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

Conflict of Interest Author declare no conflict of interest.

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