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Immunology of Ageing

Graham Pawelec and Ludmila Müller

G. Pawelec
Department of Immunology, University of Tübingen, Tübingen, Germany

Health Sciences North Research Institute, Sudbury, ON, Canada
e-mail: graham.pawelec@uni-tuebingen.de

L. Müller
Max Planck Institute for Human Development, Berlin, Germany
e-mail: lmueller@mpib-berlin.mpg.de

Contents

Abstract

Immunity protects the host against infection, but becomes dysregulated with increasing age and can be a dangerous ally. Older adults tend to respond less well to infections but at the same time suffer more immunopathology. Better understanding of age-related changes to immunity will lead to more appropriate interventions to enhance protective immunity and at the same time reduce immunopathology. To this end, this chapter briefly overviews what is known about the processes leading to human immunosenescence, considering age-associated changes

to innate and adaptive immunity and their clinical consequences.

Keywords
Immunity · Aging · Immunosenescence · Hematopoiesis · Vaccination · Immune memory · Infectious disease · T-cell and B-cell repertoire · Cancer · Degenerative diseases of aging

1 Introduction

Despite a great deal of interindividual heterogeneity, it is the universal geriatric experience that older adults, even "successfully aged" oldest old adults, manifest multiple features implying a deterioration of immunity with age. However, as with other manifestations of aging, biomarkers of this so-called "immunosenescence" process may not track with chronological age, raising a great deal of scientific, medical, and commercial interest in methods for establishing the "immune age" of an individual [1]. This has great practical consequences given the age-associated higher incidence and greater severity of most infectious diseases, generally poorer responses to vaccination in older adults and the increased incidence of degenerative diseases with an inflammatory component, such as cancer and Alzheimer's.

However, as used in the literature, immunosenescence is a vague appellation, the very loose use of which has resulted in some confusion as to the definition of the term and ways in which the state can be assessed, and the implications of such measures. We have argued that clear differences in any measured immune parameters between younger and older adults should only be considered as marking immunosenescence if they have been robustly associated with negative health consequences [2, 3]. Thus, many age-associated changes to immune measures are by the very nature of the memory function of the immune system adaptive rather than maladaptive. The problem is in distinguishing between these two effects, rendered even more difficult by the fact that some measures may reflect both states at the same time. In the present chapter, we summarize what is currently known about age-associated differences in human immune parameters that are most likely to reflect detrimental changes and therefore deserve the epithet "senescence." In many instances, however, this is not clearly established in humans and recourse to animal models may be necessary.

2 Basic Principles and Constraints on Studies of Age-Associated Changes to Immunity in Humans

There are many constraints on studying age-associated changes in long-lived animals. In humans, most data thus far have been derived from cross-sectional studies and so refer only to differences and not to changes, for which longitudinal studies are optimal. However, that is not to say that comparisons of younger and older individuals are not meaningful as indicators for biomarkers that might be dynamically relevant at the individual level, or informative for a specific measured condition or symptom. For example, as shown in mice, greater frequencies of regulatory T cells (Tregs) in the blood of older adults in association with impaired delayed-type hypersensitivity (DTH) might be informative and indicate a mechanistic link to that particular outcome [4]. Such a possibility could then be followed up by establishing whether frequencies of Tregs do indeed increase with aging in the same individuals over time, paralleled by increasing impairment of DTH. Nonetheless, thus far there are very few reported studies that have attempted to accomplish this in humans, with most comparing young and old cross-sectionally. These data are commonly interpreted as evidence for associations between immunosenescence (as assessed by whichever biomarker is studied) and deleterious outcomes (as assessed by some clinical parameter). However, it has rarely been demonstrated that this is actually the case. Although longitudinal studies are better than cross-sectional studies, it is still true that they only provide biomarker data and cannot prove causation. Only

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properly controlled trials assessing the impact of an intervention on an outcome can show that age-associated alterations to proposed biomarkers of “immunosenescence” are mechanistically linked to that particular outcome. As can easily be understood, such trials that are not aimed at treating a specific disease, but rather at the “aging process” itself, are scientifically, financially, and ethically challenging in older people. So far, few have been published, other than difficult-to-interpret interventions involving exercise, or nutritional supplementation. Pharmacological interventions currently remain very much in the experimental realm and require proper validation.

To add to the difficulties of studying this field in people, most human data on age and immunity relate to investigations of peripheral blood immune cells and their behavior. Moreover, care must be taken when interpreting the published literature to distinguish between those studies reporting immune phenotypes expressed as percentages of subpopulations and those reporting absolute numbers per microliter. Differences and changes in the frequencies of certain cell subsets may be recorded even when there are no alterations to the actual absolute numbers of cells. This potential for confusion has resulted in the argument that reporting frequencies is therefore meaningless. However, this argument actually applies to both absolute numbers and frequencies of cells because both can only be viewed as biomarkers that can be valuable when shown to correlate closely with a defined measurable clinical outcome. Causality can only be imputed (without challenge/intervention studies). Moreover, a final caveat is that changes in absolute numbers or frequencies of peripheral blood immune cell phenotypes and functions may not reflect differences in immune function in target organs because the majority of immune cells are not circulating.

3 What Is Immunosenescence?

Given the above considerations, in our opinion the term “immunosenescence” should only be applied to describe changes to immune parameters that have been established as progressing with increasing age in the same individual and that are clearly deleterious for that individual [2,3]. This strict definition excludes many parameters that merely reflect differences between younger and older individuals, many of which are likely to be adaptive and beneficial rather than degenerative and detrimental [5]. Many studies have documented that both innate and adaptive immunity is influenced by age, but the actual clinical impact of the majority has not been well-established. Indeed, most earlier published studies did not attempt to demonstrate that the reported age-associated differences were in fact detrimental. In the meantime, several longitudinal studies have been initiated in humans, aimed inter alia at documenting immune system alterations and their associations with detrimental outcomes [1, 6, 7] Additionally, alternative animal models that may be more appropriate than the commonly employed murine models are now beginning to appear (e.g., in dogs, sharing a human environment and not specific pathogen-free as are most mouse models [8]). Also “real world” studies of animals in the wild are shedding light on the impact of immune aging under natural conditions [9]. Clearly, there are more controlled and extensive data from murine models, but these animals have a different evolutionarily adapted lifespan trajectory very different from humans. They may nonetheless provide potentially informative basic data supplementing those from the newer aging models and from the increasing numbers of longitudinal human studies. Over the last decade, data from human studies have greatly extended our knowledge of the impact of aging on immunity mostly gleaned from cross-sectional studies and the limited number of very small longitudinal studies which were mostly conducted on the oldest old (at least 85 years of age). All-cause mortality represented a robust and unequivocal clinical outcome in these studies in which sufficient mortality could be recorded over a feasible study time in such old cohorts. Several studies are now revealing constellations of immune and nonimmune parameters correlating with survival or other specific outcomes of clinical importance (e.g., responses to vaccination; prevalence of age-associated degenerative disease) [10].

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Importantly, some studies are now beginning to report on changes also in younger populations, rather than only in highly selected oldest old cohorts [11]. Furthermore, it is important to investigate different human cohorts other than those from the Western Educated Industrialized Rich Democratic (WEIRD) which are still the most well-studied – but not necessarily representative for economically and racially different areas [12]. Earlier studies in the oldest old had defined “immune risk profiles” (IRPs; clusters of simple immune parameters), but their similarity to those being defined in newer studies including younger individuals is not yet clear. Currently, many efforts are focused on predictive biomarkers, including IRPs and multiple additional health parameters, in order to increase predictive power. It is highly likely that immune biomarkers together with other relevant parameters, rather than single biomarkers alone, will yield the closest associations with clinical outcomes, as is the case in the Berlin BASE-II study [13]. Understanding associations of immune parameters with frailty in aging and with impaired responses to vaccines like influenza [14] and at the moment particularly to the new Coronavirus SARS-CoV-2 [15] is especially urgent. Thus, to establish robust and clinically meaningful insights on immunity and aging, and their implications for acute and chronic disease, tools for accurately assessing the degree and impact of immunosenescence at the individual level are required [1]. As alluded to above, many earlier mostly cross-sectional studies have provided some valuable data on commonly observed age-associated immune differences in different populations, not exclusively WEIRD. Some of these have been noted also in longitudinal studies. Thus, lower frequencies and also lower absolute numbers of circulating antigen-unexposed so-called “naïve” CD8＋ T-cells (mostly cytotoxic cells) are consistently found in almost all studies. These reductions in CD8＋ naïve T cells are usually accompanied by reciprocal accumulations of memory CD8＋ T-cells (specific for previously encountered pathogens). These differences are also seen to a lesser degree in CD4＋ T-cells (mostly “helper” T cells or “regulatory” T cells. Similar types of changes to the antibody-producing B-cells are usually also reported, as well as differences in different cell types within the innate immune system. In this chapter, space permits only a very brief overview of these differences, considering their clinical implications and potential interventions to restore appropriate immune function in older adults.

4 Hematopoiesis in Older Adults

Blood cells, including immune cells, must be constantly replenished throughout the lifespan. Hence, aging effects on hematopoietic stem cells (HSC) or their niche would be expected to alter the output of immune cells. There is relatively little information available on this in humans, but a large body of data in animals mostly mice (see Fig. 1). The bone marrow (BM) architecture changes with age in terms of the numbers and proportions of stromal cells and osteoblasts, accompanied by a changed balance of secreted cytokines, which affects the HSC niche and impacts on the release of immune cells to the periphery [16]. HSC niches are located in proximity to the BM vasculature which is also changed with age [17]. Thus, the endothelial, mesenchymal and other cell types in the HSC microenvironment have an essential role in supporting these cells [18] such that the age-related changes to these cells influence the HSC themselves. The end result of these changes is that the output of myeloid cells and platelets is increased, at the same time as lymphoid cell output decreases, reflected in marked changes in epigenetics and patterns of gene expression [19]. Not only is there skewing away from lymphoid cell production, but there are (intrinsic and/or niche-induced) impairments in HSC in older animals which are associated with poorer immune function (as reflected in responsiveness to vaccines). If similar phenomena occur in humans, for which there is some circumstantial evidence, it may be possible to consider pharmacological intervention at this very earliest stage of the evolution of immunosenescence [20, 21].

These age-related changes to the HSC (Fig. 1) are reflected in the accumulation of DNA damage

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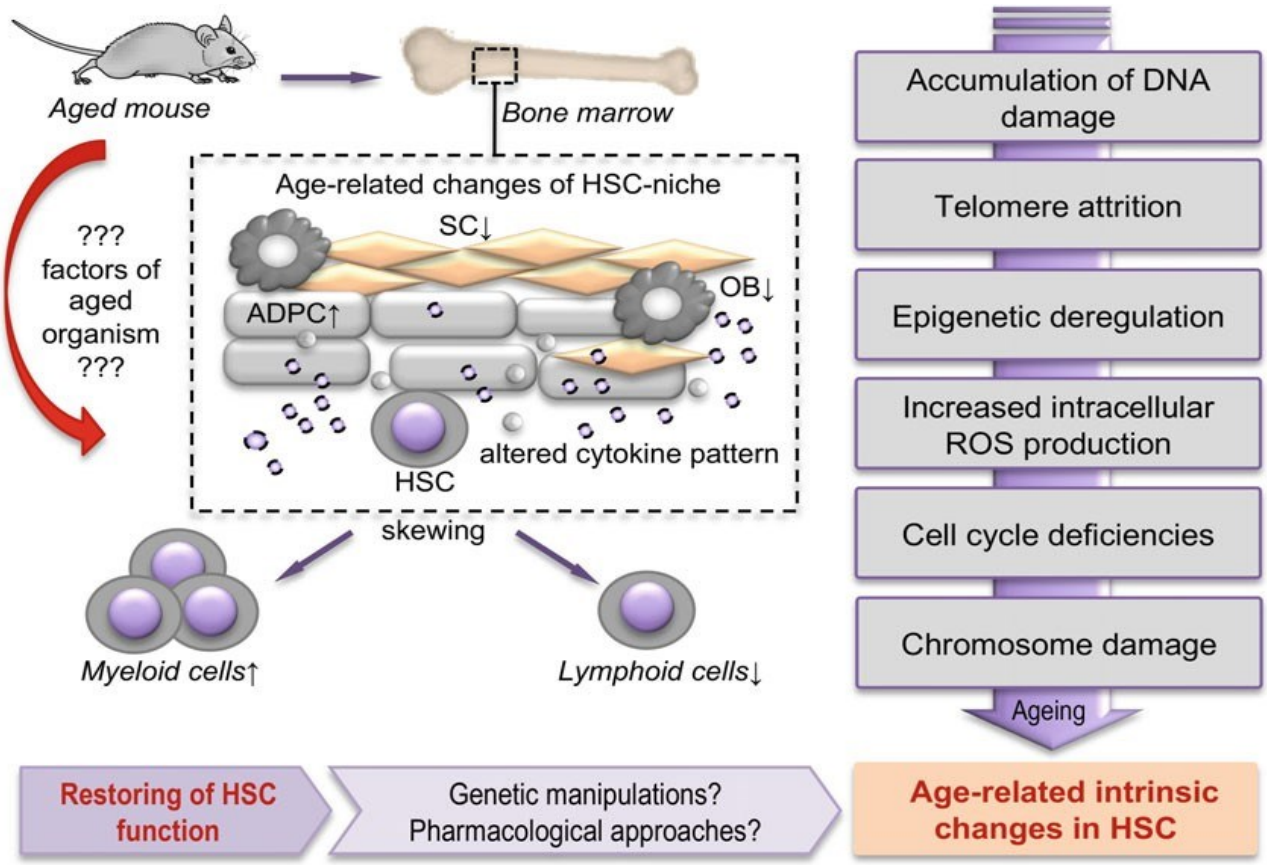

Fig. 1 Age-related alterations in bone marrow.

in cells with shorter telomeres and with evidence of epigenetic dysregulation. Physiologically, there appears to be a higher release or less control of intracellular reactive oxygen species [22]. More cell cycle deficiencies and more chromosome damage are seen in HSC from older animals, accompanying decreased integrity of the mini-chromosome maintenance (MCM) helicase system that may be in large responsible for this [23]. Thus, restoring MCM DNA helicases to young levels might be feasible in future therapies, but requires genetic manipulation that would be challenging to translate to the clinic at present. Alternatively, exploitation of pharmacological approaches that have been shown to be effective in mice might be more feasible. Thus, old HSCs treated with a specific inhibitor of the RhoGTPase cdc42 known as “casin” [2-((6-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-yl)amino)ethanol}], or Pirl1-related Compound 2 [20], have been reported to reconstitute the response of old animals to hepatitis vaccination [20] and to reduce inflammation and extend the animals’ lifespan [24].

5 Age-Associated Changes to Innate Immunity

5.1 Phagocytic Cells

The majority of white blood cells are polymorphonuclear leukocytes (PMNs), which, together with monocytes/macrophages, mediate “first responder” protection against entry of infectious agents into the body. Skewing of the output of immune cells from the BM towards the myeloid lineage (Fig. 2) maintains the numbers of these cells or even increases them in older humans, but there are qualitative differences in their functions. This may suggest that the increased numbers of myeloid cells produced may be compensatory for

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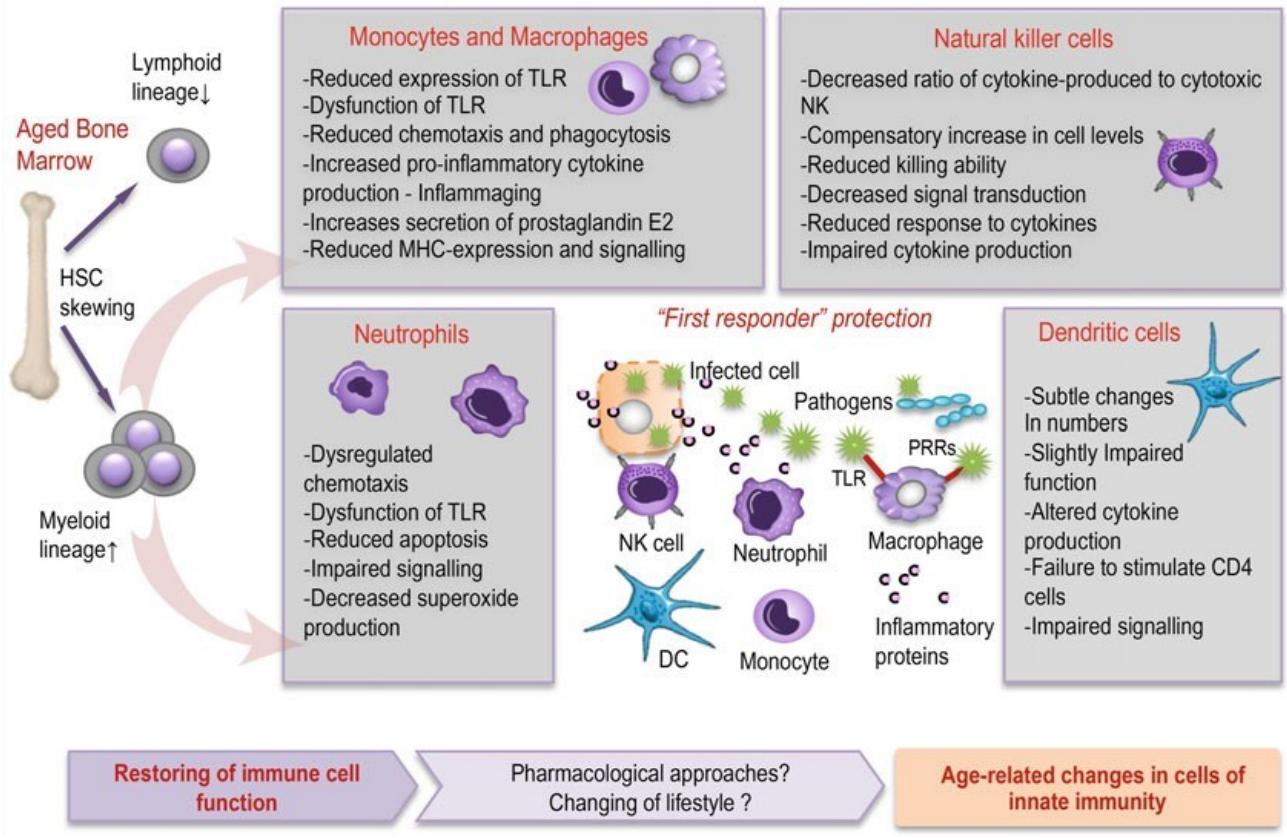

Fig. 2 Age-associated changes in the cells of innate immunity

their reduced functionality. These cells recognize microbial structures absent from mammalian cells via their expression of so-called “surface pattern-recognition receptors” (PRRs), of several major subtypes, particularly Toll-like receptors (TLRs). TLR2 and TLR4 recognize bacterial components, whereas TLR3, 7, 9 recognize viral structures. TLR signal transduction then triggers the initiation of an acute inflammatory response involving the central transcription factor NFκB, which results in pro-inflammatory cytokine and chemokine production [25]. In general, the level of expression and the functionality of TLRs is decreased in older adults, thus affecting the integrity of the immune response [26]. Herein lies a paradox – the ability of the system to respond to external stimuli is decreased but at the same time the basal level of activation is increased. This is a theme repeated in many facets of the immune system in older adults.

Thus, the resulting age-associated mildly elevated basal level of inflammation has been proposed to cause many of the degenerative changes seen with advancing age and which has been dubbed “inflammaging” [27]. Although the phagocytic cells are not the sole contributors to inflammaging, it has been proposed that they are primarily responsible for it. Hence, compromised functionality of these innate immune cells, which results in decreased responses to pathogens, also results in elevated basal free radical and pro-inflammatory cytokine production [28]. This dysfunction is compounded by aberrant responses to chemotactic signals resulting in more “collateral damage” as neutrophils passage through tissues in an attempt to reach the source of infection [29].

Thus, a major characteristic of the innate immune system in older adults is the heightened baseline activity but “immune paralysis” on challenge [30]. Whether the baseline activation is solely pathological is open to debate, as it may also reflect an adaptive response resulting from earlier exposures and now sometimes referred to as “trained innate immune memory.” [31] This may be necessary to maintain surveillance in

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older adults but also contribute to inflammaging. As so often, the immune system is both friend and foe, and the balance between the two can be fine and become dysregulated in later life. Rechallenge may then result either in enhanced responses or in stimulation of negative feedback, contributing to immune paralysis [32]. An example of this is that macrophages secrete more prostaglandin E2, thus suppressing T-cell activation in older adults, but at the same time exhibit reduced phagocytotic capacity, produce less free radicals, and also have impaired chemotaxis relative to macrophages from younger people [33]. This parallels the finding mentioned above that neutrophils show dysregulated chemotaxis, phagocytosis, and cytotoxicity because of their changed cellsurfacereceptor expression and signal trasnduction [34]. Other functional deficits of neutrophils include their reduced ability to extrude "neutrophil extracellular traps" (NETs) that capture extracellular pathogens as part of the defense against infections [35]. Finally, it should be noted that as with all HSC products, there are robust feedback mechanisms for regulating haematopoiesis [36] which may also directly affect skewed BM output.

5.2 Natural Killer Cells

Natural killer cells (NK cells) are lymphoid cells that appear to be little influenced by age (Fig. 2), with the exception that their percentages tend to be increased in older people. As with the phenomenon of trained immunity mentioned above, this may be due to the "immunobiography" of the individual, that is, the immunological history of preexposures. This is reflected by findings that the ratio of $CD56^{bright}CD16^{-}$ "naïve" NK cells (secreting more cytokine) to $CD56^{dim}CD16^{+}$ NK cells (more cytotoxic) is lower in older adults. Expression of CD16 is altered by age per se [37], and NK activating receptors such as NKp30 and NKp46 and costimulatory molecules such as DNAM-1 are lower in NK cells from older adults. Reciprocally, the fraction of NK cells expressing inhibitory receptors is higher [38]. Here, one is permitted to speak of age-associated changes because these differences have been documented not only in cross-sectional studies but also in longitudinal studies [39]. These changes translate into reduced killing ability against cells infected with viruses, although their mediation of antibody-dependent cytotoxicity seems unaffected by aging [40]. It has been documented that these age-associated changes to NK cell status do have clinical relevance in numerous disease states [41]. This may provide an argument for seeking interventions to restore appropriate function, as discussed earlier in general terms by Fulop et al. [42]

5.3 Dendritic Cells

Dendritic cells (DCs) are major regulators of both innate and adaptive immunity (Fig. 2). There are two major DC subsets: monocytic and plasmocytoid; the former take up, process, and present antigen to T-cells for initiation of adaptive immune responses, and the latter are crucial components of the immediate antiviral host defense due to their rapid release of type I interferons (IFN). There may be subtle changes in DC numbers and functions with age but there remain some conflicting results on the clinical implications of these and DC functions in older adults [43]. Clearly there are certain differences and possible impairments with increasing age [44], but in general DCs appear to retain a high degree of "youthful" ability to secrete pro-inflammatory cytokines and carry out other essential functions such as activating CD8＋ T-cells or inducing IL-17 as a mechanism for neutrophil recruitment. As so often observed, changes with age cannot be ascribed to age alone, due to the increasing level of pathology and history of previous exposures in older people. DCs are no exception and, for example, the effects of age on these cells may be amplified by pathologies such as cancer [45] . Decreased activating capacity for naïve CD4＋ T-cells may compromise successful antigen presentation to initiate an adaptive immune response [46]. This has been implicated, for example, in a study on vaccination against Yellow Fever in which one cause of the observed poorer responses of older adults was a DC deficit [47]. This DC malfunction may be due to the disruption of a

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major signaling pathway crucial for multiple different cell functions via decreased phosphoinositide 3-kinase (PI3K) activity, although the reason for this is not known. Overall, lower levels of activated PI3K result in heightened NF-kB activity that could exacerbate inappropriate secretion of pro-inflammatory cytokines such as IL-6 and TNF [48]. Dysregulated production of such factors may play a role in many chronic diseases ("inflammaging") and also over-exuberant inflammatory responses in acute infections ("cytokine storm").

6 Age-Associated Changes to Adaptive Immunity

6.1 B and T Lymphocyte Development and Antigen Recognition Repertoire

6.1.1 B-cells

B-cells are produced in the BM and exported to the periphery (Fig. 3), whereas T-cells are formed only as progenitors in the BM and require complex positive and negative selection processes for maturation. These processes can only take place in a specialized organ, the thymus (see next Section). As noted above, the production of immune cells by the BM in older individuals is skewed away from lymphoid cells toward myeloid cells, but the former are still generated at a lower level in the aged. B-cell function may be affected by the low-level chronic inflammation characterized as inflammaging, as described above. Due to their capacity to secrete inflammatory cytokines, B-cells may also contribute to this state, as well as impacting on adipose tissue function [49–51]. B-cell development occurs in two phases: production of naïve B-cells following a differentiation process from stem cells in the BM and after antigen contact and stimulation in the periphery (Fig. 3). Gene rearrangements of components of the membrane-bound immunoglobulin which acts as the antigen receptor on B-cells create an enormous repertoire of recognition potential for a universe of antigens. However, the BM of older adults is unable to support B-cell development as efficiently as in younger individuals, which has been attributed to dysregulated control of the transcription factors necessary for B-cell development [52]. Nonetheless, the exact mechanistic explanation for why such dysregulated processing occurs remains unclear. What is known is that critical developmental processes that result in the induction of self-tolerance in the BM, which are essential for removing autoreactive B-cells from the repertoire, are impaired in older adults. This suggests that, as with T cells (see next section), the selection processes in early B-cell development ensuring that the immune system does not react to self-antigens are weakened with age [53]. Again, the exact nature of these processes and their dysregulation remains obscure at the present time.

Once B-cells are released to the periphery (naïve B-cells, because they have not been exposed to cognate antigen), they may remain unstimulated for decades. However, on contact with specific antigen, and under correct conditions of T-cell-dependent "help," B-cells are activated and differentiate into antibody-producing cells and memory cells (Fig. 3). This involves clonal expansion to generate a sufficient number of cells to deal with the challenge and also the important "affinity maturation" step whereby mutations of the antigen receptor result in the selection of cells carrying receptors with a higher affinity for antigen than the original receptors at first antigen contact. Not only increased antibody affinity is selected for, but antibody-producing cells also change the type of soluble Ig that they produce. This process of "class switching" results in the alteration of antibody production from initially IgM to IgG and IgA (or sometimes IgE). Both affinity maturation and class switching can only take place in a highly specialized supportive environment termed the "germinal center" without the proper formation of which these processes cannot optimally take place. In this differentiation pathway, a central player has been identified as the enzyme "activation-induced cytidine deaminase" (AID). The end result of this and other processes is activation and differentiation of naïve B-cells, and the distribution of B-cells shifts towards an accumulation of memory cells, according to the individual's history of pathogen exposure. Thus,

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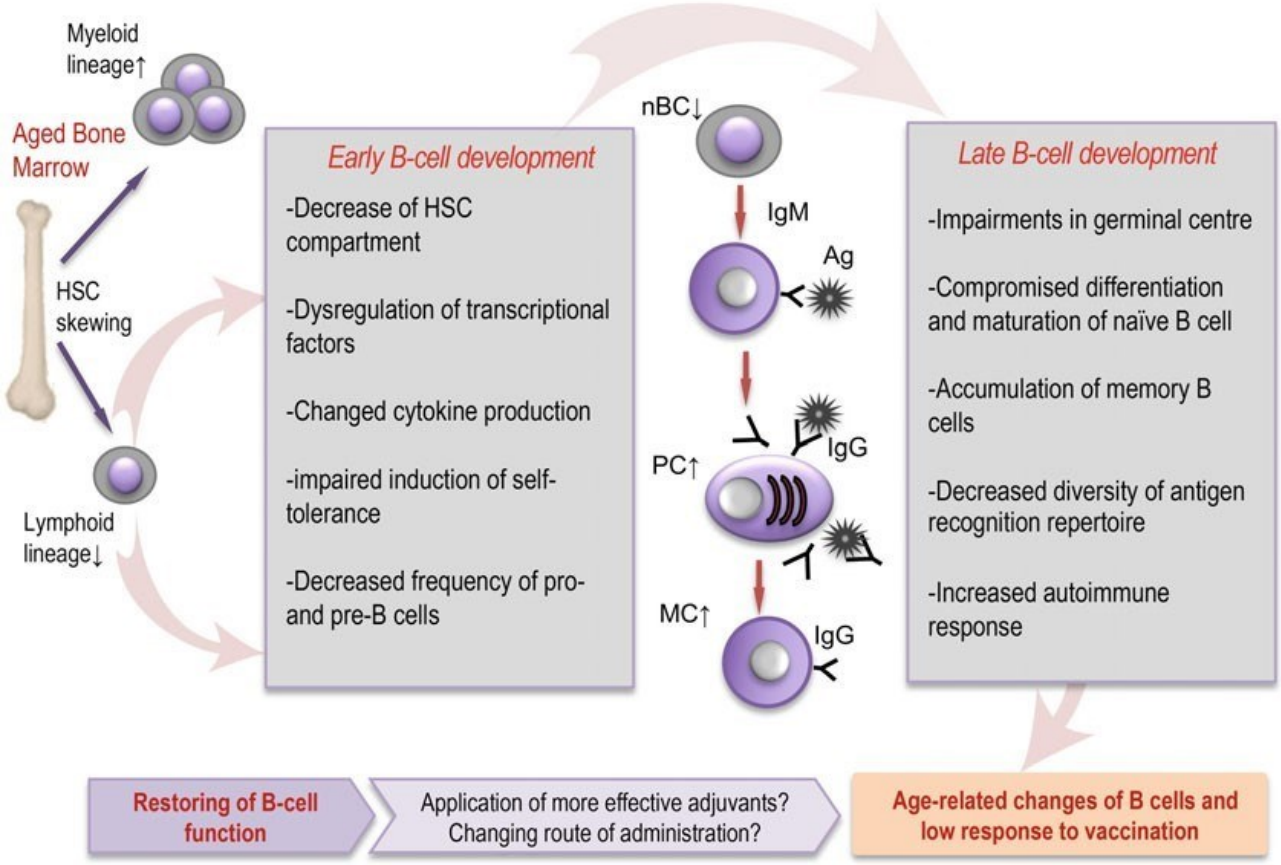

Fig. 3 Age-related changes occur in both phases of B-cell development

due to this personal “immunobiography,” the diversity of the antibody gene repertoire is lower in older adults, but there are also inappropriate expansions of B-cells without foreign antigen challenge, often with autoreactivity, which are not normally present in younger individuals [54]. There may be a distinct lack of ability for clonal expansion of B-cells in response to challenge (naïve cell compromised due to intrinsic factors or extrinsic factors related to germinal center architecture or compromised T-cell help) or rechallenge (due to memory cell dysfunction or suppression). The opposite problem may also occur, consistent with the overall theme that regulatory processes are becoming unbalanced in older adults, as illustrated, for example, by an inability to resolve the expansion response in IgA_2-bearing cells [55]. Thus, there are two major age-associated changes to be considered: those resulting from the adaptive processes reflecting the physiological function of the system (immunobiography; as confirmed, for example, by sequencing of the repertoire, confirming expanded memory cell clones and reduced naïve B cells [55, 56]) and the other resulting from dysregulation of these responses (“immunosenescence”). Hence, in young individuals, there are close correlations between the measured diversity of the antigen recognition repertoire and effective responses to, for example, influenza and pneumococcal responses, but this is not the case in older people [57]. Additionally, differences in the repertoire of the remaining naïve B-cells are also reported in older adults. Thus, the CDR-H3 region of the Ig gene, encoding the major variable portion of the antibody most influential for antigen-binding specificity, is longer in naïve B-cells from older adults, whereas efficient immune responses are associated with the shorter CDR-H3 regions seen in younger individuals [55, 57]. Again, the mechanistic reasons for these differences at older age are not perfectly understood [53, 58]. Other significant differences between the B-cells from younger and older adults

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are the relative proportions of IgG2 to IgG1-expressing B-cells, which are higher in the latter, and are relevant to immune function because IgG2 is a less effective antibody due to its low affinity for the FcgR [55, 59]. Nonetheless, memory cell functionality in older adults can be well-maintained, as witnessed by the life-long immunity that can be engendered against some (but not all) pathogens. This is reflected in the fact that the fraction of CD27+ memory B-cells, which, as noted above, is higher in older adults, is positively correlated with response to influenza vaccination when the majority of the seasonal strains circulating were present in that individual's early life [60, 61]. Emphasizing the qualitative (immunosenescent) aspect in addition to the adaptive (immunobiographical) aspect are the findings that atypical memory cell populations are also more numerous in older adults and are associated with poorer responses to vaccination [62].

6.1.2 T-cells

T-cells differ from B-cells in that they are released as progenitors from the BM (Fig. 4) and must migrate from the periphery to the thymus where they undergo negative selection of self-antigen-reactive cells but positive selection for self-MHC recognition. Due to the random nature of genetic recombination generating clonal antigen receptors at the cell surface, the majority of progenitors either fail to respond and eliminated ("death by neglect") or respond to self-antigens and are removed by clonal deletion. Hence, thymic selection is a wasteful and dangerous process and is only fully active when the organism is exposed to the maximum pathogen challenge during the life course. Thus, the thymus is large and highly active in infancy and childhood, but is developmentally programmed to cease large-scale activity at puberty and the residual thymic function gradually decreases to zero in most older adults (Fig. 4) [63]. Most naïve T-cells are therefore generated very early in life as soon as the infant is exposed to the pathogens prevalent in the local environment, which until evolutionarily recently were also those most likely to be re-encountered over the lifetime. Memory T-cells are generated at this time and may remain present to better protect the individual for the entire lifespan (which would most likely have been only 30 years for most of human history). In later life, beyond the expected lifespan, few naïve T-cells are produced but memory for the local common pathogens that the individual survived is retained. Naïve T-cells in the older adult have thus mostly been produced in early life and have persisted perhaps for decades without responding to their specific antigens. Hence, older adults possess a shrunken naïve T-cell repertoire which is composed of cells that are functionally compromised due to long exposure to an aged environment, and the individual mostly relies on the adaptive immune cells already formed earlier on (Fig. 4). Thus, both adaptive and "senescence" phenomena coexist to different degrees in different individuals due to their history of exposures ("immunobiography") and presumably multiple additional "senescence" phenomena [64]. Not only the remaining naïve cells but also the memory cells formed early in life will be affected by exposure to the aged environment as shown in mice [65] and very likely in humans also, representing the effect of organismal aging on the immune system and negatively impacting on health.

Thus, the most pressing challenges in long-lived species in general, and specifically for humans now commonly living much longer than evolution "foresaw," are (1) insufficient naïve T-cells are present to respond to new pathogens, or pathogen variants, or neoantigens from other sources (especially cancers), due to both holes in the repertoire as well as compromised functionality of the cells that are present and (2) the maintenance of memory cells for the better control of pathogen re-exposures and to maintain control of chronic infections over the entire lifespan. In low- and middle-income countries, chronic exposures will include helminths and other parasites, as well as viruses, and in high-income countries, these will mostly be viruses. Here, limited data from several longitudinal studies of the oldest old, consistent with many cross-sectional studies, have documented the extraordinary focus of adaptive CD8+ T-cell-dependent immune memory on the β-herpesvirus HHV5 (Cytomegalovirus, CMV), but not other latent herpesviruses. The T-cell

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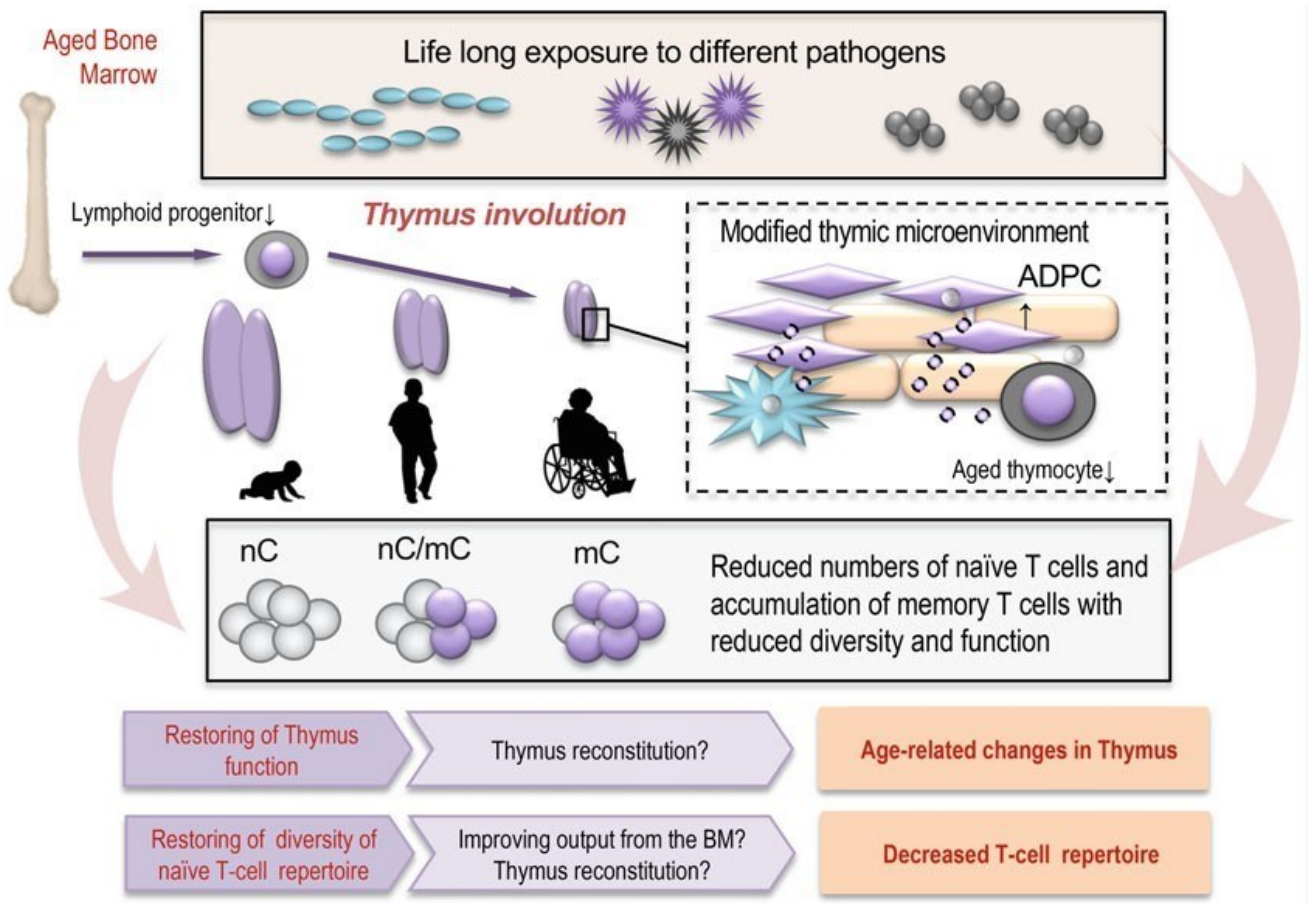

Fig. 4 Thymic involution and age-related changes in the T-cell repertoire

clones composing the memory T-cell repertoire for CMV antigens are present in high numbers in older donors, almost all of whom are CMV infected, but the loss of these cells from the periphery over time was found to be related to the survival time on follow-up in one small study [66]. Why only CMV, and not, for example, EBV, VZV, or HSV has this dramatic effect is still unclear but emphasizes the notion that maintaining appropriate T-cell responses against persistent pathogens is crucial for survival. However, it must be borne in mind that studies on individuals comprising the oldest old (who are >85 years of age today) may only be relevant to that particular age group who will have been exposed to a much different pathogen environment 85 years ago than younger individuals today. Hence, data relevant to these cohorts may not apply to younger people who will reach that age in 50 years' time. It is to be expected that maintaining diversity of the naïve T-cell repertoire will be more important for older people today, because they are likely to be exposed to newly emerging pathogens or those new to their immune system. Under these circumstances, the chance of possessing functional naïve T-cells competent to react to new exposures is likely to be reduced due to "holes" in the naïve cell repertoire. This is probably contributing to poor protection against previously unencountered pathogens, including new variants of old pathogens like influenza, as has been shown in mice [67], and as shown most dramatically by the greater susceptibility of older adults to SARS-CoV-2.

6.2 T-cell Immune Function

As outlined above, effective immune protection relies on a constellation of diverse interacting components providing immediate ("innate") responses to insults and then generating an adaptive immune response depending on T-cells and B-cells to control the pathogen and retain memory

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for enhanced responses to any future challenge by the same (or closely related) pathogen. All of these complex components and interactions are known to be at least to some extent different in older individuals. Responses to previously unseen pathogens require not only the presence and functional integrity of naïve antigen-specific T-cells, but also appropriate activation signals for clonal expansion in order to generate effector cells to control initial infection and memory cells for later protection (Fig. 5). The process of T-cell activation is strictly controlled, depending not only on the presence of a T-cell receptor (TCR) able to recognize the antigenic epitopes of the pathogen (peptide fragments) as presented by the innate immune antigen-presenting cells (APC – most often the specialized dendritic cells described above) bound to major histocompatibility complex (MHC) molecules. Recognition by the TCR by itself triggers one required signal cascade to activate the T-cell (so-called signal 1). Signal 1 alone does not activate the T-cell, for this, signal 2 is required, that is provided by costimulation (which for CD8+ T-cells is mostly commonly transmitted via the CD28 receptor on the T-cell-binding CD80 and CD86 on the APC). Additionally, CD28 controls expression and production of multiple cytokines including IL-2 (Fig. 5). Signal 1 plus signal 2 can lead to full T-cell activation through the NF-kB pathway. However, in older adults, numerous steps in this signal transduction pathway have been shown to be impaired [68]. A crucial component of TCR signaling, the Lck molecule, is regulated by the CD45 protein tyrosine phosphatase (PTPase) and the cytoplasmic moiety Csk. These pathways are different in T-cells from older people, and the activity the SHP-1 enzyme is constitutively greater. Inhibiting the SHP-1 enzyme can recover of TCR/CD28-dependent T-cell activation in T-cells from older adults, which may be able to restore T-cell reactivity of remaining naïve T-cells that have become functionally compromised by long-term residence in an aged environment. Several other pathways are clearly different in T-cells from older adults, modulation of which might also assist in the restoration of functionality. For example, blockade of one or more inhibitory coreceptors such as PD-1 (signaling via SHP-1 as well) may restore CD8+ T-cell functionality [69]. Several other possibilities for pharmacological intervention in signaling molecule pathways, such as mitogen-activated protein kinases (MAPKs) including Erk, Jnk, and p38, may also succeed in restoring functionality [70]. The cause of these compromised signal transduction pathways in naïve T-cells from older individuals remains unclear, but seems to be related to soluble factors present in the circulation of older but not younger donors. Identifying and modulating these is currently a subject of intense investigation, although most studies in this field do not refer to immune function but focus on other organ systems, particularly neurodegeneration[71]. Clearly, a deeper understanding of these basic ageing processes would be of benefit for improving immune function in older adults, but would still be unlikely to solve the problem of holes in the TCR repertoire. For restitution of a wider repertoire, efforts to improve output of T cell progenitors from the BM, together with thymic reconstitution, would be required [72].

7 Conclusions: Immune Correlates of Successful Vaccination and With Mortality

Immunosenescence may manifest itself in many deleterious ways, but dissecting out the multiple different reasons for pathological conditions to which we believe immunosenescence contributes is challenging. However, perhaps the clearest impacts are in the context of increased susceptibility and severity of infections and analogous poorer response to vaccination in older adults, although even this well-established phenomenon is not as well understood as it should be. Hence, many immunogerontologists focus on discovering the mechanisms responsible for poor responses to vaccines and to identify biomarkers predicting responsiveness in order to improve vaccination efficiency in older adults. Recently, many direct and indirect age-associated changes are being tested for their contribution to this, including a hitherto unsuspected impact of the

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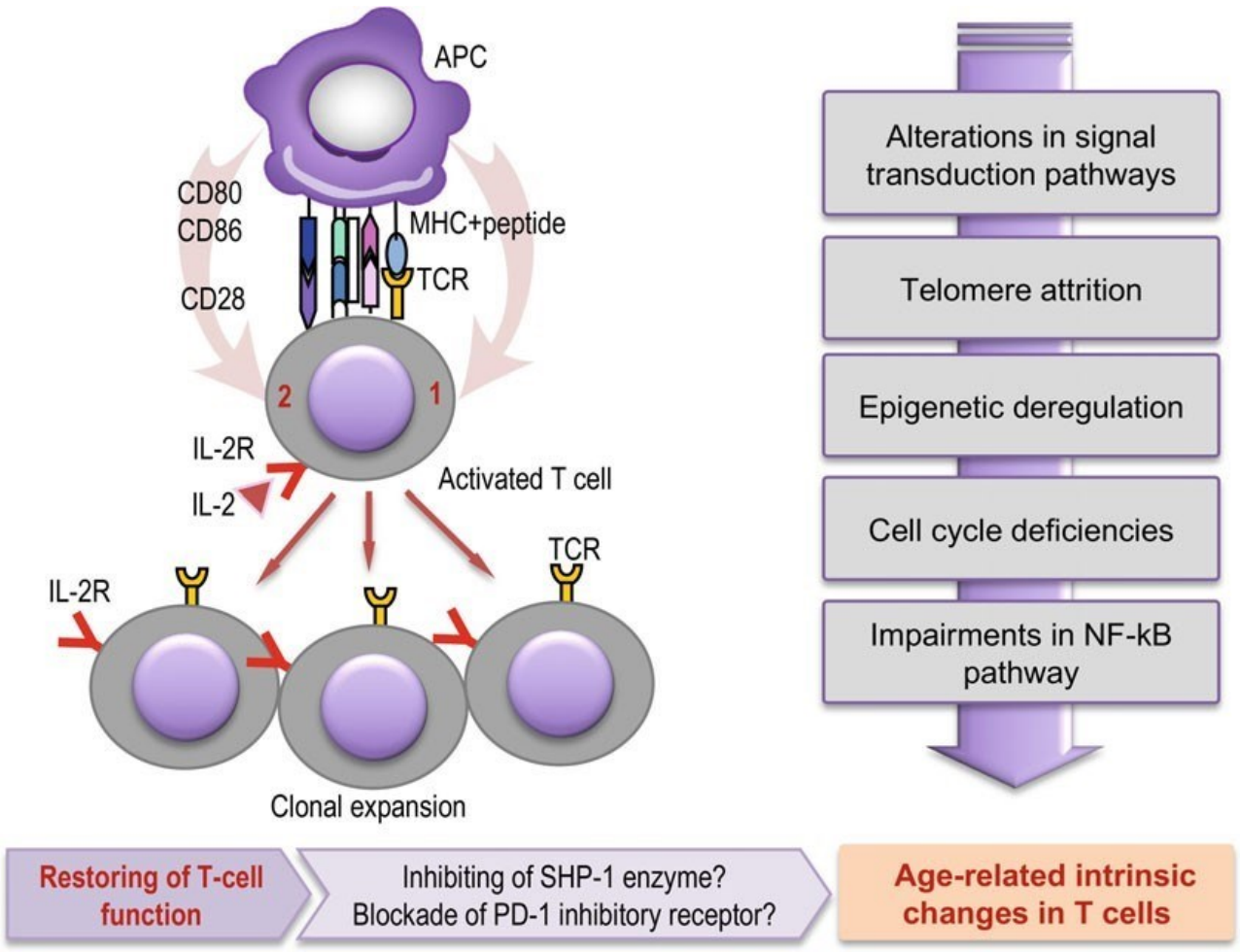

Fig. 5 Activation, stimulation, and clonal expansion of T-cell and age-related impairments of T-cell function

gut microbiota [73], as the microbiome changes with age [74]. The most common correlates of protection explored in studies of vaccination efficacy are measurements of the quantity and quality of antigen-specific antibodies, sometimes including IgM and IgA as well as IgG, all of which may be crucial for effective protection, especially in older people [57]. Thus, responses to pneumococcal antigens are decreased in older adults, parallel to a decline with age in the numbers of IgM memory (CD27 + IgD+) B-cells present in the blood [75]. B-cells from older individuals express high constitutive levels of TNF, which correlates negatively with the response to influenza vaccine [76]. As well as intrinsic changes, like all immune cell components, B-cells and their functions are guided by signals from other cells and their soluble products. However, there are data pertaining to intrinsic age-related changes to B-cells that contribute to poorer responses, albeit mostly in mice. Such experiments have shown that provision of helper T cells from younger animals cannot compensate for these and that, for example, the antibody affinity maturation response is impaired because the old B-cells cannot interact appropriately with the young T-cells. This may reflect the lower amounts of E47 and AID in B-cells from older animals, which has also been observed in human B-cells [77].

Antibody responses provide sterilizing immunity, but T-cells are also required not only as helper cells but as cytotoxic cells to delete infected host cells prior to viral replication. Several studies suggest that CMV-infection associates with a poorer response to influenza vaccines in older adults relative to CMV seronegatives [78]. The age-associated accumulation of CD8 + CD28-T-cells which is seen predominantly in CMV-infected individuals correlates with poor antibody responses to influenza vaccination.

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Indeed, the presence of T-cells with this simple phenotype was accepted for many years as a bio-marker of immunosenescence, but is in fact driven by CMV infection, and possibly some other pathogens. The reason for any associations of this phenotype with detrimental age-associated effects is unclear, but some of these late-stage differentiated CD8 + T-cells may indeed be in a senescent state and could contribute to inflammaging. Harmful “side effects” of the vital requirement for CMV immunosurveillance in this and other contexts remain controversial [79]. Hence, an accumulation of CD8 + CD28-memory cells is one robust simple biomarker of immunosenescence but it marks a physiological, not pathological phenotype and includes some cells which are senescent and others which are not [80]. More sophisticated biomarkers of immunosenescence are required to subdivide this heterogeneous population [2].

It is clear that one result of interventions to restore appropriate immunity in older adults would be to improve vaccine responsiveness, which would have a large impact on public health. At least for some pathogens, vaccine efficacy can be improved by simple measures such as increasing the antigen dose to compensate for the blunted function of APC. This approach has been applied for influenza vaccines tailored specifically to older adults, but improvements are marginal [81]. For chronic infections like VZV, where viral reactivation on escaping immunosurveillance causes overt disease, including an adjuvant in the vaccine to boost APC function may already suffice, as witnessed by the very strong boosting effect of Shingrix even in the oldest old [82]. This and other approaches under investigation involve the application of different types of adjuvant such as TLR ligands for DC activation, or antibody-mediated blockade of inhibitory receptors upregulated by chronically stimulated (“exhausted” CD8+ T-cells), as well as changing the route of administration from intramuscular to intradermal [14]. Blockade of the PD1 negative receptor has been shown to restore T-cell responses to persistent antigens and has in fact emerged as a treatment of choice in many types of cancer where the tumor serves as the chronic source of antigen. It is extremely encouraging that accumulating evidence suggests that older cancer patients may respond to treatment with anti-PD-1 antibodies at least as well if not better than younger patients [83]. This may be at least partly due to a dearth of regulatory T cells entering the tumor [84]. Clearly, vaccination against any antigen, whether of pathogen or cancer origin, cannot be effective unless DC, T-, and B-cells are present and functional, and the in vivo environment (lymph nodes, spleen, systemic circulation) is permissive. Again, the ability to generate a protective adaptive immune response depends not only on whether naïve T- and B-cells are still present in the repertoire of old individuals, and whether there is no untoward hole in antigen receptor repertoire, but also whether they retain functionality in the old environment. Clearly, it is unlikely that a single mechanism will be found responsible for decreased vaccine responsiveness. Surprisingly few studies have been published on this in humans, but available data are consistent with the view that responses to neoantigens may be impaired due to holes in the repertoire and also due to impaired DC function [47].

The major impact of chronic infection and antigenic stress in older adults as exemplified by CMV has perhaps emerged as the by-product of an originally beneficial effect of infection in early life which becomes potentially damaging much later, after evolutionary selection pressures have decreased post reproduction. The effect of CMV is seen mostly in CD8+ T-cells, but there is also an impact on CD4+ T-cells as well as NK cells [39]. Interventions to eliminate the virus, or at least reduce the viral antigenic load, which increases with age [85] paralleled by the CD8+ T-cell (and anti-CMV antibody titers), might also be of benefit in restoring appropriate immunity in older adults [86]. The impact of CMV infection and whether other pathogens or commensals such as TTV may have additive effects is still controversial. An early series of longitudinal studies proposed a set of immune biomarkers in oldest old Swedes that correlated with subsequent mortality over a 2-, 4-, and 6-year follow-up. This so-called “immune risk profile” (IRP) included low peripheral B cell numbers and a CMV-driven accumulation of CD8 + CD27 − CD28 − late-differentiated T-cells,

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which seems to start to manifest itself in people from the age of 60 up [87]. Not all older adults are CMV-positive and it is likely that the fraction of the population that is infected is decreasing now (in industrialized countries). Hence, other sources of chronic antigenic stress, be they viral, bacterial, parasitic, cancer, or auto-antigens, may become more important drivers of immunosenescence for future older populations – but whatever their nature, their reduction would likely be a necessary part of any immunorestorative interventions in older adults.

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