lymphoid tissue (MALT) contains major part of immune cells at mucosal sites. The MALT is a complex system where immune cells are integrated in a large network of tissue and mucosal epithelial cells, including its effector molecules and secreting factors, and plays an important role in protection against infectious disease (Martelli et al. 2016). This prominent role in protection is not only related to its immunological monitoring functions, but also to its function as the first physical barrier for invading pathogens. This physical barrier is formed by epithelial cells lining the mucosa, which are closely connected by tight junctions and

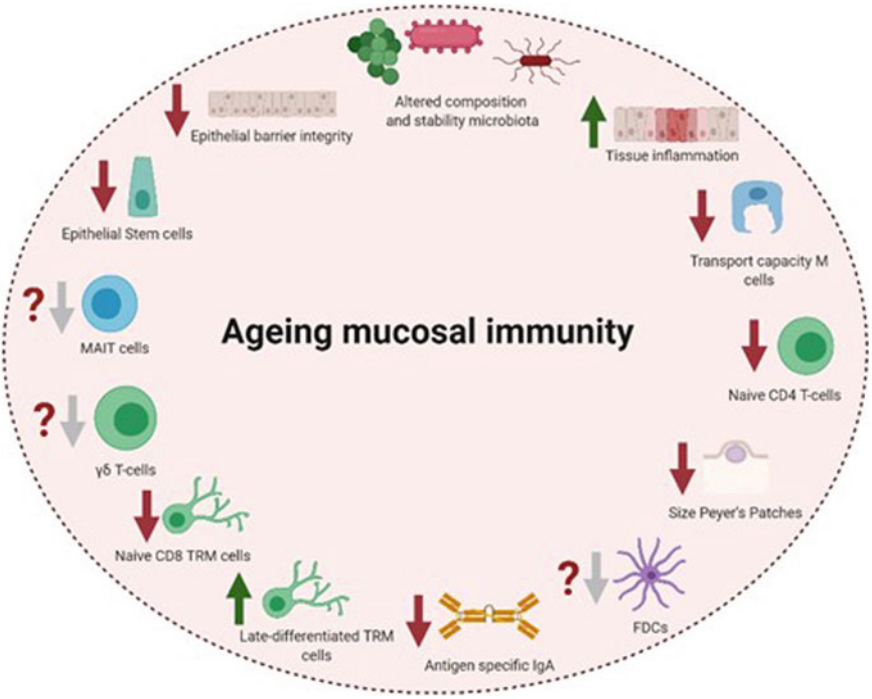

Fig. 6.1 Schematic overview of the ageing mucosal immune system

cadherin/catenin complexes (Parrish 2017). In addition, lymphocyte populations are present to maintain these epithelial tight junctions in response to infection (Dalton et al. 2006).

The MALT can further be divided into the gut-associated lymphoid tissue (GALT) (Buford 2017), nasopharyngeal-associated lymphoid tissue (NALT) and bronchus-associated lymphoid tissue (BALT) (Martelli et al. 2016; Fujihashi and Kiyono 2009). Currently, knowledge on mucosal immunity is mainly based on findings in the GALT, whereas the latter two are studied to a lesser extent. Below the most prominent aspects of the MALT as well as its relation with advancing age are described.

6.2.1 The Epithelial Barrier

First and foremost, ageing affects the first physical epithelial barrier that prevents pathogenic microbes to enter the body. With advancing age the epithelial barrier integrity diminishes, resulting in enhanced epithelial permeability and subsequent enhanced risks for invading pathogens (Man et al. 2014; Branca et al. 2019). This reduced barrier integrity is attributed to on the one hand increased damage to the

barrier, while on the other hand cell renewal by epithelial stem cells is reduced (Kirkwood 2004). In addition, this process is accelerated by an age related drop in mucus production which leads to a thinning of the mucus barrier overlaying the epithelial cells (Branca et al. 2019; Sovran et al. 2019). The increased incidence of the leaky gut syndrome with advancing age is clearly linked to this diminished epithelial barrier function (Kavanagh et al. 2019).

6.2.2 The Microbiota

Secondly, compositional changes and reduced stability of the microbial community lining the epithelia, have been observed with advancing age, where *bacteriodes* and *bifidobacteria* decline in abundance and pathogenic bacteria thrive (Buford 2017; Fujihashi and Kiyono 2009; Jeffery et al. 2016; Biagi 2010; Popkes and Valenzano 2020). These compositional changes have been found associated with age related tissue inflammation and contribute to the deterioration of the gut barrier integrity. Importantly, research in mice has also indicated associations between the ageing microbiota and systemic inflammation (Fransen et al. 2017), suggesting an important role for the microbiota in the functioning of the immune system at older age. Therefore, alterations in the microbiota with advancing age could potentially contribute to the often observed low grade inflammation in the aged, commonly referred to as *inflammageing* (Fülöp et al. 2012, 2019; Pawelec 2020). This *inflammageing* is often associated with age related diseases as well as frailty (Fülöp et al. 2019; Samson 2019). Increased use of antibiotics in community-dwelling elderly combined with a poor diet enlarge these microbiota compositional changes at old age (Buford 2017). Importantly, a recent study observed clear compositional changes in the microbiota during an event of Influenza like illness (ILI) as well as clear associations between the abundance of certain bacteria and the vulnerability to ILI, proposing clear roles for the microbiota composition in the vulnerability towards respiratory infections (Fuentes et al. 2021).

6.2.3 M Cells

Moreover, specialized cells for transportation of antigens over the mucosal barrier, referred to as M cells, show reduced capacity for transportation as well as reduced maturation with advancing age. These M cells overlay the mucosal lymphatic follicles, referred to as Peyer's patches (Fujihashi and Kiyono 2009; Kobayashi et al. 2013; Donaldson et al. 2020). Consequently, reduced transportation leads to an altered gut antigen monitoring in the aged as well as diminished initiation of immune responses following pathogen encounter. Interestingly, this altered functionality of

the M cells was found to be directly influenced by the changed microbiota in aged mice, whereas transplanted microbiota from young mice was able to rejuvenate this function (Donaldson et al. 2020).

6.2.4 Follicular Dendritic Cells (FDCs)

Underlying the epithelial barrier, FDCs patrol the mucosa in search for antigens and present them to immune cells gathered in the Peyer's patches and mesenteric lymph nodes (MLN), where adaptive immune responses are initiated. While in old mice a clear reduction in number and function of these FDCs is observed, this phenomenon is currently less clear in humans (Fujihashi and Kiyono 2009).

6.2.5 T Cells

Peyer's patches are key in mucosal immunity. However, knowledge on the composition of Peyer's patches in humans is limited and suggests that these lymphoid follicles mainly contain CD4 + T cells that are highly polarized towards the Th1 phenotype, while a minor proportion of CD8+ T cells is present (Martelli et al. 2016; Jung et al. 2010). Research in mouse models indicates that large part of these CD4+ T cells are of the effector/memory phenotype, while naïve T cells are a minority (Jung et al. 2010). Despite extensive studies on effects of age on the systemic T-cell compartment, knowledge on association between age and mucosal T-cell immunity is scarce. It is however known that with age Peyer's Patches reduce in size and contain fewer naïve CD4+ T cells, potentially resulting in decreased T-cell help during immune responses (Martelli et al. 2016). This decline in naïve T cells accompanies the findings observed in the periphery and relates to the reduced production of naïve T cells in the aged as a result of thymic shrinkage (den Braber et al. 2012; Herndler-Brandstetter et al. 2013; Goronzy and Weyand 2019). As a consequence of these reduced naïve T-cell numbers, systemic homeostatic proliferation of T cells is enhanced to maintain T-cell numbers, which is generally accepted to maintain sufficient levels of CD4+ T cells but leads to a large reduction in the CD8 T-cell compartment (Herndler-Brandstetter et al. 2013; Goronzy and Weyand 2019; Whiting et al. 2015; Pawelec 2020). Defects in this homeostatic proliferation with age could potentially lead to a reduced T-cell receptor repertoire diversity affecting responses to infections (Goronzy and Weyand 2019; Whiting et al. 2015; Egorov et al. 2018; Lanfermeijer et al. 2020). Moreover, as a result of antigenic pressure over the life course, increased numbers of late-differentiated T cells, persisting a lower proliferative capacity (Goronzy and Weyand 2019; Appay et al. 2008) are observed with advancing age in the periphery. Furthermore, as a consequence of accumulating DNA damage in ageing T cells, part of the circulating T cells develops into senescent cells. Even though the exact phenotype of senescent T cells is still topic of fierce debate, consensus exists that these senescent

cells contribute to the age-associated low grade inflammation, due to the secretion of inflammatory mediators, indicated as the senescence-associated-secretory phenotype (Goronzy and Weyand 2019; Zhu et al. 2014). Finally, elevated numbers of regulatory T cells (Tregs) are observed with age (Gregg et al. 2005; Jagger et al. 2016). These are mainly of the memory phenotype (van der Geest et al. 2014), which suggests an enhanced suppression of immune responses at older age. Currently, it is largely unknown whether these signs of systemic immunological ageing are equally observed at mucosal sites, which urges the need for future research on the ageing T-cell compartment in the MALT.

6.2.6 Tissue Resident Memory (TRM) Cells

More recently, TRM cells have been discovered in mouse models, which are specialized mucosal T cells that mainly refrain from the circulation (Szabo et al. 2019). These TRMs are observed for both the CD4+ and CD8+ T-cell compartments and have demonstrated important roles in protection against infectious disease as well as in the initiation of effective secondary immune responses in mice (Behr et al. 2020; Mueller and Mackay 2016). However, translation of these finding to the human situation is complicated due to major differences in T-cell homeostasis between mice and men, especially at older age (den Braber et al. 2012). Besides the discovery of TRM cells at human mucosal sites and the phenotypic characterization of these cells in human tissue, the specificity of the cells as well as the effects of age remain largely unknown (Sathaliyawala et al. 2013; Thome et al. 2016; Wong et al. 2016; Smolders et al. 2018; Kumar et al. 2017; Thome et al. 2014). However, consistent with findings in the periphery, scarce human evidence points to an age-related reduction in naïve CD8+ TRM cells accompanied by an expansion of late differentiated CD8+ TRM cells (Gordon et al. 2017).

6.2.7 IgA and B Cells

Based on murine models, Peyer's patches contain high number of B cells (Jung et al. 2010). These B cells are important in the production of IgA, the most abundant antibody present at mucosal sites and important in protection and tolerance. Currently, human data on the effect of age on mucosal B cells is lacking, whereas age related changes are observed in the human circulating B-cell compartment, of which major changes relate to a reduced production of B-cell progenitors (Siegrist and Aspinall 2009; Dunn-Walters 2016; Frasca et al. 2017). Moreover, reduced B-cell receptor diversity (Dunn-Walters 2016), proliferation (Siegrist and Aspinall 2009) and capacity for class-switching (Frasca et al. 2011) have been observed in circulating B cells with advancing age.

Remarkably, ageing models in mice indicate increased levels of IgA+ B cells in Peyer's patches and diminished numbers in the lamina propria with advancing age, suggesting altered homing capacity of IgA + B cells in aged mice (Martelli et al. 2016). Interestingly, maintained or even slightly increased levels of total non-specific IgA have been observed with advancing age in human gut lavages, whereas specific IgA levels were found to decrease in aged mice (Arranz et al. 1992; Fujihashi and Kiyono 2009). These findings are consistent with findings of elevated IgA levels in the serum of aged humans (Beharka et al. 2001; Finkelstein et al. 1984) and do suggest a general continuous production of IgA. Nevertheless, it is of importance to investigate de novo IgA responses at the mucosa against new incoming pathogens in a human setting.

6.2.8 Mucosal-Associated Invariant T (MAIT) and the Unconventional γδ T Cells

Finally, while present in low frequencies in the periphery, the innate like MAIT cells as well as γδ T cells are perceived to play important roles in the mucosal immune response against microbial infections (Loh et al. 2020; McCarthy and Eberl 2018). Despite observations of reduced frequencies of circulating MAIT and γδ T cells with advancing age (Loh et al. 2020; Novak et al. 2014; Lee et al. 2014; Rubino et al. 2019; Kallemeijn et al. 2017; Xu et al. 2019), the effects of age on both cell types at the mucosal sites is largely unknown. Interestingly, this age related reduction of MAIT cells in the circulation was not observed in centenarian offspring (Rubino et al. 2019). Moreover, at old age, circulating MAIT cells were found to gain central and effector memory-phenotypes, as well as to express a low-grade basal inflammatory profile. These observations are suggestive of terminal differentiation of MAIT cells with advancing age. Nevertheless, these MAIT cells continued to show plasticity in vitro, as well as express broad expansions and effector profiles (Loh et al. 2020). Finally, comparable with the conventional αβ T cells, alterations in the phenotype of circulating γδ T cells were observed with advancing age. Importantly, within the circulation, the major Vδ2 + γδ T cell subtype was found resistant against these age related changes and maintains its function until old age (Xu et al. 2019). It is of interest to investigate whether their mucosal counterparts, which are presumed to be abundant at mucosal tissues and to possess prominent functions in mucosal immunity, mirror the findings in the periphery.

Depicted are important cell types and functions involved in mucosal immunity and the changes occurring with ageing. The dark red arrows indicate a reduction with age, while the green arrow indicates an increase. Gray arrows indicate knowledge obtained from the circulation or research on mice, and have to be evaluated in human mucosal sites. Created with Biorender.

6.3 The Infectious Disease Burden in the Elderly: Crucial Roles for the Ageing MALT?

The large burden of infectious diseases in the elderly is mainly attributed to acute respiratory infections, as exemplified by the ongoing COVID19 pandemic as well as the annual burden of influenza illness, but chronic virus infections also have their significant share. The latter is mainly caused by reactivation of the chronic latent herpesviruses Varicella Zoster Virus (VZV) and Cytomegalovirus (CMV) with advancing age (Stowe et al. 2007). The ageing MALT has a potential large contribution to this disease vulnerability, although knowledge on direct associations in humans is scarce. Below we describe the major acute and chronic infections posing a threat in the elderly and discuss the potential associations with the ageing MALT.

6.3.1 Acute Infections

6.3.1.1 Influenza

Influenza Disease Burden in the Elderly

Global seasonal influenza epidemics result in about 3–5 million severe cases and 290.000–650.000 deaths each year, mainly affecting the elderly and chronically ill (World Health Organization 2018; McElhaney et al. 2020). This high influenza disease burden is accompanied by high medical costs (Klepser 2014), which are predicted to rise in light of the rapid ageing of the population. Influenza viruses are negative-stranded RNA viruses and the strains able to infect humans are influenza A, B, and C viruses (World Health Organization 2018; Bouvier and Palese 2008). The majority of human seasonal influenza illnesses are caused by influenza A and B viruses. Influenza A viruses are classified by the expression of the glycoproteins hemagglutinin (HA) and neuraminidase (NA), of which the currently circulating strains are of the H1N1 and H3N2 subtypes (World Health Organization 2018). In contrast, influenza B viruses are typed by their lineages and currently mostly found as either B/Yamagata and B/Victoria (World Health Organization 2018).

Influenza A viruses are known for their high mutation rates as a consequence of error-prone RNA polymerases, often referred to as *antigenic drift* (Bouvier and Palese 2008). Moreover, combinations of new influenza strains frequently arise, a process called *antigenic shift* (Bouvier and Palese 2008). As a consequence, influenza viruses master immune evasion, which enables a high annual disease burden. In addition, influenza viruses pose a large threat for the emergence of pandemic strains (Bouvier and Palese 2008).

Correlates of Protection

Currently, full knowledge on human correlates of protection (COPs) against influenza disease is lacking and complicates the development of protective treatments and vaccines. Historically, HA specific antibodies were considered essential in protection against influenza disease (Hobson et al. 1972). However, current consensus indicates a multifaceted antibody mediated protection and many questions remain unanswered (Krammer 2019). One complicating factor is the large influence of pre-existing immunity from previous infections on the immune response against subsequent influenza infections. Theoretically, this phenomenon is referred to as *imprinting* and explained in the *antigenic sin theory* (Krammer 2019; Francis 1960). On the basis of this theory, the first exposure to influenza viruses during a lifetime, determines the responses towards subsequent influenza infections. This phenomenon complicates research on the associations between the ageing immune system and the high influenza burden in the elderly. A large potential influence of pre-existing immunity was clearly visualized during the H1N1/09 pandemic, during which elderly suffered less from disease as compared to other age groups. The observation was partly explained by a difference in pre-existing immunity (Bansal et al. 2010; Hancock et al. 2009).

In addition, the complex interplay between antibodies and cells of the innate and adaptive immune system in response to influenza infection is incompletely understood (McElhaney et al. 2020). As of today, cell-mediated-immunity, mainly obtained by T cells, is considered to play essential roles in viral protection (McElhaney et al. 2020). Importantly, influenza specific memory CD4+ T cells were found to recognize conserved viral proteins and cross-react between multiple influenza strains (Zens and Farber 2014).

Influenza Specific Mucosal Immunity

Mucosal immunity might play essential roles in protection against influenza disease, which is evidenced by the discovery of a protective role of influenza specific nasal IgA against disease in a human challenge model, whereas serum influenza specific IgG was only poorly predictive for protection (Gould 2017). Moreover, research in mice has indicated the initiation of protective CD8+ T-cell responses against influenza A disease in the mucosal tissue of the respiratory tract (Nguyen et al. 1999), as well as the importance of alveolar macrophages in protection, as a result of their role in antibody-induced inflammation and antibody dependent phagocytosis (He et al. 2017). Consequently, mucosal immune responses in the BALT might play key roles in protection against influenza disease and warrant additional investigation in a human setting (Table 6.1).

Table 6.1 Association between mucosal immune responses and immunity and/or protection against infections with a high disease burden in the elderly

Infection	Mucosal immunity associated with infection specific immunity and/or protection	Species	References
Influenza	• Nasal influenza specific IgA	Human	Gould et al. (2017)
	• Influenza specific CD8+ T cells in respiratory tract	Mice	Nguyen et al. (1999)
	• Alveolar macrophages	Mice	He et al. (2017)
RSV	• Nasal RSV specific IgA	Human	Habibi et al. (2015)
	• RSV specific CD8+ TRM cells in BAL	Human	Jozwik (2015)
	• Neutrophil preparedness	Human	Habibi (2020)
	• Alveolar macrophages	Mice	Pribul et al. (2008)
Streptococcus	• Nasal pneumococcal specific IgG	Human	Mitsi et al. (2017)
Pneumoniae	• Total CD8+ TRM and MAIT cells in nasal mucosa	Human	Jochems et al. (2019)
	• Nasal pneumococcal specific IL17 +CD4+ TRM cells	Mice	O'Hara et al. (2020)
SARS-CoV2	• SARS-CoV2 specific airway CD8+ TRM cells	MHP	McMahan et al. (2021)
	• SARS-Cov2 specific IgA in BAL	Human	Sterlin et al. (2021)
VZV	• VZV specific CD4+ TRM cells in skin	Human	Vukmanovic-Stejic et al. (2015)
	• Innate immune responses in skin and dorsal ganglia	Human	Laing et al. (2018)
CMV	• CMV specific cells in diverse tissues (bone marrow, lymph nodes, spleen and lung)	Human	Gordon et al. (2017)
	• CMV specific T cells in salivary glands	Mice	Smith et al. (2015)

Ageing and Influenza Specific Mucosal Immunity

Currently, our understanding of influenza specific mucosal immunity in relation to ageing is highly limited in a human setting (Fulton and Varga 2009). Nevertheless, a decrease of influenza specific CD8+ TRM cells with age was observed in human lung biopsies, as well as a reduced expression of activation markers on lung T cells after in vitro stimulation with influenza virus (Nguyen 2021). These findings were accompanied by a reduced type 1 interferon response in lung biopsies after in vitro influenza specific stimulation (Nguyen 2021). In addition, results from mouse models shed some light on differences in the mucosal immune response following influenza infection between adult and aged mice and indicate a delayed activation of innate immunity in the lungs of the aged mice, which came along with altered cytokine and chemokine production in macrophages and DCs in the lung (Toapanta and Ross 2009). These results were recently complemented with findings of reduced

Table 6.2 Current limited knowledge on ageing associated alterations in infection specific mucosal immunity

Infection	Age related change in infection specific mucosal immunity	Species	References
Influenza	• Delayed activation innate immunity in lung	Mice	Toapanta (2009)
	• Altered cytokine and chemokine production in lung macrophages and DCs		
	• Reduced influenza specific CD4+ and CD8+ T cell responses in the lung		
	• Reduced phagocytic function alveolar macrophages	Mice	Wong et al. (2017)
	• Decay of influenza specific CD8+ TRM cells in lung	Human Mice	Nguyen et al. (2021) Bader and McKinsey (2005)
	• Reduced expression of activation markers lung T cells following in vitro influenza stimulation		
	• Reduced type 1 IFN in lung after in vitro influenza stimulation		
	• Relative increase in mall-functioning influenza specific CD8 + TRM cells		
Streptococcus	• Impaired innate nasal mucosal immunity	Mice	Krone et al. (2013)
Pneumoniae	• Dysbiosis nasal microbiome	Human	Steenhuijsen Piters et al. (2016)
VZV	• Increased expression regulatory markers on VZV specific CD4+ TRM cells in skin	Human	Vukmanovic-Stejic et al. (2015)

phagocytic function of alveolar macrophages in response to influenza infection in ageing mice (Wong et al. 2017). Finally, reduced influenza specific CD4+ and CD8+ responses were observed in the lungs from aged mice (Wong et al. 2017), combined with a relative increase of mall-functioning influenza specific CD8+ TRM cells that have the potential to exacerbate lung inflammation (Golpen et al. 2020). Combined, these results illustrate the potential importance of ageing mucosal immunity in light of the high influenza disease vulnerability in the aged (Table 6.2).

6.3.1.2 Respiratory Syncytial Virus (RSV)

RSV Disease Burden in the Elderly

In addition to influenza, elderly individuals are increasingly vulnerable to infection with the enveloped RNA respiratory syncytial virus (RSV) (Bader and McKinsey

2005; Ebbert and Limper 2005). Infection with RSV occurs frequently throughout life, already starting at young age, but causes complications in very young children, the immunocompromised and elderly (Olson and Varga 2008; Shi et al. 2020). Globally, the number of RSV related hospital admissions in 2015 was estimated at about 336.000 and the associated number of deaths at 14.000. These numbers were found substantially elevated in individuals over 65 years of age (Bader and McKinsey 2005). Importantly, an elevated RSV disease burden was observed in both community-dwelling older adults as well as elderly living in nursing homes (Van Erp et al. 2019).

Correlates of Protection

As of today, no COPs have been established for RSV, mainly hampered by our incomplete understanding on the role of antibodies in protection against disease. Besides their role in virus neutralization, RSV specific antibodies might also enhance infection, via the so-called process of *antibody dependent enhancement (ADE)*. Full knowledge on antibody characteristics that contribute to ADE is currently lacking, but it is hypothesized to occur when insufficient neutralizing antibodies levels are present for full protection (Habibi et al. 2015). Also, it is currently incompletely understood whether ADE plays a role in the higher RSV disease burden in the elderly. However, this is the current dogma based on the previously observed presence of high RSV specific antibody levels with low neutralizing capacity in elderly (Habibi et al. 2015). Up until now, clear association between circulating RSV specific T cells and disease progression were not observed. Even though a decline of circulating long-lasting CD8+CD127 +SV specific T cells was observed in the elderly, combined with a lower proliferative capacity and increased RSV specific Th2 responses at the expense of Th1 responses, it is questionable whether these findings contribute to the disease vulnerability in the aged (Cusi et al. 2010).

RSV Specific Mucosal Immunity

Investigation of human immune responses following experimental RSV infection indicates an important role for nasal IgA in protection against RSV infection. However, these antibodies wane quickly after infection (Habibi et al. 2015). Moreover, in contrast to circulating CD8+ T cells, RSV specific CD8+ TRM cells in the bronchoalveolar lavage (BAL) were associated with improved viral control and less severe symptoms. Interestingly, these airway RSV specific TRMs did not alter much after infection, showed low proliferative responses and reduced expression of cytotoxic molecules, as compared to their circulating counterparts (Jozwik 2015). These findings indicate a fundamental difference between RSV-specific circulating T cells and TRM cells and underline the importance of mucosal immune responses in protection against RSV (Jozwik 2015).

In addition, neutrophil preparedness in the lung was found associated with disease susceptibility in a human RSV challenge model (Habibi 2020). Finally, mouse models indicated a critical role for alveolar macrophages in the early immune response towards RSV infection. However, these alveolar al. macrophages did not affect subsequent adaptive immune responses or disease development, suggesting a role for local T cells in disease protection (Pribul et al. 2008) (Table 6.1).

Ageing and RSV Specific Mucosal Immunity

Knowledge on RSV specific mucosal immunity in relation to ageing is currently lacking, which limits our understanding on the vulnerability of elderly towards severe RSV disease and once again urges the need for studies on mucosal RSV immunity in relation to ageing (Wiseman et al. 2020). Human challenge models in older individuals will shed light on these and other aspects of protective immunity in future research.

6.3.1.3 Streptococcus Pneumoniae

Pneumococcal Disease Burden in the Elderly

Streptococcus pneumoniae (S.pneumoniae), a Gram-positive encapsulated diplococcus, is the leading causative microorganism for community-acquired pneumonia and bacterial meningitis among the elderly worldwide (Torres et al. 2018; Drijkoningen and Rohde 2014; Cabellos et al. 2009). S. pneumoniae is estimated to cause approximately one million deaths each year, greatly affecting elderly above 70 years of age (Vos et al. 2017). Consequently, the medical and economic costs of pneumococcal disease are high and expected to rise in light of the ageing population and growing antibiotic resistance (Lynch and Zhanel 2010; Bogaert et al. 2004; Tacconelli et al. 2018).

More than 90 different pneumococcal serotypes are known, of which the serotypes most associated with severe disease and high mortality in the elderly, serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F, are included in the 13-valent pneumococcal conjugate vaccine (Torres et al. 2018; Garde et al. 2019). At young age, asymptomatic carriage of *S. pneumoniae* in the nasopharynx is common, which reduces towards below 10% at older age (Garde et al. 2019; Hussain et al. 2005). Following nasal carriage, *S. pneumoniae* is able to cause invasive disease. Up until now, we do not fully understand the factors driving the process of innocent nasal carriage to invasive disease. Therefore, it is of ongoing debate whether protective measures should aim to prevent invasive disease or already start by prevention of colonization (Bogaert et al. 2004).

Correlates of Protection

The capsular polysaccharides (PS) are the most important pneumococcal virulence factors, and hence immunity towards these PS is important in protection (Garde et al. 2019). The current opinion in the field is that antibodies that are able to induce opsonophagocytosis are most essential in the protection against pneumococcal disease, even though no clear COPs have been established yet (Kim et al. 1999; Van Deursen et al. 2017). Nevertheless, PS immunity is serotype specific and might still allow other pneumococcal strains to colonize and cause disease, a process called *strain replacement* (Bogaert et al. 2004). Subsequently, broader protection against pneumococci might be prerequisite and therefore pneumococcal vaccines with increasing numbers of serotypes are being developed. Additionally, protective antibody levels in infants were found to differ between pneumococcal serotypes in children (Voysey et al. 2018), suggesting pneumococcal serotype specific COPs. As of today, no COP in elderly is identified and the immunological causes of the increased vulnerability towards pneumococcal disease in the elderly is poorly understood. Studies indicate a decrease in pneumococcal antibody concentrations, albeit this phenomenon differed per serotype (Van Deursen et al. 2017).

Pneumococcal Specific Mucosal Immunity

Pneumococcal specific mucosal immunity in the nasal cavity is expected to prevent pneumococcal nasal carriage. As a consequence of the bacteria's IgA1 proteases dismantling IgA mediated immunity, IgG antibodies in the nasal mucosa are required to prevent colonization (Janoff et al. 2014). Human pneumococcal carriage research discovered protective roles of this nasal IgG against pneumococcal colonization, due to its agglutinating activity. Interestingly, these nasal IgG concentrations correlated with its serum counterpart (Mitsi et al. 2017) and therefore serum IgG concentrations can be used as a surrogate for nasal protection. In addition to antibodies, CD8+ TRM and CD8+ MAIT cells mediated protection was observed against pneumococcal colonization in a human challenge model (Jochems et al. 2019). Interestingly, these MAIT cells respond to precursors from the riboflavin synthesis pathway highly present on pneumococci and have a potential for broad protection, surpassing the stains specific protection of PS antibodies (Jochems et al. 2019). In addition, mouse studies indicated nasal IL17+ CD4+ TRM cells mediated protection against pneumococcal colonization (O'Hara et al. 2020). (Table 6.1).

Ageing and Pneumococcal Specific Immunity

While knowledge of human mucosal pneumococcal specific immunity in relation to age is scarce, studies in mice relate age associated inflammation as well as cellular senescence to a higher burden of pneumococcal pneumonia (Hinojosa et al. 2009; Shivshankar et al. 2011). Moreover, mouse studies indicated reduced innate immunity

following pneumococcal challenge in older mice, which potentially resulted from higher baseline inflammation levels in the nasal (Krone et al. 2013). Furthermore, human upper respiratory tract microbiome research indicated a relation between pneumococcal pneumonia and dysbiosis of the respiratory tract microbiome (de Steenhuijsen Piters et al. 2016). Hence, advanced knowledge of pneumococcal specific mucosal immunity in humans in relation to age is highly needed to develop preventive measures against the high disease burden in the elderly (Table 6.2).

6.3.1.4 SARS-CoV2

Covid19 Disease Burden in the Elderly

The ongoing COVID19 pandemic, caused by the SARS-CoV2 virus, painfully exemplifies the vulnerability of the elderly towards emerging viral infections. Data from China indicates a case fatality ratio (CFR) of on average 1.38%, where the CFR in the age groups below 60 years, 60–80 years of age, and above 80 years, was estimated to be 0.32%, 6.4% and 13.4% respectively (Verity et al. 2020). Likewise, research in 16 countries overarching more than 2.4 billion people predicts that people aged 55–64 years had an 8.1 times and those 65 years and older a 62 times higher incident rate ratio as compared to those aged below 54 (Yanez et al. 2020). This increased risk of severe COVID19 disease in the elderly is often linked to underlying co-morbidities, such as cardiovascular diseases and diabetes type2 (Smorenberg et al. 2021). In order to overcome this pandemic and be better prepared for potential future pandemics, it is of crucial importance to understand the vulnerability for severe SARS-CoV2 infection in the elderly.

SARS-CoV2 enters the human body by binding of its spike protein to the ACE2 receptor on endothelial cells. This receptor is not only expressed on endothelial cells of the lung and respiratory tract, but also on endothelial cells present in the heart, kidney, blood vessels, brain, intestine and fat tissue (Perico et al. 2021). After binding with SARS-CoV2, the ACE2 receptor is downregulated on the endothelial cells, which may contribute to the inflammatory response and vascular permeability in the lung (Mcmurray et al. 2020). Inflammatory responses and cytokine storms are frequently observed in severe COVID19 patients and are most pronounced by elevated plasma levels of the pro-inflammatory cytokines TNFα and IL6 (Huang et al. 2020; Schurink et al. 2020; Cunha et al. 2020). These inflammatory responses were found persistent and not associated with viral presence, which indicates a pathological response of the immune system following infection (Schurink et al. 2020). Moreover, these inflammatory responses were accompanied by high neutrophil infiltrations in the lung of severe patients (Schurink et al. 2020) as well as a high circulating neutrophil to lymphocyte ratio (Cunha et al. 2020; Zhang et al. 2020). The underlying *inflammageing* in the elderly, might worsen the inflammatory outcome after SARS-CoV2 infection and contribute to the enhanced pathology and mortality in the aged, especially in those with underlying chronic inflammatory diseases (Yanez et al. 2020; Cunha et al. 2020; Diao et al. 2020). Moreover, extreme reduced numbers

of CD4+ and CD8+ T cells following infection associated with both inflammatory responses and survival in the elderly (Diao et al. 2020; Rydyznski Moderbacher et al. 2020). Overall, an unbalanced immune responses following SARS-CoV2 infection is observed in the elderly, which potentially enhances the development of severe disease (Rydyznski Moderbacher et al. 2020).

Correlates of Protection

At the moment of writing, the establishment of COPs for COVID19 disease is hampered by our limited understanding of the complex interplay between immunity and disease severity (Rydyznski Moderbacher et al. 2020; Mathew et al. 2020). Despite the association of COVID19 specific antibodies and T cells with disease protection, specific characteristics of these responses were also associated with severe disease (Mathew et al. 2020). For example, low affinity SARS-CoV2 spike specific CD4+ T cells (Bacher et al. 2020), and high levels of afucosylation of the SARS-CoV2 IgG antibodies were associated with severe disease (Larsen et al. 2020; Fu et al. 2020). Evidence for a dual protection of both antibodies and T cells against COVID19 disease was provided by SARS-CoV2 challenge studies in non-human primates (NHP). These studies indicated a clear role for neutralizing IgG antibodies in protection against COVID19 disease. Interestingly this antibody mediated protection was partially diminished following depletion of CD8+ T cells and the challenge studies suggest substantial roles for cellular immune responses once suboptimal antibody levels are present (McMahan et al. 2021). Therefore, based on current data, a correlate of protection is expected based on the combined actions of both humoral and cellular SARS-CoV2 specific immunity (Jin et al. 2021).

SARS-CoV2 Specific Mucosal Immunity

Albeit the current incomplete understanding of mucosal immunity in COVID19 disease, we speculate on paramount roles for immune responses in the respiratory tract in disease protection. This is evidenced by the large influence of CD8+ TRM cells in disease protection in the NHP challenge models (McMahan et al. 2021). Moreover, human data derived from research on other emerging coronaviruses indicates the importance of airway CD4+ T-cells in protection (Zhao et al. 2016), knowledge that is expected to be translatable to SARS-CoV2 infection. The longevity of these TRM cells is however questionable. I addition, mucosal IgA was previously found protective against infection with other emerging respiratory viruses. Consistently, recent research also indicates a dominant neutralizing role for IgA in the early antibody response towards SARS-CoV2 (Sterlin et al. 2021). This neutralizing IgA was found in the BAL of all ICU admitted COVID19 patients and suggest roles for mucosal IgA in the immune response against SARS-CoV2. Nevertheless, SARS-CoV2 specific IgA antibodies in serum and saliva waned quickly following infection

(Sterlin et al. 2021) and consequently the long-term presents of SARS-CoV2 specific IgA warrants thorough investigation (Siggins et al. 2021) (Table 6.1).

Ageing and SARS-Cov2 Specific Immunity

Knowledge on association between ageing and SARS-CoV2 mucosal immunity is slowly gathered. Here it is importance to note that the majority of knowledge on SARS-CoV2 immunity is gathered from severely ill patients, which are mainly of older age. Therefore, comparison of these mucosal immune responses with younger age groups is as of today hardly possible. Nevertheless, some interesting observations have been done, such as a reduced expression of ACE2 on endothelial cells in aged mice that is potentially exacerbate the inflammatory responses in the lung (Smorenberg et al. 2021; Yoon et al. 2016). Moreover, infection of the airway epithelial cells with SARS-CoV2 might break the already deteriorating epithelial barrier integrity in the elderly which results in enhanced inflammatory responses and infiltration of immune cells. In addition, this diminished barrier integrity could lead to invasion of secondary bacterial infections (Fu et al. 2020; Wolfe et al. 2020).

6.3.2 Chronic Infections

6.3.2.1 Varicella Zoster Virus (VZV)

VZV Disease Burden in the Elderly

Herpes Zoster, also known as Shingles, possess a large disease burden in the elderly, with an approximate yearly incidence rate of 3–5 per 10,000 individuals (Kawai et al. 2014). Herpes Zoster is caused by the Varicella Zoster Virus (VZV), which becomes latent in the ganglia of the human body following primary infection at childhood age, that is also known as Chickenpox. Advancing age and immunosuppression are major risk factors for disease development, with most cases revealing itself after the age of 50 (Johnson et al. 2015; de Melker et al. 2006). The disease mainly manifests itself as painful rashes on the skin, but in parts of the cases develops into long-lasting and painful post herpetic neuralgia (Kawai et al. 2014; Arvin 1996). The disease burden and economic costs of this painful disease are expected to rise in the context of the ageing population (Friesen et al. 2017).

Correlates of Protection

VZV-specific cell mediated immunity (CMI), especially IFNγ producing T cells, is perceived essential in the protection against virus reactivation, whereas the role of antibodies in disease protection is unclear (Steain et al. 2014; Schub et al. 2015). This

perception was strengthened by a decrease of VZV-specific CMI with advancing age that was associated with enhanced disease susceptibility (Schub et al. 2015; Weinberg et al. 2010; Levin et al. 2003), whereas antibody levels were found stable over the lifespan (van Lier et al. 2013).

VZV Specific Mucosal Immunity

Interestingly, high levels of VZV specific CD4+ T cells expressing a TRM phenotype, were observed in human skin biopsies and outweighed the amount of VZV-specific T cells in blood. This finding indicates important roles for VZV CMI in the skin (Vukmanovic-Stejic et al. 2015; Laing et al. 2018). Knowledge on the role of CD8+ TRM cells in protection against VZV reactivation is currently lacking (Laing et al. 2018). Contrarily, innate immune responses in the skin and ganglia were important in the control of VZV infection and was mediated by the secretion of type I interferons and pro-inflammatory cytokines. Until now, VZV specific T cells have not been found in the ganglia (Laing et al. 2018) (Table 6.1).

Ageing and VZV Specific Mucosal Immunity

Contrary to their circulatory counterparts, skin specific VZV CD4+ T cells did not decrease in numbers towards old age and showed comparable functionality over the lifespan. Nevertheless, an increased expression of regulatory markers on these T cells was observed in older adults, potentially limiting the T-cell response due to enhanced regulation (Vukmanovic-Stejic et al. 2015). Future research on mucosal and local immunity in protection against VZV reactivation is highly needed to understand the vulnerability of the elderly for painful VZV reactivation and to improve protective strategies (Table 6.2).

6.3.2.2 Cytomegalovirus (CMV)

CMV Disease Burden in the Elderly

Even though reactivation of CMV is often asymptomatic, its association with accelerated ageing is often discussed, as well as its association with the development of an immune risk profile, co-morbidity, and even increased mortality (Wikby et al. 2008; Araújo Carvalho et al. 2018; Savva et al. 2013; Gkrania-Klotsas et al. 2012. Globally, CMV infects 40–100% of adults, after which the virus establishes a latent infection in myeloid and epithelial cells (Stempel et al. 2019; van den Berg et al. 2019). CMV often reactivates over the life course and large CMV specific T-cell clones were observed in the human T-cell compartment (Lanfermeijer et al. 2020). Moreover, strong associations between CMV seropositivity and late-differentiation of large part of the peripheral CD8 + T-cell compartment were detected (van den Berg

et al. 2019), an effect that is already visible before reaching old age (van der Heiden et al. 2016; van den Heuvel et al. 2016). Interestingly, a recent human longitudinal study indicated that the size of the CMV specific T-cell compartment was associated with age of primary CMV infection and not the duration of CMV infection per se. In addition, this study found no evidence of CMV related frailty, but a potential association with an increased prevalence of cardiovascular disease (Samson et al. 2020). Therefore, it remains topic of fierce debate whether CMV indeed contributes to frail health and accelerated ageing in the elderly (Gordon et al. 2017).

Correlates of Protection

Although CMV-specific T cells are thought to be crucial in protecting against latent infection, as evidenced by the many immune evasion strategies of CMV targeting the class I presentation pathway (Jackson et al. 2017), the exact correlates of protection remain unclear, specifically against reactivation of CMV. Given the role of T cells in the early phase of infection, a large role for CMV specific T-cell immunity is however expected. As human studies remain difficult to execute, mouse models have the potential to shed more light on this.

CMV Specific Mucosal Immunity

As T cells have been the major focus of CMV-specific immunity in general, also investigation of mucosal immunity focused on T cells. TRM cells at mucosal sites might be important in the control over CMV reactivation. Recently, the presence of these CMV specific TRM cells has been observed both in mice and humans (Gordon et al. 2017; Smith et al. 2015), whereas their precise distribution, role and function in viral control remains unclear (Table 6.1).

Ageing and CMV Specific Mucosal Immunity

Although ageing and CMV-infection have been topic of a lot of research, this has mainly been focused on the influence of CMV on the ageing process from an immunological point of view and not so much on how CMV immunity is altered with ageing. The latter is of high importance as altered CMV immunity may play a significant role in the potential detrimental effects of CMV with ageing[163]. Given the fact that research on local immune responses is in its early phase, the effect of ageing on CMV specific mucosal immunity is still unexplored in human settings.

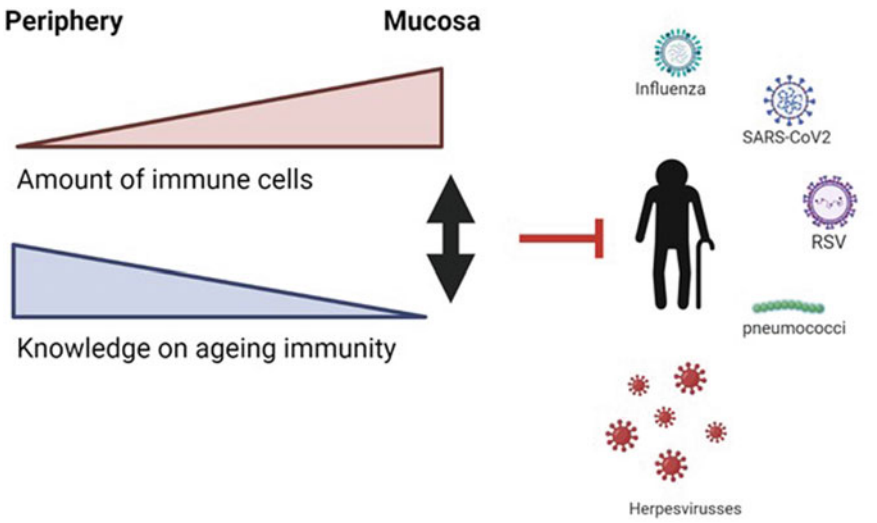

Fig. 6.2 Changes occurring in the immune system during the ageing process and pathogens

6.4 Conclusions/ Future Perspective

Besides the increased attention in the past years, knowledge on ageing of mucosal immunity remains scarce in comparison to its systemic counterpart. Nevertheless, research suggests essential roles for nasal IgA as well as lung harboring CD8+ TRM cells in the protection against influenza, RSV, pneumococcal and SARS-CoV2 disease. Combined this substantiates the importance of mucosal immunity in the respiratory tract and nasal cavity in the protection against acute respiratory infections. Therefore, future research should aim to identify protective levels of these mucosal immune response, especially in relation to ageing. On the contrary, roles for mucosal immunity in the protection against herpes virus reactivation is currently less unambiguous, as it is understudied and the mucosal site under study is specific for every herpesvirus (Fig. 6.2).

Historically, the study of mucosal immunity in a human setting has been complicated due to the limited availability of study material, but recent extensive collaborations and innovative techniques broaden our possibilities. It is essential to utilize these tools to study human mucosal immunity and improve our knowledge on correlates of protection against infectious disease as well as the disease susceptibility in the elderly. Moreover, profound knowledge of mucosal immunity in relation to age and disease is prerequisite for the development of targeted preventive measures, such as mucosal vaccines, to protect the rapidly ageing population against recurrent and potentially emerging infectious diseases.

Compliance with Ethical Standards Both authors declare that they have no conflict of interest.

This chapter does not contain any studies with human participants or animals performed by any of the authors.

References

Appay et al., 2008. Appay V, Van Lier RAW, Sallusto F, Roederer M (2008) Phenotype, function of human Tlymphocyte subsets: consensus, issues.Cytometry Part A. 73:975–983

Araújo Carvalho, et al., 2018. Araújo Carvalho AC et al (2018) Association between human herpes virus seropositivity and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev 48:145–152

Arranz E, O'Mahony S, Barton JR, Ferguson A (1992) Immunosenescence and mucosal immunity: significant effects of old age on secretory IgA concentrations and intraepithelial lymphocyte counts. Gut 33:882–886

Arvin ANNM (1996) Varicella-Zoster Virus. 9:361–381

Bacher P et al (2020) Low-avidity CD4+ T cell responses to SARS-CoV-2 in unexposed individuals and humans with severe COVID-19. Immunity 53:1258-1271.e5

Bader MS, McKinsey DS (2005) Viral infections in the elderly: the challenges of managing herpes zoster, influenza, and RSV. Postgrad Med 118:45–54

Bansal S, Pourbohloul B, Hupert N, Grenfell B, Meyers LA (2010) The shifting demographic landscape of pandemic influenza. PLoS ONE 5:1–8

Beharka AA et al (2001) Effect of age on the gastrointestinal-associated mucosal immune response of humans. J. Gerontol Ser Biol Sci Med Sci 56:218–223

Behr FM et al (2020) Tissue-resident memory CD8 + T cells shape local and systemic secondary T cell responses. Nat Immunol 21:1070–1081

Biagi E et al (2010) Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS ONE 5

Bogaert D, de Groot R, Hermans PWM (2004) Dynamics of nasopharyngeal colonization: the key to pneumococcal disease. Lancet Infect Dis 4:144–154

Boraschi D et al (2013) The gracefully aging immune system. Sci Transl Med 5:1–10

Bouvier NM, Palese P (2008) The biology of influenza viruses. Vaccine 26:49–53

Branca JJV, Gulisano M, Nicoletti C (2019) Intestinal epithelial barrier functions in ageing. Ageing Res Rev 54:100,938

Brodin P et al (2015) Variation in the human immune system is largely driven by non-heritable influences. Cell 160:37–47

Buford TW (2017) (Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease. Microbiome 5:80

Cabellos C et al (2009) Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine 88:115–119

Chang AY, Skirbekk VF, Tyrovolas S, Kassebaum NJ, Dieleman JL (2019) Measuring population ageing: an analysis of the Global Burden of Disease Study 2017. Lancet Public Health 4:e159–e167

Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV (2020) Remodeling of the immune response with aging: immunosenescence and its potential impact on COVID-19 immune response. Front Immunol 11:1–11

Cusi MG et al (2010) Age related changes in T cell mediated immune response and effector memory to Respiratory Syncytial Virus (RSV) in healthy subjects. Immun Ageing 7:1–8

Dalton JE et al (2006) Intraepithelial $\gamma\delta$ + Lymphocytes maintain the integrity of intestinal epithelial tight junctions in response to infection. Gastroenterology 131:818–829

de Melker H et al (2006) The epidemiology of varicella and herpes zoster in The Netherlands: implications for varicella zoster virus vaccination. Vaccine 24:3946–3952

de Steenhuijsen Piters WAA et al (2016) Dysbiosis of upper respiratory tract microbiota in elderly pneumonia patients. ISME J 10: 97–108
den Braber I et al (2012) Maintenance of peripheral naive T cells is sustained by thymus output in mice but not humans. Immunity 36:288–297
Diao B et al (2020) Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 11:1–7
DonaldsonDS, Pollock J, Vohra P, Stevens MP, Mabbott NA (2020) Microbial stimulation reverses the age-related decline in M cells in aged mice. iScience 23:101,147
Drijkoningen JJC, Rohde GGU (2014) Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect 20:45–51
Dunn-Walters DK (2016) The ageing human B cell repertoire: a failure of selection? Clin Exp Immunol 183:50–56
Ebbert JO, Limper AH (2005) Respiratory syncytial virus pneumonitis in immunocompromised adults: clinical features and outcome. Respiration 72:263–269
Egorov ES et al (2018) The changing landscape of naive T cell receptor repertoire with human aging. Front Immunol 9:1–12
Finkelstein MS, Tanner M, Freedman ML (1984) Salivary and serum IgA levels in a geriatric outpatient population. J Clin Immunol 4:85–91
Francis T (1960) On the doctrine of original antigenic sin author (s): Thomas Francis, Jr. Published by: American Philosophical Society Stable URL: http://www.jstor.org/stable/985534 REFERENCES Linked references are available on JSTOR for this article: you may need. Proceedings of the American philosophical society 104:572–578
Fransen F et al (2017) Aged gut microbiota contributes to systemical inflammaging after transfer to germ-free mice. Front Immunol 8:1–12
Frasca D, Diaz A, Romero M, Landin AM, Blomberg BB (2011) Age effects on B cells and humoral immunity in humans. Ageing Res Rev 10:330–335
Frasca D, Diaz A, Romero M, Blomberg BB (2017) Human peripheral late/exhausted memory B cells express a senescent-associated secretory phenotype and preferentially utilize metabolic signaling pathways. Exp Gerontol 87:113–120
Friesen KJ, Chateau D, Falk J, Alessi-Severini S, Bugden S (2017) Cost of shingles: population based burden of disease analysis of herpes zoster and postherpetic neuralgia. BMC Infect Dis 17:1–8
Fu Y et al (2020) secondary bacterial infections in critical Ill patients with coronavirus disease 2019. Open Forum Infect Dis 7:3–6
Fuentes S et al (2021) Associations of faecal microbiota with influenza-like illness in participants aged 60 years or older: an observational study. Articles Lancet Healthy Longev 2:13–23
Fujihashi K, Kiyono H (2009) Mucosal immunosenescence: new developments and vaccines to control infectious diseases. Trends Immunol 30:334–343
Fülöp T et al (2012) The innate immune system and aging: What is the contribution to immunosenescence? Open Longev Sci 6:121–132
Fülöp T et al (2018) Immunosenescence and inflamm-aging as two sides of the same coin: friends or Foes? Front Immunol 8
Fülöp T, Larbi A, Witkowski JM (2019) Human inflammaging. Gerontology 65:495–504
Fulton RB, Varga SM (2009) Effects of aging on the adaptive immune response to respiratory virus infections. Aging Health 5:775–787
Ganusov VV, De Boer RJ (2007) Do most lymphocytes in humans really reside in the gut? Trends Immunol 28:514–518
Gkrania-Klotsas E et al (2012) Higher immunoglobulin G antibody levels against cytomegalovirus are associated with incident ischemic heart disease in the population-based EPIC-norfolk cohort. J Infect Dis 206:1897–1903
Golpen NP et al (2020) Tissue-resident CD8+ T cells drive age-associated chronic lung sequelae after viral pneumonia. Sci Immunol 5: eabc4557

Gordon CL et al (2017) Tissue reservoirs of antiviral T cell immunity in persistent human CMV infection. J Exp Med 214:651–667
Goronzy JJ, Weyand CM (2019) Mechanisms underlying T cell ageing. Nat Rev Immunol 19:573–583
Gould VMW et al (2017) Nasal IgA provides protection against human influenza challenge in volunteers with low serum influenza antibody titer. Front Microbiol 8
Gregg R et al (2005) The number of human peripheral blood CD4+ CD25high regulatory T cells increases with age. Clin Exp Immunol 140:540–546
Habibi MS et al (2015) Impaired antibody-mediated protection and defective iga b-cell memory in experimental infection of adults with respiratory syncytial virus. Am J Respir Crit Care Med 191:1040–1049
Habibi MS et al (2020) Neutrophilic inflammation in the respiratory mucosa predisposes to RSV infection. Science 370
Hancock K et al (2009) Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N Engl J Med 361:1945–1952
He W et al (2017) Alveolar macrophages are critical for broadly-reactive antibody-mediated protection against influenza A virus in mice. Nat Commun 8:1–13
Herndler-Brandstetter D, Ishigame H, Flavell RA (2013) How to define biomarkers of human t cell aging and immunocompetence? Front Immunol 4:2011–2014
Hinojosa E, Boyd AR, Orihuela C (2009) Age-associated inflammation and Toll-like receptor dysfunction prime the lungs for pneumococcal pneumonia. J Infect Dis 200:546–554
Hobson D, Curry RL, Beare AS, Ward-Gardner A (1972) The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hygiene 70:767–777
Huang C et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. Lancet 395:497–506
Hussain M et al (2005) A longitudinal household study of Streptococcus pneumoniae nasopharyngeal carriage in a UK setting. Epidemiol Infect 133:891–898
Jackson SE et al (2017) CMV immune evasion and manipulation of the immune system with aging. GeroScience 39:273–291
Jagger AT, Shimojima Y, Goronzy JJ, Cornelia M (2016) T regulatory cells and the immune aging process. Gerontology 60:130–137
Janoff EN et al (2014) Pneumococcal IgA1 protease subverts specific protection by human IgA1. Mucosal Immunol 7:249–256
Jeffery IB, Lynch DB, O'Toole PW (2016) Composition and temporal stability of the gut microbiota in older persons. ISME J 10:170–182
Jin P et al (2021) Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. Signal Transduct Target Therapy 6
Jochems SP et al (2019) Innate and adaptive nasal mucosal immune responses following experimental human pneumococcal colonization. J Clin Investig 129:4523–4538
Johnson RW et al (2015) Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccin 3:109–120
Jozwik A et al (2015) RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection. Nat Commun 6
Jung C, Hugot J-P, Barreau F (2010) Peyer's patches: the immune sensors of the intestine. Int J Inflamm 2010:1–12
Kallemeijn MJ et al (2017) Ageing and latent CMV infection impact on maturation, differentiation and exhaustion profiles of T-cell receptor gammadelta T-cells. Sci Rep 7:1–14
Kavanagh K et al (2019) Biomarkers of leaky gut are related to inflammation and reduced physical function in older adults with cardiometabolic disease and mobility limitations. GeroScience 41:923–933
Kawai K, Gebremeskel BG, Acosta CJ (2014) Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open 4

Kim JO et al (1999) Relationship between cell surface carbohydrates and intrastrain variation on opsonophagocytosis of Streptococcus pneumoniae. Infect Immun 67:2327–2333
Kirkwood TBL (2004) Intrinsic ageing of gut epithelial stem cells. Mech Ageing Dev 125:911–915
Klepser ME (2014) Socioeconomic impact of seasonal (epidemic) influenza and the role of over-the-counter medicines. Drugs 74:1467–1479
Kobayashi A et al (2013) The functional maturation of M cells is dramatically reduced in the Peyer's patches of aged mice. Mucosal Immunol 6:1027–1037
Krone CL, Trzciński K, Zborowski T, Sanders EAM, Bogaert D (2013) Impaired innate mucosal immunity in aged mice permits prolonged streptococcus pneumoniae colonization. Infect Immun 81:4615–4625
Kumar BV et al (2017) Human tissue-resident memory T cells are defined by core transcriptional and functional signatures in lymphoid and mucosal sites. Cell Rep 20:2921–2934
Krammer F (2019) The human antibody response to influenza A virus infection and vaccination. Nat Rev Immunol 19:383–397
Laing KJ, Ouwendijk WJD, Koelle DM, Verjans GMGM (2018) Immunobiology of Varicella-Zoster virus infection. J Infect Dis 218:S68–S74
Lanfermeijer J, Borghans JAM, van Baarle D (2020) How age and infection history shape the antigen-specific CD8+ T-cell repertoire: implications for vaccination strategies in older adults. Aging Cell 19:1–14
Larsen MD et al (2020) Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science
Lee OJ et al (2014) Circulating mucosal-associated invariant T cell levels and their cytokine levels in healthy adults. Exp Gerontol 49:47–54
Levin MJ et al (2003) Decline in Varicella-Zoster Virus (VZV)-Specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis 188:1336–1344
Loh L et al (2020) Human Mucosal-associated invariant T cells in older individuals display expanded TCRαβ Clonotypes with potent antimicrobial responses. J Immunol 204:1119–1133
Lynch JP, Zhanel GG (2010) Streptococcus pneumoniae: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. Curr Opin Pulm Med 16:217–225
Man AL, Gicheva N, Nicoletti C (2014) The impact of ageing on the intestinal epithelial barrier and immune system. Cell Immunol 289:112–118
Martelli S, Pender SLF, Larbi A (2016) Compartmentalization of immunosenescence: a deeper look at the mucosa. Biogerontology 17:159–176
Mathew D et al (2020) Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science 369
McCarthy NE, Eberl M (2018) Human γδ T-cell control of mucosal immunity and inflammation. Front Immunol 9
McElhaney JE et al (2020) The immune response to influenza in older humans: beyond immune senescence. Immun Ageing 17:1–10
McMahan K et al (2021) Correlated of protection against SARS-CoV-2 in rhesus macaques. Nature 590:630–634
Mcmurray JJv, Pfeffer MA., Ph, D, Solomon SD (2020) Special Report Renin – Angiotensin – aldosterone system inhibitors in patients with Covid-19, 1653–1659
Mitchell WA, Lang PO, Aspinall R (2010) Tracing thymic output in older individuals. Clin Exp Immunol 161:497–503
Mitsi E et al (2017) Agglutination by anti-capsular polysaccharide antibody is associated with protection against experimental human pneumococcal carriage. Mucosal Immunol 10:385–394
Mueller SN, Mackay LK (2016) Tissue-resident memory T cells: local specialists in immune defence. Nat Rev Immunol 16:79–89
Nguyen HH et al (1999) Heterosubtypic immunity to lethal influenza A virus infection is associated with virus-specific CD8+ cytotoxic T lymphocyte responses induced in mucosa-associated tissues. Virology 254:50–60

Nguyen THO et al (2021) Influenza, but not SARS-CoV-2, infection induces a rapid interferon response that wanes with age and diminished tissue-resident memory CD8+ T cells. Clinic Trans Immunol 10

Novak J, Dobrovolny J, Novakova L, Kozak T (2014) The decrease in number and change in phenotype of mucosal-associated invariant T cells in the elderly and differences in men and women of reproductive age. Scand J Immunol 80:271–275

O'Hara JM et al (2020) Generation of protective pneumococcal-specific nasal resident memory CD4+ T cells via parenteral immunization. Mucosal Immunol 13:172–182

Olson MR, Varga SM (2008) Pulmonary immunity and immunopathology: lessons from respiratory syncytial virus. Expert Rev Vaccines 7:1239–1255

Parrish AR (2017) The impact of aging on epithelial barriers. Tissue Barriers 5

Pawelec G, Solana R (1997) Immunosenescence

Pawelec G et al (2020) The conundrum of human immune system "senescence." Mech Ageing Develop 192

Perico L et al (2021) Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol 17:46–64

Popkes M, Valenzano DR (2020) Microbiota–host interactions shape ageing dynamics. Philos Trans Royal Soc B Biol Sci 375:20190596

Pribul PK et al (2008) Alveolar macrophages are a major determinant of early responses to viral lung infection but do not influence subsequent disease development. J Virol 82:4441–4448

Pritz T, Weinberger B, Grubeck-Loebenstein B (2014) The aging bone marrow and its impact on immune responses in old age. Immunol Lett 162:310–315

Rubino G et al (2019) Sicilian centenarian offspring are more resistant to immune ageing. Aging Clin Exp Res 31:125–133

Rydyznski Moderbacher C et al (2020) Antigen-specific adaptive immunity to SARS-CoV-2 in Acute COVID-19 and associations with age and disease severity. Cell 183, 996–1012.e19

Samson LD et al (2019) Frailty is associated with elevated CRP trajectories and higher numbers of neutrophils and monocytes. Exp Gerontol 125: 110674

Samson LD et al (2020) Limited effect of duration of CMV infection on adaptive immunity and frailty: insights from a 27-year-long longitudinal study. Clinic Trans Immunol 9

Sathaliyawala T et al (2013) Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. Immunity 38:187–197

Savva GM et al (2013) Cytomegalovirus infection is associated with increased mortality in the older population. Aging Cell 12:381–387

Schub D et al (2015) Altered phenotype and functionality of varicella zoster virus-specific cellular immunity in individuals with active infection. J Infect Dis 211:600–612

Schurink B et al (2020) Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe 1:e290–e299

Shi T et al (2020) Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. J Infect Dis 222:S577–S583

Shivshankar P, Boyd AR, le Saux CJ, Yeh IT, Orihuela CJ (2011) Cellular senescence increases expression of bacterial ligands in the lungs and is positively correlated with increased susceptibility to pneumococcal pneumonia. Aging Cell 10:798–806

Siegrist CA, Aspinall R (2009) B-cell responses to vaccination at the extremes of age. Nat Rev Immunol 9:185–194

Siggins MK et al (2021) Durability of immunity to SARS-CoV-2 and other respiratory viruses. Trends Microbiol

Smith CJ, Caldeira-Dantas S, Turula H, Snyder CM (2015) Murine CMV infection induces the continuous production of mucosal resident T cells. Cell Rep 13:1137–1148

Smolders J et al (2018) Tissue-resident memory T cells populate the human brain. Nat Commun 9:1–14

Smorenberg A, Peters EJ, van Daele P, la, Nossent, E. J. & Muller, M. (2021) How does SARS-CoV-2 targets the elderly patients? a review on potential mechanisms increasing disease severity. Eur J Intern Med 83:1–5
Sovran B et al (2019) Age-associated impairment of the mucus barrier function is associated with profound changes in microbiota and immunity. Sci Rep 9:1–13
Steain M et al (2014) Analysis of T Cell responses during active Varicella-Zoster Virus Reactivation in human ganglia. J Virol 88:2704–2716
Stempel M, Chan B, Brinkmann MM (2019) Coevolution pays off: Herpesviruses have the license to escape the DNA sensing pathway. Med Microbiol Immunol 208:495–512
Sterlin D et al (2021) IgA dominates the early neutralizing antibody response to SARS-CoV-2. Sci Trans Med 13
Stowe RP et al (2007) Chronic herpesvirus reactivation occurs in aging. Exp Gerontol 42:563–570
Szabo PA, Miron M, Farber DL (2019) Location, location, location: tissue resident memory T cells in mice and humans. Sci Immunol 4:1–12
Tacconelli E et al (2018) Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 18:318–327
Toapanta FR, Ross TM (2009) Impaired immune responses in the lungs of aged mice following influenza infection. Respir Res 10
Thome JJC et al (2014) Spatial map of human t cell compartmentalization and maintenance over decades of life. Cell 159:814–828
Thome JJC et al (2016) Early-life compartmentalization of human T cell differentiation and regulatory function in mucosal and lymphoid tissues. Nat Med 22:72–77
Torres A et al (2018) Burden of pneumococcal community-acquired pneumonia in adults across Europe: a literature review. Respir Med 137:6–13
United Nations, World Population Ageing (2019) Economic and Social Affairs, Population Division
van den Berg SPH et al (2019) The hallmarks of CMV-specific CD8 T-cell differentiation. Med Microbiol Immunol 208:365–373
van den Heuvel D et al (2016) Cytomegalovirus- and epstein-barr virus-induced T-cell expansions in young children do not impair naive T-cell populations or vaccination responses: the Generation R study. J Infect Dis 213:233–242
van der Geest KSM et al (2014) Aging disturbs the balance between effector and regulatory CD4+ T cells. Exp Gerontol 60:190–196
van der Heiden M et al (2016) Differential effects of Cytomegalovirus carriage on the immune phenotype of middle-aged males and females. Sci Rep 6:1–12
Van Deursen AMM et al (2017) Immunogenicity of the 13-valent pneumococcal conjugate vaccine in older adults with and without comorbidities in the community-acquired pneumonia immunization trial in adults (capita). Clin Infect Dis 65:787–795
Van Erp EA, Luytjes W, Ferwerda G, Van Kasteren PB (2019) Fc-mediated antibody effector functions during respiratory syncytial virus infection and disease. Front Immunol **10**
van Lier A et al (2013) Varicella zoster virus infection occurs at a relatively young age in the Netherlands. Vaccine 31:5127–5133
Van De Garde MDB, Van Westen E, Poelen MCM, Rots NY, Van Els ACM (2019) Prediction and validation of immunogenic domains of pneumococcal proteins recognized by human CD4+ T-cells. Infect Immun 1–18
Verity R et al (2020) Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 20:669–677
Vos T et al (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390:1211–1259
Voysey M et al (2018) Serotype-specific correlates of protection for pneumococcal carriage: an analysis of immunity in 19 countries. Clin Infect Dis 66:913–920
Vukmanovic-Stejic M et al (2015) The characterization of varicella zoster virus-specific T cells in skin and blood during aging. J Investig Dermatol 135:1752–1762

Weinberg A et al (2010) Influence of age and nature of primary infection on varicella-zoster virus-specific cell-mediated immune responses. J Infect Dis 201:1024–1030
Whiting CC et al (2015) Large-scale and comprehensive immune profiling and functional analysis of normal human aging. PLoS ONE 10:1–21
Wikby A, Månsson IA, Johansson B, Strindhall J, Nilsson SE (2008) The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20–100 years of age. Biogerontology 9:299–308
Wiseman DJ et al (2020) Immunological and inflammatory biomarkers of susceptibility and severity in adult respiratory syncytial virus infections. J Infect Dis 222:S584–S591
Wolfe A et al (2020) Co-occurrence of SARS-CoV-2 and respiratory pathogens in the frail elderly. medRxiv. https://doi.org/10.1101/2020.06.24.20138941
Wong CK et al (2017) Aging impairs alveolar macrophage phagocytosis and increases influenza-induced mortality in mice. J Immunol 199:1060–1068
Wong MT et al (2016) A High-dimensional atlas of human T cell diversity reveals tissue-specific trafficking and cytokine signatures. Immunity 45:442–456
World Health Organization (2018) Influenza fact sheets. https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)
Xu W et al (2019) Mapping of γ/δ T cells reveals Vδ2+ T cells resistance to senescence. EBioMedicine 39:44–58
Yanez ND, Weiss NS, Romand JA, Treggiari MM (2020) COVID-19 mortality risk for older men and women. BMC Public Health 20:1–7
Yoon HE et al (2016) Age-associated changes in the vascular renin-angiotensin system in mice. Oxid Med Cell Longev
Yoshikawa TT (2002) Antimicrobial resistance and aging: beginning of the end of the Antibiotic Era? J Am Geriatr Soc 50:S226–S229
Zens KDZ, Farber DL (2014) Memory CD4 T cells in Influenza. Influenza pathogenesis and Control Volume II
Zhang B et al (2020) Immune phenotyping based on the Neutrophil-to-Lymphocyte Ratio and IgG level predicts disease severity and outcome for patients with COVID-19. Front Mol Biosci 7:1–7
Zhao J et al (2016) Airway memory CD4+ T cells mediate protective immunity against emerging respiratory coronaviruses. Immunity 44:1379–1391
Zhu Y, Armstrong JL, Tchkonia T, Kirkland JL (2014) Cellular senescence and the senescent secretory phenotype in age-related chronic diseases. Curr Opin Clin Nutr Metab Care 17:324–328

Chapter 7
Vaccines and Vaccination Strategies for Older Adults

Birgit Weinberger

Abstract Age-related changes of the immune system contribute to increased incidence and severity of infections in older adults. With demographic changes, prevention of infections becomes increasingly important to ensure healthy aging for the individual, but also to ease the socio-economic impact on societies. Vaccination is the most effective measure to achieve this and vaccination guidelines in most countries include specific recommendations for older adults. This chapter summarizes the benefits and limitations of vaccines for the older population (influenza, pneumococcal disease, herpes zoster, SARS-CoV-2), and briefly discusses the importance of other vaccines for this age group. Strategies to improve vaccine-induced immune responses in older adults include increased antigen dose, the use of adjuvants, and the development of conjugated vaccines to overcome some of the limitations of T cell-independent polysaccharide antigens. Research on universal vaccines against influenza and *S. pneumoniae* is ongoing in order to resolve the constraints of the current strain-specific vaccines. There are still many infectious diseases causing substantial morbidity in the older population, for which no vaccines are available. Extensive research is ongoing to develop vaccines against novel targets with several vaccine candidates already being clinically tested, which have the potential to substantially reduce health care costs and to save many lives. In addition to novel vaccine developments, it is crucial to optimize the use of existing vaccines and to increase awareness for the importance of vaccines for all age groups, as vaccination coverage is still far from optimal for the older population.

Keywords Vaccine · Older adults · Immunosenescence · Vaccination strategies · Influenza · Pneumococcal disease · Herpes zoster · COVID-19

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7.1 Importance of Vaccines for the Older Population

The percentage of persons older than 65 years of age is projected to increase from 18% to 25% in Europe and Northern America and from 9% to 16% worldwide between 2019 and 2050. The rise in numbers of persons older than 80 is even faster (United Nations et al. 2019). This demographic change leads to socio-econonomic and health care challenges on many levels. The focus of this chapters lies on vaccines and vaccination for older adults to prevent infectious disease. The incidence of many infections is higher in older compared to younger adults (Gavazzi and Krause 2002; Chaps. 5 and 6). In addition, morbidity and mortality is higher in old age and infectious diseases are frequently associated with long-term sequelae. Many older persons do not recover fully after an acute episode of infection as described e.g. for influenza, pneumonia and herpes zoster. This can lead to onset or increase of frailty, impairments in activities of daily living, or even the loss of independence (Janssens 2005; Herpes Zoster and Functional Decline Consortium 2015). This impacts not only the individual patient, but also needs to be reflected in socio-economic and health care considerations for an aging population. The prevention of infectious diseases can therefore contribute to healthy aging and is an important measure to improve the quality of life. Vaccination is the most promising strategy to achieve these goals. The reasons for the increased incidence and severity of infections in the older populations are multifaceted and include age-associated anatomical and physiological changes such as functional and cellular alterations in the respiratory and gastrointestinal tract, increased frequency of medical interventions (e.g. hospitalization, invasive procedures and devices), which represent risk factors for infections, as well as age-related changes of the immune system, referred to as immunosenescence. A detailed review of immunosenescence is beyond the scope of this chapter, but can be found elsewhere (Pinti et al. 2016; Crooke et al. 2019; Chaps. 1, 2, and 3). Age-related functional deficits and dysregulation of many immune mechanisms are also responsible for decreased immunogenicity and clincial efficacy of many currently available vaccines. At the site of vaccine injection innate immune cells are crucial for an efficient induction of vaccine-specific immune responses. Neutrophils elicit a pro-inflammatory state at the site of injection, which leads to recruitment and activation of monocytes/macrophages, dendritic cells (DC) and other innate immune cells. Neutrophils derived from older perons show reduced chemotaxis, as well as altered signal transduction and cytokine production upon antigen recognition (Drew et al. 2018). Similar observations have been made for DC and monocytes/macrophages, which in addition are deficient in antigen processing and presentation (Agrawal et al. 2017). Adjuvants are used in many vaccines to activate innate immune responses and improve immunogenicity and can also be helpful to overcome age-associated limitations of vaccines. This aspect will be discussed in the context of individual vaccines below. A hallmark of immunosenescence is the involution of the thymus, which - together with changes in hematopoiesis- leads to a dramatic decrease in the output of newly generated naïve T cells, potentially limiting responses to neo-antigens. Concomitantly, antigen-experienced and in particular chronically stimulated, highly

differentiated T cells accumulate, which produce preferentially pro-inflammatory cytokines, respond less efficient to antigenic stimulation, and limit the diversity of the T cell repertoire (Goronzy et al. 2015; Jergović et al. 2018; Lorenzo et al. 2018). T cell responses are crucial for protection against many pathogens and therefore T cell deficits can have a direct impact on vaccine efficacy. However, as T cell help provided by follicular T helper cells in the germinal center is required for optimal antibody responses, the effect of aged T cells on vaccine efficacy is even more substantial (Gustafson et al. 2018). The composition of the B cell compartment also changes with age. Intrinsic defects of B cells, such as reduced isotype switch and somatic hypermutation can be observed with age, and a reduced number of plasma cells further contributes to reduced antibody responses after vaccination (Frasca et al. 2020). In addition to chronological age, many other factors can influence immune responses to vaccination. Frailty, obesity and underlying co-morbidities are risk factors for many infectious diseases, but are also associated with lower immunogenicity and efficacy of vaccines. These additional risk factors are very prevalent in the older population and further aggravate age-associated immunological deficits. Comprehensive reviews of these aspects have recently been published (Frasca and Blomberg 2020; Kwetkat and Heppner 2020). As an example, in the clinical trial investigating the efficacy of the 13-valent conjugated pneumococcal vaccine in persons older than 65 years 80% of the pneumonia cases observed in the placebo cohort occurred in persons with at least one co-morbidity (e.g. chronic heart, kidney or liver disease, diabetes, asthma). This translates to a 4.2-fold higher risk for community-acquired pneumonia in this at-risk group compared to healthy participants. Concomitantly, vaccine efficacy against pneumonia caused by vaccine-type *S. pneumoniae* was 40.3% in participants with comorbidities compared to 66.7% in the healthy vaccinees (Suaya et al. 2018). Whether latent infection with the human herpesvirus Cytomegalovirus (CMV) is an additional factor influencing vaccine-induced immune responses is controversially discussed. Some studies show that CMV-seropositivity or antibody levels are associated with reduced responses to influenza vaccination (Trzonkowski et al. 2003; Frasca and Blomberg 2016) and long-term persistence of diphtheria-specific antibodies was lower in CMV-positive older persons compared to CMV-negative individuals in one study (Weinberger et al. 2017), while others demonstrated the absence of a CMV-related effect on vaccine-induced immune responses (van den Berg et al. 2019). In contrast, the impact of latent CMV-infection on immunosenescence, particularly on T cells and NK cells is well established (Weltevrede et al. 2016; Goodier et al. 2018).

This chapter summarizes the benefits and limitations of vaccines for the older population (influenza, pneumococcal disease, herpes zoster, SARS-CoV-2), key strategies, which have been tested or are under development in order to enhance vaccine responses in the older population, and discusses policies to not only improve vaccines, but also vaccination strategies for this vulnerable age group.

7.2 Vaccines for Older Adults

7.2.1 Influenza

The course of infection with influenza virus can vary from asymptomatic and mild self-limiting cases to severe disease requiring hospitalization and death, and older adults are at higher risk for severe outcomes compared to younger age groups (Iuliano et al. 2018). Influenza causes approximately 100,000 hospitalizations and 36,000 deaths annually in the USA, which occur mainly in persons over 65 years (Thompson et al. 2003, 2004). In addition, complications, such as bacterial co-infections and exacerbations of chronic pulmonary diseases, further contribute to morbidity and mortality following influenza infection in older adults (Dugan et al. 2020). Prevention of influenza infection by vaccination is therefore highly desirable in this age group. Based on worldwide surveillance of circulating virus strains, the composition of influenza vaccines is adjusted annually to reflect antigenic shift or drift. Historically, influenza vaccines comprised two influenza A strains (H1N1 and H3N2) and one influenza B strain (Victoria or Yamagata lineage). As both B lineages have co-circulated for several years, quadrivalent influenza vaccines containing two A and two B strains have been developed and are now in widespread use (Tisa et al. 2016). A variety of different influenza vaccines are available each year. Virosomal vaccines comprising only of the virus envelope have been used in the past, but, have not been available for the last years and live-attenuated vaccines, which are used in younger age groups, are not licensed for older adults and will therefore not be discussed in this chapter. Standard influenza vaccines are either split virus vaccines, which contain disrupted viral envelopes that lost infectivity but retained immunogenicity, or subunit vaccines, which undergo further purification steps that remove the nucleocapsid from the split virus (Kon et al. 2016). It has been shown in many studies that immunogenicity of standard trivalent influenza vaccines (TIV) is lower in older compared to young adults (Goodwin et al. 2006) and that frailty and comorbidities further decrease vaccine-induced immune responses (Myśliwska et al. 2004; Yao et al. 2011). In addition, influenza-specific antibody titers decline faster in older persons leading to loss of seroprotection until the following season, and possibly rendering vaccinees susceptible to some influenza strains even towards the end of the same season (Kissling et al. 2016; Carlock et al. 2019). It is important to note, that haemagglutinin antibodies are widely used as surrogate of protection in the context of influenza vaccination (McElhaney et al. 2017). However, HA antibodies might not be an ideal measure in older adults as vaccinees with low titers may be still protected and vice versa (Ward et al. 2018). It has been reported that memory B cells and plasmablasts are retained in older adults, despite lower antibody titers compared to young adults even after repeated vaccination, and it has been suggested that impaired differentiation from memory B cells towards plasma cells is responsible for this (Frasca et al. 2016). Additionally, cell-mediated immune responses are important to combat influenza virus infection and cellular parameters (e.g. IFN-γ and IL-10 production, Granzyme B activity) might be better predictors

of clinical protection (Shahid et al. 2010; Merani et al. 2018). Clinical efficacy of TIV in preventing laboratory-confirmed influenza reaches up to 70% in placebo-controlled trials enrolling young adults (Beran et al. 2009; Demicheli et al. 2018), but is lower in older adults (Govaert et al. 1994; Kwong et al. 2013). Meta-analysis of influenza vaccine immunogenicity, efficacy and effectiveness is difficult as vaccine composition changes each year, different vaccine formulations are used (split vs. subunit), clinical endpoints are variable (laboratory-confirmed influenza, hospitalization, influenza-like illness etc.) and history of exposure (infection and prior vaccination) may vary between cohorts. Despite these uncertainties there is consensus that influenza vaccines are less immunogenic and efficient in older compared to younger adults and that improved vaccines for the older population are required.

An obvious strategy to improve immunogenicity of vaccines is to increase the amount of antigen per dose. A higher antigen dose presumably results in increased uptake and presentation by antigen-presenting cells and therefore in stronger activation of adaptive immune cells. A trivalent high-dose influenza vaccine containing 60 μg hemagglutinin for each strain instead of the standard 15 μg has been used in the US, Canada, Australia, Brazil and the UK for several years in older adults. Recently, this vaccine was modified to contain four instead of three different influenza strains and is currently licensed in this form in the US and Canada as well as in many European countries for older adults. Trials with the trivalent high-dose influenza vaccine showed higher hemagglutinin antibody titers and seroprotection rates in older adults compared to the standard vaccine (DiazGranados et al. 2014) as well as increased numbers of specific IFN-γ^+ $CD4^+$ and $CD8^+$ T cells (Cowling et al. 2019). However, PBMC of aged high-dose vaccine recipients produced significantly higher IL-10 levels after live influenza virus stimulation, which might work against the positive effect of higher antigen doses due to the potential immunosuppressive properties of IL-10 (Merani et al. 2018). Meta-analyses also reported increased clinical efficacy based on a lower risk to develop laboratory-confirmed influenza (relative risk 0.76) (Wilkinson et al. 2017) and a higher relative efficacy against pneumonia (rVE 24.3%), hospitalization for influenza (rVE 17.8%), and influenza-like illness (rVE 19.5%) (Lee et al. 2018) for older adults vaccinated with the high-dose versus the standard dose vaccine. Recent studies with the quadrivalent high-dose vaccine confirmed higher immunogenicity compared to standard dose vaccine (Sanchez et al. 2020) and non-inferiority to trivalent high-dose vaccines (Chang et al. 2019). None of the above-mentioned studies reported safety concerns regarding high-dose vaccines.

Adjuvants are used in various vaccines in order to enhance immunogenicity and/or to direct the immune response in a favorable direction. As a result, adjuvants can be beneficial in order to protect cohorts, which develop unsatisfactory immune responses after standard immunization (e.g. older adults), or to induce broader immune responses, which can confer cross-protection against viral variants not present in the vaccine.

Aluminum salts were the first adjuvants in human vaccines and have been administered in various vaccines for approximately 100 years, but are not used for influenza vaccines. The oil-in-water emulsion MF59, which comprises squalene and the surfactants Tween 80 and Span85 was one of the first “modern” adjuvants and was first

licensed as an adjuvant in a seasonal influenza vaccine for older adults in 1997. It has subsequently also been approved for other age groups including children (6–24 months) and in pandemic influenza vaccines. The molecular mechanisms behind the adjuvanticity of MF59 have been studied extensively, but are probably still not fully revealed. It has been shown that MF59 induces proinflammatory chemokines and cytokines at the site of injection thereby recruiting innate immune cells and facilitating efficient antigen uptake. In addition, MF59 enhances differentiation of dendritic cells in the lymph nodes and is involved in shaping the germinal center reaction (Lofano et al. 2015; Weinberger 2018).

The immunogenicity of the adjuvanted seasonal vaccine has been investigated in numerous clinical trials (summarized in (Black 2015; Camilloni et al. 2015)), and antibody responses are generally slightly higher compared to TIV. In addition, the $CD4^+$ T cell response is elevated, but the cytokine profile with high IL-2, but lower IFN-γ production is similar (Galli et al. 2009). Interestingly, antibodies elicited by the adjuvanted vaccine recognize additional epitopes within the influenza hemagglutinin and thereby recognize drifted influenza strains more efficiently (Ansaldi et al. 2008; Orsi et al. 2013). A meta-analysis reported greater efficacy of the trivalent adjuvanted vaccine in preventing laboratory-confirmed influenza (adjusted odds ratio 0.37 (95% CI: 0.14–0.96) and hospitalizations due to pneumonia/influenza (adjusted risk ratio 0.75 (95% CI: 0.57–0.98)) compared to standard influenza vaccine (Domnich et al. 2017). Immunogenicity and safety of the quadrivalent adjuvanted vaccine have been shown to be similar to the adjuvanted trivalent formulation in older adults (Essink et al. 2020). Recently, two studies directly compared clinical efficacy for high-dose and adjuvanted influenza vaccines. In a retrospective cohort study, which analyzed data of persons above 65 years during the 2016/2017 and the 2017/2018 influenza seasons, van Aalst et al. reported that high-dose trivalent influenza vaccine provided better protection from respiratory-related hospitalizations compared to adjuvanted trivalent vaccine, with a pooled relative vaccine effectiveness (rVE) of 12% (95% CI: 3.3%–20%) (van Aalst et al. 2020). In a similar study, Boikos et al. reported that the effectiveness against any influenza-related medical encounter was higher for the adjuvanted trivalent vaccine 7.7% (95% CI: 2.3%-12.85) compared to the high-dose trivalent vaccine during the 2017/2018 influenza season. Similar results were obtained for the following season (Boikos et al. 2021). The quadrivalent adjuvanted or high-dose vaccines, which have recently been licensed had not yet been available at the time of these studies.

Intradermal administration of vaccines also is a promising strategy to improve vaccine-induced immune responses. Antigen-presenting cells, such as dendritic cells reside in the dermis and should theoretically facilitate efficient antigen uptake and presentation upon intradermal delivery of vaccines. While some studies reported increased antibody responses in older adults after intradermal influenza vaccination compared to standard intramuscular vaccine (Nunzi et al. 2017), meta-analyses of randomized controlled trials came to the conclusion that seroconversion and seroprotection rates in older adults are similar after intradermal or intramuscular influenza vaccination (Pileggi et al. 2015; Hung and Yuen 2018). Higher reactogenicity at the site of injection has been described after intradermal vaccination, but was classified

as mild and transient and did not raise further concerns (Marra et al. 2013; Scheifele et al. 2013; Hung and Yuen 2018). There are no comparative data available on vaccine efficacy or effectiveness for intradermal influenza vaccines (Young and Marra 2011). Intradermal influenza vaccines have been used for several years, but are currently not available in many countries.

Annual vaccination against influenza is recommended in many countries. Most of the national recommendations include influenza vaccination for everybody with a specific focus on vulnerable groups, e.g. older adults. In light of the recent developments of improved vaccines for this group some countries have issued specific recommendations for preferred vaccine formulations for older adults. For the last few years, the decision which influenza vaccine to choose was complicated by the fact that only standard vaccines were available in the quadrivalent formulation, whereas high-dose and adjuvanted vaccines were only trivalent and e.g. the trivalent adjuvanted vaccine was only licensed in Europe, whereas the high-dose trivalent vaccine was only used in the US. Only very recently, these "improved" influenza vaccines were licensed as quadrivalent formulations e.g. in Europe and the US but availability was limited in some countries. Specific recommendations are therefore still quite complex. For the season 2020/2021 Austria for instance recommended the trivalent adjuvanted vaccine for persons older than 65 years of age over the quadrivalent standard vaccine, but suggested an additional dose of quadrivalent standard vaccine should the second B strain become dominant during the season. In addition, very limited quantities of the high-dose quadrivalent vaccine were available for very high-risk populations (e.g. nursing homes) (BMASGK 2021a). For the season 2021/2022 both adjuvanted and high-dose quadrivalent vaccines are expected to be available and are preferentially recommended for older adults (BMASGK 2021b). Germany issued its first recommendation for a specific vaccine for the 2021/2022 season when the quadrivalent high-dose vaccine should be used for older adults (Michaelis et al. 2021). In the UK, trivalent adjuvanted or high-dose vaccine was recommended for older adults during the 2020/2021 season (Joint Committee on Vaccination and Immunisation 2019), whereas for the 2021/2022 season quadrivalent adjuvanted or high-dose vaccines should be used (Joint Committee on Vaccination and Immunisation 2020). In contrast, the Advisory Committee on Immunization Practices in the US did not recommend a specific vaccine formulation for the older population for 2020/2021 despite the fact that adjuvanted and high-dose quadrivalent formulations were expected to be available (Grohskopf et al. 2020).

7.2.2 Pneumococcal Disease

Based on their polysaccharide capsule, which also is an essential virulence factor, *Streptococcus pneumoniae* (pneumococcus) can be classified into more than 90 distinct serotypes. Only a limited number of serotypes of these gram-positive diplococci are pathogenic (Henrichsen 1995). According to the World Health Organization (WHO) *S. pneumoniae* is among the top 12 bacterial pathogens for which research

and development of new antimicrobial strategies are desirable (Tacconelli et al. 2018). Clinical presentation of *S. pneumoniae* infection can be non-invasive (otitis media, sinusitis, conjunctivitis, pneumonia) or invasive (bacteremic pneumonia, meningitis, sepsis). Incidence for pneumococcal pneumonia as well as invasive pneumococcal disease (IPD) increases with age. Incidence rates of community-acquired pneumonia (CAP) are estimated to be 18.2 per 1000 person-years in people aged 65–69 years, and up to 52.3 per 1,000 person-years in those aged over 85 years, with *S. pneumoniae* being the most frequently isolated pathogen in this age group. In the US nearly 30,000 cases of invasive pneumococcal diseases (IPD) and over 500,000 cases of non-bacteremic pneumococcal pneumonia were estimated to occur yearly in persons older than 50 years, resulting in more than 25,000 pneumococcus-related deaths (Drijkoningen and Rohde 2014). Antimicrobial resistance of *S. pneumoniae* is an increasing problem (Kim et al. 2016).

Transient colonization of the upper respiratory tract by *S. pneumoniae* (asymptomatic carriage) is frequent in children (up to 85%), but less prevalent in the elderly (approx. 20%). Due to differences in detection methods and sampling sites study results vary greatly (Adler et al. 2017). Colonizing bacteria spreading to tissues of the lower respiratory tract, the ear, the eye or the blood stream are responsible for pneumococcal disease. Bacterial co- or secondary infection is a frequent complication of influenza infection. A meta-analysis reported a rate of bacterial co- or secondary infection in influenza patients between 11% and 35% in most cohorts. The exact numbers of co-infections vary greatly in different studies, but *S. pneumoniae* was the most common pathogen, which accounted for 35% (95% CI: 14%-56%) of the bacterial co-infections (Klein et al. 2016).

The first vaccines against *S. pneumoniae* were developed based on the purified bacterial capsule polysaccharides. The 23-valent polysaccharide vaccine (PPV-23), which contains the serotypes 1, 2, 3, 4, 5, 6B, 7F, 8 9 N, 9 V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F (Table 7.1), was licensed for adults in the early 1980s and is still in use. Purified polysaccharides are T cell-independent antigens, and as such elicit a distinct immune response. They directly cross-link the B cell receptor, which leads to B cell activation and differentiation into antibody-producing plasma cells. Without T cell help this happens independently of germinal centers resulting in short-term antibody production, a lack of B cell memory and mainly IgM and IgG_2 responses (Kelly et al. 2006). In addition, the B cell pool might be depleted of the relevant specificities, which potentially leads to hyporesponsiveness upon re-vaccination (Pollard et al. 2009). In addition to the burden of pneumococcal disease in the older population, non-invasive and invasive pneumococcal disease is most prevalent in infants. However, the immune system is not able to elicit immune responses to most polysaccharide antigens in the first two years of life (Smith et al. 1973; van den Biggelaar and Pomat 2013), and therefore the PPV-23 vaccine is not suitable for young children. It has only been licensed for adults and has been recommended and utilized for the older population in many countries. A second generation of pneumococcal vaccines was developed with the goal to make them available for infants. Chemical conjugation of carrier proteins to the polysaccharides leads to uptake of the conjugate by polysaccharide-specific

Table 7.1 Serotypes included in pneumococcal polysaccharide (PPV) and conjugate (PCV) vaccines

Serotype	PPV-23§	PCV-7*	PCV-10*	PCV-13§	PCV-15&	PCV-20&
1	■		■	■	■	■
2	■					
3	■			■	■	■
4	■	■	■	■	■	■
5	■		■	■	■	■
6A	■			■	■	■
6B		■	■	■	■	■
7F	■		■	■	■	■
8	■					■
9N	■					
9V	■	■	■	■	■	■
10A	■					■
11A	■					■
12F	■					■
14	■	■	■	■	■	■
15B	■					■
17F	■					
18C	■	■	■	■	■	■
19A	■			■	■	■
19F	■	■	■	■	■	■
20	■					
22F	■				■	■
23F	■	■	■	■	■	■
33F	■				■	■

*licensed, but not for older adults
§licensed for older adults
&in development

B cells, which then process and present the protein component in the context of MHC-II molecules to $CD4^+$ T cells recognizing these peptides. Thereby carrier-specific T cells provide T cell help for polysaccharide-specific B cells eliciting T cell-dependent immune responses to the polysaccharides (Pollard et al. 2009). Class switch and avidity maturation can take place, memory B cells are generated, and the conjugate vaccines (PCV) are immunogenic in infants. The first conjugated vaccine (PCV-7) contained the serotypes 4, 6B, 9 V, 14, 18C, 19F, 23F (Table 7.1) and the carrier protein Crm-197, a derivative of diphtheria toxin, and was introduced in the late 1990s/early 2000s for young children. Subsequently the incidence of invasive pneumococcal disease caused by the seven vaccine serotypes decreased not only in the targeted age group of infants and toddlers, but also to a lesser degree

in the older population (Pilishvili et al. 2010). PCV does not only prevent disease, but also carriage of *S. pneumoniae* in children, potentially reducing transmission to older adults and providing benefits to them via herd immunity effects. In the following years a certain degree of serotype replacement was observed in children and older adults and particularly the increased number of cases caused by serotype 19A was a reason for concern (Pilishvili et al. 2010). Conjugated vaccines containing 10 (PCV-10; PCV-7 serotypes plus 1, 5, and 7F) and PCV-13 (PCV-10 serotypes plus 3, 6A, and 19A) (Table 7.1) were developed and replaced PCV-7 in childhood vaccination programs in many countries. PCV-13 was licensed also for adults and is now used for the older population in many countries. Serotype replacement was again observed in all age groups, but the epidemiological situation is very heterogenous in different countries and depends on the interplay of childhood vaccination programs, vaccination coverage in different age groups, dynamics of transmission and other factors. As an example, the incidence of IPD per 100.000 persons older than 65 years in England and Wales was 24.67, 14.97, and 6.25 for PCV-13 serotypes in 2000–2006, 2008–2010, and 2016–2017, respectively, while at the same time the incidence of non-PCV-13 serotypes increased from 9.55 to 12.76 and 22.68 (Ladhani et al. 2018).

Detection and quantification of polysaccharide-specific antibodies in clinical studies is complex. ELISA-based methods measure the amount of antibodies binding to the antigen. This assay usually only detects IgG antibodies but no other antibody classes. Early ELISA methods were often unspecific, and improvements of the protocols solved this problems, but some older studies need to interpreted with caution (Henckaerts et al. 2006). Many studies measure also functional antibodies by opsonophagocytosis assay (OPA). Whereas the antibody titers obtained by these two assays show a strong correlation in young children, this is not the case in older adults and immunocompromised patients (Song et al. 2013). As an example, despite persisting IgG antibodies measured by ELISA, opsonizing antibodies were found to considerably wane in a cohort of frail elderly over 6 years following vaccination (MacIntyre et al. 2019). Probably due to a decline in the generation of IgM-producing memory B cells and a lack of IgM antibodies, which have opsonizing function, OPA-titers are frequently lower in older adults even after natural infection (Park and Nahm 2011; Adler et al. 2017). Vaccination with seroptype 19F does not protect against 19A and this clinical finding is confirmed in OPA-assays, where there is no cross-reactivity of antibodies for these serotypes. In contrast, cross-reactivity can be observed in ELISA-assays (Lee et al. 2009). OPA titers are also more suitable to predict vaccine failures compared to data obtained by ELISA (Oishi et al. 2013). In conclusion, OPA-measurements are probably a more reliable correlate of protection and should be utilized, despite the fact that they are more complex and expensive and less standardized. Local antibody responses after pneumococcal vaccination have been investigated in tears and saliva, but nasal secretions were not analyzed and the clinical relevance of local IgM, IgG or IgA antibodies is unclear (Lue et al. 1988).

Immunogenicity of PPV-23 decreases with age as shown by reduced opsonophagocytic activity in older adults and alterations in class and subclass usage as well as in somatic hypermutation (Romero-Steiner et al. 1999; Kolibab et al. 2005; Wu et al. 2012). PCV-13 was the first conjugated pneumococcal vaccine licensed for

all age groups (children, young and old adults), whereas PCV-7 and PCV-10 are only licensed for children. With two different vaccines available for older adults direct comparisons of immune responses elicited by polysaccharide versus conjugate vaccines are of interest and have already been performed with PCV-7 prior to the development of PCV-13. Several studies reported similar antibody responses to PCV-7 and PPV-23 (Miernyk et al. 2009; Ridda et al. 2009; MacIntyre et al. 2014), but other trials demonstrated higher antibody levels (OPA and ELISA) elicited by PCV-7 in a cohort of older adults receiving their first pneumococcal vaccine (de Roux et al. 2008). Most of these studies were relatively small, the patient populations were heterogenous and previous vaccination with PPV-23 impacts the immunogenicity, which might explain the discrepancies in results. One of these studies also showed that antibody responses after pneumococcal vaccination are lower in frail older individuals (Ridda et al. 2009). Similar to the situation with influenza vaccines, higher antigen dose can increase antibody responses. A two-fold higher antigen dose of PCV-7 induced significantly higher OPA titers compared to PPV-23 for five of the seven serotypes (Jackson et al. 2007). Systematic meta-analyses of more recent studies, which compare PPV-23 and PCV-13 reported significantly higher antibody levels for 10 of the serotypes after vaccination with PCV-13. For serotype 6A this finding has to be taken with a grain of salt as it is not included in PPV-23. For the remaining 3 serotypes, namely 3, 7F and 14, immunogenicity of both vaccines is similar (Marra and Vadlamudi 2019; Vadlamudi et al. 2019). There is ongoing discussion regarding the benefit of sequential vaccination with both vaccines and/or regular booster vaccination. Early studies showed that a second dose of PCV-7 one year after primary vaccination with PPV-23 or PCV-7 leads to similar or slightly higher antibody responses compared to the first vaccination (de Roux et al. 2008). OPA titers were observed to wane already in the first year after vaccination with PPV-23, but not in persons who received PCV-7 followed by PPV-23 (MacIntyre et al. 2014), indicating that sequential vaccination is beneficial for long-term maintenance of antibodies. A meta-analysis showed that prior vaccination with PPV-23 did not influence the immunological response PCV-13 and that safety profiles were similar for both vaccines (Vadlamudi et al. 2019).

But of course, the ultimate read-out parameters for vaccination success are efficacy and effectiveness, which have been mainly studied for IPD and to a lesser extent for pneumococcal pneumonia. Pooled vaccine efficacy/effectiveness (VE) of PPV-23 against IPD was 73% (95% CI: 10–92%) in clinical trials, 45% (95% CI: 15–65%) in cohort studies and 59% (95% CI: 35–74%) in case-control studies in systematic meta-analysis, while VE against pneumococcal pneumonia was 64% (95% CI: 35–80%) and 48% (95% CI: 25–63%) in clinical trials, or cohort studies, respectively (Falkenhorst et al. 2017). The authors of this meta-analysis excluded several studies in their calculations, because they suspected a high risk of bias, due to insufficient specificity of the antibody test used to diagnose cases of pneumococcal pneumonia. This might explain the discrepancy with other meta-analyses, which did not demonstrate efficacy of PPV-23 against pneumococcal pneumonia (Moberley et al. 2013; Diao et al. 2016; Kraicer-Melamed et al. 2016; Schiffner-Rohe et al. 2016). Lower VE

estimates for cohort and case-control studies can be explained e.g. by longer follow-up times compared to clinical trials, which suggests waning protection over time. In a large Phase IV randomized, placebo-controlled trial (>84,000 participants over 65 years) VE of PCV-13 against first episodes of community-acquired pneumonia (CAP) caused by vaccine-type strains was 45.6% (95% CI: 21.8–62.5%) and against vaccine-type IPD 75.0 (95% CI: 41.1–90.8%), respectively in the per-protocol analysis. The protective effect was stable for the 4-year follow-up period (Bonten et al. 2015). Data on clinical efficacy of combined schedules or repeated doses of either vaccine are lacking and it is still debated which pneumococcal vaccination strategies provide optimal protection for the older population. Antibody responses are stronger after vaccination with PCV-13, seem to be longer lasting and have the potential to be boostered with additional doses. However, with high vaccination rates in the pediatric population and the accompanying herd immunity effects, prevalence of the PCV-13 serotypes in older adults decreases and other serotypes become more clinically relevant (serotype replacement). PPV-23 covers additional serotypes, but the immune responses are shorter-lived and lack memory generation. In addition, there are concerns that PPV might induce tolerance or hyporesponsiveness upon repeated vaccination, similar to the meningococcal polysaccharide vaccine (Richmond et al. 2000). Vaccination recommendations are very heterogenous in different countries. In Europe, various countries recommend either PCV-13 or PPV-23, or a combination of both. This combination tries to exploit the advantages of both vaccines and should include PCV-13 as the first vaccine administered. After recommending sequential use of both vaccines for several years, only PPV23 is generally recommended in the US since 2019 and the addition of PCV should be considered for the individual patient in a shared decision process (Matanock et al. 2019). Vaccination coverage for pneumococcal vaccine is still low in many countries and the uncertainties and inconsistencies in national recommendations might contribute to this phenomenon (Black et al. 2017; Norris et al. 2017; Kaplan et al. 2019; Vila-Córcoles et al. 2019).

7.2.3 Herpes Zoster

As a member of the herpes viruses, varicella-zoster virus (VZV) establishes lifelong latency in the sensory ganglia after primary infection, which usually occurs in childhood and manifests as varicella (chickenpox). Reactivation of VZV is usually controlled by T cell-mediated immunity (CMI) and is clinically silent. Upon decline of VZV-specific immune responses, e.g. with age, retrograde viral spread through the sensory nerve to the corresponding dermatome can occur upon reactivation, manifesting as herpes zoster (HZ). The typical unilateral, segmented skin rash on the abdomen or face can be painful and affection of the eye can lead to severe consequences. The risk of developing HZ increases substantially with age. In a systematic review of 130 studies from 26 countries a sharp increase in the incidence rate was observed around age 50 rising from approximately 2/1,000 person-years to 6–8/1,000 person-years at 60 years of age and 8–12/1,000 person-years at 80 years

of age (Kawai et al. 2014). Patients with a compromised immune system due to underlying conditions (HIV infection, hematological malignancies etc.) or immunosuppressive therapy also have an increased risk of developing HZ (Weinberg et al. 2010). Post-herpetic neuralgia (PHN) is a frequent complication of HZ and is defined as pain occurring or persisting more than 3 months after onset of the rash. The incidence of PHN also rises with age from 18% in HZ patients older than 50 years to 33% in HZ patients older than 80 years (Yawn and Gilden 2013). PHN can persist for several months and is associated with often severe pain. Management of this pain is frequently of limited success leading to a substantial impact on activities of daily living and quality of life (Opstelten et al. 2010; Johnson and Rice 2014). HZ and PHN are prominent examples of infectious disease leading to long-term sequelae including loss of independence and institutionalization. In contrast to other vaccines, herpes zoster vaccination does not aim to prevent infection, but to restore and boost the VZV-specific immunity that was generated in response to the primary infection, but waned over time. Thereby the clinical consequences of viral reactivation, namely HZ and PHN can be prevented improving quality of life for the individual, but also relieving social and health care systems.

A live-attenuated vaccine based on the Oka Merck virus strain, which prevents primary infection with VZV (chickenpox), is available for children, and the same attenuated virus strain was used in a 14-fold higher dose as the first vaccine for older adults. This vaccine has a well-tolerated reactogenicity profile and is safe in immunocompetent persons. Similar to other live-attenuated vaccines it cannot be used in immunocompromised patients, which is problematic considering that they are at high risk for developing HZ. In a large Phase III randomized, double-blinded, placebo-controlled trial with more than 38,000 participants above 60 years of age the vaccine was 51% efficient in preventing HZ and 67% in preventing PHN, respectively (Oxman et al. 2005). However, efficacy was declining with age and was shown to be 64% in the age group 60–69y, 41% in the age group 70–79y, and <20% for persons older than 80y. An additional study confirmed this trend demonstrating better efficacy of 70% in a younger cohort aged 50–59 years (Schmader et al. 2012). The age-dependent decline in efficacy was mirrored by reduced humoral and cellular immune responses in older participants. Neither T cell responses nor antibody levels were found to be suitable correlates of protection for further vaccine development (Levin et al. 2008). The protective effect of the vaccine waned over time and was lost approximately 10 years after vaccination (Morrison et al. 2015). Re-vaccination after 10 years results in a booster effect and would be a feasible strategy to overcome the waning protective effect (Weinberg et al. 2019). As live-attenuated vaccines usually elicit robust humoral and cellular immune responses, the limited efficacy of this vaccine is somewhat unexpected.

A second-generation HZ vaccine was developed and introduced in Europe, Canada, the US, Japan and many other countries. It contains the viral envelope glycoprotein E (gE) and the adjuvant system AS01B. This adjuvant consists of 3-O-desacyl-4´-monophosphoryl lipid A (MPL), which is a detoxified derivative of *Salmonella minnesota* lipopolysaccharide and QS-21, a saponin found in the bark of the tree *Quillaja Saponaria* Molina, fraction 21. The two adjuvant components

are formulated in liposomes, which act as antigen delivery systems. This combination activates innate immune functions via the toll-like receptor (TLR) 4 pathway, targets subcapsular macrophages in the lymph node and enables uptake of the antigen via endocytosis. (Garçon and Van Mechelen 2011; Detienne et al. 2016; Welsby et al. 2017; Del Giudice et al. 2018; Lacaille-Dubois 2019) The AS01B-mediated activation of the innate immune system at the site of injection and in the draining lymph node is rapid and transient leading to efficient activation of adaptive immune responses (Didierlaurent et al. 2017).

More than 30,000 participants were enrolled in two randomized placebo-controlled phase III trails in order to demonstrate efficacy in persons older than 50 or 70 years, respectively (Lal et al. 2015; Cunningham et al. 2016). Two doses of the vaccine were administered 8 weeks apart. The majority of adverse effects were transient reactions at the site of injection, but systemic symptoms, such as headache, fatigue or myalgia were also relatively frequent. However, no major safety concerns were identified. Autoimmune reactions in response to the adjuvant system were raised as a potential concern, but after administration of more than three million doses within the first year following licensure there was no evidence of an increased risk (Heineman et al. 2019). Immunogenicity of the vaccine was analyzed in subcohorts of the large trials. As expected, immune responses peaked 4 weeks after the second dose and robust humoral and cellular immune responses were found during the follow-up period of 3 three years (Cunningham et al. 2018). The kinetics of gE-specific T cell responses were comparable to VZV-specific responses induced by the live-attenuated vaccine, but overall the immune response was stronger after the recombinant vaccine (Levin et al. 2008). In a longer follow-up study, gE-specific $CD4^+$ T cell responses substantially above pre-vaccination levels were detected for at least 9 years (Schwarz et al. 2018). A small negative effect of age on T cell responses was observed (Cunningham et al. 2018), confirming previous reports on slightly declining T cell, but not antibody responses with age (Leroux-Roels et al. 2012; Chlibek et al. 2013, 2014).Clinical efficacy against HZ was 97.2% (95% CI: 93.7–99.0) in persons over 50 years of age and did not significantly decrease in older age groups in the first study (Lal et al. 2015). In the second study, the vaccine prevented 89.8% (95% CI: 86.8–94.5) of HZ cases in vaccinees older than 70 years and in a combined analysis of both trials vaccine efficacy did not differ between age groups 70–79 and $\geq$80 years (Cunningham et al. 2016). Efficacy dropped slightly over time, but remained above 85% for the first 4 years after vaccination. PHN did not occur in any participant younger than 70 years of age in the vaccine arm and for persons older than 70 efficacy against PHN was 88.8% (95% CI: 68.7–97.1) (Cunningham et al. 2016). Long-term follow-up is ongoing to determine the duration of protection.

Frailty status was determined for more than 90% of the participants of the two studies, and 45.6% and 11.3% were classified as pre-frail or frail, respectively. As expected, prevalence of frailty increased with age. Vaccine efficacy against HZ was 95.8% (95% CI, 91.6–98.2) for non-frail, 90.4% (95% CI, 84.4–94.4) for pre-frail and 90.2% (95% CI, 75.4–97.0) for frail participants, indicating that the adjuvanted HZ vaccine is also very potent in frail elderly. Reactogenicity was slightly lower in the frail cohorts compared to non-frail (Curran et al. 2021).

In contrast to the live-attenuated vaccine, the recombinant vaccine is suitable for immunocompromised patients. Safety and immunogenicity have been demonstrated in patients after renal transplantation (Vink et al. 2019), in HIV-positive patients (Berkowitz et al. 2015) and in patients receiving chemotherapy or immunosuppressive treatment for hematologic malignancies (Dagnew et al. 2019). Vaccination before chemotherapy against solid tumors elicited higher immune responses compared to vaccine administration at the start of therapy (Vink 2017). Clinical efficacy was 68.2% (95% CI 55.6–77.5) in adult patients after autologous hematopoietic stem cell transplantation (Bastidas et al. 2019). Safety profiles were acceptable in all of these studies. In an observational post-licensure study vaccine effectiveness was 70.1% (95% CI, 68.6–71.5), independent of age (65–79y vs. ≥80y). This study also showed that timing of the second dose (<180 days or >180 days after dose 1) did not make a difference, but that the second dose is required as protection is lower after the first dose and that effectiveness was slightly lower in immunocompromised patients (Izurieta et al. 2021).

7.2.4 COVID-19

The current SARS-CoV-2 pandemic poses tremendous challenges for the whole world. The highest incidence of severe disease and death from COVID-19 is seen in older adults, obese individuals, and persons with underlying co-morbidities, with male sex being an additional risk factor (Booth et al. 2021; Flook et al. 2021; Pijls et al. 2021). In addition to the impact of the acute infection for the individual patient many more aspects need to be considered in this extraordinary situation. Reports of long-lasting health sequelae after recovery from COVID-19 ("long COVID") are accumulating (Korompoki et al. 2021; Nalbandian et al. 2021), financial, socio-economic and psychological repercussions of lock-down and quarantine measures are obvious and the impact of the pandemic on health care for patients with COVID-19-unrelated health problems needs to be taken into account (Hassan and Arawi 2020; Rosenbaum 2020). The long-term impact on health, economy and societies is still unforeseeable and depends substantially on our ability to develop and implement efficient treatment options and vaccines. Due to the high incidence of severe disease, older adults are an important target population for vaccines against SARS-CoV-2 and have been prioritized in national vaccination programs. Several vaccines against SARS-CoV-2 have been licensed in different countries, clinical trials with additional vaccine candidates are ongoing and a plethora of vaccine candidates are in pre-clinical development (World Health Organisation 2021). This summary focusses on the SARS-CoV-2 vaccines currently licensed in Europe, namely the mRNA-based vaccines of BioNTech/Pfizer and Moderna and the adenoviral vectors of AstraZeneca (chimpanzee adenovirus ChAdOx1) and Johnson&Johnson/Janssen (human Adenovirus-26) and highlights their safety, immunogenicity, efficacy and effectiveness in older adults. With the exception of the AstraZeneca vaccine, they are also licensed for emergency use in the US. All four vaccines deliver genetic information for the SARS-CoV-2

spike protein, which is then expressed by cells of the vaccinated person. A complete overview of SARS-CoV-2 vaccine development is beyond the scope of this article (McDonald et al. 2021).

First-in-human clinical trials are usually performed in young, healthy adults. In case of SARS-CoV-2 vaccines clinical development moved quickly towards the inclusion of older adults, as they are an important target group for vaccination. As an example, the phase-1 dose escalation trial for the Moderna vaccine was extended to include participants >55 and >70 years and showed similar humoral and T cell cellular immunogenicity for the older age groups compared to the original cohort of 18–55 years (Anderson et al. 2020b). A similar study with the BioNTech/Pfizer vaccine included the age groups 18–55 and 65–85 years and also found no differences in antibody responses between the two age groups (Walsh et al. 2020). Immunogenicity was also investigated in Phase II and in subcohorts of larger Phase III studies. For the adenoviral AstraZeneca vaccine participants were stratified into three age groups (18–55y, 56–69y, ≥70y). Antibody levels and neutralizing titers after two standard doses of the vaccine and T cell responses after the first and second dose were similar for all age groups. Until now immunogenicity data on the Johnson&Johnson/Janssen vaccine were only published for adults under the age of 55 (Stephenson et al. 2021), but antibody and T cell responses in aged non-human primates were similar to those of younger animals (Solforosi et al. 2021). Several immunogenicity trials including older adults are still ongoing for the different vaccines.

Safety of the SARS-CoV-2 vaccines has been investigated in Phase I, II and III clinical trials. This summary focusses on age-related aspects and therefore mainly on the safety data from the later stage trials, which included more older adults. The safety profiles of the mRNA vaccines (Moderna and BioNTech/Pfizer) are very similar. Local pain at the site of injection was reported by the majority of vaccine recipients, whereas redness and swelling were rare. Fatigue, headache, muscle pain and chills were the most frequent systemic events. Local and systemic reactogenicity was higher after the second than after the first dose, and older participants (>65 years for Moderna or >55 years for BioNTech/Pfizer, respectively) reported less reactogenicity (Polack et al. 2020; Baden et al. 2021).

Reactogenicity of the AstraZeneca adenoviral vaccine is described in detail in the assessment report of the European Medicines Agency with pain and tenderness reported as the most common local, and fatigue and headache as the most common systemic reactions, respectively. Reactogenicty was generally lower after the second compared to the first dose (European Medicines Agency 2021a), which is in contrast to the profile of the mRNA vaccines. Reactogenicity for older adults was reported for a small cohort (18–55y, 56–69y, ≥70y; n ≤ 50 in each group) and showed a very similar pattern of reactions with reduced incidence and severity after the second dose. As observed for the mRNA vaccines, reactogenicity was lower in the older age groups (Ramasamy et al. 2020). The profile of reactogenicity after the single dose of the Johnson&Johnson/Janssen adenoviral vaccine was very similar, with pain being the most frequent local reaction, and headache, fatigue and myalgia reported as most prevalent systemic events. Reactogenicity was also higher in the younger (18–59y) compared to the older (≥60y) age group (Sadoff et al. 2021).

Severe adverse events were rare for all vaccines and mostly not vaccine related. After introduction of the vaccines and use in a large number of persons very rare severe adverse events were observed including allergic reactions, mainly against the mRNA vaccines (Banerji et al. 2021; Shimabukuro et al. 2021) and thrombosis with thrombocytopenia syndrome (TTS) after vaccination with the adenoviral vector vaccines (Cines and Bussel 2021). Very recently, cases of myocarditis have been reported in adolescents and young adults (<30y) after vaccination with mRNA vaccines. Investigations whether there is a causal link to vaccination are still ongoing (Centers for Disease Control and Prevention 2021). These rare complications are more relevant for younger adults and will therefore not be discussed in detail.

Clinical efficacy has been determined for all four vaccines in Phase III clinical trials. Older adults have been included in the pivotal trials, but not in every trial in sufficient numbers, particularly for the oldest age groups. More than 40% of the participants in the BioNTech/Pfizer Phase III trial were older than 55 years, but less than 5% were over 70 years. Overall vaccine efficacy after 2 doses with a 3-week interval was 95.0% (95% CI: 90.0–97.9) against symptomatic SARS-CoV2 infection, and did not differ in the age groups 16–55y, >55y, and ≥65y. Due to the limited number of participants over 75 years, analysis in this age group was not statistically significant, with 5 cases of COVID-19 in the placebo group versus zero cases in the vaccinated group (Polack et al. 2020). In the pivotal Moderna mRNA vaccine trial approximately 25% of the participants were older than 65 years and efficacy against symptomatic SARS-CoV-2 infection after two doses of vaccine with a 4-week interval was 86.4% (95% CI: 61.4–95.2) in this age group compared to 95.6% (95% CI: 90.6–97.9) in younger adults (overall efficacy 94.1% (95% CI: 89.3–96.8)) (Baden et al. 2021). More detailed sub-group analyses are provided in the assessment report of the European Medicines Agency showing an efficacy of 82.4% (95% CI: 46.9–93.9) for persons aged 65–75y. In the subgroup older than 75 years no COVID-19 cases occurred in the vaccinated group, whereas 7 cases were reported in the placebo group (European Medicines Agency 2021b). Despite the limited data on the oldest age groups, it can be concluded that efficacy of both mRNA vaccines against COVID-19 disease is high, even in older adults. The first publications on efficacy of the Oxford/AstraZeneca adenovirus vector vaccine included data from several clinical trials with differences in age of participants, dosing of the vaccine and interval between the two doses. Overall clinical efficacy against symptomatic SARS-CoV-2 infection was 62.1% (95% CI: 41.0–75.7) after two standard-dose vaccinations. Twelve percent of the participants were older than 55 years, but no age-based subgroup analysis was provided (Voysey et al. 2020). Press releases announced 79.9% efficacy against symptomatic disease in persons older than 65 years for a Phase III trial, which is ongoing in the US, but the data are not published yet (NCT04516746; (News Releases 2021)). In the pivotal trial for the single-dose Adenovirus-26 vector vaccine (Johnson&Johnson/Janssen) 33% of the participants were older than 60 years. 28 days after the vaccination clinical efficacy against moderate to severe COVID-19 disease was 66.1% (95% CI: 55.0–74.8) without differences between the age groups younger or older than 60 years (Sadoff et al. 2021).

Efficacy of the SARS-CoV-2 vaccines against asymptomatic infections is more difficult to assess. In theory, this can be achieved in two ways. The first strategy is regular testing for viral RNA or antigen e.g. in nasopharyngeal swabs or saliva in all participants, irrespective of symptoms. This has to be done in quite high frequency, e.g. once per week for PCR testing and even more often for antigen tests in order to catch all infections. An alternative strategy is to monitor seroconversion to viral proteins other than spike after a longer observation period, e.g. after 6 months.

A fraction of the participants in the AstraZeneca Phase III trials were monitored for asymptomatic infection by weekly self-swabs, which were tested for viral RNA, but efficacy was not statistically significant for the subgroup receiving the full-dose vaccine regimen (Voysey et al. 2020). The trial investigating the single-dose adenoviral vaccine (Johnson&Johnson/Janssen) determined antibodies against the viral N protein at day 71 after vaccination. Based on this preliminary analysis (not all participants had already reached day 71) vaccine efficacy against asymptomatic infection was 65.5% (95% CI: 39.9–81.1) (Sadoff et al. 2021). The pivotal trials investigating the BioNTech/Pfizer and Moderna mRNA vaccines (Polack et al. 2020; Baden et al. 2021) announced to provide seroconversion follow-ups at a later time point.

The goal of many countries was to vaccinate their population as quickly and as completely as possible. As vaccine supply was extremely limited in the beginning and still by far falls short of world-wide demand, priorization of risk groups was implemented. Despite differences in the details, there was consensus that the first groups to be vaccinated are health-care workers, particularly those treating COVID-19 patients, and the very old, as they are at highest risk for severe disease outcomes. Vaccine effectiveness has been and is still studied extensively after licensure and wide-spread use in various countries. Several studies confirmed that effectiveness in the "real-world" situation matches efficacy in clinical trials, but in addition, substantial information regarding asymptomatic infection and the impact of vaccination in older age groups, which were underrepresented in the efficacy trials, is emerging. Investigations of asymptomatic infections are mainly performed in health care workers. Irrespective of vaccination, they are routinely tested for active infection on a regular basis, which facilitates this type of study. In summary, several studies demonstrate high effectiveness of the mRNA vaccines against asymptomatic infection, which can already be observed after the first dose, but increases after full vaccination (Hall et al. 2021; Thompson et al. 2021). In some instances, age has been considered in the analyses and does not seem to decrease efficacy, but that of course is limited by the age-range in the health care work force and does not include very old individuals. However, effectiveness against COVID-19 disease has been investigated also in older adults and this confirms data obtained in clinical trials. Most studies also include analyses after the first dose of vaccine, and in general, protection is already seen approximately 2 weeks after the first dose, but increases after the second dose. Israel´s national vaccination campaign with the BioNTech/Pfizer vaccine was carried out exceptionally fast and therefore nation-wide data from Israel was available early after vaccine licensure. Vaccine effectiveness was calculated against SARS-CoV-2 infection (and separately for asymptomatic and symptomatic infection), COVID-19-related hospitalization and COVID-19-related death for different age groups (16–44y; 45–64y;

≥65y). The lowest effectiveness was 85.9% (95% CI: 80.2–89.9) for asymptomatic infection in the oldest age group, all other outcomes were higher, most of them above 95% (Haas et al. 2021). No differences were observed, when further stratifying the oldest age group into subgroups ≥65y, ≥75y, and ≥85y. These findings demonstrate excellent effectiveness against infection and disease of any severity in all age groups, even in the very old. Additional effectiveness studies were performed in other countries confirming these results. Effectiveness of mRNA vaccines was 94% (95% CI: 49–99) among hospitalized adults ≥65 years of age in the US (Tenforde et al. 2021). Persons older than 80 years were vaccinated with the BioNTech/Pfizer vaccine in the UK. Vaccine effectiveness against symptomatic disease was 89% (95% CI: 85–93) after the second dose. In the same study persons older than 70 years vaccinated with the AstraZeneca vaccine were followed, and effectiveness in this group was 73% (95% CI: 27–90) (Lopez Bernal et al. 2021).

The "real-world" scenario is even more complicated, but a detailed discussion of all these aspects is beyond the scope of this chapter. In brief, it has to be considered that optimal vaccination schedules are still being evaluated. There is clear evidence that longer time-intervals between two doses of AstraZeneca vaccine are beneficial (Voysey et al. 2021), and preliminary results suggest a similar effect for the BioNTech/Pfizer vaccine (Parry et al. 2021). Heterologous prime-boost schedules with AstraZeneca and mRNA vaccines are tested and first results indicate slightly higher reactogenicity of the heterologous regime (Shaw et al. 2021), but no data on immunogenicity or efficacy are available yet. There is a lively discussion whether and when booster vaccinations will be necessary. To address this question, the duration of protection needs to be determined. The initial clinical trials continue their follow-up and observations in the large number of persons vaccinated in the national vaccine campaigns will contribute to our understanding of (hopefully) long-term protection. It is important to monitor long-term protection specifically in high-risk populations, such as older adults, and to consider specific recommendations for these groups. In addition, newly emerging virus variants endanger the protective effect of vaccines and extensive research is ongoing to evaluate the existing vaccines in the context of virus variants and to develop modified vaccines, which incorporate the crucial changes in the viral genome. In the future, SARS-CoV-2 vaccines might become part of our "regular" vaccination schedules for everybody, or at least for risk groups. First studies are already ongoing investigating co-administration of SARS-CoV-2 vaccines with other vaccines, such as influenza or pneumococcal vaccines (NCT04848467, NCT04790851). In addition, development of combination vaccines (e.g. SARS-CoV-2 and influenza) has started (Massare et al. 2021).

7.2.5 Other Vaccines

Vaccinations, which are recommended for all adults should also be considered in the context of aging. The most prominent example for this is regular booster vaccination against tetanus and diphtheria, in some cases combined with pertussis and/or

polio, which is recommended in many countries. Regular vaccinations against other pathogens are advocated in some countries, e.g. against tick-borne encephalitis in endemic areas. Most countries do not specifically mention older adults, but some countries such as e.g. in Europe Austria, Liechtenstein, France and Portugal recommend shortened booster intervals for older adults. Tetanus- and diphtheria-specific antibody concentrations are frequently below the levels considered to be protective for adults, and are even lower in older age groups (Bayas et al. 2001; Van Damme and Burgess 2004; Kaml et al. 2006; Launay et al. 2009; Weinberger et al. 2013). In one of our studies in Austria a single booster shot of a combined vaccine was administered and approximately 10% of the older cohort (>60y) did not develop protective diphtheria-specific antibody levels. Almost half of the participants did no longer have protective antibody concentrations five years later, and a second booster vaccination at this time point did again not provide long-term protection (Weinberger et al. 2013; Grasse et al. 2016). Antibody levels for tetanus and diphtheria vary greatly in different European countries. In general, protection against tetanus is adequate in most countries, whereas diphtheria-specific antibody levels are below the protective level for a substantial fraction of the population in some countries, and are decreasing with age (Weinberger et al. 2018b). A more extensive summary of vaccination against tetanus and diphtheria can be found elsewhere (Weinberger 2017). Antibody responses after booster vaccination against tick-borne encephalitis are also lower in old compared to young adults and decline over time (Weinberger et al. 2010; Stiasny et al. 2012).

Over the last years, an increased incidence of pertussis has been observed in adults, and particularly in older age groups, for whom infection can be severe (Gil et al. 2001; Rendi-Wagner et al. 2010; Ridda et al. 2012). Adults can also transmit the infection to newborns, who are too young to be vaccinated. Therefore, vaccination against pertussis is not only relevant for children, where it is widely accepted, but also needs to be considered for adults. Few countries recommend regular booster immunization with combination vaccines containing the pertussis component (Tdap) and some recommend one booster dose during adulthood, but many countries do not include pertussis in their recommendations for adults. Regular booster doses of Tdap vaccine are well tolerated and immunogenic in young and older adults, but antibody concentrations are lower in the older age groups (Kaml et al. 2006; Halperin et al. 2012).

Health, mobility and financial prospects of older adults have improved over the last years and decades leading to an increased number of older long-distance travelers. As a consequence, travel vaccines are becoming more important in this age group, particularly as some tropical diseases such as typhoid fever and Japanese encephalitis are more frequent and severe in older adults (Taylor et al. 1983; Hennessy et al. 1996). Unfortunately, little data are available regarding immune responses of older adults to travel vaccines and immunization guidelines rely primarily on studies with young adults. Many travel vaccines represent neo-antigens for older travelers (e.g. rabies, yellow fever, Japanese encephalitis) and most older travelers probably also never had contact with Hepatitis B and to a lesser extent Hepatitis A. The loss of naïve adaptive immune cells is a hallmark of immunosenescence, and experiments

in animal models have demonstrated an impaired generation of memory responses in old age (Haynes et al. 2003; Haynes 2005), suggesting that primary vaccination in old age might be impaired. A reduction in antibody production after Hepatitis A and B vaccination can already be observed in middle-aged adults and the percentage of non-responders to Hepatitis B vaccine increases with age (Fisman et al. 2002; Wolters et al. 2003; Stoffel et al. 2003; Weinberger et al. 2018a). Vaccination against Hepatitis B is of relevance for older adults beyond the travel setting. Other risk groups for whom HBV-vaccination is of importance are e.g. health care workers, household contacts of infected patients and hemodialysis patients, and all of these groups also include older persons. The live-attenuated yellow fever vaccine is highly immunogenic also in older adults, but a higher risk for rare severe adverse events such as e.g. yellow fever vaccine-associated viscerotropic disease, which mimics infection with the wild-type virus and has a high mortality of up to 60% (Rafferty et al. 2013), has been reported. Therefore, the decision to vaccinate the individual older traveler needs to weigh the risks and benefits carefully. However, yellow fever vaccination is mandatory for travels to some countries in Africa and South America and therefore a next-generation yellow fever vaccine with an improved safety profile in the older population would be useful. A detailed summary of vaccines for older travelers has recently been published (Jilg 2020).

7.3 The Future of Vaccines for Older Adults

7.3.1 Novel Adjuvants

Novel adjuvants for older adults would need to counteract the diminished responsiveness of the aged immune system and the accelerated decline of protection and to overcome the low-grade inflammatory state observed in older adults. (Ciabattini et al. 2018). Several novel adjuvants are evaluated in the context of influenza vaccines and some also in combination with other antigens. This summary highlights examples of adjuvants, which are in clinical development without claiming to be complete (Table 7.2). Basic research and pre-clinical development are ongoing for a large number of additional adjuvant candidates. More extensive reviews on this topic can be found elsewhere (Tregoning et al. 2018; Weinberger 2018).

MF59® in influenza vaccines and AS01B in the recombinant herpes zoster vaccine are currently the only adjuvants specifically licensed for older adults (see above). AS03, another squalene-based oil-in-water based adjuvant has been used in the pandemic influenza vaccine of 2009 and induced higher antibody concentrations and seroprotection levels in older adults compared to a whole virus vaccine (Nicholson et al. 2011). A second study found higher antibody concentrations in young and older adults after vaccination with the adjuvanted pandemic vaccine compared to the non-adjuvanted split vaccine (Yang et al. 2013). In both studies the amount of antigen in the adjuvanted vaccine was substantially lower than in the

Table 7.2 Overview of adjuvants in vaccines and vaccines candidates for older adults[a]

Adjuvant	Adjuvant type	Vaccine	Licensed
MF59	Squalene-based oil-in-water emulsion	Seasonal influenza	+
		Pandemic influenza	+
AS01B	Liposomes, saponin, TLR4-agonist (MPL)	Herpes zoster	+
AS02V	Oil-in-water emulsion, saponin, TLR4-agonist (MPL)	S. pneumoniae (protein and conjugate)	–
AS03	Squalene-based oil-in-water emulsion	pandemic influenza	+
AF03	Squalene-based oil-in-water emulsion	Pandemic influenza	+[§]
		Seasonal influenza	–
Montanide ISA51	Non-squalene-based oil-in-water emulsion	Seasonal influenza	–
		Universal influenza (peptide)	–
Matrix M	Saponin	Influenza (HA nanoparticles)	–
GLA-SE	Squalene-based oil-in-water emulsion, TLR4-agonist (GLA)	Pandemic influenza	–
		RSV	–
Flagellin	TLR5-agonist	Influenza (fusion protein)	–
Imiquimod	TLR7/8-agonist	Intradermal influenza	–
1018	TLR9-agonist (CpG-oligonucleotide)	Hepatitis B	+
AdVax-CpG55.2	Inulin, TLR9-agonist (CpG-oligonucleotide)	Seasonal influenza	–

[a]This table summarizes the adjuvants and their use as mentioned in this chapter and does not provide a complete overview of all substances and vaccine candidates in development
[§]licensed, but not marketed
TLR: Toll-like receptor
MPL: 3-O-desacyl-4´-monophosphoryl lipid A
HA: hemagglutinin
GLA: glucopyranosyl Lipid A
RSV: respiratory syncytial virus

comparator vaccines. The adjuvant mechanism of AS03 includes the stimulation cytokine and chemokine production leading to local influx of innate immune cells, the induction of $CD4^+$ T helper cells with potential cross-reactive specificities and the generation of memory B cells resulting in longer antibody persistence (Moris et al. 2011; Shi et al. 2019). In a Phase III trial enrolling more than 43,000 older adults clinical efficacy of trivalent seasonal influenza vaccine adjuvanted with AS03 was compared to standard TIV. Superiority of the adjuvanted vaccine could be demonstrated for protection against influenza A, and particularly A/H3N2 infection, but not against infection with any influenza strain. In addition this study showed higher efficacy against hospital admission for pneumonia and all cause death in

descriptive estimates (McElhaney et al. 2013). Another H1N1 pandemic influenza vaccine containing AF03, which is also a squalene-based oil-in-water emulsion was licensed, but has never been marketed (Tregoning et al. 2018). AF03 is currently tested in a Phase I trial in combination with a seasonal influenza vaccine in young adults in parallel with Advax-CpG55.2, an adjuvant containing the plant-derived polysaccharide inulin and a CpG oligonucleotide targeting TLR9 (NCT03945825). A detailed summary of squalene-based adjuvants and their mode of action can be found elsewhere (Nguyen-Contant et al. 2021).

GLA-SE combines the approach of squalene-based oil-in-water emulsions with GLA (glucopyranosyl Lipid A), which is a synthetic variant of *Salmonella minnesota* LPS and acts as a TLR4 agonist. It is a promising adjuvant for influenza vaccines. Antibody responses to GLA-SE adjuvanted influenza vaccine are higher only in mice, but of broader specificity in mice and non-human primates compared to standard influenza vaccine (Baldwin et al. 2009; Coler et al. 2010). In vitro studies showed that the stimulatory effect of GLA on innate immune cells is well preserved in cells from old donors (Weinberger et al. 2016) and that T cells from old donors respond with enhanced cytokine production to influenza virus in the presence of GLA-SE (Behzad et al. 2012). GLA-SE-adjuvanted H1N1 influenza vaccine induces higher immune responses in aged mice compared to unadjuvanted vaccine (Baldwin et al. 2018). GLA-SE has been used in a clinical study in combination with a recombinant H5 pandemic influenza vaccine candidate and showed increased immunogenicity in healthy young adults (Treanor et al. 2013). GLA-SE has also been tested in vaccine candidates against Respiratory Syncytial Virus (RSV), which are discussed below (Sect. 7.3.2). Other TLR agonists have also been tested together with influenza vaccines. The TLR5 agonist flagellin has been tested as a fusion protein with different influenza proteins, namely the head domain of hemagglutinin (VAX125) and the ectodomain of matrix protein (M2e; VAX102). High levels of antibodies and seroprotection in persons over 65 years were reported for VAX125, but this study did not include a direct comparison with standard TIV (Taylor et al. 2011). Concomitant administration of VAX102 and standard TIV improved hemagglutinin-specific antibody responses compared to TIV alone, and induced a M2e-specific antibody response in young adults (Keipp Talbot et al. 2010). Imiquimod is a TLR7/8 agonist, which-applied as an ointment prior to intradermal trivalent influenza vaccination-could elicit higher antibody titers, seroconversion and long-term seroprotection over one year in older adults with comorbidities (Hung et al. 2014). Stimulation of TLRs has also been shown to improve immunogenicity and protection in mouse models of pneumococcal vaccination (Moffitt et al. 2014; Vecchi et al. 2014).

The adjuvant 1018, containing a TLR9 agonist (CpG oligonucleotide), has been approved by the FDA recently in the context of a hepatitis B vaccine. Primary vaccination of healthy individuals between 40 and 70 years of age led to higher seroprotection and antibody titers after a 2-dose regimen at 0 and 4 weeks compared to the licensed alum-adjuvanted vaccine containing the same antigen amount (20 μg HBsAg) applied three times at weeks 0, 4 and 24 (Heyward et al. 2013). Although seroprotection rates were lower in the 60–70 year old participants, levels were still

higher with the 1018-containing vaccine compared to alum (Jackson et al. 2018). Overall, TLR agonists seem to be a promising class of adjuvants for use in older adults.

Several adjuvants based on oil-in-water emulsions are successfully used in vaccines for older adults (see above) and a variety of alternative oil-in-water formulations are being developed. Montanide ISA 51 (mineral oil plus mannide monooleate surfactant), has been applied with TIV in a phase I trial to adults between 55 to 75 years, however results are not yet published (NCT01010737) and has also been investigated in two broad spectrum/universal peptide-based influenza vaccine candidate in young adults (Atsmon et al. 2012; Pleguezuelos et al. 2020). The antibody concentrations elicited by peptide vaccines cannot be compared to the HAI titers induced by conventional influenza vaccines, as they contain different antigens. The adjuvant effect of Montanide ISA51 is based on depot formation, stimulation of inflammatory signals, and enhancing lymphocyte interaction in lymph nodes leading to increased antibody and $CD8^+$ T cell responses (Van Doorn et al. 2016). The adjuvant $AS02_V$ (oil-in-water emulsion, combined with MPL and QS21) enhances humoral and cellular immune responses to the pneumococcal protein PhtD, PhtD-dPly and an 8-valent conjugated polysaccharide formulation in young and older adults (Pauksens et al. 2014; Leroux-Roels et al. 2015). Saponins are used in several multi-component adjuvants e.g. in AS01 and AS02. Matrix M, is also based on saponin and has been tested in combination with quadrivalent recombinant influenza hemagglutinin nanoparticles. This vaccine candidate induced higher hemagglutination inhibiting antibodies against homologous and drifted influenza strains compared to standard quadrivalent seasonal influenza vaccine and to high-dose trivalent seasonal influenza vaccine in older adults (Shinde et al. 2020). Results of a phase 3 trial in older adults have not yet been published (NCT04120194).

There are many more potential adjuvants, such as e.g. cytokines, T cell stimulating adjuvants, DNA-based adjuvants etc., which might be good candidates to boost vaccine-induced immune responses in older adults, but have not yet been tested in this age group or other high-risk groups. Many of them are investigated in the context of influenza and pneumococcal vaccines.

7.3.2 Novel Target Antigens and Pathogens

But even with novel adjuvants, which improve immune responses in older adults, pneumococcal and influenza vaccines suffer from the limitations of strain-specific immune responses. Therefore, many studies investigate the potential of broad spectrum or universal vaccines for these pathogens. Pneumococcal vaccines induce only antibodies specific for the polysaccharides present in the vaccine. There is almost no cross-reactivity with other pneumococcal serotypes, no protection against other serotypes, and serotype replacement has been observed after the introduction of conjugated pneumococcal vaccines containing a limited number of

different serotypes (see above). Therefore, development of next-generation conjugated vaccines containing additional serotypes is ongoing. Safety and immunogenicity of a 15-valent conjugated vaccine (Table 7.1) in older adults was similar to that of 13-valent PCV in early stage clinical trials (Stacey et al. 2019). This vaccine candidate has been tested in Phase III trials in older adults (NCT03950622, NCT03950856, NCT03615482, NCT03547167) demonstrating adequate efficacy when administered alone or concomitantly with influenza vaccine or followed by the23-valent polysaccharide vaccine and has been submitted for licensure. A 20-valent PCV (Table 7.1) also showed promising safety and immunogenicity in older adults (Hurley et al. 2020). Phase III trials are ongoing in older adults (NCT03835975, NCT04875533, NCT03760146, NCT04526574). It might be worthwhile to consider the option of including different serotypes in pediatric compared to adult vaccines in order to reflect the distinct pattern of serotype prevalence in the different age groups. However, to fully overcome the risk of serotype replacement universal vaccines against *S. pneumoniae* would be needed. A whole cell vaccine utilizing an engineered pneumococcal strain, which lacks a polysaccharide capsule and bacterial toxins has been tested successfully in animal models (Lu et al. 2010a, b; Campos et al. 2017), and induced T cell responses and antibodies to conserved epitopes of several pneumococcal proteins in early clinical trials (Campo et al. 2018; Keech et al. 2019). Various vaccine candidates are developed, which utilize individual pneumococcal proteins or peptides and most of them focus on virulence factors and well-conserved surface proteins, frequently in combination with adjuvants. The most prominent proteins selected for potential vaccines are pneumococcal histidine triad protein D (PhtD), detoxified pneumolysin derivative (PlyD) and pneumococcal surface protein (PspA) or combinations of those. Several of them have been tested in early-stage clinical trials demonstrating an acceptable safety profile and immunogenicity in humans. Several more are still in pre-clinical development (Pichichero et al. 2016; Pichichero 2017; Lagousi et al. 2019; Masomian et al. 2020). The situation is similar for influenza vaccines. Despite the fact that influenza-specific antibodies show some degree of cross-reactivity towards related viral strains and that influenza-specific T cells can recognize conserved epitopes, clinical data show that efficacy and effectiveness of influenza vaccines are decreased in situations where there is a mismatch between circulating virus strains and the vaccine strains. As an example, in the 2014/2015 season the circulating influenza A H3N2 strains changed significantly (antigenic drift) after selection of the vaccine strains (Xie et al. 2015), and due to this mismatch vaccine effectiveness was only 19% against influenza and only 6% against the drifted H3N2 strains in this season (Zimmerman et al. 2016). Similar effects were observed in the seasons 2004/2005 and 2005/2006 (Belongia et al. 2009). In contrast, overall vaccine effectiveness is usually 40–60% in years with adequate matching of vaccine and circulating virus strains (Zimmerman et al. 2016). It has been shown that currently used (MF59, AS03) and novel adjuvants (e.g. TLR agonists and saponin-based formulations) are capable of inducing cross-reactive antibodies, which recognize drifted strains and therefore potentially offer broader protection. A detailed overview of this topic has recently been published (Li et al. 2021). But to effectively tackle the immense antigenic variability of influenza

viruses universal vaccines are desirable. They need to be able to induce broadly neutralizing antibodies to highly conserved epitopes and other effector mechanisms, such as FcR-mediated phagocytosis or cellular cytotoxicity. For optimal protection they should induce long-lasting immunity for more than one season and should cover Influenza A and B strains (Nachbagauer and Krammer 2017; Krammer 2019). Various approaches, such as antigens based on the stem-region of hemagglutinin, chimeric hemagglutinin proteins, peptides and nucleic acid platforms, are currently tested in clinical trials. Antibody responses as well as T cell-mediated cytotoxicity will probably be important for clinical efficacy and it is very likely that adjuvants and/or vaccine-delivery platforms will be essential for optimal vaccine responses, particularly in the older population (Estrada and Schultz-Cherry 2019; Nachbagauer and Palese 2020; Wei et al. 2020). It has also been reported in a small study that priming with a universal recombinant protein vaccine can enhance immune responses to subsequent seasonal influenza vaccination (Atsmon et al. 2014).

There are many additional pathogens, which cause high morbidity and mortality in the older population, and for which vaccines would be highly desirable. Respiratory syncytial virus (RSV) is a major cause of severe respiratory infection in infants but also older and particularly frail individuals and patients with underlying co-morbidities can experience severe RSV disease. An estimated 18,000 hospitalizations and 8,400 deaths per year are caused by RSV in the UK, and most of these cases occur in the older population (Fleming et al. 2015). The first RSV vaccine in the 1960s was associated with risk for disease enhancement in infants and this experience has substantially slowed down RSV vaccine development in the following decades. Over the last years several candidate vaccines against RSV have been developed and are in clinical testing. However, despite promising safety and immunogenicity data, several failed to provide protection for older adults in clinical trials (Mazur et al. 2018). As an example, a RSV F-protein nanoparticle vaccine failed in a phase III trial in older adults (NCT02608502), and also adjuvantation of F protein with GLA-SE did not confer clinical efficacy (Falloon et al. 2017b), despite positive results during immunogenicity testing (Falloon et al. 2016, 2017a). An alternative strategy is the use of viral vectors. An MVA-BN (Modified Vaccinia Ankara—Bavarian Nordic) poxviral vector encoding five RSV proteins induces broad cellular and antibody responses in older adults (Jordan et al. 2021), but clinical data is not yet available for this vaccine candidate.

Due to more frequent invasive procedures, hospitalization and residence in long-term care facilities the risk of nosocomial infections is high in older adults. Antibiotic resistance of bacterial nosocomial pathogens is a growing problem and vaccination could be an effective strategy to prevent such infections. *Clostridium difficile*, which is the most common cause of nosocomial diarrhea, *Staphylococcus aureus*, which is responsible for infections of prostheses, catheters or surgical wounds and *Escherichia coli*, which causes mainly catheter-associated urinary tract infections, but also surgical wound infections are among the most relevant bacterial nosocomial pathogens (Poolman and Anderson 2018). Clinical development of two vaccine

candidates against *C. difficile* utilizing different modifications of bacterial toxins has been terminated (Tian et al. 2012; Sanofi 2017) and only one toxoid-based candidate is still actively investigated in a Phase III study (NCT03090191). Two vaccine candidates against *S. aureus* have been clinically tested in the past in high-risk patients, but did not confer protection (Shinefield et al. 2002; Fowler et al. 2013). Two newer vaccine candidates, one containing conjugated polysaccharides and bacterial proteins, the other an adjuvanted protein vaccine are in early stages of clinical development (Levy et al. 2015; Creech et al. 2017). It still remains to be seen, whether they will be able to provide clinical protection. There are currently no vaccines to prevent *E. coli* infection. However, *E.coli* is also relevant as the cause of recurrent urinary tract infections outside of health-care settings and whole cell as well as subunit (bioconjugates of polysaccharides) vaccines have been developed for prevention of recurrent episodes. Clinical outcomes were mixed and can be found in detail elsewhere (Aziminia et al. 2019). Norovirus is also highly relevant as a nosocomial pathogen. Outbreaks in hospitals and other institutions, such as long-term care facilities are frequent, and the disease can be severe in older adults. Virus-like particles, which lack the viral genome, have been tested as a vaccine candidate and showed limited clinical efficacy in healthy adults (Bernstein et al. 2015), but older adults have only been included in safety and immunogenicity studies (NCT02661490).

Vaccines against these and other nosocomial pathogens, such as *Klebsiella pneumoniae*, *Acinetobacter* ssp., *Pseudomonas aeruginosa* and fungal pathogens such as *Candida* spp. have the potential to substantially reduce health care costs and to save many lives (McIntosh 2018). A detailed summary on vaccines for nosocomial infections of older adults has recently been published (Anderson et al. 2020a)

7.4 Vaccination Strategies

Improvements of existing vaccines and the development of novel vaccines for older adults have the potential to prevent substantial morbidity and mortality. However, even the best vaccines can only provide protection if they are actually administered. It is important to not only optimize vaccines for older adults, but also vaccination strategies, schedules and implementation. This section will discuss these aspects for selected vaccines, exemplifying data from individual countries, mainly in Europe and the US. Even within Europe, there are major differences between countries and of course the situation is even more distinct for middle- and low-income countries, where additional factors need to be considered.

7.4.1 Vaccination Coverage and Documentation of Vaccination

Vaccination coverage is unsatisfactory in the older population for many vaccines. Various barriers to vaccine uptake exist including access to vaccines, personal decisions for or against vaccines, as well as financial aspects. Systematic data on vaccination coverage is not collected in all countries, and the mode of data collection varies substantially, with some countries documenting only the number of vaccines distributed, which may not reflect the number of doses actually administered, and also does not allow analysis of individual risk groups, e.g. based on age. A summary of the WHO on influenza vaccine uptake among older adults in Europe provides data for 72% of the eligible countries for the season 2014/2015. Vaccination uptake ranged from 0.03% to 76% and only one country reached the WHO goal of 75% coverage in this season. For more than half of the countries where data were available for the seasons 2008/2009 and 2014/2015 vaccination coverage dropped during this time span (Jorgensen et al. 2018). In the US, influenza vaccine coverage was approximately 50% in all adults (>18y; 2017/2018) and pneumococcal vaccination coverage was 72.6% (at least one dose, irrespective of vaccine type) in persons older than 65 years (Lu et al. 2021). Uptake of pneumococcal vaccine in older adults also varies greatly in European countries. Some countries reach quite high coverage, such as e.g. Spain, where a survey reported coverage with the 23-valent pneumococcal polysaccharide vaccine of 63.1% and 81.2% for persons aged 65–79y or ≥80y, respectively (Vila-Córcoles et al. 2019), whereas other countries do not generally recommend pneumococcal vaccine for older adults. Vaccine uptake of the live-attenuated herpes zoster vaccine was low in many countries, e.g. 31.8% (95% CI: 31.4–32.2) coverage was estimated for 2014 in the US (Lu et al. 2017), which is substantially lower than the rates for influenza and pneumococcal vaccine. Data are still scarce for the recombinant adjuvanted herpes zoster vaccine, as it was only introduced 2–3 years ago. Two doses are required for full protection and first studies reported completion of the vaccination series for 70–80% of persons, who received the first dose (Ackerson et al. 2021; Patterson et al. 2021). Vaccine uptake for other adult vaccinations is not sufficiently documented in most countries and e.g. data on adult vaccination coverage against tetanus and diphtheria is only available for 5 of 29 European countries (Kanitz et al. 2012). On the national level, documentation of vaccine uptake is crucial to identify gaps in coverage, and to target groups for efforts to improve vaccine uptake. Ideally, this includes data, which are detailed enough to stratify for age, underlying co-morbidities or other risk factors for optimal targeting. However, vaccination documentation is also of utmost importance for the individual person and is crucial, e.g. to deliver booster vaccinations at the right time points, and is the basis for any kind of reminder system. Unfortunately, this documentation is often fragmentary for older adults, and it is therefore difficult to reliably assess adequate primary vaccination earlier in life and the number of booster immunizations received throughout life. Several studies on tetanus/diphtheria vaccination reported only incomplete immunization histories (Van Damme and Burgess 2004;

Kaml et al. 2006; Launay et al. 2009). It has been reported that the number of vaccine doses received in life decreases from 7.1 (95% CI: 6.9–7.2) doses of tetanus vaccine in young adults, which corresponds well with recommendations of 5 doses during childhood/adolescence and 10 year-booster intervals afterwards, to only 5.7 (95% CI: 4.6–6.8) doses for adults aged 50–60 years (Launay et al. 2009). This indicates a lack of regular booster immunizations during adulthood for this age group.

7.4.2 Life-Long Vaccination Strategies and Harmonization of Vaccine Recommendations

Childhood vaccination programs are well-accepted and widely used, but awareness for adult vaccination is by far less prominent. Historically, the burden of infectious disease was highest in infants and young children, but changes in epidemiology and demography, and the development of vaccines against pathogens, which affect adolescents, adults or the older population have altered the objectives of immunization strategies. Today, vaccination is a highly relevant topic for all age groups, and if it is not perceived as such, we should strive to achieve this goal. A life-long vaccination strategy is required to ensure protection of all target groups. This includes adolescents (e.g. human papillomavirus vaccine), pregnant women and their surroundings (e.g. pertussis and influenza vaccine), older adults and persons with underlying medical conditions (influenza, pneumococcal and herpes zoster vaccine). In addition, regular booster vaccinations (e.g. tetanus/diphtheria/pertussis vaccine) need to be considered throughout adulthood. National vaccination guidelines must be tailored to fit the local requirements, e.g. consider local epidemiology, but inconsistencies of vaccine recommendations can also contribute to insecurity and vaccine hesitancy within the population. In many countries financial considerations also play an important role in decisions on vaccine recommendations. Vaccination schedules need to be as easy and convenient as possible. It seems that age-based recommendations are followed better than recommendations based on other risk factors. The option of concomitant administration of vaccines could also improve uptake. Studies demonstrating safety and efficacy of co-administration are available for combinations of influenza vaccination with pneumococcal vaccines (Ofori-Anyinam et al. 2017; Thompson et al. 2019) and adjuvanted herpes zoster vaccine (Schwarz et al. 2017). There have been efforts to harmonize adult vaccine recommendations in Europe, but so far this endeavor has not been successful. A plethora of statements have been published advocating life-long vaccination and harmonization of vaccine schedules and suggesting strategies to improve vaccine uptake throughout adulthood (Gusmano and Michel 2009; Michel et al. 2009; Bonanni et al. 2014; Esposito et al. 2016, 2018; Antonelli Incalzi et al. 2020; Ecarnot et al. 2020). For childhood vaccines it is obvious that pediatricians are the primary providers and programs of regular early childhood visits including scheduled vaccinations are implemented in the health care systems of industrialized countries. But who is providing vaccinations later in life? Family

physicians and general practitioners play an important role, as they often take care of patients over long periods of time and are familiar with underlying conditions. They are also highly suited to keep track of vaccination histories and to provide reminders, e.g. for booster vaccinations. However, specialist physicians such as cardiologists or pneumologists also need to be aware that vaccination is relevant for their patients suffering from chronic conditions which increase the risk for severe infection. Every contact with a physician should be an opportunity to check the vaccination status and to offer the appropriate vaccines. As mentioned above, adequate documentation of immunizations is essential for the success of all implementation strategies.

7.5 Conclusions

Older adults are at high risk for infections and vaccination is an important strategy to prevent disease and facilitate healthy aging. Several vaccines against influenza, *S. pneumoniae* and herpes zoster are available for older adults and vaccines that are used throughout adulthood, such as tetanus, diphtheria and pertussis, are also relevant for seniors. The first step towards optimal protection of older adults is the comprehensive use of existing vaccines. Vaccination recommendations for older adults differ from country to country and increased efforts to harmonize them e.g. throughout Europe would be desirable in order to increase confidence in vaccination programs and to increase vaccine uptake. Awareness needs to be raised that vaccination is important for all age groups, and could be accomplished by educating medical personnel and decision makers, as well as by increasing health literacy in the general public. In addition, easy access and financial coverage are crucial to improve vaccination coverage.

Improved vaccines against influenza, pneumococcal disease and herpes zoster have been developed over the last years and continuous effort is put into further increasing their potential to provide broad and long-lasting protection. Novel vaccines are needed to target the many infectious diseases causing substantial morbidity in the older population, for which no vaccines are available so far, such as RSV or nosocomial pathogens. And finally, a more detailed knowledge about age-related changes of the immune system will enable us to rationally design vaccines, which specifically target the aged immune system and are hopefully able to overcome its limitations.

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References

Ackerson B, Qian L, Sy LS, et al (2021) Completion of the two-dose recombinant zoster vaccine series in adults 50 years and older. Vaccine 39:926–932. https://doi.org/10.1016/j.vaccine.2020.12.076

Adler H, Ferreira DM, Gordon SB, Rylance J (2017) Pneumococcal capsular polysaccharide immunity in the elderly. Clin Vaccine Immunol 24:1–18

Agrawal A, Agrawal S, Gupta S (2017) Role of dendritic cells in inflammation and loss of tolerance in the elderly. Front Immunol 8:1–8. https://doi.org/10.3389/fimmu.2017.00896

Anderson AS, Scully IL, Pride MW, Jansen KU (2020a) Vaccination against nosocomial infections in elderly adults. Interdiscip Top Gerontol Geriatr 43:193–217. https://doi.org/10.1159/000504481

Anderson EJ, Rouphael NG, Widge AT, et al (2020b) Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 383:2427–2438. https://doi.org/10.1056/nejmoa2028436

Ansaldi F, Bacilieri S, Durando P, et al (2008) Cross-protection by MF59^{TM}-adjuvanted influenza vaccine: Neutralizing and haemagglutination-inhibiting antibody activity against A(H3N2) drifted influenza viruses. Vaccine 26:1525–1529. https://doi.org/10.1016/j.vaccine.2008.01.019

Antonelli Incalzi R, Bernabei R, Bonanni P, et al (2020) Vaccines in older age: moving from current practice to optimal coverage—a multidisciplinary consensus conference. In: Aging clinical and experimental research, pp 1405–1415

Atsmon J, Caraco Y, Ziv-Sefer S, et al (2014) Priming by a novel universal influenza vaccine (Multimeric-001)-A gateway for improving immune response in the elderly population. Vaccine 32:5816–5823. https://doi.org/10.1016/j.vaccine.2014.08.031

Atsmon J, Kate-Ilovitz E, Shaikevich D, et al (2012) Safety and immunogenicity of multimeric-001—A novel universal influenza vaccine. J Clin Immunol 32:595–603. https://doi.org/10.1007/s10875-011-9632-5

Aziminia N, Hadjipavlou M, Philippou Y, et al (2019) Vaccines for the prevention of recurrent urinary tract infections: a systematic review. BJU Int 123:753–768. https://doi.org/10.1111/bju.14606

Baden LR, El Sahly HM, Essink B, et al (2021) Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 384:403–416. https://doi.org/10.1056/nejmoa2035389

Baldwin SL, Hsu F-C, Van Hoeven N, et al (2018) Improved immune responses in young and aged mice with Adjuvanted vaccines against H1N1 influenza infection. Front Immunol 9:295. https://doi.org/10.3389/fimmu.2018.00295

Baldwin SL, Shaverdian N, Goto Y, et al (2009) Enhanced humoral and Type 1 cellular immune responses with Fluzone adjuvanted with a synthetic TLR4 agonist formulated in an emulsion. Vaccine 27:5956–63. https://doi.org/10.1016/j.vaccine.2009.07.081

Banerji A, Wickner PG, Saff R, et al (2021) mRNA vaccines to Prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. J Allergy Clin Immunol Pract 9:1423–1437. https://doi.org/10.1016/j.jaip.2020.12.047

Bastidas A, De La Serna J, El Idrissi M, et al (2019) Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. JAMA J Am Med Assoc 322:123–133. https://doi.org/10.1001/jama.2019.9053

Bayas JM, Vilella A, Bertran MJ, et al (2001) Immunogenicity and reactogenicity of the adult tetanus-diphtheria vaccine: how many doses are necessary? Epidemiol Infect 127:451–460. https://doi.org/10.1017/S095026880100629X

Behzad H, Huckriede ALW, Haynes L, et al (2012) GLA-SE, a synthetic toll-like receptor 4 agonist, enhances T-cell responses to influenza vaccine in older adults. J Infect Dis 205:466–473. https://doi.org/10.1093/infdis/jir769

Belongia EA, Kieke BA, Donahue JG, et al (2009) Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004–2005 season to the 2006-2007 season. J Infect Dis 199:159–167. https://doi.org/10.1086/595861

Beran J, Vesikari T, Wertzova V, et al (2009) Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: a prospective, randomized, placebo-controlled trial. J Infect Dis 200:1861–1869. https://doi.org/10.1086/648406

Berkowitz EM, Moyle G, Stellbrink HJ, et al (2015) Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: A phase 1/2a randomized, placebo-controlled study. J Infect Dis 211:1279–1287. https://doi.org/10.1093/infdis/jiu606

Bernstein DI, Atmar RL, Lyon GM, et al (2015) Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. J Infect Dis 211:870–878. https://doi.org/10.1093/infdis/jiu497

Black CL, Williams WW, Warnock R, et al (2017) Pneumococcal vaccination among medicare beneficiaries occurring after the advisory committee on immunization practices recommendation for routine use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults . Morb Mortal Wkly Rep 66:728–733. https://doi.org/10.15585/mmwr.mm6627a4

Black S (2015) Safety and effectiveness of MF-59 adjuvanted influenza vaccines in children and adults. Vaccine 33:B3–B5. https://doi.org/10.1016/j.vaccine.2014.11.062

BMASGK (2021a) Impfplan Österreich 2021

BMASGK (2021b) Empfehlungen zur Influenza Impfung Saison 2021/2022. https://www.sozialministerium.at/Themen/Gesundheit/Impfen/Impfempfehlungen-Allgemein/Empfehlung-Influenza-Impfung-(-Grippeimpfung-)-Saison-2021-2022.html. Accessed 23 May 2021

Boikos C, Fischer L, O'Brien D, et al (2021) Relative effectiveness of Adjuvanted trivalent inactivated influenza vaccine versus egg-derived quadrivalent inactivated influenza vaccines and high-dose trivalent influenza vaccine in preventing influenza-related medical encounters in US adults ≥65 years. Clin Infect Dis 1–8. https://doi.org/10.1093/cid/ciab152

Bonanni P, Sacco C, Donato R, Capei R (2014) Lifelong vaccination as a key disease-prevention strategy. Clin. Microbiol. Infect. 20:32–36

Bonten MJM, Huijts SM, Bolkenbaas M, et al (2015) Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 372:1114–1125. https://doi.org/10.1056/NEJMoa1408544

Booth A, Reed AB, Ponzo S, et al (2021) Population risk factors for severe disease and mortality in COVID-19: a global systematic review and meta-analysis. PLoS One 16:e0247461. https://doi.org/10.1371/journal.pone.0247461

Camilloni B, Basileo M, Valente S, et al (2015) Immunogenicity of intramuscular MF59- Adjuvanted and intradermal administered influenza enhanced vaccines in subjects aged over 60: A literature review. Hum Vaccines Immunother 11:553–563. https://doi.org/10.1080/21645515.2015.1011562

Campo JJ, Le TQ, Pablo J V., et al (2018) Panproteome-wide analysis of antibody responses to whole cell pneumococcal vaccination. Elife 7:e37015. https://doi.org/10.7554/eLife.37015

Campos IB, Herd M, Moffitt KL, et al (2017) IL-17A and complement contribute to killing of pneumococci following immunization with a pneumococcal whole cell vaccine. Vaccine 35:1306–1315. https://doi.org/10.1016/j.vaccine.2017.01.030

Carlock MA, Ingram JG, Clutter EF, et al (2019) Impact of age and pre-existing immunity on the induction of human antibody responses against influenza B viruses. Hum Vaccines Immunother 15:2030–2043. https://doi.org/10.1080/21645515.2019.1642056

Centers for Disease Control and Prevention (2021) Myocarditis and Pericarditis Considerations. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html

Chang LJ, Meng Y, Janosczyk H, et al (2019) Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: A phase 3 randomized clinical trial. Vaccine 37:5825–5834. https://doi.org/10.1016/j.vaccine.2019.08.016

Chlibek R, Bayas JM, Collins H, et al (2013) Safety and immunogenicity of an ASO1 -adjuvanted varicella-zoster virus subunit candidate vaccine against herpes zoster in adults ≥50 years of age. J Infect Dis 208:1953–1961. https://doi.org/10.1093/infdis/jit365

Chlibek R, Smetana J, Pauksens K, et al (2014) Safety and immunogenicity of three different formulations of an adjuvanted varicella-zoster virus subunit candidate vaccine in older adults: A phase II, randomized, controlled study. Vaccine 32:1745–1753. https://doi.org/10.1016/j.vaccine.2014.01.019

Ciabattini A, Nardini C, Santoro F, et al (2018) Vaccination in the elderly: the challenge of immune changes with aging. Semin Immunol 40:83–94. https://doi.org/10.1016/j.smim.2018.10.010

Cines DB, Bussel JB (2021) SARS-CoV-2 Vaccine–induced immune thrombotic thrombocytopenia. N Engl J Med. https://doi.org/10.1056/nejme2106315

Coler RN, Baldwin SL, Shaverdian N, et al (2010) A synthetic adjuvant to enhance and expand immune responses to influenza vaccines. PLoS One 5:e13677. https://doi.org/10.1371/journal.pone.0013677

Cowling BJ, Perera RAPM, Valkenburg SA, et al (2019) Comparative immunogenicity of several enhanced influenza vaccine options for older adults: a randomized, controlled trial. Clin Infect Dis. https://doi.org/10.1093/cid/ciz1034

Creech CB, Frenck RW, Sheldon EA, et al (2017) Safety, tolerability, and immunogenicity of a single dose 4-antigen or 3-antigen Staphylococcus aureus vaccine in healthy older adults: Results of a randomised trial. Vaccine 35:385–394. https://doi.org/10.1016/j.vaccine.2016.11.032

Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB (2019) Immunosenescence and human vaccine immune responses. Immun Ageing 16:1–16. https://doi.org/10.1186/s12979-019-0164-9

Cunningham AL, Heineman TC, Lal H, et al (2018) Immune responses to a recombinant glycoprotein e herpes zoster vaccine in adults aged 50 years or older. J Infect Dis 217:1750–1760. https://doi.org/10.1093/infdis/jiy095

Cunningham AL, Lal H, Kovac M, et al (2016) Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 375:1019–1032. https://doi.org/10.1056/NEJMoa1603800

Curran D, Kim JH, Matthews S, et al (2021) Recombinant zoster vaccine is efficacious and safe in frail individuals. J Am Geriatr Soc 69:744–752. https://doi.org/10.1111/jgs.16917

Dagnew AF, Ilhan O, Lee WS, et al (2019) Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis 19:988–1000. https://doi.org/10.1016/S1473-3099(19)30163-X

de Roux A, Schmöele-Thoma B, Siber GR, et al (2008) Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. Clin Infect Dis 46:1015–1023. https://doi.org/10.1086/529142

Del Giudice G, Rappuoli R, Didierlaurent AM (2018) Correlates of adjuvanticity: a review on adjuvants in licensed vaccines. Semin Immunol 39:14–21. https://doi.org/10.1016/j.smim.2018.05.001

Demicheli V, Jefferson T, Ferroni E, et al (2018) Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2:CD001269. https://doi.org/10.1002/14651858.CD001269.pub6

Detienne S, Welsby I, Collignon C, et al (2016) Central role of CD169 + lymph node resident macrophages in the adjuvanticity of the QS-21 component of AS01. Sci Rep 6:1–14. https://doi.org/10.1038/srep39475

Diao W qi, Shen N, Yu P xi, et al (2016) Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. Vaccine 34:1496–1503. https://doi.org/10.1016/j.vaccine.2016.02.023

DiazGranados CA, Dunning AJ, Kimmel M, et al (2014) Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med 371:635–645. https://doi.org/10.1056/NEJMoa1315727

Didierlaurent AM, Laupèze B, Di Pasquale A, et al (2017) Adjuvant system AS01: helping to overcome the challenges of modern vaccines. Expert Rev Vaccines 16:55–63. https://doi.org/10.1080/14760584.2016.1213632

Domnich A, Arata L, Amicizia D, et al (2017) Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. Vaccine 35:513–520. https://doi.org/10.1016/j.vaccine.2016.12.011

Drew W, Wilson D V., Sapey E (2018) Inflammation and neutrophil immunosenescence in health and disease: Targeted treatments to improve clinical outcomes in the elderly. Exp Gerontol 105:70–77. https://doi.org/10.1016/j.exger.2017.12.020

Drijkoningen JJC, Rohde GGU (2014) Pneumococcal infection in adults: Burden of disease. Clin Microbiol Infect 20:45–51. https://doi.org/10.1111/1469-0691.12461

Dugan HL, Henry C, Wilson PC (2020) Aging and influenza vaccine-induced immunity. Cell Immunol 348:103998. https://doi.org/10.1016/j.cellimm.2019.103998

Ecarnot F, Maggi S, Michel J-P (2020) Strategies to improve vaccine uptake throughout adulthood. Interdiscip Top Gerontol Geriatr 43:234–248. https://doi.org/10.1159/000504486

Esposito S, Bonanni P, Maggi S, et al (2016) Recommended immunization schedules for adults: clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid). Hum. Vaccines Immunother. 12:1777–1794

Esposito S, Principi N, Rezza G, et al (2018) Vaccination of 50 + adults to promote healthy ageing in Europe: The way forward. Vaccine 36:5819–5824

Essink B, Fierro C, Rosen J, et al (2020) Immunogenicity and safety of MF59-adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-adjuvanted trivalent influenza vaccines in older adults. Vaccine 38:242–250. https://doi.org/10.1016/j.vaccine.2019.10.021

Estrada LD, Schultz-Cherry S (2019) Development of a universal influenza vaccine. J Immunol 202:392–398. https://doi.org/10.4049/jimmunol.1801054

European Medicines Agency (2021a) Assessment report: COVID-19 Vaccine AstraZeneca. https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf

European Medicines Agency (2021b) Assessment report: COVID-19 Vaccine Moderna. https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf

Falkenhorst G, Remschmidt C, Harder T, et al (2017) Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (ppv23) against pneumococcal disease in the elderly: Systematic review and meta-analysis. PLoS One 12:1–18. https://doi.org/10.1371/journal.pone.0169368

Falloon J, Ji F, Curtis C, et al (2016) A phase 1a, first-in-human, randomized study of a respiratory syncytial virus F protein vaccine with and without a toll-like receptor-4 agonist and stable emulsion adjuvant. Vaccine 34:2847–54. https://doi.org/10.1016/j.vaccine.2016.04.002

Falloon J, Talbot HK, Curtis C, et al (2017a) Dose Selection for an Adjuvanted respiratory syncytial virus f protein vaccine for older adults based on humoral and cellular immune responses. Clin Vaccine Immunol 24. https://doi.org/10.1128/CVI.00157-17

Falloon J, Yu J, Esser MT, et al (2017b) An adjuvanted, postfusion F protein-based vaccine did not prevent respiratory syncytial virus illness in older adults. J Infect Dis 216:1362–1370. https://doi.org/10.1093/infdis/jix503

Fisman DN, Agrawal D, Leder K (2002) The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. Clin Infect Dis 35:1368–1375. https://doi.org/10.1086/344271

Fleming DM, Taylor RJ, Lustig RL, et al (2015) Modelling estimates of the burden of Respiratory Syncytial virus infection in adults and the elderly in the United Kingdom. BMC Infect Dis 15:. https://doi.org/10.1186/s12879-015-1218-z

Flook M, Jackson C, Vasileiou E, et al (2021) Informing the public health response to COVID-19: a systematic review of risk factors for disease, severity, and mortality. BMC Infect Dis 21:342. https://doi.org/10.1186/s12879-021-05992-1

Fowler VG, Allen KB, Moreira ED, et al (2013) Effect of an investigational vaccine for preventing Staphylococcus aureus infections after cardiothoracic surgery: a randomized trial. JAMA J Am Med Assoc 309:1368–1378. https://doi.org/10.1001/jama.2013.3010

Frasca D, Blomberg BB (2020) The impact of obesity and metabolic syndrome on vaccination success. in: weinberger b (ed) vaccines for older adults: current practices and future opportunities. Interdiscp Top Gerontol Geriatr. Karger, Basel, pp 86–97

Frasca D, Blomberg BB (2016) Aging, cytomegalovirus (CMV) and influenza vaccine responses. Hum Vaccines Immunother 12:682–690. https://doi.org/10.1080/21645515.2015.1105413

Frasca D, Blomberg BB, Garcia D, et al (2020) Age-related factors that affect B cell responses to vaccination in mice and humans. Immunol Rev 296:142–154. https://doi.org/10.1111/imr.12864

Frasca D, Diaz A, Romero M, Blomberg BB (2016) The generation of memory B cells is maintained, but the antibody response is not, in the elderly after repeated influenza immunizations. Vaccine 34:2834–2840. https://doi.org/10.1016/j.vaccine.2016.04.023

Galli G, Medini D, Borgogni E, et al (2009) Adjuvanted H5N1 vaccine induces early CD4 + T cell response that predicts long-term persistence of protective antibody levels. Proc Natl Acad Sci U S A 106:3877–3882. https://doi.org/10.1073/pnas.0813390106

Garçon N, Van Mechelen M (2011) Recent clinical experience with vaccines using MPL- and QS-21-containing Adjuvant Systems. Expert Rev Vaccines https://doi.org/10.1586/erv.11.29

Gavazzi G, Krause K (2002) Ageing and infection. Lancet 2:659–666

Gil A, Oyagüez I, Carrasco P, González A (2001) Hospital admissions for pertussis in Spain, 1995–1998. Vaccine 19:4791–4. https://doi.org/10.1016/s0264-410x(01)00213-4

Goodier MR, Jonjić S, Riley EM, Juranić Lisnić V (2018) CMV and natural killer cells: shaping the response to vaccination. Eur J Immunol 48:50–65. https://doi.org/10.1002/eji.201646762

Goodwin K, Viboud C, Simonsen L (2006) Antibody response to influenza vaccination in the elderly: A quantitative review. Vaccine 24:1159–1169. https://doi.org/10.1016/j.vaccine.2005.08.105

Goronzy JJ, Fang F, Cavanagh MM, et al (2015) Naive T cell maintenance and function in human aging. J Immunol 194:4073–4080. https://doi.org/10.4049/jimmunol.1500046

Govaert TME, Thijs CTMCN, Masurel N, et al (1994) The efficacy of influenza vaccination in elderly individuals a randomized double-blind placebo-controlled trial from the departments of general practice. JAMA 272:1661–1665

Grasse M, Meryk A, Schirmer M, et al (2016) Booster vaccination against tetanus and diphtheria: insufficient protection against diphtheria in young and elderly adults. Immun Ageing 13:26. https://doi.org/10.1186/s12979-016-0081-0

Grohskopf LA, Alyanak E, Broder KR, et al (2020) Prevention and control of seasonal influenza with vaccines: Recommendations of the advisory committee on immunization practices-United States, 2020–21 influenza season. MMWR Recomm Reports 69. https://doi.org/10.15585/MMWR.RR6908A1

Gusmano MK, Michel JP (2009) Life course vaccination and healthy aging. Aging Clin Exp Res 21:258–263. https://doi.org/10.1007/BF03324907

Gustafson CE, Weyand CM, Goronzy JJ (2018) T follicular helper cell development and functionality in immune ageing. Clin Sci 132:1925–1935. https://doi.org/10.1042/CS20171157

Haas EJ, Angulo FJ, McLaughlin JM, et al (2021) Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 397:1819–1829. https://doi.org/10.1016/S0140-6736(21)00947-8

Hall VJ, Foulkes S, Saei A, et al (2021) Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in england, multicentre prospective cohort study (the SIREN Study). SSRN Electron J. https://doi.org/10.2139/ssrn.3790399

Halperin SA, Scheifele D, De Serres G, et al (2012) Immune responses in adults to revaccination with a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 10 years after a previous dose. Vaccine 30:974–982. https://doi.org/10.1016/j.vaccine.2011.11.035

Hassan B, Arawi T (2020) The Care for Non-COVID-19 Patients: a matter of choice or moral obligation? Front Med 7. https://doi.org/10.3389/fmed.2020.564038

Haynes L (2005) The effect of aging on cognate function and development of immune memory. Curr Opin Immunol 17:476–9. https://doi.org/10.1016/j.coi.2005.07.003

Haynes L, Eaton SM, Burns EM, et al (2003) CD4 T cell memory derived from young naive cells functions well into old age, but memory generated from aged naive cells functions poorly. Proc Natl Acad Sci U S A 100:15053–15058. https://doi.org/10.1073/pnas.2433717100

Heineman TC, Cunningham A, Levin M (2019) Understanding the immunology of Shingrix, a recombinant glycoprotein E adjuvanted herpes zoster vaccine. Curr Opin Immunol 59:42–48. https://doi.org/10.1016/j.coi.2019.02.009

Henckaerts I, Goldblatt D, Ashton L, Poolman J (2006) Critical differences between pneumococcal polysaccharide enzyme-linked immunosorbent assays with and without 22F inhibition at low antibody concentrations in pediatric sera. Clin Vaccine Immunol 13:356–360. https://doi.org/10.1128/CVI.13.3.356-360.2006

Hennessy S, Liu Z, Tsai TF, et al (1996) Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. Lancet (London, England) 347:1583–6. https://doi.org/10.1016/s0140-6736(96)91075-2

Henrichsen J (1995) Six newly recognized types of Streptococcus pneumoniae. J Clin Microbiol 33:2759–2762

Herpes Zoster and Functional Decline Consortium (2015) Functional decline and herpes zoster in older people: an interplay of multiple factors. Aging Clin Exp Res 27:757–765. https://doi.org/10.1007/s40520-015-0450-0

Heyward WL, Kyle M, Blumenau J, et al (2013) Immunogenicity and safety of an investigational hepatitis B vaccine with a Toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40–70 years of age. Vaccine 31:5300–5305. https://doi.org/10.1016/j.vaccine.2013.05.068

Hung IFN, Yuen KY (2018) Immunogenicity, safety and tolerability of intradermal influenza vaccines. Hum Vaccines Immunother 14:565–570. https://doi.org/10.1080/21645515.2017.1328332

Hung IFN, Zhang AJ, To KKW, et al (2014) Immunogenicity of intradermal trivalent influenza vaccine with topical imiquimod: a double blind randomized controlled trial. Clin Infect Dis 59:1246–1255. https://doi.org/10.1093/cid/ciu582

Hurley D, Griffin C, Young M, et al (2020) Safety, Tolerability, and Immunogenicity of a 20-valent pneumococcal conjugate vaccine (PCV20) in adults 60 to 64 Years of age. Clin Infect Dis 1–9. https://doi.org/10.1093/cid/ciaa1045

Iuliano AD, Roguski KM, Chang HH, et al (2018) Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 391:1285–1300. https://doi.org/10.1016/S0140-6736(17)33293-2

Izurieta HS, Wu X, Forshee R, et al (2021) Recombinant Zoster Vaccine (Shingrix) real-world effectiveness in the first two years post- licensure. ClinInfectDis ciab125. https://doi.org/10.1093/cid/ciab125

Jackson LA, Neuzil KM, Nahm MH, et al (2007) Immunogenicity of varying dosages of 7-valent pneumococcal polysaccharide-protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine 25:4029–4037. https://doi.org/10.1016/j.vaccine.2007.02.062

Jackson S, Lentino J, Kopp J, et al (2018) Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. Vaccine 36:668–674. https://doi.org/10.1016/j.vaccine.2017.12.038

Janssens JP (2005) Pneumonia in the elderly (geriatric) population. Curr Opin Pulm Med 11:226–230

Jergović M, Smithey MJ, Nikolich-Žugich J (2018) Intrinsic and extrinsic contributors to defective CD8 + T cell responses with aging. Exp Gerontol 105:140–145. https://doi.org/10.1016/j.exger.2018.01.011

Jilg W (2020) Vaccines for Older Travelers. In: Interdisciplinary topics in gerontology and geriatrics. Interdiscip Top Gerontol Geriatr, pp 158–181

Johnson RW, Rice ASC (2014) Postherpetic neuralgia. N Engl J Med 371:1526–1533. https://doi.org/10.1056/NEJMcp1403062

Joint Committee on Vaccination and Immunisation (2019) Advice on influenza vaccines for 2020/2021. https://app.box.com/s/t5ockz9bb6xw6t2mrrzb144njplimfo0/file/529004924372. Accessed 23 May 2021

Joint Committee on Vaccination and Immunisation (2020) Advice on influenza vaccines for 2021/2022

Jordan E, Lawrence SJ, Meyer TPH, et al (2021) Broad antibody and cellular immune response from a phase 2 clinical trial with a novel multivalent poxvirus-based respiratory syncytial virus vaccine. J Infect Dis 223:1062–1072. https://doi.org/10.1093/infdis/jiaa460

Jorgensen P, Mereckiene J, Cotter S, et al (2018) How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine 36:442–452. https://doi.org/10.1016/j.vaccine.2017.12.019

Kaml M, Weiskirchner I, Keller M, et al (2006) Booster vaccination in the elderly: their success depends on the vaccine type applied earlier in life as well as on pre-vaccination antibody titers. Vaccine 24:6808–6811

Kanitz EE, Wu LA, Giambi C, et al (2012) Variation in adult vaccination policies across Europe: An overview from VENICE network on vaccine recommendations, funding and coverage. Vaccine 30:5222–5228. https://doi.org/10.1016/j.vaccine.2012.06.012

Kaplan A, Aresnault P, Aw B, et al (2019) Vaccine strategies for prevention of community-acquired pneumonia in Canada. Candadian Fam Physician 65:625–633

Kawai K, Gebremeskel BG, Acosta CJ (2014) Systematic review of incidence and complications of herpes zoster: Towards a global perspective. BMJ Open 4:e004833. https://doi.org/10.1136/bmjopen-2014-004833

Keech CA, Morrison R, Anderson P, et al (2019) Trial to evaluate the safety and immunogenicity of inactivated streptococcus pneumoniae whole-cell vaccine in adults. Pediatr Infect Dis J Epub ahead of print. https://doi.org/10.1097/INF.0000000000002567

Keipp Talbot H, Rock MT, Johnson C, et al (2010) Immunopotentiation of trivalent influenza vaccine when given with VAX102, a recombinant Influenza M2e vaccine fused to the TLR5 Ligand Flagellin. PLoS One 5:6–12. https://doi.org/10.1371/journal.pone.0014442

Kelly DF, Snape MD, Cutterbuck EA, et al (2006) CRM197-conjugated serogroup C meningococcal capsular polysaccharide, but not the native polysaccharide, induces persistent antigen-specific memory B cells. Blood 108:2642–2647. https://doi.org/10.1182/blood-2006-01-009282

Kim L, McGee L, Tomczyk S, Beall B (2016) Biological and epidemiological features of antibiotic-resistant Streptococcus pneumoniae in pre- and post-conjugate vaccine eras: a United States perspective. Clin Microbiol Rev 29:525–552. https://doi.org/10.1128/CMR.00058-15

Kissling E, Nunes B, Robertson C, et al (2016) I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination? Eurosurveillance 21:30201. https://doi.org/10.2807/1560-7917.ES.2016.21.16.30201

Klein EY, Monteforte B, Gupta A, et al (2016) The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respi Viruses 10:394–403. https://doi.org/10.1111/irv.12398

Kolibab K, Smithson SL, Shriner AK, et al (2005) Immune response to pneumococcal polysaccharides 4 and 14 in elderly and young adults. I Antibody concentrations, avidity and functional activity. Immun Ageing 2:1–9. https://doi.org/10.1186/1742-4933-2-10

Kon TC, Onu A, Berbecila L, et al (2016) Influenza vaccine manufacturing: effect of inactivation, splitting and site of manufacturing. Comparison of influenza vaccine production processes. PLoS One 11:e0150700. https://doi.org/10.1371/journal.pone.0150700

Korompoki E, Gavriatopoulou M, Hicklen RS, et al (2021) Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. https://doi.org/10.1016/j.jinf.2021.05.004

Kraicer-Melamed H, O'Donnell S, Quach C (2016) The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. Vaccine 34:1540–1550. https://doi.org/10.1016/j.vaccine.2016.06.045

Krammer F (2019) The human antibody response to influenza A virus infection and vaccination. Nat Rev Immunol 19:383–397. https://doi.org/10.1038/s41577-019-0143-6

Kwetkat A, Heppner HJ (2020) Comorbidities in the elderly and their possible influence on vaccine response. In: Weinberger B (ed) Vaccines for Older Adults: Current Practices and Future Opportunities. Interdiscp Top Gerontol Geriatr. Karger, Basel, pp 73–85

Kwong JC, Campitelli MA, Gubbay JB, et al (2013) Vaccine effectiveness against laboratory-confirmed influenza hospitalizations among elderly adults during the 2010-2011 season. Clin Infect Dis 57:820–827. https://doi.org/10.1093/cid/cit404

Lacaille-Dubois MA (2019) Updated insights into the mechanism of action and clinical profile of the immunoadjuvant QS-21: A review. Phytomedicine 60. https://doi.org/10.1016/j.phymed.2019.152905

Ladhani SN, Collins S, Djennad A, et al (2018) Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis 18:441–451. https://doi.org/10.1016/S1473-3099(18)30052-5

Lagousi T, Basdeki P, Routsias J, Spoulou V (2019) Novel protein-based pneumococcal vaccines: Assessing the use of distinct protein fragments instead of full-length proteins as vaccine antigens. Vaccines 7:1–18. https://doi.org/10.3390/vaccines7010009

Lal H, Cunningham AL, Godeaux O, et al (2015) Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 372:2087–2096. https://doi.org/10.1056/NEJMoa1501184

Launay O, Toneatti C, Bernède C, et al (2009) Antibodies to tetanus, diphtheria and pertussis among healthy adults vaccinated according to the French vaccination recommendations. Hum Vaccin 5:341–6. https://doi.org/10.4161/hv.5.5.7575

Lee H, Nahm MH, Burton R, Kim KH (2009) Immune response in infants to the heptavalent pneumococcal conjugate vaccine against vaccine-related serotypes 6A and 19A. Clin Vaccine Immunol 16:376–381. https://doi.org/10.1128/CVI.00344-08

Lee JKH, Lam GKL, Shin T, et al (2018) Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines 17:435–443. https://doi.org/10.1080/14760584.2018.1471989

Leroux-Roels I, Devaster JM, Leroux-Roels G, et al (2015) Adjuvant system AS02V enhances humoral and cellular immune responses to pneumococcal protein PhtD vaccine in healthy young and older adults: Randomised, controlled trials. Vaccine 33:577–584. https://doi.org/10.1016/j.vaccine.2013.10.052

Leroux-Roels I, Leroux-Roels G, Clement F, et al (2012) A phase 1/2 clinical trial evaluating safety and immunogenicity of a varicella zoster glycoprotein e subunit vaccine candidate in young and older adults. J Infect Dis 206:1280–1290. https://doi.org/10.1093/infdis/jis497

Levin MJ, Oxman MN, Zhang JH, et al (2008) Varicella-Zoster Virus–Specific Immune Responses in Elderly Recipients of a Herpes Zoster Vaccine. J Infect Dis 197:825–835. https://doi.org/10.1086/528696

Levy J, Licini L, Haelterman E, et al (2015) Safety and immunogenicity of an investigational 4-component Staphylococcus aureus vaccine with or without AS03B adjuvant: Results of a randomized phase I trial. Hum Vaccines Immunother 11. https://doi.org/10.1080/21645515.2015.1011021

Li Z, Zhao Y, Li Y, Chen X (2021) Adjuvantation of influenza vaccines to induce cross-protective immunity. Vaccines 9:1–22. https://doi.org/10.3390/vaccines9020075

Lofano G, Mancini F, Salvatore G, et al (2015) Oil-in-water emulsion MF59 increases germinal center B cell differentiation and persistence in response to vaccination. J Immunol 195:1617–1627. https://doi.org/10.4049/jimmunol.1402604

Lopez Bernal J, Andrews N, Gower C, et al (2021) Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. Bmj n1088. https://doi.org/10.1136/bmj.n1088

Lorenzo EC, Bartley JM, Haynes L (2018) The impact of aging on CD4 + T cell responses to influenza infection. Biogerontology 19:437–466. https://doi.org/10.1007/s10522-018-9754-8

Lu P-J, Hung M-C, Srivastav A, et al (2021) Surveillance of vaccination coverage among adult populations—United States, 2018. MMWR Surveill Summ 70:1–26. https://doi.org/10.15585/mmwr.ss7003a1

Lu P jun, O'Halloran A, Williams WW, Harpaz R (2017) National and state-specific shingles vaccination among adults aged ≥60 years. Am J Prev Med 52:362–372. https://doi.org/10.1016/j.amepre.2016.08.031

Lu YJ, Leite L, Gonçalves VM, et al (2010a) GMP-grade pneumococcal whole-cell vaccine injected subcutaneously protects mice from nasopharyngeal colonization and fatal aspiration-sepsis. Vaccine 28:7468–7475. https://doi.org/10.1016/j.vaccine.2010.09.031

Lu YJ, Yadav P, Clements JD, et al (2010b) Options for inactivation, adjuvant, and route of topical administration of a killed, unencapsulated pneumococcal whole-cell vaccine. Clin Vaccine Immunol 17:1005–1012. https://doi.org/10.1128/CVI.00036-10

Lue C, Tarkowski A, Mestecky J (1988) Systemic immunization with pneumococcal polysaccharide vaccine induces a predominant IgA2 response of peripheral blood lymphocytes and increases of both serum and secretory anti-pneumococcal antibodies. J Immunol 140:3793–3800

MacIntyre CR, Ridda I, Gao Z, et al (2014) A randomized clinical trial of the immunogenicity of 7-valent pneumococcal conjugate vaccine compared to 23-valent polysaccharide vaccine in frail, hospitalized elderly. PLoS One 9:e94578. https://doi.org/10.1371/journal.pone.0094578

MacIntyre CR, Ridda I, Trent MJ, McIntyre P (2019) Persistence of immunity to conjugate and polysaccharide pneumococcal vaccines in frail, hospitalised older adults in long-term follow up. Vaccine 37:5016–5024. https://doi.org/10.1016/j.vaccine.2019.07.005

Marra F, Vadlamudi NK (2019) Efficacy and safety of the pneumococcal conjugate-13 valent vaccine in adults. Aging Dis 10:404–418. https://doi.org/10.14336/AD.2018.0512

Marra F, Young F, Richardson K, Marra CA (2013) A Meta-analysis of intradermal versus intramuscular influenza vaccines: Immunogenicity and Adverse Events. Influenza Other Respi Viruses 7:584–603. https://doi.org/10.1111/irv.12000

Masomian M, Ahmad Z, Gew LT, Poh CL (2020) Development of next generation streptococcus pneumoniae vaccines conferring broad protection. Vaccines 8:. https://doi.org/10.3390/vaccines8010132

Massare MJ, Patel N, Zou B, et al (2021) combination respiratory vaccine containing recombinant SARS-CoV-2 spike and quadrivalent seasonal influenza hemagglutinin nanoparticles with matrix-M Adjuvan. bioRxiv. https://doi.org/10.1101/2021.05.05.442782

Matanock A, Lee G, Gierke R, et al (2019) Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep 68:1069–1075. https://doi.org/10.15585/mmwr.mm6846a5

Mazur NI, Higgins D, Nunes MC, et al (2018) The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Lancet Infect Dis 18:e295–e311. https://doi.org/10.1016/S1473-3099(18)30292-5

McDonald I, Murray SM, Reynolds CJ, et al (2021) Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. npj Vaccines 6:1–14. https://doi.org/10.1038/s41541-021-00336-1

McElhaney JE, Andrew MK, McNeil SA (2017) Estimating influenza vaccine effectiveness: Evolution of methods to better understand effects of confounding in older adults. Vaccine 35:6269–6274. https://doi.org/10.1016/j.vaccine.2017.09.084

McElhaney JE, Beran J, Devaster J-M, et al (2013) AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. Lancet Infect Dis 13:485–96. https://doi.org/10.1016/S1473-3099(13)70046-X

McIntosh EDG (2018) Healthcare-associated infections: potential for prevention through vaccination. Ther Adv Vaccines Immunother 6:19–27. https://doi.org/10.1177/2515135518763183

Merani S, Kuchel GA, Kleppinger A, McElhaney JE (2018) Influenza vaccine-mediated protection in older adults: Impact of influenza infection, cytomegalovirus serostatus and vaccine dosage. Exp Gerontol 107:116–125. https://doi.org/10.1016/j.exger.2017.09.015

Michaelis K, Scholz S, Buda S, et al (2021) Beschluss und Wissenschaftliche Begründung der Ständigen Impfkommission für die Aktualisierung der Influenza-Impfempfehlung für Personen im Alter von ≥60 Jahren. Epid Bull 1:3–25

Michel JP, Chidiac C, Grubeck-Loebenstein B, et al (2009) Coalition of advocates to vaccinate of Western European citizens aged 60 years and older. Aging Clin. Exp. Res

Miernyk KM, Butler JC, Bulkow LR, et al (2009) Immunogenicity and Reactogenicity of Pneumococcal Polysaccharide and Conjugate Vaccines in Alaska Native Adults 55–70 Years of Age. Clin Infect Dis 49:241–248. https://doi.org/10.1086/599824

Moberley S, Holden J, Tatham T, Andrews R (2013) Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 1:CD000422

Moffitt K, Skoberne M, Howard A, et al (2014) Toll-like receptor 2-dependent protection against pneumococcal carriage by immunization with lipidated pneumococcal proteins. Infect Immun 82:2079–2086. https://doi.org/10.1128/IAI.01632-13

Moris P, Van Der Most R, Leroux-Roels I, et al (2011) H5N1 influenza vaccine formulated with AS03 A induces strong Cross-reactive and polyfunctional CD4 T-Cell responses. J Clin Immunol 31:443–454. https://doi.org/10.1007/s10875-010-9490-6

Morrison VA, Johnson GR, Schmader KE, et al (2015) Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 60:900–909. https://doi.org/10.1093/cid/ciu918

Myśliwska J, Trzonkowski P, Szmit E, et al (2004) Immunomodulating effect of influenza vaccination in the elderly differing in health status. Exp Gerontol 39:1447–1458. https://doi.org/10.1016/j.exger.2004.08.005

Nachbagauer R, Krammer F (2017) Universal influenza virus vaccines and therapeutic antibodies. Clin Microbiol Infect 23:222–228. https://doi.org/10.1016/j.cmi.2017.02.009

Nachbagauer R, Palese P (2020) Is a universal influenza virus vaccine possible? Annu Rev Med 71:315–327. https://doi.org/10.1146/annurev-med-120617-041310

Nalbandian A, Sehgal K, Gupta A, et al (2021) Post-acute COVID-19 syndrome. Nat. Med. 27:601–615

News Releases (2021) Investigational AstraZeneca vaccine prevents COVID-19. https://www.nih.gov/news-events/news-releases/investigational-astrazeneca-vaccine-prevents-covid-19

Nguyen-Contant P, Sangster MY, Topham DJ (2021) Squalene-based influenza vaccine adjuvants and their impact on the hemagglutinin-specific b cell response. Pathogens 10:. https://doi.org/10.3390/pathogens10030355

Nicholson KG, Abrams KR, Batham S, et al (2011) Immunogenicity and safety of a two-dose schedule of whole-virion and AS03 A-adjuvanted 2009 infl uenza A (H1N1) vaccines: a randomised, multicentre, age-stratifi ed, head-to-head trial. Lancet Infect Dis 11:91–101. https://doi.org/10.1016/S1473

Norris T, Vahratian A, Cohen RA (2017) Vaccination coverage among adults aged 65 and over: United States, 2015. NCHS Data Brief 1–8

Nunzi E, Iorio AM, Camilloni B (2017) A 21-winter seasons retrospective study of antibody response after influenza vaccination in elderly and very elderly institutionalized subject. Hum Vaccines Immunother 13:2659–2668. https://doi.org/10.1080/21645515.2017.1373226

Ofori-Anyinam O, Leroux-Roels G, Drame M, et al (2017) Immunogenicity and safety of an inactivated quadrivalent influenza vaccine co-administered with a 23-valent pneumococcal polysaccharide vaccine versus separate administration, in adults ≥50 years of age: Results from a phase III, randomized, non-inferiori. Vaccine 35:6321–6328. https://doi.org/10.1016/j.vaccine.2017.09.012

Oishi T, Ishiwada N, Matsubara K, et al (2013) Low opsonic activity to the infecting serotype in pediatric patients with invasive pneumococcal disease. Vaccine 31:845–849. https://doi.org/10.1016/j.vaccine.2012.11.010

Opstelten W, McElhaney J, Weinberger B, et al (2010) The impact of varicella zoster virus: Chronic pain. J Clin Virol 48:S8–S13. https://doi.org/10.1016/S1386-6532(10)70003-2

Orsi A, Ansaldi F, De Florentiis D, et al (2013) Cross-protection against drifted influenza viruses: Options offered by adjuvanted and intradermal vaccines. Hum Vaccines Immunother 9:582–590. https://doi.org/10.4161/hv.23239

Oxman MN, Levin MJ, Johnson GR, et al (2005) A vaccine to prevent herpse zoster and postherpetic neuralgia in older adults. N Engl J Med 352:2271–2284

Park S, Nahm MH (2011) Older adults have a low capacity to opsonize pneumococci due to low igm antibody response to pneumococcal vaccinations. Infect Immun 79:314–320. https://doi.org/10.1128/IAI.00768-10

Parry H, Bruton R, Stephens C, et al (2021) Extended interval BNT162b2 vaccination enhances peak antibody generation in older people. medRxiv. https://doi.org/10.1101/2021.05.15.21257017

Patterson BJ, Chen CC, McGuiness CB, et al (2021) Early examination of real-world uptake and second-dose completion of recombinant zoster vaccine in the United States from October 2017 to September 2019. Hum Vaccines Immunother. https://doi.org/10.1080/21645515.2021.1879579

Pauksens K, Nilsson AC, Caubet M, et al (2014) Randomized controlled study of the safety and immunogenicity of pneumococcal vaccine formulations containing PhtD and detoxified pneumolysin with alum or adjuvant system AS02Vin elderly adults. Clin Vaccine Immunol 21:651–660. https://doi.org/10.1128/CVI.00807-13

Pichichero ME (2017) Pneumococcal whole-cell and protein-based vaccines: changing the paradigm. Expert Rev Vaccines 16:1181–1190. https://doi.org/10.1080/14760584.2017.1393335

Pichichero ME, Khan MN, Xu Q (2016) Next generation protein based Streptococcus pneumoniae vaccines. Hum Vaccines Immunother 12:194–205. https://doi.org/10.1080/21645515.2015.1052198

Pijls BG, Jolani S, Atherley A, et al (2021) Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. BMJ Open 11:e044640. https://doi.org/10.1136/bmjopen-2020-044640

Pileggi C, Mascaro V, Bianco A, et al (2015) Immunogenicity and safety of intradermal influenza vaccine in the elderly: a meta-analysis of randomized controlled trials. Drugs and Aging 32:857–869. https://doi.org/10.1007/s40266-015-0303-8

Pilishvili T, Lexau C, Farley MM, et al (2010) Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 201:32–41. https://doi.org/10.1086/648593

Pinti M, Appay V, Campisi J, et al (2016) Aging of the immune system: focus on inflammation and vaccination. Eur J Immunol 46:2286–2301. https://doi.org/10.1002/eji.201546178

Pleguezuelos O, Dille J, de Groen S, et al (2020) Immunogenicity, safety, and efficacy of a standalone universal influenza vaccine, Flu-V, in healthy adults a randomized clinical trial. Ann Intern Med 172:453–462. https://doi.org/10.7326/M19-0735

Polack FP, Thomas SJ, Kitchin N, et al (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 383:2603–2615. https://doi.org/10.1056/nejmoa2034577

Pollard AJ, Perrett KP, Beverley PC (2009) Maintaining protection agaisnt invasive bacteria with protein-polysaccharide conjugate vaccines. Nat Rev Immunol 426:422–426

Poolman JT, Anderson AS (2018) Escherichia coli and Staphylococcus aureus: leading bacterial pathogens of healthcare associated infections and bacteremia in older-age populations. Expert Rev Vaccines 17:607–618. https://doi.org/10.1080/14760584.2018.1488590

Rafferty E, Duclos P, Yactayo S, Schuster M (2013) Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: a systematic review. Vaccine 31:5798–805. https://doi.org/10.1016/j.vaccine.2013.09.030

Ramasamy MN, Aley PK, Angus B, et al (2020) Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 396:1979–1993

Rendi-Wagner P, Tobias J, Moerman L, et al (2010) The seroepidemiology of Bordetella pertussis in Israel–Estimate of incidence of infection. Vaccine 28:3285–90. https://doi.org/10.1016/j.vaccine.2010.02.104

Richmond P, Kaczmarski E, Borrow R, et al (2000) Meningococcal C polysaccharide vaccine induces immunologic hyporesponsiveness in adults that is overcome by meningococcal C conjugate vaccine. J Infect Dis 181:761–764. https://doi.org/10.1086/315284

Ridda I, MacIntyre CR, Lindley R, et al (2009) Immunological responses to pneumococcal vaccine in frail older people. Vaccine 27:1628–1636. https://doi.org/10.1016/j.vaccine.2008.11.098

Ridda I, Yin JK, King C, et al (2012) The importance of pertussis in older adults: a growing case for reviewing vaccination strategy in the elderly. Vaccine 30:6745–52. https://doi.org/10.1016/j.vaccine.2012.08.079

Romero-Steiner S, Musher DM, Cetron MS, et al (1999) Reduction in functional antibody activity against streptococcus pneumoniae in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. Clin Infect Dis 29:281–288. https://doi.org/10.1086/520200

Rosenbaum L (2020) The untold toll—the pandemic's effects on patients without Covid-19. N Engl J Med 382:2368–2371. https://doi.org/10.1056/nejmms2009984

Sadoff J, Gray G, Vandebosch A, et al (2021) Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 1–15. https://doi.org/10.1056/nejmoa2101544

Sanchez L, Matsuoka O, Inoue S, et al (2020) Immunogenicity and safety of high-dose quadrivalent influenza vaccine in Japanese adults ≥65 years of age: a randomized controlled clinical trial. Hum Vaccines Immunother 16:858–866. https://doi.org/10.1080/21645515.2019.1677437

Sanofi (2017) Sanofi ends development of Clostridium difficile vaccine. https://www.sanofi.com/en/media-room/press-releases/2017/2017-12-01-22-00-00

Scheifele DW, McNeil SA, Ward BJ, et al (2013) Safety, immunogenicity, and tolerability of three influenza vaccines in older adults: Results of a randomized, controlled comparison. Hum Vaccines Immunother 9:2460–2473. https://doi.org/10.4161/hv.25580

Schiffner-Rohe J, Witt A, Hemmerling J, et al (2016) Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk—A systematic review and meta-analysis. PLoS One 11:1–21. https://doi.org/10.1371/journal.pone.0146338

Schmader KE, Levin MJ, Gnann JW, et al (2012) Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis 54:922–928. https://doi.org/10.1093/cid/cir970

Schwarz TF, Aggarwal N, Moeckesch B, et al (2017) Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine coadministered with seasonal influenza vaccine in adults aged 50 years or older. In: Journal of Infectious Diseases. pp 1352–1361

Schwarz TF, Volpe S, Catteau G, et al (2018) Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults. Hum Vaccines Immunother 14:1370–1377. https://doi.org/10.1080/21645515.2018.1442162

Shahid Z, Kleppinger A, Gentleman B, et al (2010) Clinical and immunologic predictors of influenza illness among vaccinated older adults. Vaccine 28:6145–6151. https://doi.org/10.1016/j.vaccine.2010.07.036

Shaw RH, Stuart A, Greenland M, et al (2021) Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet. https://doi.org/10.1016/s0140-6736(21)01115-6

Shi S, Zhu H, Xia X, et al (2019) Vaccine adjuvants: understanding the structure and mechanism of adjuvanticity. Vaccine 37:3167–3178. https://doi.org/10.1016/j.vaccine.2019.04.055

Shimabukuro TT, Cole M, Su JR (2021) Reports of Anaphylaxis after Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA J Am Med Assoc 325:1101–1102. https://doi.org/10.1001/jama.2021.1967

Shinde V, Cai R, Plested J, et al (2020) Induction of cross-reactive hemagglutination inhibiting antibody and polyfunctional CD4 + T-Cell responses by a recombinant matrix-M–adjuvanted hemagglutinin nanoparticle influenza vaccine. Clin Infect Dis 1–10. https://doi.org/10.1093/cid/ciaa1673

Shinefield H, Black S, Fattom A, et al (2002) Use of a staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. N Engl J Med 346:491–496. https://doi.org/10.1056/nejmoa011297

Smith DH, Peter G, Ingram DL, et al (1973) Responses of children immunized with the capsular polysaccharde of hemophilus influenzae type b. Pediatrics 52:637–644

Solforosi L, Kuipers H, Jongeneelen M, et al (2021) Immunogenicity and efficacy of one and two doses of Ad26.COV2.S COVID vaccine in adult and aged NHP. J Exp Med 218. https://doi.org/10.1084/jem.20202756

Song JY, Moseley MA, Burton RL, Nahm MH (2013) Pneumococcal vaccine and opsonic pneumococcal antibody. J Infect Chemother 19:412–425

Stacey HL, Rosen J, Peterson JT, et al (2019) Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults. Hum Vaccines Immunother 15:530–539. https://doi.org/10.1080/21645515.2018.1532249

Stephenson KE, Le Gars M, Sadoff J, et al (2021) Immunogenicity of the Ad26.COV2.S Vaccine for COVID-19. JAMA J Am Med Assoc 325:1535–1544. https://doi.org/10.1001/jama.2021.3645

Stiasny K, Aberle JH, Keller M, et al (2012) Age affects quantity but not quality of antibody responses after vaccination with an inactivated flavivirus vaccine against tick-borne encephalitis. PLoS One. https://doi.org/10.1371/journal.pone.0034145

Stoffel M, Lievens M, Dieussaert I, et al (2003) Immunogenicity of Twinrix^{TM} in older adults: a critical analysis. Expert Rev Vaccines 2:9–14. https://doi.org/10.1586/14760584.2.1.9

Suaya JA, Jiang Q, Scott DA, et al (2018) Post hoc analysis of the efficacy of the 13-valent pneumococcal conjugate vaccine against vaccine-type community-acquired pneumonia in at-risk older adults. Vaccine 36:1477–1483. https://doi.org/10.1016/j.vaccine.2018.01.049

Tacconelli E, Carrara E, Savoldi A, et al (2018) Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 18:318–327. https://doi.org/10.1016/S1473-3099(17)30753-3

Taylor DN, Pollard RA, Blake PA (1983) Typhoid in the United States and the risk to the international traveler. J Infect Dis 148:599–602. https://doi.org/10.1093/infdis/148.3.599

Taylor DN, Treanor JJ, Strout C, et al (2011) Induction of a potent immune response in the elderly using the TLR-5 agonist, flagellin, with a recombinant hemagglutinin influenza-flagellin fusion vaccine (VAX125, STF2.HA1 SI). Vaccine 29:4897–4902. https://doi.org/10.1016/j.vaccine.2011.05.001

Tenforde MW, Olson SM, Self WH, et al (2021) Effectiveness of Pfizer-BioNTech and Moderna vaccines Against COVID-19 among hospitalized adults aged ≥65 Years —January-March 2021. Mmwr 70:674–679

Thompson AR, Klein NP, Downey HJ, et al (2019) Coadministration of 13-valent pneumococcal conjugate and quadrivalent inactivated influenza vaccines in adults previously immunized with polysaccharide pneumococcal vaccine 23: a randomized clinical trial. Hum Vaccines Immunother 15:444–451. https://doi.org/10.1080/21645515.2018.1533777

Thompson MG, Burgess JL, Naleway AL, et al (2021) Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers—Eight U.S. Locations, December 2020–March . MMWR Morb Mortal Wkly Rep 70:495–500. https://doi.org/10.15585/mmwr.mm7013e3

Thompson WW, Shay DK, Weintraub E, et al (2004) Influenza-associated hospitalizations in the United States. J Am Med Assoc 292:1333–1340. https://doi.org/10.1001/jama.292.11.1333

Thompson WW, Shay DK, Weintraub E, et al (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. J Am Med Assoc 289:179–186. https://doi.org/10.1001/jama.289.2.179

Tian JH, Fuhrmann SR, Kluepfel-Stahl S, et al (2012) A novel fusion protein containing the receptor binding domains of C. difficile toxin A and toxin B elicits protective immunity against lethal toxin and spore challenge in preclinical efficacy models. Vaccine 30:. https://doi.org/10.1016/j.vaccine.2012.04.045

Tisa V, Barberis I, Faccio V, et al (2016) Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden. J Prev Med Hyg 57:E28–E33

Treanor JJ, Essink B, Hull S, et al (2013) Evaluation of safety and immunogenicity of recombinant influenza hemagglutinin (H5/Indonesia/05/2005) formulated with and without a stable oil-in-water emulsion containing glucopyranosyl-lipid A (SE + GLA) adjuvant. Vaccine 31:5760–5. https://doi.org/10.1016/j.vaccine.2013.08.064

Tregoning JS, Russell RF, Kinnear E (2018) Adjuvanted influenza vaccines. Hum Vaccines Immunother 14:550–564. https://doi.org/10.1080/21645515.2017.1415684

Trzonkowski P, Myśliwska J, Szmit E, et al (2003) Association between cytomegalovirus infection, enhanced proinflammatory response and low level of anti-hemagglutinins during the anti-influenza vaccination—An impact of immunosenescence. Vaccine 21:3826–3836. https://doi.org/10.1016/S0264-410X(03)00309-8

United Nations, Department of Economic and Social Affairs, Population Division (2019) World Population Prospects 2019: Highlights. (ST/ESA/SER.A/423)

Vadlamudi NK, Parhar K, Altre Malana KL, et al (2019) Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis. Vaccine 37:1021–1029. https://doi.org/10.1016/j.vaccine.2019.01.014

van Aalst R, Gravenstein S, Mor V, et al (2020) Comparative effectiveness of high dose versus adjuvanted influenza vaccine: A retrospective cohort study. Vaccine 38:372–379. https://doi.org/10.1016/j.vaccine.2019.09.105

Van Damme P, Burgess M (2004) Immunogenicity of a combined diphtheria-tetanus-acellular pertussis vaccine in adults. Vaccine 22:305–308. https://doi.org/10.1016/j.vaccine.2003.08.012

van den Berg SPH, Warmink K, Borghans JAM, et al (2019) Effect of latent cytomegalovirus infection on the antibody response to influenza vaccination: a systematic review and meta-analysis. Med Microbiol Immunol 208:305–321. https://doi.org/10.1007/s00430-019-00602-z

van den Biggelaar AHJ, Pomat WS (2013) Immunization of newborns with bacterial conjugate vaccines. Vaccine 31:2525–2530. https://doi.org/10.1016/j.vaccine.2012.06.019

Van Doorn E, Liu H, Huckriede A, Hak E (2016) Safety and tolerability evaluation of the use of Montanide ISATM51 as vaccine adjuvant: A systematic review. Hum Vaccines Immunother 12:159–169. https://doi.org/10.1080/21645515.2015.1071455

Vecchi S, Bufali S, Uno T, et al (2014) Conjugation of a TLR7 agonist and antigen enhances protection in the S. pneumoniae murine infection model. Eur J Pharm Biopharm 87:310–317. https://doi.org/10.1016/j.ejpb.2014.01.002

Vila-Córcoles A, Ochoa-Gondar O, de Diego C, et al (2019) Pneumococcal vaccination coverages by age, sex and specific underlying risk conditions among middle-aged and older adults in Catalonia, Spain, 2017. Eurosurveillance 24:1–9. https://doi.org/10.2807/1560-7917.ES.2019.24.29.1800446

Vink P (2017) Immunogenicity and safety of a candidate subunit adjuvanted herpes zoster vaccine in adults with solid tumors vaccinated before or during immunosuppressive chemotherapy treatment: a Phase II/III, randomized clinical trial. Open Forum Inf Dis 4:S417–S418

Vink P, Ramon Torrell JM, Sanchez Fructuoso A, et al (2019) Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in chronically immunosuppressed adults following renal transplant: a Phase III, randomized clinical trial. Clin Infect Dis 70:181–190. https://doi.org/10.1093/cid/ciz177

Voysey M, Ann S, Clemens C, et al (2020) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2 : an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 1–13

Voysey M, Costa Clemens SA, Madhi SA, et al (2021) Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 19:1–11. https://doi.org/10.1016/S0140-6736(21)00432-3

Walsh EE, Frenck RW, Falsey AR, et al (2020) Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 383:2439–2450. https://doi.org/10.1056/nejmoa2027906

Ward BJ, Pillet S, Charland N, et al (2018) The establishment of surrogates and correlates of protection: Useful tools for the licensure of effective influenza vaccines? Hum Vaccines Immunother 14:647–656. https://doi.org/10.1080/21645515.2017.1413518

Wei C-J, Crank MC, Shiver J, et al (2020) Next-generation influenza vaccines: opportunities and challenges. Nat Rev Drug Discov 19:239–252. https://doi.org/10.1038/s41573-019-0056-x

Weinberg A, Lazar AA, Zerbe GO, et al (2010) Influence of age and nature of primary infection on varicella-zoster virus–specific cell-mediated immune responses. J Infect Dis 201:1024–1030. https://doi.org/10.1086/651199

Weinberg A, Popmihajlov Z, Schmader KE, et al (2019) Persistence of varicella-zoster virus cell-mediated immunity after the administration of a second dose of live herpes zoster vaccine. J Infect Dis 219:335–338. https://doi.org/10.1093/infdis/jiy514

Weinberger B (2017) Adult vaccination against tetanus and diphtheria: the European perspective. Clin Exp Immunol 187:93–99. https://doi.org/10.1111/cei.12822

Weinberger B (2018) Adjuvant strategies to improve vaccination of the elderly population. Curr Opin Pharmacol 41:34–41. https://doi.org/10.1016/j.coph.2018.03.014

Weinberger B, Haks MC, de Paus RA, et al (2018a) Impaired immune response to primary but not to booster vaccination against hepatitis B in older adults. Front Immunol. https://doi.org/10.3389/fimmu.2018.01035

Weinberger B, Joos C, Reed SG, et al (2016) The stimulatory effect of the TLR4-mediated adjuvant glucopyranosyl lipid A is well preserved in old age. Biogerontology 17:177–187. https://doi.org/10.1007/s10522-015-9576-x

Weinberger B, Keller M, Fischer KH, et al (2010) Decreased antibody titers and booster responses in tick-borne encephalitis vaccinees aged 50–90 years. Vaccine. https://doi.org/10.1016/j.vaccine.2010.03.024

Weinberger B, Keller M, Grubeck-Loebenstein B (2017) Long-term maintenance of diphtheria-specific antibodies after booster vaccination is hampered by latent infection with Cytomegalovirus. Immun Ageing 14:16. https://doi.org/10.1186/s12979-017-0099-y

Weinberger B, Keller M, Putzer C, et al (2018b) Protection against Tetanus and Diphtheria in Europe: The impact of age, gender and country of origin based on data from the MARK-AGE Study. Exp Gerontol 105:109–112. https://doi.org/10.1016/j.exger.2017.08.037

Weinberger B, Schirmer M, Matteucci GR, et al (2013) Recall responses to tetanus and diphtheria vaccination are frequently insufficient in elderly persons. PLoSOne 8:e82967

Welsby I, Detienne S, N'Kuli F, et al (2017) Lysosome-dependent activation of human dendritic cells by the vaccine adjuvant QS-21. Front Immunol 7:663. https://doi.org/10.3389/fimmu.2016.00663

Weltevrede M, Eilers R, de Melker HE, van Baarle D (2016) Cytomegalovirus persistence and T-cell immunosenescence in people aged fifty and older: A systematic review. Exp Gerontol 77:87–95. https://doi.org/10.1016/j.exger.2016.02.005

Wilkinson K, Wei Y, Szwajcer A, et al (2017) Efficacy and safety of high-dose influenza vaccine in elderly adults: A systematic review and meta-analysis. Vaccine 35:2775–2780. https://doi.org/10.1016/j.vaccine.2017.03.092

Wolters B, Junge U, Dziuba S, Roggendorf M (2003) Immunogenicity of combined hepatitis A and B vaccine in elderly persons. Vaccine 21:3623–3628. https://doi.org/10.1016/S0264-410X(03)00399-2

World Health Organisation (2021) COVID-19 vaccine tracker and landscape. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Wu YCB, Kipling D, Dunn-Walters DK (2012) Age-related changes in human peripheral blood IGH repertoire following vaccination. Front Immunol 3:1–12. https://doi.org/10.3389/fimmu.2012.00193

Xie H, Wan XF, Ye Z, et al (2015) H3N2 Mismatch of 2014-15 Northern Hemisphere Influenza Vaccines and Head-to-head Comparison between Human and Ferret Antisera derived Antigenic Maps. Sci Rep 5:1–10. https://doi.org/10.1038/srep15279

Yang WH, Dionne M, Kyle M, et al (2013) Long-term immunogenicity of an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine in young and elderly adults: An observer-blind, randomized trial. Vaccine 31:4389–4397. https://doi.org/10.1016/j.vaccine.2013.07.007

Yao X, Hamilton RG, Weng N ping, et al (2011) Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine 29:5015–5021. https://doi.org/10.1016/j.vaccine.2011.04.077

Yawn BP, Gilden D (2013) The global epidemiology of herpes zoster. Neurology 81:928–930. https://doi.org/10.1212/wnl.0b013e3182a3516e

Young F, Marra F (2011) A systematic review of intradermal influenza vaccines. Vaccine 29:8788–8801. https://doi.org/10.1016/j.vaccine.2011.09.077

Zimmerman RK, Nowalk MP, Chung J, et al (2016) 2014–2015 influenza vaccine effectiveness in the united states by vaccine type. Clin Infect Dis 63:1564–1573. https://doi.org/10.1093/cid/ciw635

Chapter 8
Immunosenescence and Cancer

Gisele W. B. Colleoni and Valquiria Bueno

Abstract The probability to develop invasive cancer increases enormously for individuals aged 70 years and more. In addition, cancer has been the first cause of death for individuals aged 60–79 years. In oldest age individuals (80 years and more) cancers such as breast and colorectal are mostly diagnosed at a metastatic stage with the low survival compared to other age groups. The treatment of cancer in old individuals is a challenge and a further knowledge of the tumor development in aged host immune system is crucial to develop individualized therapy and thus benefit this population. The lifelong exposition to carcinogens and insults increases the risk for cancer development and a physiological induction of cell senescence facilitates the clearance of damaged cells by the immune system. However, senescence seems to play a dual role leading to the clearance of tumor cells but also inducing proliferation and induction of tumor vascularization. Immunosenescence is another age-related event linked to cancer progression both for the decreased immunosurveillance and for the chronic low-grade of systemic inflammation (inflammageing) observed in ageing individuals. In this context, cancer immunotherapy has been administered aiming the enhancement of the immune response against the tumor but only a fraction of patients has achieved long lasting remissions. Senolytics such as dasatinib and querceting have been developed to selectively kill senescent cells and potentiate anticancer therapies.

Keywords Ageing · Cancer · Immunosenescence · Inflammageing

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Abbreviations

ARG1	Arginase 1
B-ALL	B cell Acute Lymphoblastic Leukemia
BCG	Bacille Calmette-Guerin
Bregs	B Regulatory cells
CAR	Chimeric Antigen Receptors
CMV	Cytomegalovirus
COVID-19	Coronavirus 19
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cells
DNA	Deoxyribonucleic Acid
gMDSC	Granulocytic Myeloid-derived suppressor cells
HPV	Human Papillomavirus
IDO1	Indoleamine 2,3-dioxygenase
IL-10	Interleukin 10
iNOS	Inducible Nitric Oxide Synthase
l-Arg	**L**-Arginine
M1	Macrophage type 1
M2	Macrophage type 2
mMDSC	Monocytic Myeloid-derived suppressor cells
MDSC	Myeloid-derived suppressor cells
MHC class I	Major histocompatibility complex class I
MHC class II	Major histocompatibility complex class II
NK	Natural killer
Nor-NOHA	N-hydroxy-nor-L-arginine
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
ROS	Reactive Oxygen Species
TAA	Tumor-associated antigens
TAM	Tumor-Associated Macrophages
TCR	T cell receptor complex
TGF-β	Transforming Growth Factor beta
Th1	T cell helper 1
Th2	T cell helper 2
Tregs	T regulatory cells
USA	United States of America
UV	Ultraviolet

8.1 Cancer and Ageing

A USA study showed that the probability to develop invasive cancer in all sites during the period 2014–2016 for individuals aged 50–59 years was 6.2% for men and 6.4% women, whereas for individuals aged 60–69 years the probability was 13.3% and 10.2% respectively. These probabilities increased enormously for the individuals aged 70 years and more to 32.7% (men) and 26.7% (women). Breast (7.0%), lung (6.0% men and 4.8% women), prostate (8.2%), and colorectal cancer (3.3% men and 3.0% women) were the most incident sites for the population aged 70 years and more. In addition, cancer was the first cause of death for male and female aged 60–79 years and second cause of death for the age of 80 and more (Siegel et al. 2020). The higher incidence of cancer development and death in individuals older than 60 years compared to younger counterparts are not exclusive of the USA population but have been a common finding around the world (Bray et al. 2018). In Americans aged 85 years and more (oldest age), DeSantis et al. (2019) observed that some cancers (i.e. breast and colorectal) are mostly diagnosed at a metastatic stage with a relative lowest survival of any age group.

The treatment of cancer in oldest age individuals is a challenge due to comorbidities, decrease of the functional reserve, impaired cognition, reduced immunosurveilance, and polypharmacy which could increase the risk of toxicity to cancer therapies. A further knowledge of how tumor cells develop and escape from the aged host immune system could lead to individualized oncology and thus benefit older individuals.

8.2 Cancer Initiation and Progression

Considering that the human organism is exposed to carcinogens and insults capable to transform healthy cells in tumor cells, the lifelong exposition to these agents will increase the probability to develop malignancies (Fulop et al. 2010; Sportès and Hakim 2009). The common carcinogens such as tobacco, obesity, sedentarism, alcohol consumption, exposure to ultraviolet sunlight or tanning devices (http://cancerprogressreport.org/) could be avoided or reduced and therefore, many cases of cancer are preventable. However, several years of DNA damage in healthy cells disrupts their physiological growth and induces the development of malignant tumors. As a consequence, cancer cells present thousands of mutations, but only a small subset are "drivers" that trigger tumor growth and allow cancer cells to survive. Therefore, accumulation of mutations can be considered an age-related event that impact the pathogenesis of malignancies (Hanahan and Weinberg 2011). Another age-related cause that leads to tumor development is the lower efficacy of the immune system with decreased immunosurveillance and impaired immunity against tumor antigens (Foster et al. 2011) (Fig. 8.1).

One mechanism that fight cancer initiation and progression due to continuous DNA damage is the physiological induction of cell senescence which facilitates the clearance of damaged cells by NK cells, macrophages, and T cells (Burton and Stolzing 2018). Oncogene activation induces senescence and cell cycle arrest inhibiting thus a benign tumor progression to malignant tumor (Wajapeyee et al. 2008). In addition, the loss of tumor suppressor genes (TSG) can also induce cell senescence (Ahmad et al. 2011).

The senescence-associated secretory phenotype (SASP, cytokines and chemokines) activate innate and adaptive immunity for the clearance of tumor cells (Vicente et al. 2016). However, SASP play a dual role in the tumor microenvironment and can also induce tumor cell proliferation and induction of tumor vascularization (maladaptive senescence) (Toso et al. 2015). In addition, SASP is capable to attract myeloid-derived suppressor cells (MDSCs) which infiltrate the tumor microenvironment, block the immune response, and impairs the chemotherapy-induced senescence (Jackson et al. 2012).

Therapy induced-senescence (TIS) has been used to treat cancer and it can both impair the proliferation of tumor cells (Ewald et al. 2010) but also, some chemotherapy agents prevent the destruction of senescent tumor cells from the immune system. In addition, TIS enhances the process of ageing in normal cells of the patient (Marcoux et al. 2013).

8.3 Cancer and Immune System

Immune cells are attracted to tumor microenvironment and recognize molecules in senescent cells such as the receptor for CD58/ICAM (recognized by NK cells); macrophages express receptors (CD36, IgM, SIRPα, and leptins) for glycans, lipids, and vimentin that are present in senescent cells; T cells recognize antigens via TCR (Vicente et al. 2016; Burton and Stolzing 2018). Cytotoxic NK kills senescent cells via granules secretion (Sagiv et al. 2013). Macrophages polarized to M1 are essential for the adequate function of CD4+ T cells and for the phagocytosis of senescent cells (Kang et al. 2011).

During the ageing process, changes occurring in the immune system alter the immunity, increasing thus the susceptibility to cancer development (Isidori et al. 2018) (Fig. 8.1). In older individuals the different subsets of NK cells are redistributed, there is a reduced expression of activating receptors, and the cytotoxicity is impaired. NK activating receptors are also altered in cancer patients suggesting that age and cancer may have a synergistic action in NK cell by decreasing tumor immunosurveillance (Tarazona et al. 2017). T cells present senescence, anergy, and exhaustion which contributes differently for cancer progression. The reduced percentage of naïve T cells and increased percentage of effector memory T cells (mainly terminally differentiated CD8+) are common findings in aged individuals (Alves et al. 2018) and in addition to the reduced diversity of the TCR (T cell receptor) that impairs the

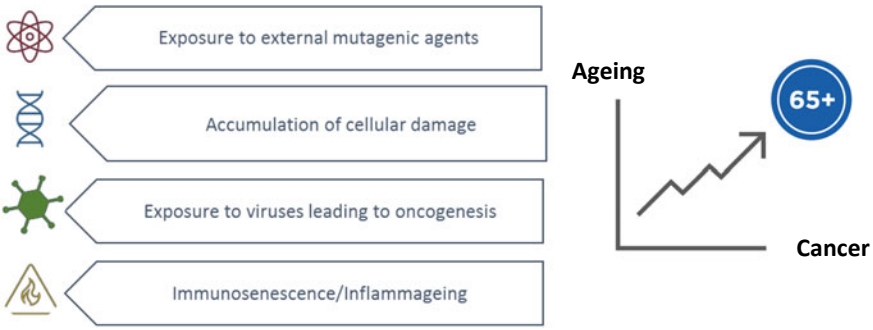

Fig. 8.1 Ageing and cancer: findings and risk factors

response to new cancer antigens (Foster et al. 2011), have been suggested as risks for the development of cancer.

The tumor microenvironment (TME) contains senescent tumor cells, stromal cells, proliferating tumor cells (non-senescent), and immune system cells. Tumor cells present suppressive mechanisms that act on healthy cells before the infiltration of cells from the immune system (Lowe et al. 2004). As T cells (CD4 and CD8) infiltrate the TME, they act as the main eliminators of tumor lesions (elimination phase). The incapacity from the immune system to total clearance of tumor cells but with prevention of tumor outgrowth (equilibrium phase), generates variants of tumor cells which are less immunogenic and thus maintained occult. Tumor cells with less immunogenic capacity expand and reach clinical stages (escape phase). Elimination, equilibrium and escape are phases described for the cancer initiation-progression and are known as cancer immunoedition (reviewed in Ostroumov et al. 2018). Thus, either tumor cells can be suppressed by the immune system or they can escape from immunosurveillance. As example Katlinski et al. (2017) showed that colorectal cancer cells resisted to cytotoxic (CTL)-mediated growth control by downregulation of interferon receptor chain (IFNAR1). In prostate and breast cancer patients with residual drug resistant tumors it was shown that MMPs in senescent cancer cells play a role to avoid immune recognition by NK receptors (NKG2D) cell (Muñoz et al. 2019). TME can also drive T cells to exhaustion causing loss of the effector function and upregulation of receptors of inhibition in T cells (Wherry et al. 2015) which leads tumor cells to escape from immune attack (Figs. 8.2 and 8.3).

Considering that "tumor promoting inflammation" is one of the Hallmarks of Cancer, some cells of the immune system with inflammatory profile are crucial as they provide conditions within the TME that contribute for tumor growth (Hanahan and Weinberg 2011). Therefore, angiogenesis, proliferation, and tissue evasion are facilitated in tumor cells due to the inflammatory cells support. As an example, macrophages polarized as M2 (anti-inflammatory) has been linked to immune suppression, angiogenesis, and tissue remodeling (Mantovani and Sica 2010). In this

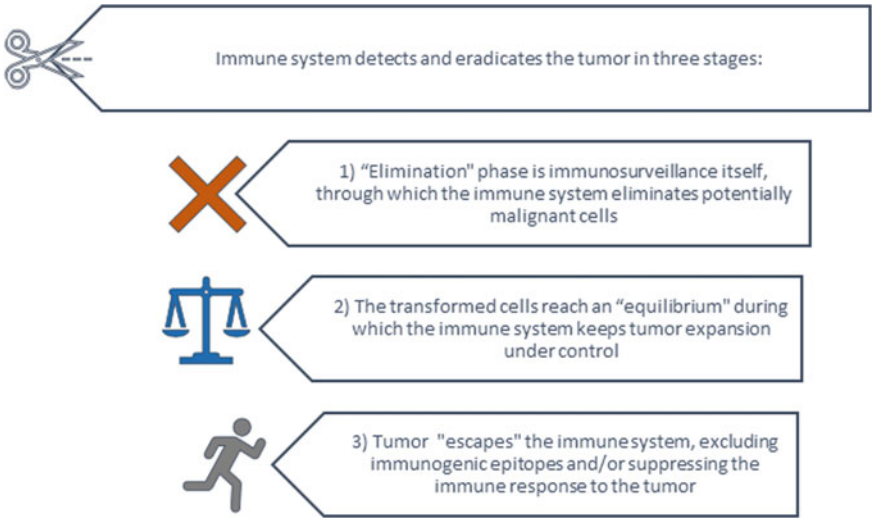

Fig. 8.2 The three phases of cancer immuno-editing: elimination, equilibrium, and escape

context, ageing has been associated with a chronic low-grade of systemic inflammation and thus, cancer and ageing could be linked by the inflammatory process (review in Leonardi et al. 2018).

The most studied group of cells in cancer in the last few decades which are also linked to inflammatory processes are myeloid-derived suppressor cells (MDSCs). In older healthy individuals, two different groups demonstrated an increase in the number of MDSC (Verschoor et al. 2013; Alves et al. 2018) and the maintenance of their suppressive capacity (Magri et al. 2020). These findings suggest an increased suppressive action on the immune system during the ageing process, thereby favoring tumor development. On the other hand, as the tumor itself induces emergency myelopoiesis, and in turn MDSCs, it is difficult to distinguish between the role played by age and by the tumor in the increased frequency and suppressive action of MDSCs. Some studies have shown that MDSCs contribute to tumor progression through suppression of tumor-specific T cell responses, stimulation of tumor angiogenesis, or facilitating tumor cell metastasis. Considering all available cancer therapies, their impaired efficacy has been related, at least in part, to the accumulation of MDSCs and their contribution to an immunosuppressive microenvironment (Shipp et al. 2016; Marvel and Gabrilovich 2015).

Since MDSCs are enhancers of other immunosuppressive cells, such as regulatory T cells (Tregs) and B cells (Bregs), we can assume that MDSCs remodel the immune system, preventing excessive inflammation during the aging process (Salminen et al. 2019).

MDSCs cause suppression of immune cells via oxygen species (ROS) generated by g-MDSCs (granulocytic MDSC), nitric oxide (NO) generated by m-MDSCs (monocytic MDSC), production of arginase and also by secretion of cytokines such

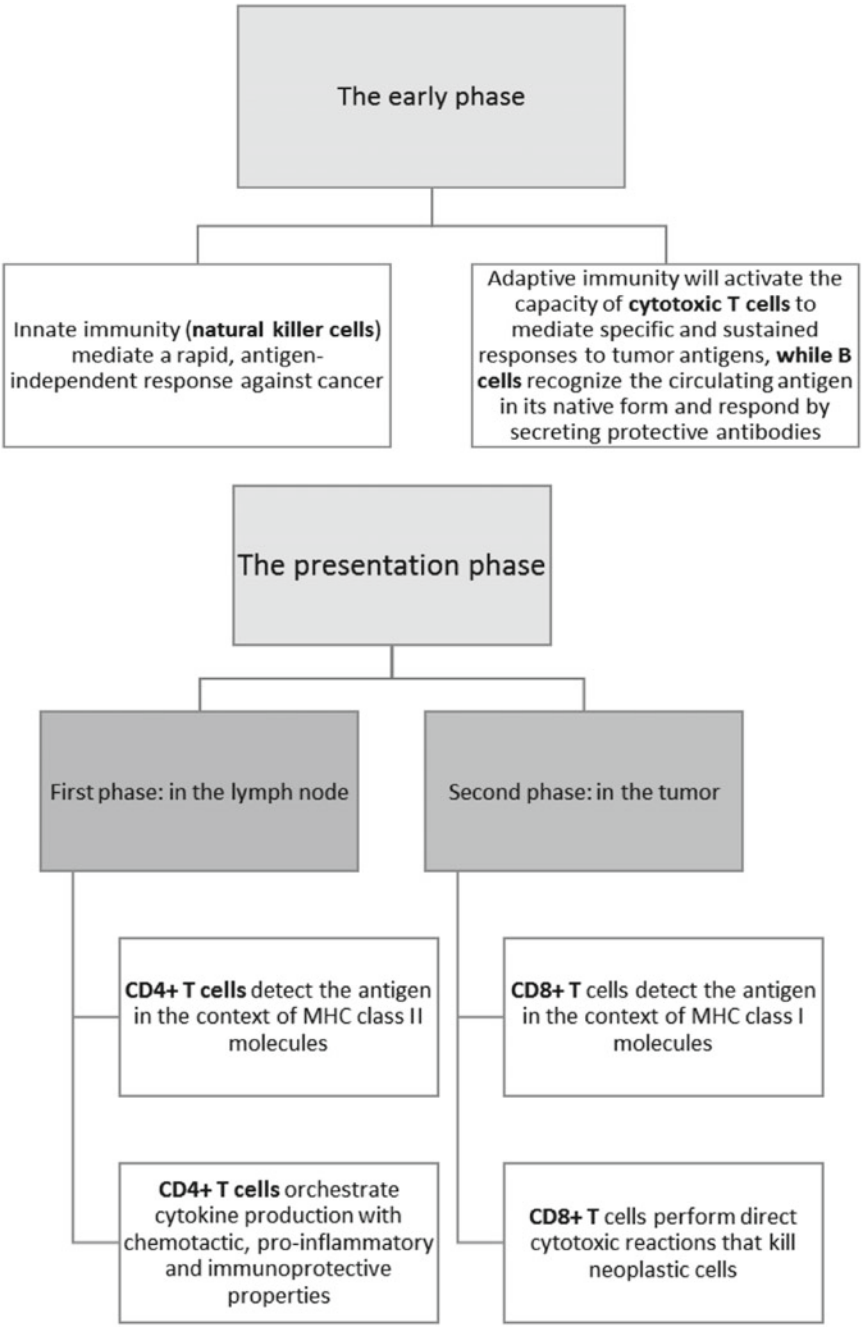

Fig. 8.3 The early and presentation phases of the immune system against cancer

as IL-10 and TGF-β. Arginine is used metabolically by MDSC and, therefore, by removing this substrate from the microenvironment that is also used by T cells, MDSC interferes with T cell proliferation. The consumption of L-arginine (Arg) to produce arginase 1 (ARG1) represents a well-known immunoregulatory mechanism explored by MDSCs and also M2 macrophages (Mondanelli et al. 2019). Another via used by MDSCs is PD-L1- and cytokine-dependent inhibitory mechanisms that inhibit the antitumor effector T cell response (Timosenko et al. 2017).

In cancer MDSCs and DCs overexpression of ARG1 and IDO1 contribute to the reduction of the host anti-tumor immunity (Mondanelli et al. 2019). The use of arginase inhibitors such as Nor-NOHA (N-hydroxy-nor-L-arginine) abrogated the arresting effects of arginase on T-cell proliferation and allowed lymphocyte-dependent tumor reduction (Rodriguez et al. 2017). In addition, as MDSCs polarizes macrophages toward the M2 phenotype, arginase inhibitors could have a double effect in favor of T cells proliferation and preventing the expansion of immunosuppressive TAMs (Mussai et al. 2013).

Considering that the relationship between the immune system and cancer is dynamic and complex, it is not a surprise that cells from the immune system can play dual role in cancer development. The immune system can not only suppress tumor growth by destroying cancer cells and inhibiting their outgrowth, but also promote tumor progression by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth. Human tumors harbor a multitude of somatic gene mutations and epigenetically dysregulated genes, the products of which are potentially recognizable as foreign antigens. The immune system must recognize danger signals and respond accordingly. In this scenario, immune escape and immunotolerance are considered the main mechanisms linked to cancer development (Hong et al. 2019). Therefore, it is essential to further understand the changes occurring in the immune system that could contribute for cancer development and response to current therapy.

In this context, cancer immunotherapy has been developed aiming the enhancement of the immune response against the tumor. The common feature of the immunotherapy is increase T-cytotoxic lymphocytes capability to attack tumor cells (Pisconti et al. 2018).

Immunotherapy approaches aim: (1) “trigger” powerful T cell responses via immune control point block (checkpoint); (2) infusion of immune cells that fight tumors in the body (adoptive cell therapies); (3) be prophylactic or therapeutic (cancer vaccines) (Waldman et al. 2020).

Monoclonal antibodies against the CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed death 1)/PD-L1 (programmed death-ligand 1) resulted in antitumor responses by regulation of activation at various stages of the immune cycle (Pisconti et al. 2018). However, despite the clinical efficacy of checkpoint block, most cancer patients do not yet have long lasting benefits from these therapies: many important types of tumor do not or minimally respond to checkpoint block, including pancreatic cancer, to most colorectal and prostate tumors.

Even in responsive tumors, such as melanoma or lung cancer, only a fraction of patients will achieve long lasting remissions.

Animal models suggest that tumors often activate several receptors in the immunosuppressive pathways. Antibodies to PD-1 / PD-L1 and CTLA-4 showed that the response to blockage in one pathway does not exclude the response to the other. Thus, combining two checkpoints with ipilimumab and nivolumab conferred a significant survival benefit in patients with metastatic melanoma and advanced renal cell carcinoma, leading to FDA approval for these conditions. In addition, some of these tumors may respond to the blocking of alternative checkpoint receptors (Dougan et al. 2019).

Allogeneic hematopoietic stem cell transplants for leukemia represented the first effective adoptive transfer approach clinically implanted, and clinical positive results were mediated by the graft of T cells against the tumor (Waldman et al. 2020).

T-cell chimeric antigen (CAR) receptors are chimeric proteins that assemble a signaling portion similar to the T cell receptor complex (TCR) and the variable domain of an antibody directed to an antigen of interest. CAR T cells designed with specificity for the CD19 cell surface molecule, which is expressed by all B cells, have been successful in treating B cell malignancies. The first clinical implantation of second generation CD19-specific CAR T cells led to durable responses in chronic lymphocytic leukemia (Waldman et al. 2020).

Prophylactic vaccines are used for the prevention of infection with oncogenic viruses. Vaccines against hepatitis B and human papillomavirus reduced the incidence of hepatocellular carcinoma and cervical cancer, respectively. Therapeutic vaccines action is based on the immune system cells which eliminate disease-causing cells that are already neoplastic. The bacillus vaccine Calmette-Guérin (BCG, attenuated *Mycobacterium bovis*), which is generally used as a prophylactic vaccine against tuberculosis, has been reused as a primitive therapeutic vaccine for bladder cancer. Tumor-associated antigens (TAAs) which are highly expressed in tumor cells but not in normal tissues led to new approaches based on therapeutic vaccines, and are in clinical trials for specific tumors, associated or not with other immunotherapies (Waldman et al. 2020).

In summary, despite the promising results of immunotherapy, a minority of cancer patients achieve long-lasting responses against tumor. Therefore, immunotherapies are in expansion mainly approaching checkpoints (Dougan et al. 2019. Moreover, the decline in the incidence of some common cancers after age 80, such as prostate and breast cancer, has directed research for the further understanding of the age process and its effect on the immune system. Senolytics such as dasatinib and querceting have been developed to selectively kill senescent cells and potentiate anticancer therapies (Birch and Gil 2020).

In conclusion:

- Cancer is a leading cause of morbidity and mortality worldwide
- > 50% of new cancer cases are diagnosed in people aged 65+ years
- Exposure to carcinogens and accumulation of cellular damage are important cancer risk factors in all populations, mainly in 65+ patients
- Immunosenescence is extremely important for cancer development, including immunotolerance and immune escape
- Immunotherapy is an important tool to enhance loss of function in immune system in cancer patients, in special in old individuals

Compliance with Ethical Standards

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Conflict of Interest All authors declare they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Ahmad I, Patel R, Singh LB et al (2011) HER2 overcomes PTEN (loss)-induced senescence to cause aggressive prostate cancer. Proc Natl Acad Sci USA 108:16392–16397. https://doi.org/10.1073/pnas.1101263108

Alves AS, Isimura M, Duarte YAO, Bueno V (2018) Parameters of the immune system and vitamin D levels in old individuals. Front Immunol 9:1122

Birch J, Gil J (2020) Senescence and the SASP: many therapeutic avenues. Genes Dev 1;34(23–24):1565–1576. https://doi.org/10.1101/gad.343129.120

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424. https://doi.org/10.3322/caac.21492

Burton DGA, Stolzing A (2018) Cellular senescence: immunosurveillance and future immunotherapy. Ageing Res Rev 43:17–25. https://doi.org/10.1016/j.arr.2018.02.001

DeSantis CE, Miller KD, Dale W, Mohile SG, Cohen HJ, Leach CR, Goding Sauer A, Jemal A, Siegel RL (2019) Cancer statistics for adults aged 85 years and older, 2019. CA Cancer J Clin 69(6):452–467. https://doi.org/10.3322/caac.21577

Dougan M, Dranoff G, Dougan SK (2019) Cancer immunotherapy: beyond checkpoint blockade. Ann Rev Cancer Biol 3(1):55–75

Ewald JA, Desotelle JA, Wilding G et al (2010) Therapy-induced senescence in cancer. J Natl Cancer Inst 102:1536–1546. https://doi.org/10.1093/jnci/djq364

Foster AD, Sivarapatna A, Gress RE (2011) The aging immune system and its relationship with cancer. Aging Health 7(5):707–718

Fulop T, Kotb R, Fortin CF, Pawelec G, De Angelis F, Larbi A (2010) Potential role of immunosenescence in cancer development. Ann NY Acad Sci 1197:158–165

Hanahan D, Weinberg R (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674

Hong H, Wang Q, Li J, Liu H, Meng X, Zhang H (2019) Aging, cancer, and immunity. J Cancer 10(13):3021–3027

Isidori A, Loscocco F, Ciciarello M, Corradi G, Lecciso M, Ocadlikova D, Parisi S, Salvestrini V, Amadori S, Visani G, Curti A (2018) Immunosenescence and Immunotherapy in elderly acute Myeloid Leukemia patients: time for a biology-driven approach. Cancers 10:211

Jackson JG, Pant V, Li Q et al (2012) p53-mediated senescence impairs the apoptotic response to chemotherapy and clinical outcome in breast cancer. Cancer Cell 21:793–806. https://doi.org/10.1016/j.ccr.2012.04.027

Kang TW, Yevsa T, Woller N et al (2011) Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. Nature 479:547–551. https://doi.org/10.1038/nature10599

Katlinski KV, Gui J, Katlinskaya YV et al (2017) Inactivation of interferon receptor promotes the establishment of immune privileged tumor microenvironment. Cancer Cel 31:194–207. https://doi.org/10.1016/j.ccell.2017.01.004

Leonardi GC, Accardi G, Monastero R et al (2018) Ageing: from inflammation to cancer. Immun Ageing 15:1. https://doi.org/10.1186/s12979-017-0112-5

Lowe SW, Cepero E, Evan G (2004) Intrinsic tumour suppression. Nature 432(7015):307–315. https://doi.org/10.1038/nature03098

Magri S, Masetto E, Solito S, Francescato S, Belluzzi E, Pozzuoli A, Berizzi A, Ruggieri P, Mandruzzato S (2020) Human MDSCs derived from the bone marrow maintain their functional ability but have a reduced frequency of induction in the elderly compared to pediatric donors. Immun Ageing 9;17:27

Mantovani A, Sica A (2010) Macrophages, innate immunity and cancer: balance, tolerance, and diversity. Curr Opin Immunol 22(2):231–237. https://doi.org/10.1016/j.coj.2010.01.009

Marcoux S, Le ON, Langlois-Pelletier C et al (2013) Expression of the senescence marker p16INK4a in skin biopsies of acute lymphoblastic leukemia survivors: a pilot study. Radiat Oncol 8:252. https://doi.org/10.1186/1748-717X-8-252

Marvel D, Gabrilovich DI (2015) Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. J Clin Invest 125(9):3356–3364

Mondanelli G, Iacono A, Allegrucci M, Puccetti P, Grohmann U (2019) Immunoregulatory interplay between arginine and tryptophan metabolism in health and disease. Front Immunol 10:1565

Muñoz DP, Yannone SM, Daemen A et al (2019) Targetable mechanisms driving immunoevasion of persistent senescent cells link chemotherapy-resistant cancer to aging. JCI Insight 5(14):e124716. https://doi.org/10.1172/jci.insight.124716

Mussai F, De Santo C, Abu-Dayyeh I et al (2013) Acute myeloid leukemia creates an arginase-dependent immunosuppressive microenvironment. Blood 122(5):749–758

Ostroumov D, Fekete-Drimusz N, Saborowski M et al (2018) CD4 and CD8 T lymphocyte interplay in controlling tumor growth. Cell Mol Life Sci 75(4):689–713. https://doi.org/10.1007/s00018-017-2686-7

Pisconti S, Della Vittoria Scarpati G et al (2018) The evolving landscape of immunotherapy against cancer. WCRJ 5(1):e1042

Rodriguez PC, Ochoa AC, Al-Khami AA (2017) Arginine metabolism in myeloid cells shapes innate and adaptive immunity. Front Immunol 8. https://doi.org/10.3389/fimmu.2017.00093

Sagiv A, Biran A, Yon M et al (2013) Granule exocytosis mediates immune surveillance of senescent cells. Oncogene 32:1971–1977. https://doi.org/10.1038/onc.2012.206

Salminen A, Kaarniranta K, Kauppinen A (2019) Immunosenescence: the potential role of myeloid-derived suppressor cells (MDSC) in age-related immune deficiency. Cell Mol Life Sci 76(10):1901–1918

Shipp C, Speigl L, Janssen N et al (2016) A clinical and biological perspective of human myeloid-derived suppressor cells in cancer. Cell Mol Life Sci 73:4043–4061

Siegel RL, Miller MD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70(1):7–30. https://doi.org/10.3322/caac.21590

Sportès C, Hakim FT (2009) Aging, immunity, and cancer. In: Fulop T, Franceschi C, Hirokawa K, Pawelec G (eds) Handbook on immunosenescence: basic understanding and clinical applications. Springer, Berlin, Germany

Tarazona R, Sanchez-Correa B, Casas-Avilés I et al (2017) Immunosenescence: limitations of natural killer cell-based cancer immunotherapy. Cancer Immunol Immunother 66(2):233–245. https://doi.org/10.1007/s00262-016-1882-x

Timosenko E, Hadjinicolaou AV, Cerundolo V (2017) Modulation of cancer-specific immune responses by amino acid degrading enzymes. Immunotherapy 9(1):83–97

Toso A, Di Mitri D, Alimonti A (2015) Enhancing chemotherapy efficacy by reprogramming the senescence-associated secretory phenotype of prostate tumors: a way to reactivate the antitumor immunity. OncoImmunology 4:e994380. https://doi.org/10.4161/2161402X.2014.994380

Verschoor CP, Johnstone J, Millar J, Dorrington MG, Habibagahi M, Lelic A, Loeb M, Bramson JL, Bowdish DM (2013) Blood CD33(+) HLA-DR(−) myeloid-derived suppressor cells are increased with age and a history of cancer. J Leukoc Biol 93(4):633–637

Vicente R, Mausset-Bonnefont AL, Jorgensen C et al (2016) Cellular senescence impact on immune cell fate and function. Aging Cell 15:400–406. https://doi.org/10.1111/acel.12455. www.cancer.gov/about-cancer/understanding/statistics

Wajapeyee N, Serra RW, Zhu X et al (2008) Oncogenic BRAF induces senescence and apoptosis through pathways mediated by secreted protein IGFBP7. Cell 132:363–374. https://doi.org/10.1016/j.cell.2007.12.032

Waldman AD, Fritz JM, Lenardo MJ (2020) A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol 20:651–668

Wherry EJ, Kurachi M (2015) Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 15:486–499. https://doi.org/10.1038/nri3862

Chapter 9
Immunosenescence and Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is the most frequent cause of dementia due to neurodegeneration. It is stated that the most important risk factor for the late onset AD development is age. AD develops during decades and appears most of the time after 65 years of age. Even though its incidence is increasing with age but not all the centenarians are suffering from AD. The most important underlying age-related factor is immunosenescence/inflammaging. Indeed, aging is associated with immune changes which are thought to be the most prevalent cause of the age-related chronic inflammatory diseases. However, it is now postulated that the changes occurring with aging in the immune system may not be only detrimental but also adaptive. Therefore,

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in this review we will describe whether and how immunosenescence/inflammaging may contribute to the development of AD. We will also examine whether this can lead to novel treatment approaches different form the current.

Keywords Alzheimer's disease (AD) · Mild cognitive impairment (MCI) · Immunosenescence · Inflammaging neuroinflammation · Monocytes · Macrophages · Phagocytosis · Free radicals · Cytokines · Signaling

9.1 Introduction

Aging is considered by many scientists as the most important risk factor for the development of the so-called chronic age-related diseases (ARD) (Fülöp et al. 2016; Franceschi et al. 2018; Barbé-Tuana et al. 2020). What are these diseases and why it is so? This concept gained popularity mainly because most of these diseases such as diabetes, neurocognitive disorders (dementia), cancers and cardiovascular diseases have a common denominator which is chronic inflammation (Hansen 2018; Kurakim and Bredsen 2020). Therefore, as aging is associated with immunosenescence including its corollary the inflammaging, the slipping extension of this fact became a true overarching paradigm (Barbé-Tuana et al. 2020). Thus, as aging is characterised by immunosenescence/inflammaging and most of the ARD have inflammation as a common root, therefore age is the most important risk factor for these chronic inflammatory diseases, especially AD (Tam and Pasternak 2012; Kern and Behl 2009). However altogether only around 10% of older subjects over 65 of age are affected by AD (Solana et al. 2018). So, could age be the greatest risk factor for AD? Considering these data, the obvious conclusion is no, however it should be recognised that the age-related immune changes may contribute.

Among these diseases one of the most frequent and devastating is dementia and most specifically the Alzheimer's disease (AD) (Prince et al. 2013). This disease was named after Alois Alzheimer who more than 100 years ago described the main pathological hallmarks of the disease from the pathological and clinical point of view (Hardy et al. 2002). This led to the extraordinary development of the research on AD but unfortunately this was not translated neither in the real understanding of the etiology of AD nor in even a minimal capacity of treatment (Mehta et al. 2017; Long et al. 2019). So, until now we struggle with a devastating disease that we do not know the cause and have no cure nor prevention. In this chapter we will briefly describe what is AD, what are the putative causes of its onset and how it may be considered as a consequence of the age-related immune changes and what could be the resulting interventions to mitigate the effects of this eventual role of immunosenescence (Fig. 9.1).

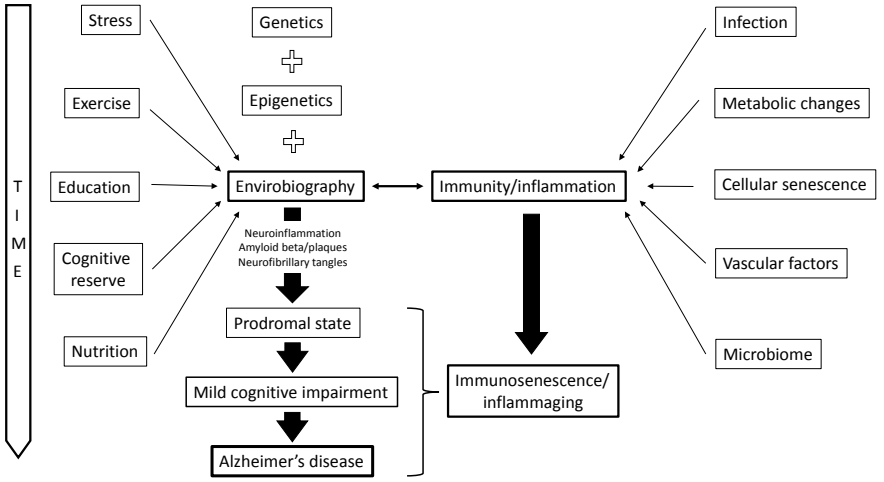

Fig. 9.1 Schematic conceptualization of the role of various factors in the development and clinical development of Alzheimer's disease

9.2 What is AD?

As a systemic inflammatory and clinical syndrome, AD is the most frequent type of dementia mainly affecting the brain (Solana et al. 2018; Paouri and Georgopoulos 2019; Walker et al. 2019). This starts in most of the cases with the loss of memory and speech capacity to continue until the complete disorganization of the whole cognitive sphere and even personality. However, the clinical presentation may be more nuanced and sometimes starting by other symptoms like frontal manifestations. From a pathological aspect, the AD is characterized by the deposition of the extracellular amyloid plaques composed by amyloid beta (Aβ) and by intracellular neurofibrillary tangles composed by hyperphosphorylated tau protein (pTau) (McGeer and McGeer 2013; Hardy and Allsop 1991). This was originally described by Alois Alzheimer, however he already noted that this was not the whole story, but some other alterations might be as important as these changes in the brain. This is even more important as the patient who served to describe the later named AD was most probably a familiar AD, and so her disease was genetically driven (causing around 5% of all cases of the disease).

It is now recognized that AD is a lifelong process which is revealed clinically as we age but the whole pathological process occurs well before old ages when we are only able to diagnose it (Shen et al. 2020). When the cognitive alterations become clinically noticeable the pathological process has been present for decades. Therefore, the pathological process whatever is its cause would not exist as a disease if some changes related to the physiological aging process would not reveal it. It could

be strongly suggested that the immune changes manifesting as so called immunosenescence/inflammaging are the driver of this clinical manifestation of the lifelong process, but not of the disease as currently conceptualized (Constantini et al. 2018; Zhao et al. 2020).

9.3 What Could Be the Cause(s) of AD?

There are many theories to explain the causes of AD. The most prevalent theory is the amyloid cascade hypothesis. This hypothesis states that the depot of Aβ, forming amyloid plaques and initiating the Tau hyperphosphorylation, causes the AD by destroying first the synapses and later leading to a neurodegeneration. Moreover, according to this hypothesis, the deposition of amyloid-beta (Aβ) in senile plaques, leads to inflammation and ultimately to the death of neurons (McGeer and McGeer 2013; Hardy and Allsop 1991; Beyreuther and Masters 1991). However, attempts to decrease the Aβ load or to prevent its formation had no effect on AD (Sacks et al. 2017; Cummings et al. 2018), even if we consider the recent very controversial approval of Aducanumab by the FDA. No cure whatsoever exists or seems to be on the horizon (Mehta et al. 2017; Long et al. 2019). These facts seriously question the validity of this mainstream hypothesis (Itzhaki et al. 2016; Herrup et al. 2015; Ricciarelli and Fedele 2017).

Therefore, new research needs to be pursued to unravel new pathomechanisms which may include the Aβ cascade hypothesis. It is certain that AD is initiated decades before its clinical diagnosis, suggesting that the driving pathological processes occur well before the appearance of symptoms. It has been also observed that AD, as an irreversible condition, displays signs of a systemic inflammation (Paouri and Georgopoulos 2019; Walker et al. 2019; McManus and Heneka 2017; Bolós et al. 2017), suggesting that systemic inflammation could precede the well-established AD hallmarks i.e. deposit of Aβ plaques, neurofibrillary tangles and neuroinflammation (Akiyama et al. 2000; Giunta et al. 2008). This implies that AD results from the chronic progression of these noxious inflammatory events in the brain, notably via Aβ production and accumulation (Webers et al. 2020). This local neuroinflammation continues at a low level throughout life with little negative effect, but repeated stimulations by infections, dysbiosis, vascular (ischemia), metabolic (glucose, lipids) or other insults (free radicals) result each time in an acute inflammatory response which culminate and is particularly severe in the elderly (Maloney and Lahiri 2016; Whalley et al. 2006; Fülöp et al. 2013; Fülöp et al. 2016; Li et al. 2010). These insults gradually cause damage to the blood–brain-barrier (BBB) (Nation et al. 2019; Noe et al. 2020) allowing brain inflammatory mediators to reach the periphery and trigger peripheral innate and adaptive inflammatory responses (Le Page et al. 2018; Ellwardt et al. 2016; Šimić et al. 2019; Dionisio-Santos et al. 2019; Shad et al. 2013).

Recent studies also suggested that neuroinflammation and systemic inflammation could progress over decades following triggering events of infectious origin. Latent virus infections e.g. cytomegalovirus (CMV) have been described as major chronic

innate immunity activators that contribute to inflammaging and therefore to AD development Bauer and Fuente 2016; Biagi et al. 2012; Thevaranjan et al. 2017). It could sound provocative to propose that AD may result from infection, but some major scientific discoveries were made from offensive hypotheses. Nobody would have bet few years ago that peptic ulcer diseases and cervical cancer were both caused by infections (respectively by Helicobacter pylori and human papillomavirus) (Kelly 1998; Caselli et al. 1997; Kessler 2017).

Infection by specific microorganisms as a plausible AD pathomechanism had been voiced several years ago but did not receive significant attention (Block 2019; Dominy et al. 2019; Osorio et al. 2019; Singhrao and Olsen 2019). The demonstration of the presence of HSV-1 viral DNA or spirochetes in AD brains was too instrumental to consider infections as contributors of AD pathogenesis (Wozniak et al. 2007, 2009; Miklossy 2016). Based on the most recent evidence, the infectious hypothesis provides a plausible stimulus for neuroinflammation. Local brain neuroinflammation may exist at a low level throughout life with little negative effect. However, when exacerbated by reactivation of infections or by the persistence of microbial metabolites, the ongoing inflammatory response combined with immunosenescence/inflammaging becomes difficult to control in order to repair the injury (Kritsilis et al. 2018; Blach-Olszewska et al. 2015; Busse et al. 2017). When it becomes chronic and a threshold of neuron death is surpassed, the disease manifests itself clinically in the brain with irreversible damages (Leszek et al. 2016; Di Benedetto et al. 2017; Goldeck et al. 2016).

It is of interest to mention that this infection hypothesis was strongly supported by the recent discovery that Aβ is an antimicrobial peptide able to protect the brain tissue from viral and bacterial infections (Bourgade et al. 2015, 2016; Soscia et al. 2010). The epidemiological data as well as the susceptibility genes (e.g. Apolipoprotein E4) also support the infection hypothesis (Lopatko et al. 2019). The fact that Aβ is an antimicrobial peptide explain also why these amyloid plaques may be found in normal brains as the so-called cemetery for microbes inside the biofilms (Miklossy 2016; Perl 2010; Fülöp et al. 2018a, b, c).

Besides this infection hypothesis since many years other hypotheses gain importance for the development of AD, the vascular hypothesis being one of the oldest. Even if there are plaques, AD is only clinically manifested when the vascular burden becomes overwhelming as it was shown in the Nunn study. Ischemia was also shown to be one of the triggers of Aβ production (Li et al. 2007; Han and Fukunaga 2009). Ischemia is a powerful trigger of the neuroinflammatory process by the production of the free radicals, pro-inflammatory cytokines and chemokines. All these processes initiated by ischemia contribute to AD development by inducing the preceding linflammation (Marchesi 2011). Recently, the cellular senescence was also favoured as the main source of the neuroinflammation (Walton et al. 2020).

Whatever is the exact cause of AD the main factors are age, genetics, epigenetics and environmental factors in its development (Kurakin and Bredesen 2020; Komleva et al. 2021; López-Otín et al. 2013). Besides central or peripheral infections, other peripheral stressors including gastrointestinal inflammation, dysbiosis, toxic products as well as metabolic disorders (diabetes, obesity and atherosclerosis)

via innate immunity activation leads to neuroinflammation resulting in AD (Komleva et al. 2021; Kowalski and Mulak 2019; Cai et al. 2013). These environmental factors contribute for at least 40% to AD development, beside the well-established genetic markers (Kremen et al. 2019). This means that age could be a risk factor but in reality, lifelong environmental factors have much more influence in the development of the disease. All the envirobiographic changes, including nutrition, physical activity, cognitive stimulation/education, hand-in-hand with the lifelong immunobiography and genetic susceptibility, contribute to the development of AD (Ngandu et al. 2015). This envirobiography is the key to explain the heterogeneity of the pathological process, the clinical manifestations and the difficulty to find a single treatment. Therefore, it seems to be much more important that age but also an elusive health parameter to measure yet.

9.4 What is Immunosenescence/Inflammaging?

Aging is accompanied by many physiological changes which lead to the decrease of the body reserves ending up with a homeostenosis condition (i.e. a reduction in the ability to maintain homeostasis/homeodynamics). The immune system is not an exception from this dynamic change leading also, due to the lifelong immunobiography/envirobiography, to a homeostenosis state composed from adaptative and maladaptative parts depending on the hormesis capacity of the entire organism (Fülöp et al. 2020a, b). The preponderance of one or the other will determine the protective role or disease-favouring-role of the older immune system.

The constant internal and external challenges are shaping the immune system through the entire life. Immune cells are able to react to various challenges via the damage associated molecular patterns (DAMPs) generated by injured cells and pathogen associated molecular patterns (PAMPs) (Kumar et al. 2011; Magrone et al. 2020). This is occurring through patterns recognition receptors (PRR) including the Toll-like receptors (TLRs), NOD-like receptors (NLR) and retinoic acid-inducible gene-I-like receptors (RLRs). As the immune system is in a such central position via its fundamental role for life by fighting all noxious stresses that its changes during aging will likely influence the clinical manifestation of most of the age-related diseases (Fülöp et al. 2018). Therefore, it is conceivable that these changes in the immune system may also drive the clinical apparition of AD (Fülöp et al. 2018a).

We will briefly describe the most important changes which may affect the development of AD. The innate immune system is an ancestral immune response assuring the first line of defence against internal and external challenges such as pathogenic microorganisms and damaged cells. In its prime, the innate immune system is able to return to a quiescent state after neutralizing the aggressions, but with the time-dependent accumulation of stressors, the innate immune cells become more permanently activated even at its "resting" state constituting the "trained innate memory" (Fülöp et al. 2016; Kleinnijenhuis et al. 2012; van der Heijden et al. 2017; Arts et al. 2016; Domínguez-Andrés et al. 2020). This is an excessively adaptable and useful

process based on epigenetic and metabolic changes in innate immune cells. This contributes at any moment of the organism life to protect earlier and stronger to each successive challenge (Ciarlo et al. 2019; Fransceschi et al. 2017).

However, constant challenges lead to an exhaustion and the system become tolerogenic and could result in detrimental effects (Salani et al. 2019). The pro-inflammatory and anti-inflammatory balance will determine the outcome of the aggression as being resolved with an innate memory or becoming chronic and harming the organism. Therefore, this permanent antigenic stimulation contributes to low but significant secretion of pro-inflammatory mediators creating an activation/inhibition disequilibrium and participating to inflammaging (Fransceschi et al. 2000, 2007, 2018a, b).

Non-infectious agents have been implicated in the spreading of inflammatory processes fueling inflammaging over time. The senescence-associated secretory phenotype (SASP) is considered as the main non-infectious trigger of inflammaging (Walton et al. 2020; Magrone et al. 2020; Coppé et al. 2018; Tchkonia et al. 2013; Birch et al. 2017). Senescent cells secrete pro-inflammatory molecules but also exosomes that can modulate immune system functions by transporting regulatory micro-RNAs and proteins through bodily fluids (Campisi 2016; Giuliani 2017; Terlecki-Zaniewicz et al. 2018). The appearance of senescent cells is primarily a protective mechanism against cancer development and reinforcing immunosurveillance, but their continuous formation is becoming detrimental along aging. Therefore, cellular senescence represents a dual process depending on its time of manifestation and the type of secretome induction (Walton et al. 2020).

The innate immune system as the main primary defense of the organism contributes to the immune changes and to inflammaging (Franceschi et al. 2000). All cells composing the innate immune response are impacted by aging but to different degrees (Müller et al. 2019; Goldberg et al. 2020; Bandaranayake and Shaw 2016). Their phenotypic and functional changes may all contribute to the development and progression of AD (Le Page et al. 2018). The monocytes are particularly changing in their phenotypes shifting towards the more inflammatory and senescent type of the so called intermediary and non-classical phenotype (Costantini et al. 2018; Zhao et al. 2020; Magrone et al. 2020). The monocytes at the periphery are also more activated than in physiological conditions. Paradoxically, essential defense functions such as chemotaxis and killing are decreased. These monocytes are able to infiltrate the brain because of the increased permeability of the BBB (Di Benedetto et al. 2017; Huang et al. 2020). Their differentiation in macrophages is skewed with mainly M2 subset with immunosuppressive functions (Nyugen et al. 2010). There is also alteration in Natural Killer (NK) cell phenotype and function with aging (Solana et al. 2018; Solana et al. 2012). Similarly, dendritic cell (DC) antigen presentation to T cells is altered with aging (Gupta 2014). Noteworthy, most of the changes are controversial as they were obtained in laboratory animal models. In humans as it was shown that controlled inflammation was a better predictor of longevity than any other previously thought biomarkers such as telomere shortening (Arai et al. 2015).

The adaptive immunity is taking over when the innate immunity may not cope efficiently with the aggression. Therefore, the adaptive immune system functioning

is basically dependent on the efficiency of the innate immune system and its antigen presenting capacity (e.g. with DCs) and the controlled cytokine production (e.g. IL-12). The antigen presenting capacity but also the number of the naïve CD4+ and CD8+ T cells are decreased with aging (Wong et al. 2013). These data led to the common concept that the adaptive immune system is profoundly altered with aging being responsible for the well-known ARD (Castelo-Branco and Soveral 2014; Pawelec 2018). However, there are still many unsettled questions to really declare that the adaptive immunity is globally decreased. We do not know to what extent the antigen presentation is altered, to what extent the naïve T cells are decreased with aging and most importantly, how these changes may be part of an adaptative process occurring with aging (Fülöp et al. 2020a, b; Pawelec 2020; Pawelec et al. 2020). Therefore, it will be important to optimize the immune resources to assure a better survival and functionality inside the already known challenges. There should be also a balance between the proinflammatory Th17 T cells and regulatory T cells (Tregs) (Magrone et al. 2020). With aging this equilibrium is perturbed; while Th17 become more inflammatory the anti-inflammatory control of Tregs is decreasing as even if their number is increasing the secretion of IL-10 by Tregs is decreased (Schmitt et al. 2013; Salminen 2020; Churov et al. 2020).

Inflammaging was introduced by Franceschi et al. (2000) as a basic characteristic of the biology of aging. Since its original description, the concept of inflammaging evolved considerably. From the concept of disbalance between the innate and adaptive immunity, in favour of the innate part other factors have been discovered and the molecular bases were also described. Thus, the roles of cellular senescence (SASP), the microbiome, the mitochondrial metabolic changes have been associated (Fülöp et al. 2019). The central role of the NF-kB is now well recognized as it is activated via various receptors and transduction pathways, but also by ROS, cellular senescence and DNA damage, in the increased production of IL-6, TNFα as hallmark of inflammaging (Smale 2011; Salvioli et al. 2013). In the meantime, another way to produce pro-inflammatory cytokines (e.g. IL-1) is via the NLR mediated the inflammasome activation (Humphries and Fitzgerald 2019). Inflammasome activation has numerous similar mediators than the NF-kB activation and among them, particularly the ROS and Aβ (Hu et al. 2019). It is also to mention that the nature has foreseen many possible control mechanisms to avoid the overactivation of inflammasome such as the stimulation of AMPK, Sirtuins, the type I interferon and autophagy (Bae et al. 2016; Price et al. 2012; de Kreutzenberg et al. 2015).

Together, inflammaging is characterized by an inflammatory status that is chronic, systemic and low grade. The level of cytokines often remains within the normal range (Sanada et al. 2018; Frasca et al. 2017; Rubino et al. 2019), justifying why inflammaging is also referred as low-grade inflammation. Considering all these factors, aging, associated with inflammaging, may be the most important risk factor for the clinical manifestation of late onset AD (Tam et al. 2012; Kern and Behl 2009; Castellani et al. 2010). Thus, this progressive pro-inflammatory situation, exacerbated with age, creates local and systemic inflammatory responses that activate cytotoxic microglia, unbalanced cytokine production, Aβ accumulation and irreversible

brain damage. Therefore, the innate immune system activation by some still unspecified triggers will result over time in a baseline inflammatory state. At younger age this is compensated by the anti-inflammatory environment however with the passage of time in susceptible individuals the ravages of the environmental damages would lead to AD as it is not anymore counterbalanced. It is of note that in many older subjects this scenario is either delayed or efficiently combatted. This once again means that aging is not the most important risk factors, but the conglomerates of pathological processes driven by lifelong bad habits/envirobiographie. Thus, the question is naturally occurring how immunosenescence/inflammaging may contribute to AD?

9.5 What is the Role of Inflammation in AD Development and Progression?

It took many years to the AD community to accept that inflammation is part of the pathogenesis of AD however it is still mainly considered as the direct result of the Aβ deposition (McGeer and McGeer 2013). In this concept the neuroinflammation is the consequence of AD and not the cause as Aβ produced under various situations would trigger the activation of microglia in the brain via TLR2 and TLR4 receptors resulting in pro-inflammatory cytokine and chemokine production (Selkoe and Hardy 2016; Kumar 2019). Assuming the antimicrobial role of Aβ as described above (Bourgade et al. 2015, 2016; Soscia et al. 2010), still this protective process becomes detrimental when the Aβ can not be anymore ingested and cleared by the cumulative exhausted/senescent microglia and become deposited in diffuse amyloid plaques which in turn continue to activate/stimulate/exhaust microglia (Costantini et al. 2018; Cunningham et al. 2013; Regen et al. 2017; Floden et al. 2011; Wyatt-Johnson and Brutkiewicz 2020). In the meantime, the peripheral immune system is also activated (as the Aβ is both an antigen and enhancer of the T cell reactivity) (Jóźwik et al. 2012) making AD a systemic disease and could be an earlier biomarker of brain inflammation. Therefore, changes in peripheral innate immune biomarkers may also precede by decades the clinical appearance of AD (Busse et al. 2017; Morgan et al. 2019).

Considering the recent progress, the picture is much more complicated than that. It is now well-recognised that the inflammation is preceding by decades the clinical manifestation of dementia. This inflammation may originate from the brain where it would be a reaction to local noxious agents of any sort which would initiate an inflammatory reaction and results in the activation of the local innate system by the stimulation of PAMP and DAMP (Paouri and Georgopoulos 2019; Walker et al. 2019; McGeer and McGeer 2013). One of the most important cytokines implicated is IL-1β which has also a dual role. IL-1β is beneficial at the beginning by activating the microglia to protect the brain, but at long-term becomes deleterious and causes microgliosis in AD (Licastro et al. 2000; Dansokho et al. 2016). The local innate system is composed mainly from microglia and astrocytes. These cells under

continuous stimulation will secrete pro-inflammatory mediators via the activation of NF-kB and inflammasome which will reinforce the secretion of antimicrobial Aβ by neurons (Kurakin and Bredesen 2020; Costantini et al. 2018). This Aβ will initially fight the infections and may neutralize other toxic substances (Kumar et al. 2016a, b). Thus, the activated microglia will try to eliminate the aggressors and create dense core plaques which will be a sort of Aβ dense cemetery for the aggressors fueled and organized by the Aβ (Fyfe 2021). These new data shed light on the complex role of microglia which at the beginning of the process, by their inflammatory action, have a strongly protective activity (Wyatt-Johnson SK and Brutkiewicz 2020). Indeed, this is a very efficient way for decades to control both the aggressions/pathogens and the Aβ deposition by creating the dense-core plaques. Therefore, amyloid plaques may be seen in almost every aging brain (Rodrigue et al. 2009). However, as we will describe later the specific changes occurring concomitantly with aging may alter this equilibrium and AD may eventually develop. Indeed, meanwhile this neuroinflammation will have progressive systemic effects and induce a peripheral inflammation. The inflammatory mediators released from the brain will stimulate the peripheral innate immune response. Among these cells at a very early stages are monocytes and NK cells (Solana et al. 2018). This will result to the maintenance of the activation of the innate immune system which will in turn activate the adaptive immune response. We should mention that this phenomenon may also occur in another way, specifically a systemic inflammation by the mediation of the inflammatory molecules and the migration of peripheral innate cells to the brain (Kurakin and Bredesen 2020). This may increase the BBB permeability which is letting to penetrate the inflammatory mediators and cells to penetrate into the brain and leading to neuroinflammation. Thus, a vicious circle will develop either whether the inflammation originate from the brain and spread to the periphery or vice versa (Paouri and Georgopoulos 2018; Tejera et al. 2019; Yang et al. 2020).

The reactive permeability of the blood brain barrier (BBB) is an important aspect of neuroinflammatory process (Nzou et al. 2020; Kowalski and Mulak 2019; Festoff 2016). In normal situation this is a semi-impermeable entity between the periphery and the central nervous system. Either aging or any inflammatory processes will impair this impermeable status of BBB (Chen 2011). This results in the passage of pro-inflammatory mediators and cells from the periphery to the brain and vice versa. Not only the BBB becomes permeable, but also the transporters are also altered. Comorbidities occurring with aging such as obesity and diabetes (diabesity) favor the increased BBB permeability and are also risk factors for AD (Chiu et al. 2015). Another probable contribution of the periphery to control the brain inflammation and physiology is the gut-brain axis (Kowalski and Mulak 2019; Cattaneo et al. 2017). This was known for a while but recently it became a major way for the interaction and mutual control between the brain and the gut. The study of this crosstalk axis is of utmost importance to understand the role of immunity and inflammation in central nervous degenerative diseases.

Collectively, this data suggest that inflammation is the basic process fighting and later maintaining the development and progression of AD.

9.6 Immunosenescence/Inflammaging and AD

From what we have described it can be easily concluded that the are-associated immune changes may contribute to the development of AD and consequently, it is very tempting to blame immunosenescence/inflammaging for the development of AD. However, it would be very reductionist to think that age-related immune changes may play a fundamental role in the development of AD. Nevertheless, considering what are the main characteristics of immunosenescence/inflammaging it is more than plausible that they play a role in the clinical manifestation/appearance of AD.

Immunosenescence/inflammaging will result in a clinically imperceptible, chronic low-grade inflammatory state which will maintain the innate immune system stimulation, the production of more than normal pro-inflammatory cytokines and finally the stimulation of the adaptive immune system (Franceschi et al. 2000; Fülöp et al. 2019). This will manifest by the decrease in naïve cells and the increase in memory cells, further contributing to the inflammation (Müller et al. 2019). This is clearly occurring as a reaction to the lifelong (immunobiography) constant external and internal challenges (Fülöp et al. 2020; Franceschi et al. 2017). Therefore, this is primarily a defense mechanism that may lead to AD in the long run. In this way the age-related immune changes may contribute by several ways.

The constant inflammation may have detrimental role and induce the neuronal death. Furthermore, the constant stimulation will result in the sustained production of pro-inflammatory mediators preventing the action of anti-inflammatory processes. We should also mention that these pro-inflammatory challenges will result in exhaustion of the immune cells mainly that of the adaptive immune system by the increase of memory CD8+ T cells. In the brain this stimulation will result in the apparition of the senescent microglia which will contribute to the inflammation and neurodegeneration instead of fighting this.

However, if we consider that AD develops through decades before its clinical apparition, immunosenescence/inflammaging will have a very little role in the development of AD as the neuroinflammation is independent of the aging process. Nevertheless, when the process proceeds the immunosenescence/inflammaging through the exhaustion of the innate and adaptive immune response, it may contribute to the clinical appearance of AD (Solana et al. 2018; Costantini et al. 2018; Magrone et al. 2020).

As mentioned, under the constant stimulation, microglia will become exhausted and instead of being protector it becomes harmful. This has been shown through the progression of AD. It was a major progress to establish the dual role of microglia (Subhramanyam et al. 2019; Colonna and Butovsky 2017). The same process may also affect the astrocytes (Garwood et al. 2017).

Another way that the aging immune system may contribute is the deregulation of the immune suppressive system. The changes in Tregs and myeloid-derived suppressor cells (MDSC) cells will favor the appearance of higher specific immune reactions suppression but concomitantly the fueling of the chronic inflammatory process (Le Page et al. 2017).

Therefore, we should be very cautious before we attribute the major risk factor title to aging with its immunological attribute because this can have far reaching conceptual and treatment consequences. However instead if we integrate these changes in a complex systems biology view of the AD development we could perhaps improve the possibilities of prevention and slowing down the disease progression (Ardura-Fabregat et al. 2017).

9.7 Cues for Intervention Targeting the Inflammation and the Immune Changes Contributing to AD

So far, most of the anti-inflammatory drug trials were failures besides many epidemiological data demonstrating the use of non-steroidal anti-inflammatory drugs (especially in arthritis patients) reduced the risk of AD (Rivers-Auty et al. 2020). This may be explained by considering that these trials did not consider the complex role of inflammation in the pathogenesis of AD. At the beginning inflammation should be sustained to fight the aggression and later it should be downsized to avoid the aggravation and the ongoing nature of the neuroinflammation reinforced by the dysregulated immunosenescence/inflammaging.

Presently many trials are ongoing targeting different molecules, pathways and cells of the immune system to modulate the inflammation (Fülöp et al. 2020, 2021). None of them directly is addressing the altered immune system with aging, with the exception perhaps the tentative reduction of Tregs (Ballard et al. 2020). All of them targets the original neuroinflammation. This should lead either to the prevention or the decreasing/delaying of the progression of AD (Munafò et al. 2020).

Presently the only way to prevent and influence the immune changes with aging is the intervention in multimodal way on the envirobiography (Ngandu et al. 2015). This intervention would consist of a very early implementation of good nutritional habits, regular exercise, decrease of bad stress (hormetically negative), cognitive reserve increase implemented since the middle age (Komleva et al. 2021; Atri 2019; Eiser and Fülöp 2020; de Oliveira Silva et al. 2019). In this way the use of a ketogenic diet may increase some cognitive functions in MCI subjects by potentially acting as a better fuel for the brain and an inhibitor of the inflammasome (Fortier et al. 2021; Myette-Côté et al. 2021; Wissler et al. 2020).

Another popular anti-aging intervention is the use of senolytics which would eliminate one source of aging, namely the senescent cells and as such would alleviate inflammaging, hoping that the organism will be capable to better fight against the aggressions (Zhao et al. 2020; Schubert et al. 2018; Mannick et al. 2014; Kang 2019). We really at this stage do not know neither the short nor the long-term effects of such interventions.

9.8 Conclusion and Translational Perspectives

AD is clearly a neuroinflammation mediated neurodegenerative disease. Aging is considered as one of the most important risk factors mainly by its attribute influencing the immune system changes. The development of inflammation is preceding decades before the clinical apparition of AD. In this way immunosenescence/inflammaging may play some role. The clear conceptualization and better understanding of AD will tone down the role of aging and will bring viable treatment opportunities. However, considering the envirobiography and the genetic origins of AD it is hardly conceivable that a monotherapy may be available, even if the aducanumab (Aduhelm) was very recently approved by the FDA. We should aim to treat AD by a multimodal approach in a system biology perspective which could lead to a real personalized approach (Gauthier et al. 2018; Fülöp et al. 2021).

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Conflict of Interest Author declare no conflict of interest.

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References

Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mrak R, Mackenzie IR, McGeer PL, O'Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T (2000) Inflammation and Alzheimer's disease. Neurobiol Aging May–June 2021;21(3):383–421. https://doi.org/10.1016/s0197-4580(00)00124-x

Arai Y, Martin-Ruiz CM, Takayama M, Abe Y, Takebayashi T, Koyasu S, Suematsu M, Hirose N, von Zglinicki T (2015) Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. EBioMedicine 2(10):1549–1558. https://doi.org/10.1016/j.ebiom.2015.07.029

Ardura-Fabregat A, Boddeke EWGM, Boza-Serrano A, Brioschi S, Castro-Gomez S, Ceyzériat K, Dansokho C, Dierkes T, Gelders G, Heneka MT, Hoeijmakers L, Hoffmann A, Iaccarino L, Jahnert S, Kuhbandner K, Landreth G, Lonnemann N, Löschmann PA, McManus RM, Paulus A, Reemst K, Sanchez-Caro JM, Tiberi A, Van der Perren A, Vautheny A, Venegas C, Webers A, Weydt P, Wijasa TS, Xiang X, Yang Y (2017) Targeting neuroinflammation to treat Alzheimer's disease. CNS Drugs 31(12):1057–1082. https://doi.org/10.1007/s40263-017-0483-3

Arts RJ, Joosten LA, Netea MG (2016) Immunometabolic circuits in trained immunity. Semin Immunol 28:425–430

Atri A (2019) Current and future treatments in Alzheimer's disease. Semin Neurol 39(2):227–240. https://doi.org/10.1055/s-0039-1678581

Bae HR, Kim DH, Park MH, Lee B, Kim MJ, Lee EK, Chung KW, Kim SM, Im DS, Chung HY (2016) β-Hydroxybutyrate suppresses inflammasome formation by ameliorating endoplasmic reticulum stress via AMPK activation. Oncotarget 7(41):66444–66454. https://doi.org/10.18632/oncotarget.12119

Ballard C, Aarsland D, Cummings J et al (2020) Drug repositioning and repurposing for Alzheimer disease. Nat Rev Neurol 16(12):661–673. https://doi.org/10.1038/s41582-020-0397-4

Bandaranayake T, Shaw AC (2016) Host resistance and immune aging. Clin Geriatr Med 32(3):415–432. https://doi.org/10.1016/j.cger.2016.02.007

Barbé-Tuana F, Funchal G, Schmitz CRR, Maurmann RM, Bauer ME (2020) The interplay between immunosenescence and age-related diseases. Semin Immunopathol 42(5):545–557. https://doi.org/10.1007/s00281-020-00806-z

Bauer ME, de la Fuente M (2016) The role of oxidative and inflammatory stress and persistent viral infections in immunosenescence. Mech Ageing Dev. 158:27–37

Beyreuther K, Masters CL (1991) Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function. Brain Pathol 1(4):241–251. https://doi.org/10.1111/j.1750-3639.1991.tb00667.x

Biagi E, Candela M, Fairweather-Tait S, Franceschi C, Brigidi P (2012) Aging of the human metaorganism: the microbial counterpart. Age (dordr) 34:247–267

Birch J, Passos JF (2017) Targeting the SASP to combat ageing: Mitochondria as possible intracellular allies? Bioessays 39(5)

Blach-Olszewska Z, Zaczynska E, Gustaw-Rothenberg K, Avila-Rodrigues M, Barreto GE, Leszek J, Aliev G (2015) The innate immunity in Alzheimer disease—relevance to pathogenesis and therapy. Curr Pharm Des 21:3582–3588

Block J (2019) Alzheimer's disease might depend on enabling pathogens which do not necessarily cross the blood-brain barrier. Med Hypotheses 125:129–136

Bolós M, Perea JR, Avila J (2017). Alzheimer's disease as an inflammatory disease. Biomol Concepts 8(1):37–43. https://doi.org/10.1515/bmc-2016-0029

Bourgade K, Garneau H, Giroux G, Le Page AY, Bocti C, Dupuis G, Frost EH, Fülöp T Jr (2015) β-Amyloid peptides display protective activity against the human Alzheimer's disease-associated herpes simplex virus-1. Biogerontology 16:85–98

Bourgade K, Le Page A, Bocti C, Witkowski JM, Dupuis G, Frost EH, Fülöp T Jr (2016) Protective effect of amyloid-β peptides against herpes simplex virus-1 infection in a neuronal cell culture model. J Alzheimers Dis 50:1227–1241

Busse M, Michler E, von Hoff F, Dobrowolny H, Hartig R, Frodl T, Busse S (2017) Alterations in the peripheral immune system in dementia. J Alzheimers Dis 58:1303–1313

Cai Z, Yan Y, Wang Y (2013) Minocycline alleviates beta-amyloid protein and tau pathology via restraining neuroinflammation induced by diabetic metabolic disorder. Clin Interv Aging 8:1089–1095. https://doi.org/10.2147/CIA.S46536

Campisi J (2016) Cellular senescence and lung function during aging. Yin and Yang. Ann Am Thorac Soc. 13(Supplement_5):S402.

Caselli M, Trevisani L, Tursi A, Sartori S, Ruina M, Luzzi I, Gaudenzi P, Alvisi V, Gasbarrini G (1997) Short-term low-dose triple therapy with azithromycin, metronidazole and lansoprazole appears highly effective for the eradication of Helicobacter pylori. Eur J Gastroenterol Hepatol 9(1):45–48

Castellani RJ, Rolston RK, Smith MA (2010) Alzheimer disease. Dis Mon 56:484–546

Castelo-Branco C, Soveral I (2014) The immune system and aging: a review. Gynecol Endocrinol 30(1):16–22. https://doi.org/10.3109/09513590.2013.852531

Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, Bianchetti A, Volta GD, Turla M, Cotelli MS, Gennuso M, Prelle A, Zanetti O, Lussignoli G, Mirabile D, Bellandi D, Gentile S, Belotti G, Villani D, Harach T, Bolmont T, Padovani A, Boccardi M, Frisoni GB; INDIA-FBP Group (2017) Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 49:60–68. https://doi.org/10.1016/j.neurobiolaging.2016.08.019

Chen RL (2011) Is it appropriate to use albumin CSF/plasma ratio to assess blood brain barrier permeability? Neurobiol Aging 32(7):1338–1339. https://doi.org/10.1016/j.neurobiolaging.2008.08.024

Chiu C, Miller MC, Monahan R, Osgood DP, Stopa EG, Silverberg GD (2015) P-glycoprotein expression and amyloid accumulation in human aging and Alzheimer's disease: preliminary observations. Neurobiol Aging 36(9):2475–2482. https://doi.org/10.1016/j.neurobiolaging.2015.05.020

Churov AV, Mamashov KY, Novitskaia AV (2020) Homeostasis and the functional roles of CD4(+) Treg cells in aging. Immunol Lett 226:83–89. https://doi.org/10.1016/j.imlet.2020.07.004

Ciarlo E, Heinonen T, Théroude C, Asgari F, Le Roy D, Netea MG, Roger T (2019) Trained immunity confers broad-spectrum protection against bacterial infections. J Infect Dis pii:jiz692

Colonna M, Butovsky O (2017) Microglia function in the central nervous system during health and neurodegeneration. Ann Rev Immunol 26(35):441–468. https://doi.org/10.1146/annurev-immunol-051116-052358

Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J (2018) Senescence-associated secretory phenotypes reveal cell- nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6:2853–2868

Costantini E, D'Angelo C, Reale M (2018) The role of immunosenescence in neurodegenerative diseases. Mediators Inflamm 8(2018):6039171. https://doi.org/10.1155/2018/6039171

Cummings J, Ritter A, Zhong K (2018) Clinical trials for disease-modifying therapies in Alzheimer's disease: a primer, lessons learned, and a blueprint for the future. J Alzheimers Dis 64(s1):S3–S22. https://doi.org/10.3233/JAD-179901

Cunningham C (2013) Microglia and neurodegeneration: the role of systemic inflammation. Glia 61(1):71–90. https://doi.org/10.1002/glia.22350

Dansokho C, Ait Ahmed D, Aid S, Toly-Ndour C, Chaigneau T, Calle V, Cagnard N, Holzenberger M, Piaggio E, Aucouturier P, Dorothée G (2016) Regulatory T cells delay disease progression in Alzheimer-like pathology. Brain 139(Pt 4):1237–1251. https://doi.org/10.1093/brain/awv408

de Kreutzenberg SV, Ceolotto G, Cattelan A, Pagnin E, Mazzucato M, Garagnani P, Borelli V, Bacalini MG, Franceschi C, Fadini GP, Avogaro A (2015) Metformin improves putative longevity effectors in peripheral mononuclear cells from subjects with prediabetes. A randomized controlled trial. Nutr Metab Cardiovasc Dis 25(7):686–693. https://doi.org/10.1016/j.numecd.2015.03.007

de Oliveira SF, Ferreira JV, Plácido J, Sant'Anna P, Araújo J, Marinho V, Laks J, Camaz DA (2019) Three months of multimodal training contributes to mobility and executive function in elderly individuals with mild cognitive impairment, but not in those with Alzheimer's disease: a randomized controlled trial. Maturitas 126:28–33. https://doi.org/10.1016/j.maturitas.2019.04.217

Di Benedetto S, Müller L, Wenger E, Düzel S, Pawelec G (2017) Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. Neurosci Biobehav Rev 75:114–128

Dionisio-Santos DA, Olschowka JA, O'Banion MK (2019) Exploiting microglial and peripheral immune cell crosstalk to treat Alzheimer's disease. J Neuroinflammation 16(1):74. 48. https://doi.org/10.1186/s12974-019-1453-0

Domínguez-Andrés J, Fanucchi S, Joosten LAB, Mhlanga MM, Netea MG (2020) Advances in understanding molecular regulation of innate immune memory. Curr Opin Cell Biol 63:68–75

Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, Nguyen M, Haditsch U, Raha D, Griffin C, Holsinger LJ, Arastu-Kapur S, Kaba S, Lee A, Ryder MI, Potempa B, Mydel P, Hellvard A, Adamowicz K, Hasturk H, Walker GD, Reynolds EC, Faull RLM, Curtis MA, Dragunow M, Potempa J (2019) Porphyromonas gingivalis in Alzheimer's disease brains: evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 5(1):eaau3333

Eiser AR, Fulop T (2020) Extra-cranial factors in the development of Alzheimer's disease. Brain Res 1(1748):147076. https://doi.org/10.1016/j.brainres.2020.147076

Ellwardt E, Walsh JT, Kipnis J, Zipp F (2016) Understanding the Role of T Cells in CNS Homeostasis. Trends Immunol 37:154–165

Festoff BW (2016) HMGB1 and thrombin mediate the blood-brain barrier dysfunction acting as biomarkers of neuroinflammation and progression to neurodegeneration in Alzheimer's disease. J Neuroinflam 13:194

Floden AM, Combs CK (2011) Microglia demonstrate age-dependent interaction with amyloid-β fibrils. J Alzheimers Dis 25(2):279–293. https://doi.org/10.3233/JAD-2011-101014

Fortier M, Castellano CA, St-Pierre V, Myette-Côté É, Langlois F, Roy M, Morin MC, Bocti C, Fulop T, Godin JP, Delannoy C, Cuenoud B, Cunnane SC (2021) A ketogenic drink improves cognition in mild cognitive impairment: results of a 6-month RCT. Alzheimers Dement 17(3):543–552. https://doi.org/10.1002/alz.12206

Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 908:244–254

Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S (2007) Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 128:92–105

Franceschi C, Salvioli S, Garagnani P, de Eguileor M, Monti D, Capri M (2017) Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. Front Immunol 8:982

Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A (2018a) Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018 Oct;14(10):576–590. https://doi.org/10.1038/s41574-018-0059-4

Franceschi C, Zaikin A, Gordleeva S, Ivanchenko M, Bonifazi F, Storci G, Bonafè M (2018b) Inflammaging 2018: an update and a model. Semin Immunol 40:1–5

Frasca D, Blomberg BB, Paganelli R (2017) Aging, obesity, and inflammatory age-related diseases. Front Immunol 8:1745

Fülöp T, Lacombe G, Cunnane S, Le Page A, Dupuis G, Frost EH, Bourgade-Navarro K, Goldeck D, Larbi A, Pawelec G (2013) Elusive Alzheimer's disease: can immune signatures help our understanding of this challenging disease? Part 2: new immune paradigm. Discov Med 15(80):33–42

Fülöp T, Dupuis G, Baehl S, Le Page A, Bourgade K, Frost E, Witkowski JM, Pawelec G, Larbi A, Cunnane S (2016) From inflamm-aging to immune-paralysis: a slippery slope during aging for immune-adaptation. Biogerontology 17(1):147–157. https://doi.org/10.1007/s10522-015-9615-7

Fülöp T, Witkowski JM, Olivieri F, Larbi A (2018a) The integration of inflammaging in age-related diseases. Semin Immunol 40:17–35. https://doi.org/10.1016/j.smim.2018.09.003

Fülöp T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, Witkowski JM, Franceschi C (2018b) Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol Jan 10;8:1960. https://doi.org/10.3389/fimmu.2017.01960

Fülöp T, Witkowski JM, Bourgade K, Khalil A, Zerif E, Larbi A, Hirokawa K, Pawelec G, Bocti C, Lacombe G, Dupuis G, Frost EH (2018c) Can an infection hypothesis explain the beta amyloid hypothesis of Alzheimer's disease? Front Aging Neurosci Jul 24;10:224. https://doi.org/10.3389/fnagi.2018.00224

Fülöp T, Larbi A, Witkowski JM (2019) Human inflammaging. Gerontology 65(5):495–504. https://doi.org/10.1159/000497375

Fülöp T, Munawara U, Larbi A, Desroches M, Rodrigues S, Catanzaro M, Guidolin A, Khalil A, Bernier F, Barron AE, Hirokawa K, Beauregard PB, Dumoulin D, Bellenger JP, Witkowski JM, Frost E (2020a) Targeting infectious agents as a therapeutic strategy in Alzheimer's disease. CNS Drugs 2020 Jul;34(7):673–695. https://doi.org/10.1007/s40263-020-00737-1

Fülöp T, Larbi A, Hirokawa K, Cohen AA, Witkowski JM (2020b) Immunosenescence is both functional/adaptive and dysfunctional/maladaptive. Semin Immunopathol 2020 Oct;42(5):521–536. https://doi.org/10.1007/s00281-020-00818-9

Fülöp T, Tripathi S, Rodrigues S, Desroches M, Bunt T, Eiser A, Bernier F, Beauregard PB, Barron AE, Khalil A, Plotka A, Hirokawa K, Larbi A, Bocti C, Laurent B, Frost EH, Witkowski JM (2021) Targeting impaired antimicrobial immunity in the brain for the treatment of Alzheimer's disease. Neuropsychiatr Dis Treat 4(17):1311–1339. https://doi.org/10.2147/NDT.S264910

Fülöp T, Dupuis G, Witkowski JM, Larbi A (2016) The role of immunosenescence in the development of age-related diseases. Rev Invest Clin March–April 2016;68(2):84–91

Fyfe I (2021) Dense-core plaques could be beneficial in AD. Nat Rev Neurol 17(6):328. https://doi.org/10.1038/s41582-021-00513-9

Garwood CJ, Ratcliffe LE, Simpson JE, Heath PR, Ince PG, Wharton SB (2017) Review: astrocytes in Alzheimer's disease and other age-associated dementias: a supporting player with a central role. Neuropathol Appl Neurobiol 43(4):281–298. https://doi.org/10.1111/nan.12338

Gauthier S, Ng KP, Pascoal TA, Zhang H, Rosa-Neto P (2018) Targeting Alzheimer's disease at the right time and the right place: validation of a personalized approach to diagnosis and treatment. J Alzheimers Dis 64(s1):S23–S31. https://doi.org/10.3233/JAD-179924

Giuliani A, Prattichizzo F, Micolucci L, Ceriello A, Procopio AD, Rippo MR (2017) Mitochondrial (Dys) function in inflammaging: do mitomirs influence the energetic, oxidative, and inflammatory status of senescent cells? Mediators Inflamm 2017:2309034

Giunta B, Fernandez F, Nikolic WV, Obregon D, Rrapo E, Town T, Tan J (2008) Inflammaging as a prodrome to Alzheimer's disease. J Neuroinflam 11(5):51. https://doi.org/10.1186/1742-2094-5-51

Goldberg EL, Shaw AC, Montgomery RR (2020) How inflammation blunts innate immunity in aging. Interdiscip Top Gerontol Geriatr 43:1–17. https://doi.org/10.1159/000504480 Epub 2020 Apr 9

Goldeck D, Witkowski JM, Fülop T, Pawelec G (2016) Peripheral immune signatures in Alzheimer disease. Curr Alzheimer Res 13(7):739–749

Gupta S (2014) Role of dendritic cells in innate and adaptive immune response in human aging. Exp Gerontol 54:47–52. https://doi.org/10.1016/j.exger.2013.12.009

Han F, Fukunaga K (2009) Beta-amyloid accumulation in neurovascular units following brain embolism. J Pharmacol Sci 111(2):101–109. https://doi.org/10.1254/jphs.09r02cp

Hansen PR (2018) Chronic inflammatory diseases and atherosclerotic cardiovascular disease: innocent bystanders or partners in crime? Curr Pharm Des 24(3):281–290. https://doi.org/10.2174/1381612824666180110102341

Hardy J, Allsop D (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 12(10):383–388. https://doi.org/10.1016/0165-6147(91)90609-v

Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297(5580):353–356. https://doi.org/10.1126/science.1072994

Herrup K (2015) The case for rejecting the amyloid cascade hypothesis. Nat Neurosci 18(6):794–799. https://doi.org/10.1038/nn.4017

Hu MY, Lin YY, Zhang BJ, Lu DL, Lu ZQ, Cai W (2019) Update of inflammasome activation in microglia/macrophage in aging and aging-related disease. CNS Neurosci Ther 25(12):1299–1307. https://doi.org/10.1111/cns.13262

Huang Z, Wong LW, Su Y, Huang X, Wang N, Chen H, Yi C (2020) Blood-brain barrier integrity in the pathogenesis of Alzheimer's disease. Front Neuroendocrinol 59:100857. https://doi.org/10.1016/j.yfrne.2020.100857

Humphries F, Fitzgerald KA (2019) Assembling the inflammasome Piece by Piece. J Immunol. 203(5):1093–1094. https://doi.org/10.4049/jimmunol.1900764

Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, Bullido MJ, Carter C, Clerici M, Cosby SL, Del Tredici K, Field H, Fulop T, Grassi C, Griffin WS, Haas J, Hudson AP, Kamer AR, Kell DB, Licastro F, Letenneur L, Lövheim H, Mancuso R, Miklossy J, Otth C, Palamara AT, Perry G, Preston C, Pretorius E, Strandberg T, Tabet N, Taylor-Robinson SD, Whittum-Hudson JA (2016) Microbes and Alzheimer's disease. J Alzheimers Dis 51(4):979–984. https://doi.org/10.3233/JAD-160152

Jóźwik A, Landowski J, Bidzan L, Fülop T, Bryl E, Witkowski JM (2012) Beta-amyloid peptides enhance the proliferative response of activated CD4CD28 lymphocytes from Alzheimer disease patients and from healthy elderly. PLoS One 7(3):e33276. https://doi.org/10.1371/journal.pone.0033276

Kang C (2019) Senolytics and senostatics: a two-pronged approach to target cellular senescence for delaying aging and age-related diseases. Mol Cells 42(12):821–827. https://doi.org/10.14348/molcells.2019.0298

Kelly DJ (1998) The physiology and metabolism of the human gastric pathogen Helicobacter pylori. Adv Microb Physiol 40:137–189

Kern A, Behl C (2009) The unsolved relationship of brain aging and late-onset Alzheimer disease. Biochim Biophys Acta 10:1124–1132. https://doi.org/10.1016/j.bbagen.2009.07.016

Kessler TA (2017) Cervical cancer: prevention and early detection. Semin Oncol Nurs 33(2):172–183

Kleinnijenhuis J, Quintin J, Preijers F, Joosten LA, Ifrim DC, Saeed S, Jacobs C, van Loenhout J, de Jong D, Stunnenberg HG, Xavier RJ, van der Meer JW, van Crevel R, Netea MG (2012) Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci USA 109:17537–17542

Komleva Y, Chernykh A, Lopatina O, Gorina Y, Lokteva I, Salmina A, Gollasch M (2021) Inflamm-aging and brain insulin resistance: new insights and role of life-style strategies on cognitive and social determinants in aging and neurodegeneration. Front Neurosci 14(14):618395. https://doi.org/10.3389/fnins.2020.618395

Kowalski K, Mulak A (2019) Brain-Gut-Microbiota axis in Alzheimer's disease. J Neurogastroenterol Motil 25(1):48–60. https://doi.org/10.5056/jnm18087

Kremen WS, Beck A, Elman JA, Gustavson DE, Reynolds CA, Tu XM, Sanderson-Cimino ME, Panizzon MS, Vuoksimaa E, Toomey R, Fennema-Notestine C, Hagler DJ Jr, Fang B, Dale AM, Lyons MJ, Franz CE (2019) Influence of young adult cognitive ability and additional education on later-life cognition. Proc Natl Acad Sci USA 116(6):2021–2026. https://doi.org/10.1073/pnas.1811537116

Kritsilis M, Rizou SV, Koutsoudaki PN, Evangelou K, Gorgoulis VG, Papadopoulos D. (2018) Ageing, cellular senescence and neurodegenerative disease. Int J Mol Sci 19(10), pii:E2937.

Kumar V (2019) Toll-like receptors in the pathogenesis of neuroinflammation. J Neuroimmunol 15(332):16–30. https://doi.org/10.1016/j.jneuroim.2019.03.012

Kumar H, Kawai T, Akira S (2011) Pathogen recognition by the innate immune system. Int Rev Immunol 30(1):16–34. https://doi.org/10.3109/08830185.2010.529976

Kumar DK, Eimer WA, Tanzi RE, Moir RD (2016a) Alzheimer's disease: the potential therapeutic role of the natural antibiotic amyloid-β peptide. Neurodegener Dis Manag 6(5):345–348

Kumar DK, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE, Moir RD (2016b) Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med 8(340):340ra72

Kurakin A, Bredesen DE (2020) Alzheimer's disease as a systems network disorder: chronic stress/dyshomeostasis, innate immunity, and genetics. Aging (Albany, NY) 12(18):17815–17844. https://doi.org/10.18632/aging.103883

Le Page A, Garneau H, Dupuis G, Frost EH, Larbi A, Witkowski JM, Pawelec G, Fülöp T (2017) Differential phenotypes of myeloid-derived suppressor and T regulatory cells and cytokine levels in amnestic mild cognitive impairment subjects compared to mild alzheimer diseased patients. Front Immunol 7(8):783. https://doi.org/10.3389/fimmu.2017.00783

Le Page A, Dupuis G, Frost EH, Larbi A, Pawelec G, Witkowski JM, Fulop T (2018) Role of the peripheral innate immune system in the development of Alzheimer's disease. Exp Gerontol 107:59–66

Leszek J, Barreto GE, Gąsiorowski K, Koutsouraki E, Ávila-Rodrigues M, Aliev G (2016) Inflammatory mechanisms and oxidative stress as key factors responsible for progression of neurodegeneration: role of brain innate immune system. CNS Neurol Disord Drug Targets 15:329–336

Li L, Zhang X, Yang D, Luo G, Chen S, Le W (2019) Hypoxia increases abeta generation by altering betaand gamma-cleavage of APP. Neurobiol Aging. 30(7):1091–1098. https://doi.org/10.1016/j.neurobiolaging.2007.10.011

Li S, Wang W, Wang C, Tang YY (2010) Possible involvement of NO/NOS signaling in hippocampal amyloid-beta production induced by transient focal cerebral ischemia in aged rats. Neurosci Lett 470(2):106–110. https://doi.org/10.1016/j.neulet.2009.12.064

Licastro F, Pedrini S, Caputo L, Annoni G, Davis LJ, Ferri C, Casadei V, Grimaldi LM (2000) Increased plasma levels of interleukin-1, interleukin-6 and alpha-1-antichymotrypsin in patients with Alzheimer's disease: peripheral inflammation or signals from the brain? J Neuroimmunol 103(1):97–102. https://doi.org/10.1016/s0165-5728(99)00226-x

Long JM, Holtzman DM (2019) Alzheimer disease: an update on pathobiology and treatment strategies. Cell 179(2):312–339. https://doi.org/10.1016/j.cell.2019.09.001

Lopatko Lindman K, Weidung B, Olsson J, Josefsson M, Kok E, Johansson A, Eriksson S, Hallmans G, Elgh F, Lövheim H (2019) A genetic signature including apolipoprotein Eε4 potentiates the risk of herpes simplex-associated Alzheimer's disease. Alzheimers Dement (n y). 4(5):697–704. https://doi.org/10.1016/j.trci.2019.09.014

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153(6):1194–1217. https://doi.org/10.1016/j.cell.2013.05.039

Magrone T, Magrone M, Russo MA, Jirillo E (2020) Peripheral immunosenescence and central neuroinflammation: a dangerous liaison—a dietary approach. Endocr Metab Immune Disord Drug Targets 20(9):1391–1411. https://doi.org/10.2174/1871530320666200406123734

Maloney B, Lahiri DK (2016) Epigenetics of dementia: understanding the disease as a transformation rather than a state. Lancet Neurol 15(7):760–774. https://doi.org/10.1016/S1474-4422(16)00065-X

Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, Glass DJ, Klickstein LB (2014) mTOR inhibition improves immune function in the elderly. Sci Transl Med 6(268):268ra179. https://doi.org/10.1126/scitranslmed.3009892

Marchesi VT (2011) Alzheimer's dementia begins as a disease of small blood vessels, damaged by oxidative-induced inflammation and dysregulated amyloid metabolism: implications for early detection and therapy. FASEB J 25(1):5–13. https://doi.org/10.1096/fj.11-0102ufm

McGeer PL, McGeer EG (2013) The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta Neuropathol 126(4):479–497. https://doi.org/10.1007/s00401-013-1177-7

McManus RM, Heneka MT (2017) Role of neuroinflammation in neurodegeneration: new insights. Alzheimers Res Ther. 9(1):14. https://doi.org/10.1186/s13195-017-0241-2

Mehta D, Jackson R, Paul G, Shi J, Sabbagh M (2017) Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010–2015. Expert Opin Investig Drugs 26(6):735–739. https://doi.org/10.1080/13543784.2017.1323868

Miklossy J (2016) Bacterial amyloid and dna are important constituents of senile plaques: further evidence of the spirochetal and biofilm nature of senile plaques. J Alzheimers Dis 53:1459–1473

Morgan AR, Touchard S, Leckey C, O'Hagan C, Nevado-Holgado AJ, NIMA Consortium, Barkhof F, Bertram L, Blin O, Bos I, Dobricic V, Engelborghs S, Frisoni G, Frölich L, Gabel S, Johannsen P, Kettunen P, Kłoszewska I, Legido-Quigley C, Lleó A, Martinez-Lage P, Mecocci P, Meersmans K, Molinuevo JL, Peyratout G, Popp J, Richardson J, Sala I, Scheltens P, Streffer J, Soininen H, Tainta-Cuezva M, Teunissen C, Tsolaki M, Vandenberghe R, Visser PJ, Vos S, Wahlund LO, Wallin A, Westwood S, Zetterberg H, Lovestone S, Morgan BP (2019) Annex: NIMA–Wellcome trust consortium for neuroimmunology of mood disorders and Alzheimer's disease. Inflammatory

biomarkers in Alzheimer's disease plasma. Alzheimers Dement 2019 Jun;15(6):776–787. https://doi.org/10.1016/j.jalz.2019.03.007

Müller L, Di Benedetto S, Pawelec G (2019) The immune system and its dysregulation with aging. Subcell Biochem 91:21–43. https://doi.org/10.1007/978-981-13-3681-2_2

Munafò A, Burgaletto C, Di Benedetto G et al (2020) Repositioning of immunomodulators: a ray of hope for Alzheimer's disease? Front Neurosci 14:614643. https://doi.org/10.3389/fnins.2020.614643

Myette-Côté É, St-Pierre V, Beaulieu S, Castellano CA, Fortier M, Plourde M, Bocti C, Fulop T, Cunnane SC (2021) The effect of a 6-month ketogenic medium-chain triglyceride supplement on plasma cardiometabolic and inflammatory markers in mild cognitive impairment. Prostaglandins Leukot Essent Fatty Acids 169:102236. https://doi.org/10.1016/j.plefa.2020.102236

Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, Sepehrband F, Nelson AR, Buennagel DP, Harrington MG, Benzinger TLS, Fagan AM, Ringman JM, Schneider LS, Morris JC, Chui HC, Law M, Toga AW, Zlokovic BV (2019) Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med Feb 2019;25(2):270–276

Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385(9984):2255–2263. https://doi.org/10.1016/S0140-6736(15)60461-5

Noe CR, Noe-Letschnig M, Handschuh P, Noe CA, Lanzenberger R (2020) Dysfunction of the blood-brain barriers—a key step in neurodegeneration and dementia. Front Aging Neurosci 12:18539

Nyugen J, Agrawal S, Gollapudi S, Gupta S (2010) Impaired functions of peripheral blood monocyte subpopulations in aged humans. J Clin Immunol 30(6):806–813. https://doi.org/10.1007/s10875-010-9448-8

Nzou G, Wicks RT, VanOstrand NR, Mekky GA, Seale SA, El-Taibany A, Wicks EE, Nechtman CM, Marrotte EJ, Makani VS, Murphy SV, Seeds MC, Jackson JD, Atala AJ (2020) Multicellular 3D neurovascular unit model for assessing hypoxia and neuroinflammation induced blood-brain barrier dysfunction. Sci Rep 10(1):9766. https://doi.org/10.1038/s41598-020-66487-8

Osorio C, Kanukuntla T, Diaz E, Jafri N, Cummings M, Sfera A (2019) The post-amyloid era in Alzheimer's disease: trust your gut feeling. Front Aging Neurosci 11:143

Paouri E, Georgopoulos S (2019) Systemic and CNS inflammation crosstalk: implications for Alzheimer's disease. Curr Alzheimer Res 16(6):559–574. https://doi.org/10.2174/1567205016666190321154618

Pawelec G (2018) Age and immunity: What is "immunosenescence"? Exp Gerontol 105:4–9. https://doi.org/10.1016/j.exger.2017.10.024

Pawelec G (2020) The human immunosenescence phenotype: does it exist? Semin Immunopathol 42(5):537–544. https://doi.org/10.1007/s00281-020-00810-3

Pawelec G, Bronikowski A, Cunnane SC, Ferrucci L, Franceschi C, Fülöp T, Gaudreau P, Gladyshev VN, Gonos ES, Gorbunova V, Kennedy BK, Larbi A, Lemaître JF, Liu GH, Maier AB, Morais JA, Nóbrega OT, Moskalev A, Rikkert MO, Seluanov A, Senior AM, Ukraintseva S, Vanhaelen Q, Witkowski J, Cohen AA (2020) The conundrum of human immune system "senescence." Mech Ageing Dev 192:111357. https://doi.org/10.1016/j.mad.2020.111357

Perl DP (2010) Neuropathology of Alzheimer's disease. Mt Sinai J Med January–February 2010; 77(1):32–42. https://doi.org/10.1002/msj.20157

Price NL, Gomes AP, Ling AJ, Duarte FV, Martin-Montalvo A, North BJ, Agarwal B, Ye L, Ramadori G, Teodoro JS, Hubbard BP, Varela AT, Davis JG, Varamini B, Hafner A, Moaddel R, Rolo AP, Coppari R, Palmeira CM, de Cabo R, Baur JA, Sinclair DA (2012) SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. Cell Metab 15(5):675–690. https://doi.org/10.1016/j.cmet.2012.04.003

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP (2013) The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 9(1):63-75.e2. https://doi.org/10.1016/j.jalz.2012.11.007

Regen F, Hellmann-Regen J, Costantini E, Reale M (2017) Neuroinflammation and Alzheimer's disease: implications for microglial activation. Curr Alzheimer Res 14(11):1140–1148. https://doi.org/10.2174/1567205014666170203141717

Ricciarelli R, Fedele E (2017) The amyloid cascade hypothesis in Alzheimer's disease: it's time to change our mind. Curr Neuropharmacol 15(6):926–935. https://doi.org/10.2174/1570159X15666170116143743

Rivers-Auty J, Mather AE, Peters R, Lawrence CB, Brough D (2020) Anti-inflammatories in Alzheimer's disease-potential therapy or spurious correlate? Brain Commun 2020 Jul 24;2(2):fcaa109. https://doi.org/10.1093/braincomms/fcaa109

Rodrigue KM, Kennedy KM, Park DC (2009) Beta-amyloid deposition and the aging brain. Neuropsychol Rev 19(4):436–450. https://doi.org/10.1007/s11065-009-9118-x

Rubino G, Bulati M, Aiello A, Aprile S, Gambino CM, Gervasi F, Caruso C, Accardi G (2019) Sicilian centenarian offspring are more resistant to immune ageing. Aging Clin Exp Res 31(1):125–133

Sacks CA, Avorn J, Kesselheim AS (2017) The failure of Solanezumab—How the FDA saved taxpayers billions. N Engl J Med 376(18):1706–1708. https://doi.org/10.1056/NEJMp1701047

Salani F, Sterbini V, Sacchinelli E, Garramone M, Bossù P (2019) Is innate memory a double-edge sword in Alzheimer's disease? A reappraisal of new concepts and old data. Front Immunol 7(10):1768. https://doi.org/10.3389/fimmu.2019.01768

Salminen A (2020) Activation of immunosuppressive network in the aging process. Ageing Res Rev 57:100998. https://doi.org/10.1016/j.arr.2019.100998

Salvioli S, Monti D, Lanzarini C, Conte M, Pirazzini C, Bacalini MG, Garagnani P, Giuliani C, Fontanesi E, Ostan R, Bucci L, Sevini F, Yani SL, Barbieri A, Lomartire L, Borelli V, Vianello D, Bellavista E, Martucci M, Cevenini E, Pini E, Scurti M, Biondi F, Santoro A, Capri M, Franceschi C (2013) Immune system, cell senescence, aging and longevity–inflamm-aging reappraised. Curr Pharm Des 19(9):1675–1679

Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, Morishita R (2018) Source of chronic inflammation in aging. Front Cardiovasc Med. 5:12

Schmitt V, Rink L, Uciechowski P (2013) The Th17/Treg balance is disturbed during aging. Exp Gerontol 48(12):1379–1386. https://doi.org/10.1016/j.exger.2013.09.003

Schubert D, Currais A, Goldberg J, Finley K, Petrascheck M, Maher P (2018) Geroneuroprotectors: effective geroprotectors for the brain. Trends Pharmacol Sci 39(12):1004–1007. https://doi.org/10.1016/j.tips.2018.09.008

Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8(6):595–608. https://doi.org/10.15252/emmm.201606210

Shad KF, Aghazadeh Y, Ahmad S, Kress B (2013) Peripheral markers of Alzheimer's disease: surveillance of white blood cells. Synapse 67(8):541–543

Shen H, Guan Q, Zhang X, Yuan C, Tan Z, Zhai L, Hao Y, Gu Y, Han C (2020) New mechanism of neuroinflammation in Alzheimer's disease: the activation of NLRP3 inflammasome mediated by gut microbiota. Prog Neuropsychopharmacol Biol Psychiatry 8(100):109884. https://doi.org/10.1016/j.pnpbp.2020.109884

Šimić G, Španić E, Langer Horvat L, Hof PR (2019) Blood-brain barrier and innate immunity in the pathogenesis of Alzheimer's disease. Prog Mol Biol Transl Sci 168:99–145

Singhrao SK, Olsen I (2019) Assessing the role of Porphyromonas gingivalis in periodontitis to determine a causative relationship with Alzheimer's disease. J Oral Microbiol 11(1):1563405

Smale ST (2011) Hierarchies of NF-κB target-gene regulation. Nat Immunol 12(8):689–694. https://doi.org/10.1038/ni.2070

Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T (2012) Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. Semin Immunol 24(5):331–341. https://doi.org/10.1016/j.smim.2012.04.008

Solana C, Tarazona R, Solana R (2018) Immunosenescence of natural killer cells, inflammation, and Alzheimer's disease. Int J Alzheimers Dis 1(2018):3128758. https://doi.org/10.1155/2018/3128758

Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, Moir RD (2010) The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One 5:e9505

Subhramanyam CS, Wang C, Hu Q, Dheen ST (2019) Microglia-mediated neuroinflammation in neurodegenerative diseases. Semin Cell Dev Biol 94:112–120. https://doi.org/10.1016/j.semcdb.2019.05.004

Tam JH, Pasternak SH (2012) Amyloid and Alzheimer's disease: inside and out. Can J Neurol Sci 39:286–298. https://doi.org/10.1017/s0317167100013408

Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL (2013) Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest 123:966–972

Tejera D, Mercan D, Sanchez-Caro JM, Hanan M, Greenberg D, Soreq H, Latz E, Golenbock D, Heneka MT (2019) Systemic inflammation impairs microglial Abeta clearance through NLRP3 inflammasome. EMBO J 2019 Sep 2;38(17):e101064. https://doi.org/10.15252/embj.2018101064. Epub 2019 Jul 30

Terlecki-Zaniewicz L, Lämmermann I, Latreille J, Bobbili MR, Pils V, Schosserer M, Weinmüllner R, Dellago H, Skalicky S, Pum D, Almaraz JCH, Scheideler M, Morizot F, Hackl M, Gruber F, Grillari J (2018) Small extracellular vesicles and their miRNA cargo are anti-apoptotic members of the senescence-associated secretory phenotype. Aging (Albany, NY) 10(5):1103–1132

Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, Loukov D, Schenck LP, Jury J, Foley KP, Schertzer JD, Larché MJ, Davidson DJ, Verdú EF, Surette MG, Bowdish DME (2017) Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe 21:455

van der Heijden CDCC, Noz MP, Joosten LAB, Netea MG, Riksen NP, Keating ST (2017) Epigenetics and trained immunity. Antioxid Redox Signal 29(11):1023–1040

Walker KA, Ficek BN, Westbrook R (2019) Understanding the role of systemic inflammation in Alzheimer's disease. ACS Chem Neurosci 10(8):3340–3342. https://doi.org/10.1021/acschemneuro.9b00333

Walton CC, Begelman D, Nguyen W, Andersen JK (2020) Senescence as an amyloid cascade: the amyloid senescence hypothesis. Front Cell Neurosci 19(14):129. https://doi.org/10.3389/fncel.2020.00129

Webers A, Heneka MT, Gleeson PA (2020) The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease. Immunol Cell Biol 98(1):28–41. https://doi.org/10.1111/imcb.12301

Whalley LJ, Dick FD, McNeill G (2006) A life-course approach to the aetiology of late-onset dementias. Lancet Neurol 5(1):87–96. https://doi.org/10.1016/S1474-4422(05)70286-6

Wissler Gerdes EO, Zhu Y, Tchkonia T, Kirkland JL (2020) Discovery, development, and future application of senolytics: theories and predictions. FEBS J 287(12):2418–2427. https://doi.org/10.1111/febs.15264

Wong C, Goldstein DR (2013) Impact of aging on antigen presentation cell function of dendritic cells. Curr Opin Immunol 25(4):535–541. https://doi.org/10.1016/j.coi.2013.05.016

Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB (2007) Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett 429:95–100

Wozniak MA, Mee AP, Itzhaki RF (2009) Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 217:131–138

Wyatt-Johnson SK, Brutkiewicz RR (2020) The complexity of microglial interactions with innate and adaptive immune cells in Alzheimer's disease. Front Aging Neurosci 19(12):592359. https://doi.org/10.3389/fnagi.2020.592359

Yang J, Wise L, Fukuchi KI (2020) TLR4 cross-talk with NLRP3 inflammasome and complement signaling pathways in Alzheimer's disease. Front Immunol 2020 Apr 23;11:724. https://doi.org/10.3389/fimmu.2020.00724. eCollection 2020

Zhao Y, Zhan JK, Liu Y (2020) A perspective on roles played by immunosenescence in the pathobiology of Alzheimer's disease. Aging Dis 11(6):1594–1607. https://doi.org/10.14336/AD.2020.0205