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

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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

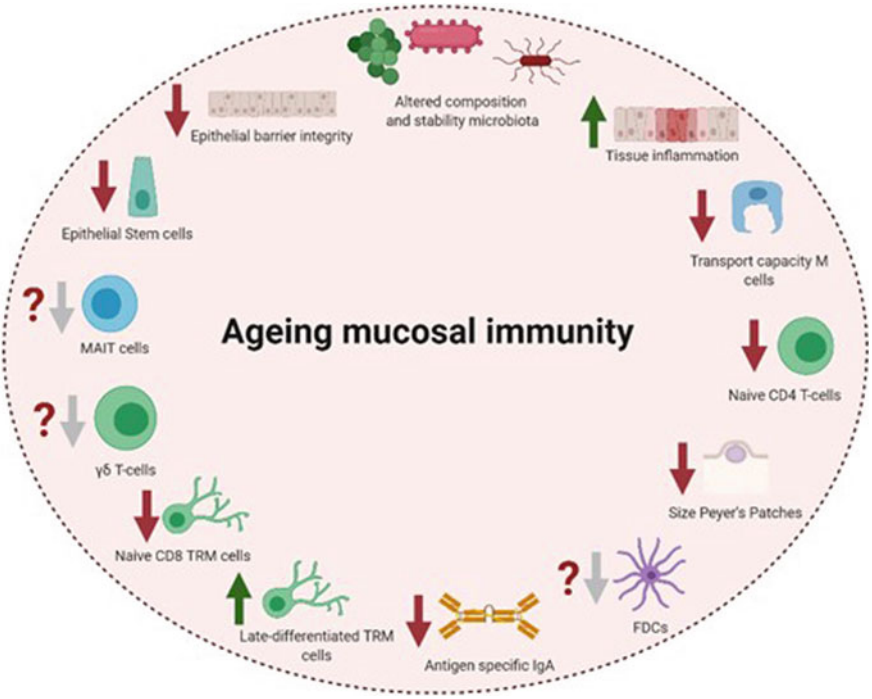

Fig. 6.1 Schematic overview of the ageing mucosal immune system

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.

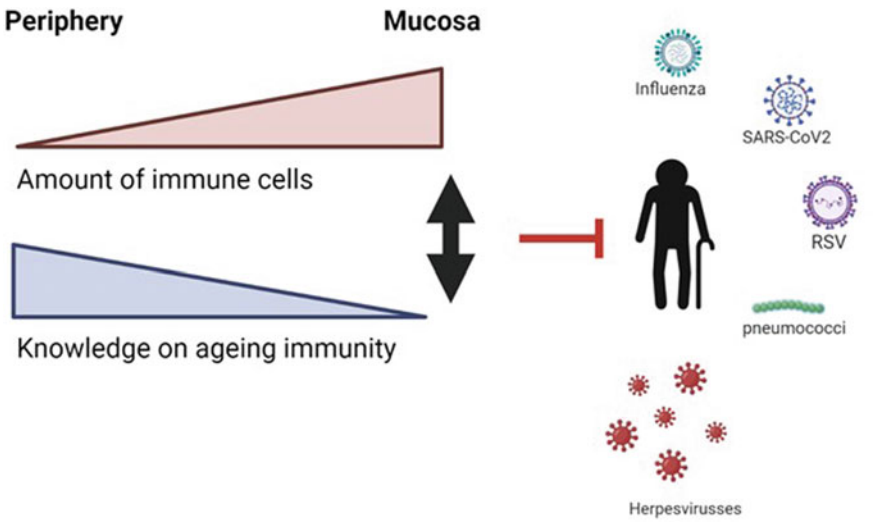

Fig. 6.2 Changes occurring in the immune system during the ageing process and pathogens

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