

Chapter 2

The Immune System and Its Dysregulation with Aging



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Abstract Aging leads to numerous changes that affect all physiological systems of the body including the immune system, causing greater susceptibility to infectious disease and contributing to the cardiovascular, metabolic, autoimmune, and neurodegenerative diseases of aging. The immune system is itself also influenced by age-associated changes occurring in such physiological systems as the endocrine, nervous, digestive, cardio-vascular and muscle-skeletal systems. This chapter describes the multidimensional effects of aging on the most important components of the immune system. It considers the age-related changes in immune cells and molecules of innate and adaptive immunity and consequent impairments in their ability to communicate with each other and with their aged environment. The contribution of age-related dysregulation of hematopoiesis, required for continuous replenishment of immune cells throughout life, is discussed in this context, as is the developmentally-programmed phenomenon of thymic involution that limits the output of naïve T cells and markedly contributes to differences between younger and older people in the distribution of peripheral blood T-cell types. How all these changes may contribute to low-grade inflammation, sometimes dubbed “inflammaging”, is considered. Due to findings implicating elevated inflammatory immunomediators in age-associated chronic autoimmune and neurodegenerative processes, evidence for their possible contribution to neuroinflammation is reviewed.

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Introduction

Aging is a highly complex process associated with numerous changes at the organismal, tissue, cellular and molecular levels, characterized by dysregulation of different physiological systems (such as the immune, central and peripheral nervous, endocrine, metabolic and other systems) from their optimal homeostatic state (Xu and Larbi 2017; Müller et al. 2013a; Müller and Pawelec 2015; Masters et al. 2017). Particularly, chronic oxidative stress affects cells of these central regulatory systems leading to modified interactions between them. This influences their functionality, disturbs homeostasis and may thereby affect longevity (De la Fuente et al. 2011).

Deleterious alterations in the immune system that accompany human aging are commonly known as immunosenescence, although many differences between young and old individuals are in fact only assumed to be detrimental without unequivocal proof. Thus, it is clear that aging per se does not always lead to inevitable decline in immune functions, but rather causes their modification. Paramount amongst these age-associated changes are the replacement of naïve T and B cells with memory cells, which is of course the basis of adaptive immune function. While some aspects of immunity deteriorate with age, some remain unchanged, while others tend to become overactive. In this sense, we should rather refer to dysregulation than deterioration that is likely to be driving force for immunosenescence. However, progressive increases in the incidence of infectious, metabolic, and autoimmune diseases, in cancer and neurological disorders occurring with aging appear likely to be at least partly caused by immunosenescence (Müller and Pawelec 2014; Menza et al. 2010; Michaud et al. 2013).

In this context, immunosenescence should be considered as a multistage process consisting of numerous developmentally regulated and interrelated changes, instead of conceiving it as an unidirectional general decay of the immune system (Accardi and Caruso 2018; Del Giudice et al. 2018). Thus far, it has not been clear which changes are truly age-related and which are adaptive and compensatory, arising as a consequence of immune exposures and other confounders (Nikolich-Zugich 2018; Pawelec 2017a, b; Fulop et al. 2017). Such events as hematopoietic stem cell dysfunction and thymus involution with decreased T-cell generation contribute to the age-related remodeling of the immune system leading to the decreased levels of naïve T-lymphocytes accompanied by increased numbers of memory cells but also manifesting as accumulations of dysfunctional potentially senescent immune cells. Additionally, intrinsic defects in development, maturation, migration, and homeostasis of peripheral immune cells contribute to this process (Gruver et al. 2007).

Along with such developmental/age-related changes and partly related to these events, low-level chronic inflammation commonly present in older adults is believed

to be implicated in age-related mortality. There have been many attempts to explain the cause of chronic inflammation in aging, considering such reasons as mitochondrial damage, redox stress, age-related alterations in endocrine function, epigenetic changes and other phenomena, linked or not to immunosenescence. It appears that no single theory or mechanism has thus far proven itself able to explain all aspects of aging and immune aging. Therefore, it is more probable that multiple interrelated processes contribute to aging, but in some way, nearly all of them might contribute to or be related to inflammation (Jenny 2012; Müller and Pawelec 2015).

Maintaining well-balanced inflammatory and anti-inflammatory homeostasis seems to be decisive to maintain functional longevity required for optimal aging. If this equilibrium is disturbed for any reason, pathological pathways may become prevalent. Fulop and colleagues hypothesize that “canalized dysregulations occur as a result of adaptations to the aging process and thus reflect an optimized response to an imperfect situation. In contrast, non-canalized dysregulations reflect a true loss of homeostatic control and may themselves be the imperfect situation causing the canalized responses” (Fulop et al. 2017).

It is widely accepted that age-associated inflammatory conditions are closely interrelated with changes in immune system function. Additionally, they are under the influence of neuroendocrine hormones, including dehydroepiandrosterone, glucocorticoids, and the catecholamines, epinephrine, and norepinephrine. In the course of aging, alterations in endocrine function can potentially modulate their interrelationships and lead to deterioration of the regulatory feedback pathways. Chronic stress, including psychological and social stressors, is also known to negatively affect both neuroendocrine and immune functions and may contribute to increased age-associated diseases and mortality in old people (Heffner 2011; Hawkey and Cacioppo 2004; Müller and Pawelec 2014). Thus, the aging immune system influences and is influenced by these other physiological systems of the body.

Components of the Immune System

After barrier functions, our immune system is the most important defender of our body’s integrity against external invaders or pathogens as well as altered or modified internal factors. At the same time, according to one school of thought, adaptive immunity has the important task “to facilitate the maintenance of a beneficial microbiota” (Pawelec 2012; Müller and Pawelec 2014). For this reason our immune system possess various sophisticated mechanisms of both the innate and adaptive branches, consisting of different cell populations, which are capable of responding to these challenges and defending the integrity of the body as well as its beneficial microbiota (Fig. 2.1). So called “first line of defense” is represented by the skin and mucosa of the gastro-intestinal, respiratory and urogenital tracts, serving not only as a mechanical and physiological barrier (Doran et al. 2013), but also containing fatty acids, anti-microbial molecules, proteases, digestive enzymes, lysozymes,

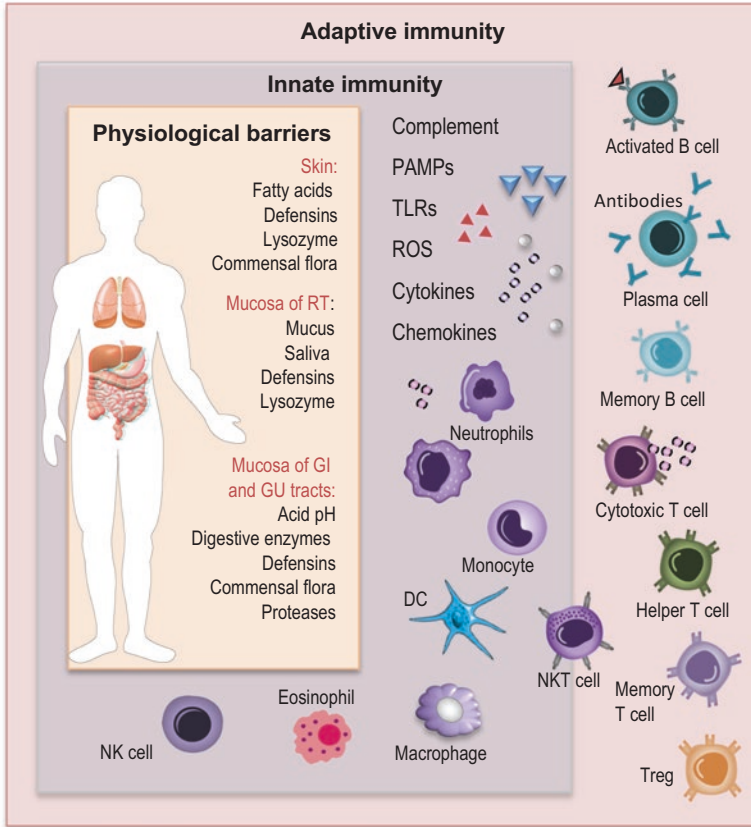


Fig. 2.1 Overview of the human immune system

RT respiratory tract, *GI* gastro-intestinal, *GU* urogenital, *PAMPs* pathogen-associated molecular patterns, *TLRs* Toll-like receptors, *ROS* reactive oxygen species, *DC* dendritic cells, *NK cells* natural killer cells, *NKT cells* natural killer T cells, *Treg* regulatory T cells

defensins, and is colonized by commensal flora to provide sophisticated defense (Müller et al. 2013b). But when barrier function is compromised, immune function is clearly paramount.

Thus, when a pathogen breaks these physiological barriers and enters the body, the innate immune system (Fig. 2.2) affords a rapid response involving immediate migration of innate cells with phagocytic activity to the lesion, and providing local release of toxic mediators. By means of specialized receptors, which are present on the surface of innate immune cells (Fig. 2.3, top), they recognise highly conserved molecules on microorganisms, so-called “PAMPs” (pathogen-associated molecular patterns), which are shared by many different pathogens but are not present on mammalian cells (Medzhitov and Janeway 2000). These interactions in turn activate different innate defence mechanisms, which include phagocytosis, release of inflammatory proteins, activation of the complement system, production of acute phase proteins, secretion

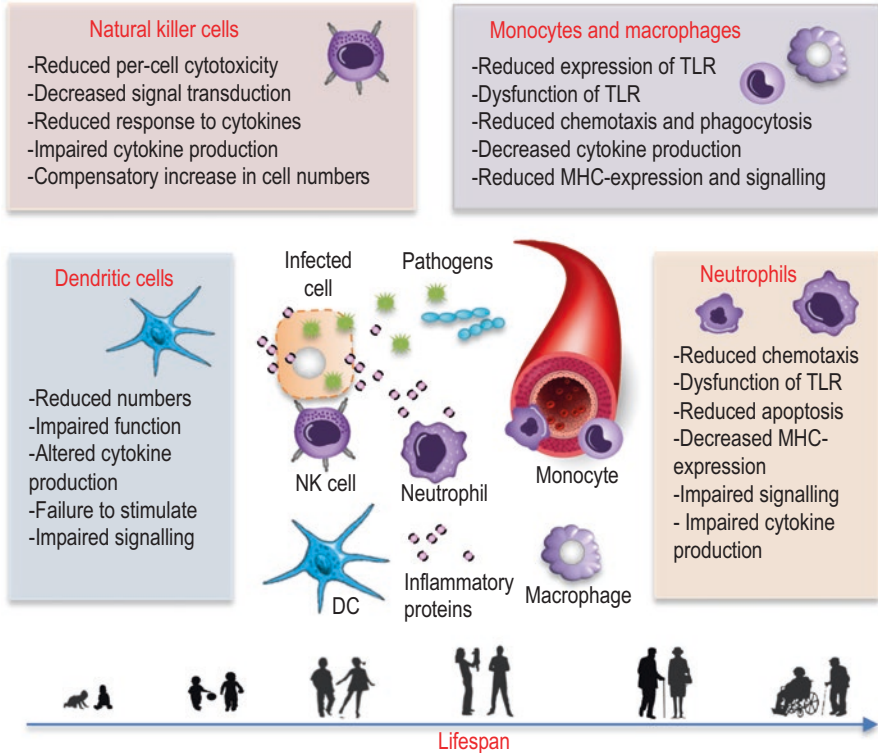


Fig. 2.2 Innate immune system and age-related changes

TLR Toll-like receptor, *MHC* major histocompatibility complex, *NK* cells natural killer cells, *DC* dendritic cells

chemokines and cytokines (Müller and Pawelec 2014). The ongoing responses of the innate immune system “call into play” adaptive immune responses and both arms act together to eliminate pathogens and develop immune memory.

Cells of the innate immune system are believed to provide much more rapid but less specific immune response than do the cells of the adaptive immune system. However, from a more recent point of view, the separation of these two arms of immunity, previously considered as completely distinct, has become muddled. It was shown that cells of the innate immune system may possess a kind of memory function under certain conditions and reciprocally, immune cells of the adaptive arm may express receptors specific for innate cells and act like these cells functionally. These receptors appear especially at late stages of differentiation, are normally elevated later in life and accompanied by other age-associated changes (Lanier and Sun 2009). Chronological aging was also shown to be associated with accumulations of immune cells combining characteristics of both the innate and adaptive arms of the immune system. This phenomenon might be partly explained by compensatory mechanisms for age-related functional defects of conventional immune cells (Pereira and Akbar 2016).

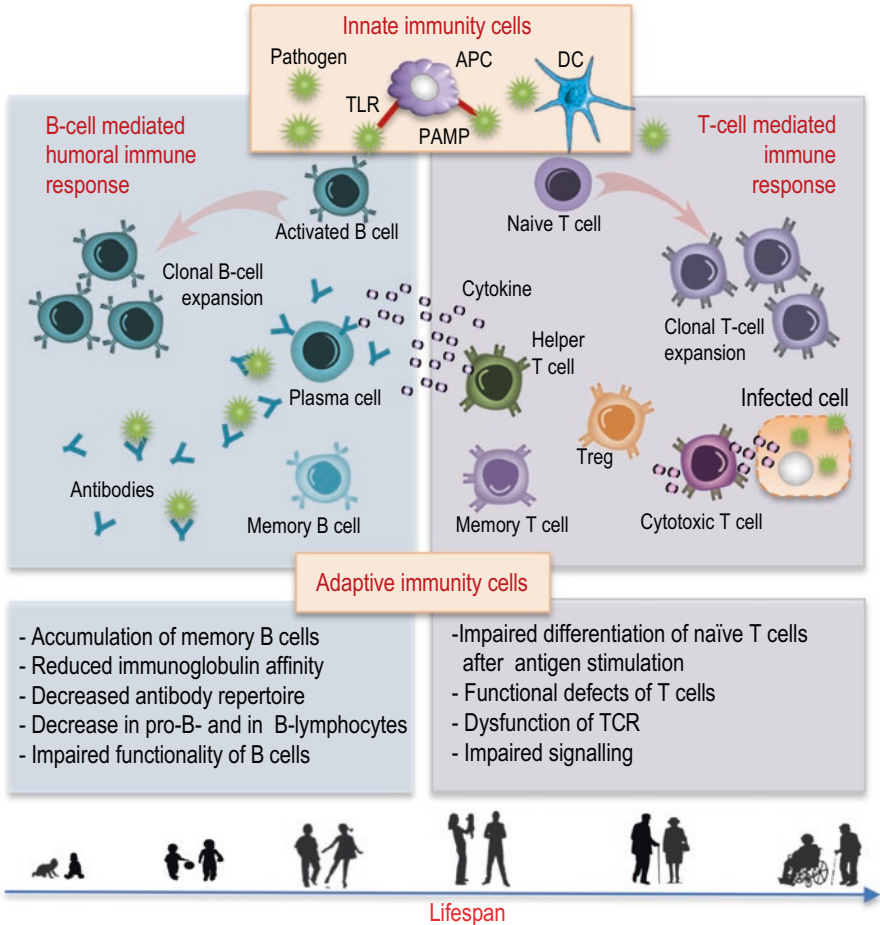


Fig. 2.3 Adaptive immune system age-related changes

APC antigen presenting cells, PAMPs pathogen-associated molecular patterns, TLRs Toll-like receptors, DC dendritic cells, Treg regulatory T cells, TCR T-cell receptor

Effects of Aging on the Innate Immune System

As mentioned above, “innate immune defences are not non-specific, but they respond to pathogens in a generic way” (Litman et al. 2010). Further important functions of innate immunity are activation of the complement cascade and generation and release of chemical humoral factors, rapid recruitment to sites of infection such cells as eosinophils, neutrophils, macrophages, natural killer cells (NK), and dendritic cells (DCs) (Figs. 2.1 and 2.2).

Neutrophils short-lived polymorphonuclear granulocytic cells representing the most abundant circulating leukocytes, and act as a very effective first line of defence

against pathogenic bacteria, yeast and fungi (Fig. 2.2). They are immediately recruited to the site of infection and act rapidly through specialised mechanisms such as phagocytosis and killing target organisms. Neutrophils mediate high oxidative burst activity, triggered after recognition of PAMPs on the pathogen. These innate cells are characterised by a relatively high turnover and have a very short lifespan. Despite these features, various age-related functional impairments have been reported in phagocytic mechanisms, in chemotaxis and generation of toxic free radicals, as well as in their susceptibility to apoptosis (Shaw et al. 2010). These alterations presumably reflect aging processes at the level of the hematopoietic stem cell. The level of expression and functional integrity of receptors recognising PAMPs, such as Toll-like receptors, and also the expression of major histocompatibility complex class II (MHC-II) molecules, together with production and release of chemokines and cytokines, are also lower in neutrophils from old individuals (Fulop et al. 2004). Thus, disturbed function and impairments in these initial defence mechanisms against infectious agents are likely to have vital importance in elderly populations (Müller and Pawelec 2014).

Monocytes and macrophages also have important roles including multiple functions in terms of phagocytosis and antigen presentation (Fig. 2.2). Monocytes act very efficiently in controlling invading bacteria – the feature that is most important for the aged population characterized by high prevalence of infectious diseases. Macrophages are involved in the initiation of inflammatory responses, in the direct destruction of pathogens and elimination of malignant cells, as well as in interactions with and activation of the adaptive immune response by means of antigen presentation (Oishi and Manabe 2016). They are then able to eliminate their target antigens directly or indirectly – through production and secretion of immune molecules and immune factors, such as interleukin (IL)-1, Tumor Necrosis factor (TNF), and Interferon (IFN)- γ , which in turn, are capable of activating and recruiting additional immune cells (Derhovannessian et al. 2008; Keller 1993).

The proportion of circulating monocytes in peripheral blood of aged individuals does not seem to be significantly different to the young, but there are fewer macrophages in the bone marrow of 80–100 year old people. This decrease can be explained by accompanying processes of an increased apoptosis as well as reduced cellularity observed with advancing age. Also expression and functionality of MHC-II antigens on macrophages are decreased with aging, with apparently epigenetic changes being responsible for this impairment. The phagocytic and apoptotic features of macrophages are also impaired with age, accompanied by decreased release of reactive oxygen species, such as NO_2 and H_2O_2 and less secretion of TNF and IL-1 (Fernandez-Morera et al. 2010; Gonzalo 2010; Müller and Pawelec 2014).

Dendritic cells (Fig. 2.2) are important players in the immune response and are said to bridge the innate and adaptive immune systems. They are capable of recognising PAMPs and take up and process pathogens to present MHC-bound antigens to T lymphocytes. They are often designated “professional” antigen-presenting cells (APCs). In fact, they represent the cell fraction “without which adaptive immune responses cannot take place. Moreover, the manner in which the DCs present antigen and co-stimulate T cells influences the type of T-cell response initiated, and thus

the quality and intensity of adaptive immune responses” as we reviewed previously (Müller et al. 2013a). Thus, it is understandable that even small age-related alterations in the function of dendritic cells could greatly affect T-cell functionality.

DCs do appear to be somewhat impaired by aging in terms of their migratory capacity and distribution, in their ability to process antigen, in their expression of costimulatory signals, and their ability to secrete cytokines (Fig. 2.2). Despite the fact that antigen presentation by DCs appears to be relatively unimpaired in the elderly, slightly decreased numbers of DC found in peripheral blood and follicles could probably explain reduced immune supportive capacity of this cell fraction in immune defence against pathogens and tumours (Gonzalo 2010; Della Bella et al. 2007; Derhovanessian et al. 2008). Results from animal studies demonstrate that the circulating levels of DCs are markedly reduced. The same may be true in elderly humans (Adema 2009; Müller and Pawelec 2014).

Natural killer (NK) cells are a class of cytotoxic lymphocytes. They are responsible for and are involved in early defence, with particular importance in recognizing virus-infected cells. They recognize and kill their target cell in an MHC-unrestricted manner, and are inhibited by the presence of self-MHC molecules (Fig. 2.2). This particular outstanding immune competence of NK cells makes them most important players in cancer immune surveillance during aging. Results of studies on elderly individuals have shown that although numbers of NK cells are often elevated with age, they tend to have an impaired cytotoxic function on a per-cell basis, and are more likely to have a mature phenotype compared to NK cells from the young. NK cells from the elderly are also characterized by decreased production and release of chemokines and cytokines, such as MIP1 α , RANTES, and IL-8. In this regard, the elevated numbers of NK cells commonly found in aged people may be required to achieve a certain baseline level of functionality as a compensatory mechanism for the decreased function of each cell. Production and secretion of such cytokines as IL-2, IFN- γ , TNF and IL-12 were also shown to be decreased with aging – which may also contribute (among other factors) for immune impairments related to advanced age (Dewan et al. 2012; Müller and Pawelec 2014).

Adaptive Immune System

As stated by Bonilla and Oettgen, “A defining feature of adaptive immunity is the somatic development by genetic rearrangements of the inherited germline of a pool of clonally diverse lymphocytes with a large repertoire of different antigen-recognition receptors” (Bonilla and Oettgen 2010). Accordingly to this definition, the hallmarks of adaptive immunity are: (i) clonal expansion – in order to generate sufficient amounts of cells to confront the pathogen; (ii) differentiation to effector cells – in order to destroy and eliminate the pathogen; and finally (iii) maintenance of a small fraction of antigen-specific memory cells – in order to respond faster and more strongly to pathogen re-exposure (Müller et al. 2013b). In other words, adaptive immunity (Figs. 2.1 and 2.3) involves a highly regulated multidirectional

interplay between innate cells such as DCs (or other antigen-presenting cells), and T- and B-lymphocytes. These specific interactions activate, induce, and promote pathogen-specific immunologic effector pathways and the generation of immunological memory mediated by subpopulations of long-lived memory T- and B cells. When the latter encounter and recognize the same pathogen later, they respond more rapidly with a stronger protective effect (Cooper 2010; Müller and Pawelec 2014).

During the course of aging, after long-term residence in the aging host, naïve T cells begin to suffer impaired differentiation into effector cells after antigen stimulation, as well as further functional impairments, such as reduced production of cytokines, and a more restricted T-cell receptor (TCR) repertoire (Ferrando-Martinez et al. 2011; Weiskopf et al. 2009). Epigenetic age-related changes, such as methylation of cytokine gene promoters can also lead to impaired immune function (Calvanese et al. 2009; Gonzalo 2010). The altered DNA methylation profiles were found to be present over the course of aging for both immune-specific genes and for the genes involved in common pathways normally related to cell homeostasis (Fernandez-Morera et al. 2010; Shanley et al. 2009).

The functional potency of T lymphocytes from aged individuals was found to be reduced relative to cells of the same phenotype from the young (Liu et al. 2002). Naïve T cells freshly exported from the thymus, are activated by APCs through binding of their TCRs to the appropriate MHC-peptide complex on the APC surface. The decisive event at the beginning of T-cell activation appears to be the reorganisation of the plasma membrane into a “lipid raft” or “immune synapse”. These assemble at the place of contact between T cell and APC. However, this step of lipid raft clustering is impaired in T lymphocytes from older people. One possible explanation for this may be the higher levels of cholesterol commonly found in aged cells. The rise in the cholesterol content impedes the motility of their rafts and in this way reduces recruitment of signalling molecules to the locality that are required for successful activation (Larbi et al. 2011; Müller and Pawelec 2014; Fulop et al. 2017).

For appropriate activation and differentiation of T cells, a necessary requirement is the integrity of the genes coding for the main key factors. This in turn may be dependent on different environmental factors, such as exposure to hormones or chemicals, infection with different pathogens etc., which influence this process. Such factors can change the epigenetic profile of T lymphocytes, affecting their gene expression and modifying these processes. The consequence of such immune remodelling that usually accompanies aging is a significantly increased morbidity and mortality commonly observed in the elderly population (Dewan et al. 2012; Larbi et al. 2008; Solana et al. 2006; Fernandez-Morera et al. 2010).

Relatively less is known about age-related alterations occurring in B cells and their subpopulations than in T cells. Some studies report that memory B-cell populations accumulate with age, in terms of proportions and numbers of CD27⁺ cells. Indeed, humoral immunity does appear to be different in older people both in quality and quantity. Such alterations as a reduced numbers of pro-B lymphocytes in the bone marrow, but also their reduced ability to differentiate into pre-B cells may be responsible for these impairments. Both antibody diversity and quality are different in older adults because of compromised somatic hypermutation in germinal centers,

but the relative contribution of intrinsic changes or microenvironmental changes is unclear (Müller et al. 2013b).

It has been consistently reported that there are decreased numbers of functional immunoglobulin-secreting B cells in aged people, correlating with decreased titres of antigen-specific antibodies. Not only the B-cell subsets themselves but also the repertoire of immunoglobulins produced by them are altered in both specificity and isotype. The consequence of this may well be the reduced duration of humoral response with reduced B-cell capacity for providing specific primary and secondary responses seen in aged individuals (Colonna-Romano et al. 2008; Ademokun et al. 2010). The entire process appears to be generally related to the specific interactions inside the germinal center where antigen-activated B cells communicate with CD4⁺ “helper” T lymphocytes. Age-associated deficiencies in T cells can have modulatory effects on these cognate interactions and reduce the quality of antibodies in terms of their avidities, and their titer (Dewan et al. 2012). Age-related alterations in epigenetic status is likely to be playing an important role here as well, and might be responsible for altered B-cell function. Such epigenetic changes may induce important modifications in cell differentiation pathways as well as in rearrangement of B-cell receptor and immunoglobulin genes and their affinity maturation (Shanley et al. 2009; Colonna-Romano et al. 2008; Müller and Pawelec 2014).

Age-Related Dysregulation of Hematopoiesis

Figure 2.4 represents the development of lymphocytes that takes place in the functionally specialised environments of the bone marrow and thymus, in a simplified manner (Fig. 2.4). The original lymphoid B- and T-cell precursors emerge from a pluripotent hematopoietic stem cell (HSC) in the bone marrow (Fig. 2.4, left). The haematopoietic stem cell compartment serves as the origin and source for the continuous replenishment of blood cells including the cells of the immune system, providing and delivering all lymphoid and myeloid cellular components. Aging alters the HSC compartment (Geiger et al. 2013) such that the output of immune cells is skewed away from lymphocytes towards myeloid cells. The stromal matrix of the aging bone marrow that normally gives rise to and regulates HSC production, undergoes structural alterations because of the diminished stromal cell numbers and decrease in IL-7 production (Pangrazzi et al. 2017). In the course of aging the bone marrow haematopoietic compartment becomes invaded by fatty adipose tissue for reasons that remain unclear (Compston 2002; Gruver et al. 2007; Müller and Pawelec 2014).

Alterations within the HSC compartment occurring with aging may be partly related to intrinsic changes to the HSCs themselves, as well as changes in the micro-environment. Age-related accumulation of DNA damage, epigenetic changes, and telomere attrition, accompanied by elevations in intracellular ROS are characteristic features of aged HSCs (Dykstra and de Haan 2008; Warren and Rossi 2009). Accidents of genomic instability may lead to increasing malignant transformation of HSCs, especially in the myeloid lineage, and thus to the development of myelo-

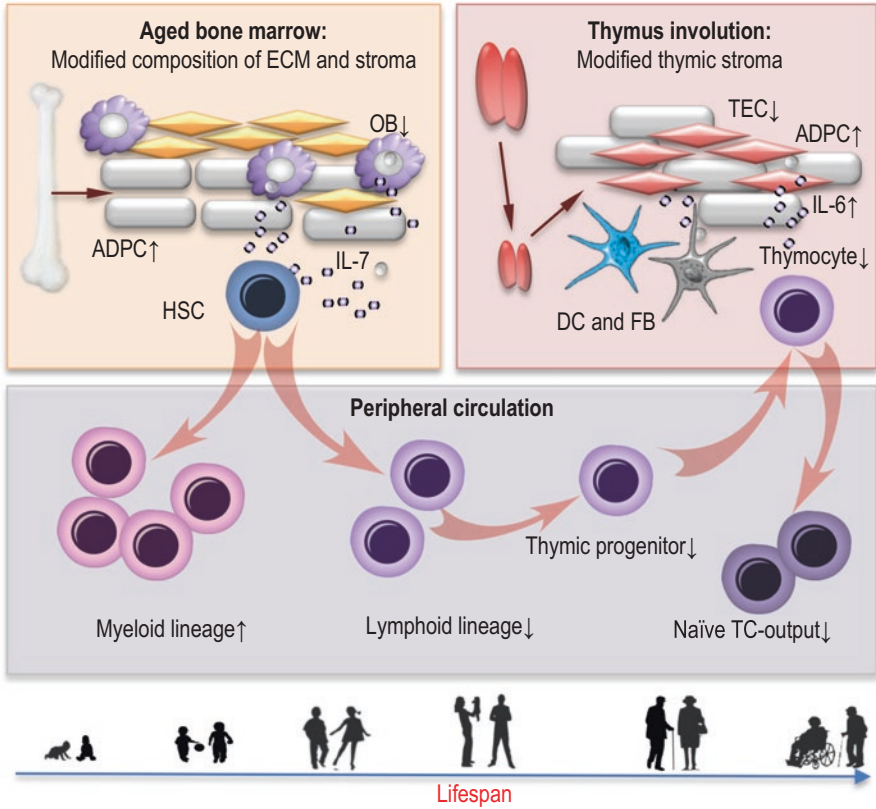


Fig. 2.4 Age-related dysregulation of hematopoiesis and thymopoiesis (Modified from Müller and Pawelec (2015))

ECM extra-cellular matrix, *ADPC* adipocytes, *OB* osteoblasts, *HSC* hematopoietic stem cell; *IL* interleukin, *TEC* thymic epithelial cells, *DC* dendritic cells, *FB* fibroblast, *TC* T cell

proliferative disorders. The consequent age-related changes in the lymphoid and myeloid lineage are likely to account for a major part of problem with immune function in the elderly and their increased susceptibility to myeloproliferative disease (Beerman et al. 2010; Dykstra and de Haan 2008; Müller and Pawelec 2014).

Thymic Involution

It is clear that a major event contributing to age-associated immune system changes is the physiological process of thymic involution (Fig. 2.4, right). After puberty, a progressive reduction in the size of the thymus size takes place, areas of active thymopoiesis decrease and the organ shrinks (Aspinall et al. 2010). This evolutionarily

programmed process is supported by increased levels thymo-suppressive cytokines, such as leukaemia inhibitory factor, oncostatin M, and IL-6 (Sempowski et al. 2000), with a simultaneous decrease of IL-7 secretion. These alterations negatively affect the numbers of thymic epithelial cells and lead to decreases in thymopoiesis. The contraction of thymic output and consequently reduced capacity to replace the circulating naïve T lymphocytes after their activation and differentiation is believed to be an important element contributing to the development of immunosenescence (Aspinall et al. 2010; Müller and Pawelec 2014).

Thymus involution is characterised not only by a diminished efficiency of T-cell development but also and by the impaired migratory capacity of naïve T lymphocytes to the periphery (Fig. 2.4, bottom). The marked decline of thymic function leads to shrinkage of the T-cell repertoire and is a decisive contributor to the age-related rise in the incidence of infectious disease – despite the fact that the thymic involution per se, beginning early in life, is a developmental not in itself an aging phenomenon (Lynch et al. 2009). Additional to this process, alterations in thymic function may also be affected by environmental surroundings, prenatally as well as postnatally, by genetic predisposition, and sexual dimorphism – men display different patterns of thymic involution than women (Gui et al. 2012). It was demonstrated that thymectomy in early childhood is associated with early onset of several age-related alterations reminiscent of immunosenescence (Appay et al. 2010; Sauce and Appay 2011). These findings emphasize the importance of potentially powerful naïve T-cell output in early life for the generation of sufficient enough reserve naïve T cells for later life.

Impact of CMV Infection on Immunosenescence

An important driver of remodeling of the peripheral T-cell compartment over the lifespan is chronic immune activation by different pathogens and particularly persistent cytomegalovirus (CMV). CMV infection is usually asymptomatic unless the host is immunosuppressed and establishes a lifelong latent infection (Dowd et al. 2009; Britt 2008). CMV resides in latent form in cells broadly distributed throughout the body, including HSC, monocytes, macrophages, dendritic cells and endothelial cells (Nikolich-Zugich and van Lier 2017). Lifelong coexistence with CMV as significant implications for the immune system, leading to functional alterations and eventually driving immunosenescence (Müller et al. 2017). It is likely that latent CMV reactivates sporadically, but whether this occurs more often in the elderly than the young has not been unequivocally demonstrated (Stowe et al. 2007). In the predominantly subclinical reactivation process, it is believed that immunogenic viral transcripts are produced, which then cause expansion of virus-specific cytotoxic memory lymphocytes. The whole persistence process requires a complex equilibrium between virus immune evasion and host immune recognition over the lifetime (Jackson et al. 2017; Nikolich-Zugich et al. 2017).

As result of such persistent CMV infection an expansion of the total CD8⁺ T-cell pool occurs that is associated with accumulation of late-stage differentiated effector memory T cells in the peripheral circulation (Müller et al. 2017). In people infected with CMV and especially in the elderly, a large proportion of circulating CD8⁺ T cells is specific for CMV. This phenomenon of successive increases of CMV-specific CD8⁺ T-cells over the lifespan is known as “memory inflation” (Karrer et al. 2003; Kim et al. 2015). Therefore, the absolute number of CMV-specific T lymphocytes assessed as functional may be even higher in the old than in the young individuals, due to memory inflation, emphasizing the over-riding importance of immunosurveillance against this virus (Ouyang et al. 2003).

In a recent systematic review, Weltevrede and colleagues considered current evidence concerning the relationship between CMV and immunosenescence (Weltevrede et al. 2016). They concluded that in the majority of studies, CMV-seropositivity seems to enhance the accumulation of T-cell phenotypes commonly associated in the literature with immunosenescence (i.e. elevated levels of Effector Memory (EM) and TEMRA (Effector Memory T cells re-expressing CD45RA) cells in both CD4⁺ and the CD8⁺ T-cell subsets) in CMV-positive relative to CMV-negative elderly. No clear evidence was found for a lower level of naïve T cells in CMV-seropositive-vs-seronegative individuals.

Due to the observed high levels of both CD4⁺ and CD8⁺ memory T lymphocytes in older people, it was suggested that CMV might contribute to and promote immunosenescence in a clinically-relevant sense (i.e. may be associated with mortality (Ouyang et al. 2003; Pawelec et al. 2009, 2012; Pawelec and Derhovanessian 2011; Müller et al. 2017)). Many reports suggest that CMV infection increases mortality in the elderly and is related to frailty and to impaired survival (Savva et al. 2013; Wikby et al. 2005; Spyridopoulos et al. 2015). Functional decline in elderly individuals has been found to be associated with altered immune characteristics and the intensity of the immune response to CMV (Moro-Garcia et al. 2012; Müller et al. 2017). However, these data remain controversial.

Aging and Loss of T-Cell Diversity

As we have seen above, age-related changes in peripheral T-cell dynamics are associated with altered hematopoiesis, with thymic involution and with lifelong immune stimulation by multitudinous antigens, but especially CMV. Such alterations contribute to lower proportions of naïve T vcells due to lower HSC output and minimal remaining thymic function, and possibly filling of the “immunological space” by memory cells, leading to reduced diversity of the T-cell repertoire (Lynch et al. 2009; Naylor et al. 2005; Holder et al. 2016). A shift occurs towards accumulations of T-cell populations with memory and effector phenotypes, as well as to accumulation of putatively senescent immune cells. Higher levels of CD28⁻ T cells in elderly Swedes, clustered together with certain other parameters, such as an altered CD4/CD8 ratio, fewer B-cells, and CMV-seropositivity, has led to the definition of a

so-called “immune risk phenotype” associated with higher 2, 4 and 6-year mortality in longitudinal studies of people 85 years old at baseline (Pawelec et al. 2009). However, these risk parameters may be different in different populations.

A broad TCR repertoire is commonly considered to be essential for maintaining adequate immune competence in the face of new pathogens. In this regard, the age-related restraints on diversity are assumed to have negative implications. It has been reported that TCR repertoire contraction, demonstrated at least for CD4⁺ T lymphocytes, may occur quite suddenly: TCR diversity was found to be well-preserved up to an age of around 60–65 years, but was thereafter shown to be abruptly reduced (Naylor et al. 2005). This contraction may lead or at least contribute to the lowered responses to new pathogens and to poor vaccination response in this age group (Müller et al. 2017), but surprisingly few data are available on this issue.

The consistently lower absolute numbers and percentages of peripheral blood naïve CD8⁺ T cells are clearly one of the universal biomarkers of human immune aging in non-Western populations as well (Fagnoni et al. 2000; Alam et al. 2013; Pawelec 2017a). While this phenomenon is consistently found in studies comparing younger and older adults, the accumulation of memory CD8⁺ T cells is not universally reported (Pawelec 2017a). This may be due to the fact that accumulation of memory T cells is apparently associated with persistent CMV infection, but not infection with other common herpesviruses, and that *de novo* infection with CMV may occur at any time of life.

Inflammaging and Its Contribution to Neuroinflammation

Aging is characterized by accumulation of senescent cells in many tissues. These cells secrete inflammatory cytokines, chemokines and other inflammatory mediators modulating their microenvironment (Grabowska et al. 2017). Aging-related accumulation of such functionally exhausted memory T lymphocytes, commonly secreting the pro-inflammatory cytokines IFN- γ and TNF, together with mediators and factors of the innate immune system, is considered to be one source contributing to the low-grade inflammation (inflammaging) often observed in old people (Franceschi et al. 2007).

Chronic activation of the adaptive immune system together with significant functional alterations in monocytes is believed to contribute to the process of aging. All these changes may also have implications for development and maintenance of a chronic state of low-grade inflammation and contribute to various age-related diseases (Hearps et al. 2012). Thus, inflammatory monocytes together with activated macrophages may contribute to inflammaging (Franceschi et al. 2000, 2007).

It was postulated that inflammaging is a decisive source of and is associated with different age-related diseases, playing an important role in their pathology (Franceschi et al. 2000, 2007). Thus, “inflammaging seems to be a universal phenomenon accompanying human aging, and is associated with frailty, morbidity and mortality in elderly individuals” (Jenny 2012; Soysal et al. 2016; Vallejo 2007).

Nevertheless, it is often difficult to determine whether inflammation per se is the cause for these pathological conditions or rather the consequence (Rymkiewicz et al. 2012). Although nearly all aged individuals exhibit low-level chronic inflammation to some extent, not all suffer from age-related diseases. Thus, factors in addition to the chronic inflammatory state must be required for the onset of age-associated diseases (Bektas et al. 2017; Coder et al. 2017; Franceschi et al. 2017b; Nikolich-Zugich 2018).

Even in overtly healthy individuals, chronic low-grade inflammation has repeatedly been identified during aging, as reflected by increased levels of circulating pro-inflammatory cytokines such as IL-6, IL-1 β , TNF, and IFN- γ (Franceschi et al. 2017a). These cytokines influence all physiological systems and affect their functional status, particularly neurological function, thus affecting behavioral and cognitive parameters (Alboni and Maggi 2015; Di Benedetto et al. 2017).

Peripheral immunosenescence, accompanied by inflammaging contributes at the systemic level to age-related alterations in the proportions and functions of cells in the circulation (Fig. 2.5). It is assumed that cytokines produced from such aged and functionally altered cells in the periphery can access the brain via several routes and affect neurological function in this way. “Chronic exposure to inflammatory mediators can compromise the blood-brain barrier and permit entry of immune cells and pro-inflammatory cytokines into the brain. These influence the phenotype and function of microglia due to low-grade brain inflammation. Other cells such as astrocytes and neurons, and including peripheral immune cells such as T cells, monocytes, and macrophages, thus all participate in neuroinflammation” (Di Benedetto et al. 2017; Liang et al. 2017).

Age-associated increased levels of certain cytokines and their modulators are found in the CNS of aged rodents (Barrientos et al. 2012; Ye and Johnson 1999; Scheinert et al. 2015). Aging microglia show characteristics of an increased inflammatory state referred to as a “primed profile” and defined by Norden et al. as (i) “increased baseline expression of inflammatory markers and mediators;” (ii) a “decreased threshold to be activated and to switch to a pro-inflammatory state”; and (iii) “exaggerated inflammatory response following immune activation” (Norden et al. 2015). In other words, immunosenescence and inflammaging in the periphery may contribute to neuroinflammation “by modulating glial cells towards a more active pro-inflammatory state”. These altered conditions may lead to loss of neuroprotective function (normally provided by microglia) and hence to neuronal dysfunction contributing to elevated brain tissue damage (Giunta et al. 2008; von Bernhardi et al. 2010; Smith et al. 2018). Thus, systemic inflammation contributes to the risk of developing age-related cognitive impairment, neurodegenerative changes and neurological disorders (Pizza et al. 2011; Harrison 2016; Goldeck et al. 2016; Di Benedetto et al. 2017).

Currently, there is no definitive answer concerning the main underlying mechanisms involved in the induction of the neuroinflammation and its role in neurodegenerative processes occurring with aging. Nevertheless, neuroinflammation seems to be the basic contributor “that links together many factors associated with cognitive aging” (Ownby 2010). Greater cognitive impairment following immune

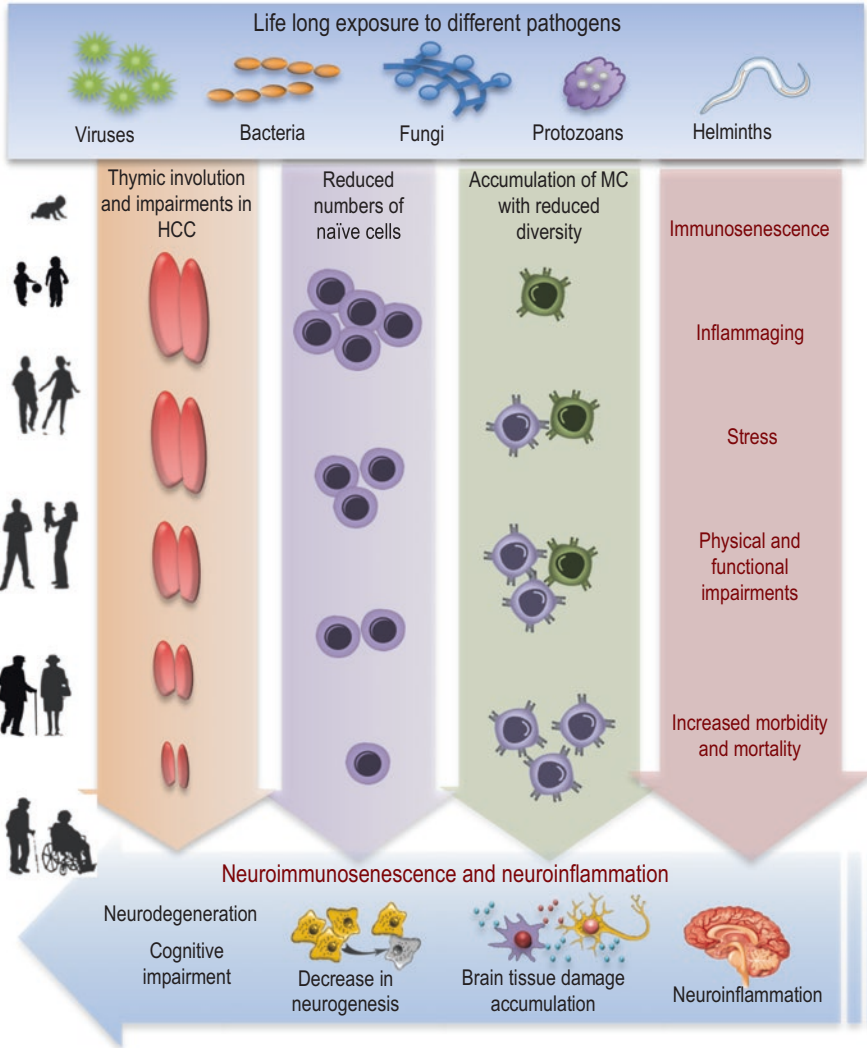


Fig. 2.5 Immunosenescence and inflammaging and their contribution to neuroinflammation (Modified from Di Benedetto et al. (2017))

“Immunosenescence affects both adaptive and innate immune systems. The most relevant changes to adaptive immunity are decreased peripheral naïve T cells and the concomitant accumulation of late-stage differentiated memory T cells with reduced antigen receptor repertoire diversity. This phenomenon results from age-related impairments in the hematopoietic stem cell compartment and thymic involution. Lifelong exposure to different pathogens is the major driver of the phenotypic changes in the distribution of T-cell subsets over the life course. Ageing is characterized by a chronic, low-grade inflammation (inflammaging). Peripheral immunosenescence and inflammaging may promote neuroinflammation by modulating glial cells towards a more active pro-inflammatory state, leading to a loss of neuroprotective function, to neuronal dysfunction accumulation of brain tissue damage and neurodegeneration” (Di Benedetto et al. 2017)

HCC hematopoietic cell compartment

challenge is often seen in the elderly compared to the young, accompanied by elevated and more prolonged release of pro-inflammatory cytokines in the otherwise healthy aged brain (Barrientos et al. 2015). It is broadly accepted that aging together with stress affects the neuroendocrine system, activating the hypothalamic-pituitary-adrenal axis to secrete corticotropin-releasing hormone from the paraventricular nucleus of the hypothalamus and further promoting the release of adrenocorticotropin by the anterior pituitary gland. As a consequence of this, the adrenal gland begins to produce glucocorticoids and release them into the circulation (Barrientos et al. 2012). The main glucocorticoid, cortisol, exerts modulatory effects on the immune system in a bidirectional way: by modulating the production and release of chemokines, cytokines, and adhesion molecules, as well as by altering maturation, differentiation, and migration of immune cells (Barrientos et al. 2015; Hansel et al. 2010). Elevated levels of cortisol can impair hippocampal neurogenesis either directly or indirectly, through modulation of cytokine release and through regulated expression of receptors on immune and brain cells (Di Benedetto et al. 2017). As a consequence of such modulation, an inflammatory milieu is produced that contains resident and peripheral immune cells, which all are engaged in complex interactions between secreted inflammatory mediators and cell surface receptors such as TLRs. TLRs are commonly expressed on cells that primarily participate in the inflammatory response, including microglia, astrocytes, and macrophages (Doty et al. 2015). Activated microglia and astrocytes alter their functional and morphological characteristics and start to release elevated levels of such pro-inflammatory cytokines as IL-6, TNF, and IL-1 β . It was suggested that brain microglia undergo a process of senescence, similar to the immune cells in the peripheral circulation. Recent studies report detection of senescent and hyperactive microglia in the aged and diseased brain (Deleidi et al. 2015). It is assumed that also the aging brain is in turn capable of regulating the immune system in terms of supporting recruitment of immune cells from the periphery. This may further contribute to immunosenescence and neuroinflammation (Gemechu and Bentivoglio 2012; Di Benedetto et al. 2017).

Concluding Remarks

Like all somatic tissues, the immune system exhibits age-related changes, sharing certain characteristics in all mammals so far studied. The root-cause of immune aging is at least two-fold; (1) “intrinsic” aging manifesting as dysregulated immune cell generation from hematopoietic stem cells and altered peripheral selection processes related to differentiation of precursor cells, especially T cells due to thymic involution; and (2) “extrinsic” aging resulting from the effects of lifelong exposures of immune cells to antigenic and other challenges from the internal and external environment. Improved understanding of the mechanisms involved in these two disparate aspects of immune aging will be required to develop rational approaches to interventions aimed at restoring appropriate immune function in the elderly.

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