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Host Resistance and Immune Aging

Thilinie Bandaranayake, MBBS, **Albert C. Shaw, MD, PhD**

Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine, New Haven, CT 06520

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INTRODUCTION

With age, immunologic function changes substantially, resulting in impaired responses to pathogens or vaccines. As a result, older adults are at increased risk for morbidity and mortality from infectious diseases and impaired responses to vaccination [1]. Clearly, non-immunologic factors also contribute to these adverse outcomes; for example, age-related changes in chest wall mechanics and lung elasticity may affect respiratory mechanics and medications may affect cough—all potential contributors to respiratory infection risk [2]. However, it is evident that immunologic changes influence host defense against infection. The aging immune system is characterized by a variety of alterations that encompass developmental impairment, diminished signaling and the effects of antigen exposure history on chronic inflammation and antigen receptor repertoire diversity —all of which contribute to defects in immune activation in response to pathogens or vaccines. However, the aged innate immune system also shows substantial inflammatory dysregulation with a paradoxical heightened pro-inflammatory environment; this may arise in part from endogenous stimuli linked to cellular damage. Here we provide an overview of age-related changes in human host defense, with an emphasis on consequences for outcomes to pathogens or vaccines in older adults.

CHANGES IN INNATE IMMUNITY WITH AGING

The innate immune system is the first line of defense in mounting a host resistance response to antigens; it is responsible for the earliest responses to pathogens or vaccines [3, 4]. Innate immune responses are mediated by a network of cell types that include neutrophils, monocytes/macrophages, dendritic cells, natural killer cells (NK cells), eosinophils, and basophils; endothelial and epithelial cells may also play roles in innate immunity [4]. Innate immune responses are closely linked to the activation of inflammatory processes including

CORRESPONDING AUTHOR: Albert C. Shaw, MD, PhD (albert.shaw@yale.edu).

phagocytosis, intracellular killing, pathogen-induced pro-inflammatory cytokine production, and upregulation of co-stimulatory proteins on antigen presenting cells (APCs) such as dendritic cells, monocytes, or macrophages. Such co-stimulatory protein expression provides additional signals facilitating T cell activation, and thus links innate to adaptive (i.e. mediated by antigen receptors on B and T cells) immune responses.

Age-related Dysregulation of Inflammation

Several lines of evidence indicate that chronic inflammation is a characteristic of the aging immune system in humans. In particular, levels of pro-inflammatory cytokines (particularly IL-6, but also TNF-α, IL-1β and others), acute phase reactants such as C-reactive protein (CRP) and clotting factors (including D-dimer) are generally elevated in older, compared to young adults [5–10]. Moreover, such increases in cytokine production have been correlated with all-cause mortality in several studies [11–13]. Basal elevation of pro-inflammatory cytokines and other products may affect the ability of the aged immune system to respond to new pathogens or vaccines; in this regard, both pro- and anti-inflammatory cytokine production may be augmented, resulting in more complex patterns of age-related inflammatory dysregulation [14]. The etiology underlying this heightened pro-inflammatory state (termed Inflamm-Aging [15, 16]) remains incompletely understood, but may in part reflect the consequences of cellular damage and endogenous activators of the innate immune system, as described below.

Neutrophils

Neutrophils are short-lived cells that are among the first to migrate in response to an infectious agent. For example, chemotaxis, describing movement toward a gradient of a stimulus (such as a chemokine or cytokine), appears impaired in neutrophils from older, compared to young adults [17–19]. Moreover, phagocytosis of pathogens such as *Streptococcus pneumoniae* as well as intracellular killing both appeared impaired in neutrophils from older, versus young individuals [20, 21]. In addition, the generation of neutrophil extracellular traps (NETs), extracellular scaffolds of extruded chromatin containing antimicrobial peptides and proteases, is also diminished in neutrophils from older adults—further affecting pathogen capture and killing [22]. Several age-related signal transduction defects have been reported in neutrophils; for example, diminished accuracy of neutrophil migration with age has been linked to increased Phosphoinositide (PI)-3 kinase neutrophil signal transduction [18]. Other alterations may influence neutrophil survival by affecting anti-apoptotic pathways mediated by Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) [23, 24]; moreover, TLR-1-dependent cytokine production, induction of activation markers and glucose utilization were all diminished in neutrophils from older, compared to young adults [25]. While most of these studies indicate that neutrophil function is diminished with age, it should also be noted that defects in chemotaxis for example may result in both impaired trafficking to sites of infection and inappropriate persistence of neutrophils during the resolution of inflammation. Indeed, such delayed neutrophil egress from the lungs has been found in a murine model of burn injury [26]; such persistence, even of neutrophils with impaired function, could contribute to a heightened pro-inflammatory milieu in the context of aging.

Monocytes

Monocytes also contribute to innate immune responses as a source for cytokine and chemokine production. They are particularly adept at migrating from the circulation to sites of infection and inflammation, where they differentiate into macrophages and also to dendritic cells [27]. Studies of monocyte function in the context of human aging have revealed evidence for both impaired function and in some cases, a dysregulated, enhanced pro-inflammatory response. For example, studies of Toll-like Receptor (TLR) function, a family of invariant membrane-associated receptors recognizing conserved portions of pathogens (so-called pathogen-associated molecular patterns, or PAMPs), reveal an age-associated decrease in IL-6 and TNF-α production following stimulation of the TLR1/2 heterodimer with triacylated bacterial lipoproteins [28, 29]. In addition, a generalized impairment in expression of co-stimulatory proteins (such as CD80) was found in monocytes from older, compared to young adults following in vitro stimulation with a variety of TLR agonists [30]; such co-stimulatory proteins interact with ligands found on the T cell surface, and together with the T cell receptor for antigen, facilitate optimal T cell activation and link innate to adaptive immune responses. These alterations in TLR-induced costimulatory protein expression could be expected to adversely affect innate and adaptive immunity, and indeed a significant association was found between TLR-induced costimulatory protein expression and antibody response to influenza vaccination [30].

Other studies of monocyte function in the context of aging reveal further evidence of age-related dysregulation of inflammatory responses. For example, monocytes partially activated following isolation by adherence to plastic *in vitro* showed an age-associated increase in TLR5-induced cytokine production, using the TLR5 ligand flagellin [31]; interestingly, an increase in TLR5-induced cytokine production was also found in macrophages from aged mice [32], suggesting a potential role for monocyte activation in augmenting some innate immune responses (and the possibility that preserved TLR5 function could be utilized for vaccine adjuvants in older adults).

Several studies suggest that the proportion of so-called inflammatory monocytes expressing high levels of both CD14 and CD16 on the cell surface (as compared to classical monocytes which are CD14+ CD16− and non-classical CD14lo CD16hi monocytes) is increased in older adults. Such inflammatory monocytes have been reported to be increased in adults with HIV, sepsis, myocardial infarction and other conditions associated with increased inflammation[27]; CD14+ CD16+ monocytes from older adults showed evidence of senescence and increased cytokine production in response to LPS stimulation of TLR4 *ex vivo* [28, 33–35]. The effects of aging on monocyte function, however, may be more complex, as studies of cytokine production in monocytes (using intracellular cytokine staining) following influenza vaccination in the absence of *ex vivo* stimulation revealed diminished production of IL-6 and TNF-α in both inflammatory (which were induced post-vaccination) and classical monocytes from older, compared to young adults. By contrast, basal levels of the anti-inflammatory cytokine IL-10 were markedly elevated in monocyte populations in older, but not young adults; an age-associated alteration in activation of a negative regulator of IL-10, Dual Specificity Phosphatase (DUSP)-1 suggested a potential basis for impaired cytokine responses following vaccination or exposure to pathogens [36]. Interestingly, some

studies have utilized CD14+CD16+ monocytes as an indicator of age-related inflammation, and have demonstrated that resistance exercise training in older adults resulted in diminished levels of such monocytes and decreased LPS-induced pro-inflammatory cytokine production [37, 38]; these findings suggest that some changes associated with age-related inflammation may be reversible.

Dendritic Cells

Dendritic cells (DCs) are professional antigen presenting cells that also undergo age related changes contributing to the impaired host resistance. These cells may be broadly divided into myeloid DCs (mDCs), which express a variety of TLRs and are critical for production of IL-12 in Th1 responses; and plasmacytoid DCs (pDCs), which express a more narrow range of TLRs (such as TLR7 and TLR9) and are particularly adept at producing type I interferons in response to viral infections. TLR-induced cytokine production (including pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12 in mDCs and type I interferons in pDCs) in both mDCs and pDCs appears diminished in cells from older, compared to young adults in response to ex vivo activation of a broad range of TLRs, and the extent of TLR-induced cytokine production was strongly correlated with influenza vaccine antibody response [39]. Several additional studies indicate that pDCs and monocyte-derived DCs (which may be generated in vitro using growth factor stimulation and likely resemble DCs generated under inflammatory conditions) are defective in type I interferon production in response to stimulation by viruses such as West Nile and influenza virus [40, 41], and indeed, gene expression microarray analyses of monocyte-derived DCs have revealed decreased expression of interferon-stimulated genes [42]. At the same time, there is evidence for inflammatory dysregulation in DC populations as well. For example, LPS or self DNA-induced cytokine production was increased in monocyte-derived DCs from older, compared to young adults, juxtaposed with in vitro impairment in migration (as assessed in vitro using a chemotaxis assay) [42–44]. In addition, basal elevation in cytokine production has been found in pDCs, mDCs, and monocyte-derived DCs from older, but not young adults in the absence of *ex vivo* stimulation [39, 45]. The findings of impaired type I interferon production but increased TLR-induced cytokine production in monocyte-derived DCs may reflect differences in signal transduction pathways mediating pro-inflammatory cytokine vs. interferon production; alternatively, innate immune signaling pathways in addition to TLRs were likely induced in these monocyte-derived DC studies, which employed viral stimulation that would also engage cytoplasmic innate immune receptors recognizing viral nucleic acids such as Retinoic Acid Inducible Gene-I (RIG-I), Melanoma Differentiation Associated Gene-5 (MDA-5), and others. Nonetheless, taken together, these studies provide evidence that DCs may reflect the aging-associated pro-inflammatory environment.

Natural Killer Cells

NK Cells are the predominant class of innate immune lymphocytes [46], and function in cytokine production (identified as CD56bright CD16- NK cells) and cytotoxicity, particularly of virus-infected or cancer cells (CD56dim CD16+ cells). Cytotoxicity functions are regulated by a balance between activating receptors and receptors such as the Killer Immunoglobulin-like Receptors (KIRs) that are inhibited by Major Histocompatibility Complex (MHC) Class I engagement. In general, NK cells in older adults show an increase

in the CD56dim CD16+ cytotoxic population, which also represents a more differentiated population compared to CD56bright NK cells [47–52]. Expression of activating cytotoxicity receptors is also diminished with age [53, 54], with diminished cytotoxic function in older adults that has been linked to decreased mobilization of perforin to the NK cell immunologic synapse [55]. The consequences of age-related NK cell dysfunction remain incompletely understood, but it is worth noting that NK function has been associated with infection risk in at least one study of nursing home residents [56].

Origins of Age-Related Inflammation

The etiology of so-called Inflamm-aging remains incompletely understood, but is likely to reflect a combination of factors, not all of which originate in the immune system. For example, hormonal changes in the context of aging likely contribute; the loss of estrogen and testosterone production with age is associated with increased inflammatory markers in humans [57, 58]. In addition, there is decreased production of dihydroepiandosterone (DHEA) in older adults, a corticosteroid with immune enhancing properties (such as promoting Th1 cytokine production and decreasing LPS-induced TNF-α production) [59]. Cells other than those typically associated with the immune system may also contribute to age-related inflammation, and indeed, a recent study of gene expression contributors to the age-related increase in IL-6 found a relatively limited contribution of elevated cytokine transcripts from leukocytes [60]. In this regard, evidence from animal models suggests that macrophages infiltrating adipose tissue shifts to a pro-inflammatory profile with age [61]. Moreover, small studies of human adipose tissue revealed an age-related accumulation of fat cell progenitors that may contribute to age-related inflammation[62], particularly in the context of the so-called senescence-associated secretory phenotype (SASP)[63]. The SASP refers to the secretome of senescent cells (induced by replicative senescence or DNA damage for example), and in adipocytes could be inhibited by treatment with Jun-activated Kinase (JAK) inhibitors [62]. Recent studies in model systems have also identified the mammalian Target of Rapamycin (mTOR, which has pleiotropic effects in regulating the balance between anabolic and catabolic metabolism[64]) as another modulator of the SASP, where mTOR inhibition with rapamycin (clinically employed in higher doses for transplant immunosuppression) also inhibited SASP pro-inflammatory cytokine production [65, 66]. mTOR inhibition using rapamycin (clinically employed for transplant immunosuppression in higher doses) has previously been shown to extend lifespan in mice and ameliorate inflammation associated with cerebral ischemia or heart failure [67–69]. Notably, low-dose rapamycin given prior to influenza vaccination in older adults resulted in a 20% increase in antibody titers compared to older adults given placebo [70]. As a result, there is considerable interest in developing mTOR inhibitors that can modulate immunosenscence-associated inflammation.

In addition to the SASP, the origins of chronic inflammation in older adults could reflect the presence of endogenous damage-associated molecular patterns (DAMPs) that activate innate immune pattern recognition receptors. For example, levels of non-cell-associated DNA, presumably released from damaged or dying cells, are elevated in older adults [71–73]; mitochondrial DNA (mtDNA) in particular is increased in older, compared to young adults, and correlates with increased levels of pro-inflammatory cytokines at baseline and in trauma patients [74,75]. Notably, human monocytes treated with mtDNA develop endotoxin tolerance,

in which they are refractory to subsequent TLR4 stimulation with LPS—a potential mechanism contributing to impaired innate immune responses in the setting of chronic inflammation [76]. The mechanisms by which mtDNA activates the innate immune system likely involve TLR9 recognition of DNA; consistent with this, mtDNA induced NET formation in human neutrophils (with impaired NET formation in older adults) was reduced with TLR9 inhibition [74]. Oxidized mtDNA generated in the context of mitochondrial dysfunction and apoptosis activates the NOD-like Receptor NLRP3, a cytoplasmic innate immune pattern recognition receptor [77]. NLRP3 activation results in the formation of the NLRP3 inflammasome, a multi-protein scaffold containing NLRP3 and the adaptor protein Apoptosis Inducing Speck-like Protein Containing a CARD Domain (ASC) [78]. When assembled, the NLRP3 inflammasome mediates the Caspase 1-dependent processing of pro-IL-18 and pro-IL-1β to their activated, cleaved forms. In addition to oxidized mtDNA, NLRP3 is also engaged by necrotic cell damage [79–81]; in fact, the wide range of endogenous (uric acid, extracellular ATP, oxidized mtDNA, ceramide, beta-amyloid), exogenous (silica, asbestos, alum), and infectious (influenza virus, bacterial pore forming toxins, fungi) NLRP3 activators suggests that this receptor could contribute substantially to age-related inflammatory dysregulation [78]. Indeed, studies in NLRP3-deficient mice revealed a decrease in age-associated inflammation and improvements in bone loss and cognitive function [82]; in addition, recent findings in mice indicate that ASC aggregates from activated inflammasomes can be released from dying cells into the extracellular space, where they may be taken up by other cells to activate new inflammasomes and amplify a pro-inflammatory stimulus [83, 84]. Taken together, these findings suggest NLRP3 as a potential target for therapeutic intervention to modulate inflammation in older adults. Changes in the innate immune system with age are depicted in Figure 1.

CHANGES IN THE ADAPTIVE IMMUNE SYSTEM WITH AGING

Activation of the innate immune system facilitates the T and B cell mediated adaptive immune response through the production of pro-inflammatory cytokines and expression of costimulatory proteins on monocyte/macrophages or dendritic cells. Such costimulatory proteins (e.g. CD80, CD86 and others) interact with ligands on T cells (such as CD28) to provide critical second signals for optimal T cell activation, in conjunction with T cell receptor (TCR) recognition of a peptide from a pathogen or vaccine bound to a major histocompatibility antigen protein on the APC cell surface. As previously discussed, this innate immune activation is dysregulated and generally impaired with aging; however, the function of the adaptive immune system is also disrupted in older adults, reflecting the effects of chronic antigenic stimulation and exposures and intrinsic alterations in B and T cell development and function. Here, we provide a brief update, emphasizing recent findings regarding adaptive immunosenescence in humans.

T cell aging

Bone marrow progenitor cells migrate to the thymus, where T cell development, or thymopoiesis, occurs. Thymopoiesis is notable for stages of proliferative expansion, and for positive selection (where T cells expressing a TCR that can recognize host MHC proteins on APCs are selected) and negative selection (where T cells recognizing autoreactive, or “self”

antigens are deleted) processes. The thymus begins to involute during childhood, and continues to involute at a rate of approximately 3% per year in adults [85]. Not surprisingly, thymic involution is accompanied by a decline in generation of new (naïve) T cells. While some studies have suggested that some degree of naïve T cell generation continues in adulthood, one study using metabolic labeling and detection of T cell Receptor Excision Circles (TRECs) (the nonreplicating products of VDJ recombination at TCR loci that are associated with naïve T cells) has concluded that the vast majority (approximately 90% of CD4 T cells) of T cells in older adults are generated not from thymic activity, but from division of cells in the existing T lymphocyte pool [86]. Consequently, in older adults most T cells appear to be antigen-experienced memory T cells. The effects of thymic involution on T cell development were demonstrated in a study of young adults who had underwent thymectomy in the first month of life in the context of surgery for congenital heart disease. Numbers of CD4 and CD8 T cells were reduced in such adults, compared to young adults who had not undergone thymectomy, with diminished proportions of naïve T cells. Notably, a subset of young adults in the thymectomy group had T cell parameters that were comparable to aged adults 75 years of age or older, including levels of non-malignant oligoclonal T cell expansions frequently found in older adults [87]. The occurrence of an aged T cell profile in thymectomized young adults was strongly associated with seropositivity to cytomegalovirus (CMV), consistent with a substantial body of literature supporting the notion that control of CMV has a profound effect on the T cell compartment in the context of aging [88–92]. CMV may reactivate throughout life without end-organ damage, such as in the setting of the stress of medical or surgical illness [93]. Notably, a recent study evaluating CMV seronegative and seropositive adults concluded that CMV appears to be the dominant factor in driving the increased proportion of effector memory T cells and likely also non-malignant oligoclonal T cell expansion seen in older adults [94]. Indeed, significant levels of CMV-specific, dysfunctional T cells can be detected in older adults [91, 95–98], and functional outcomes such as mental status testing or ability to carry out activities of daily living have been associated with CMV seropositivity or the presence of CMV-specific CD4 T cells [99].

Analyses of TCR repertoire using high throughput sequencing methods and PBMCs as starting material revealed decreased diversity with age [100]; another analysis of purified naïve and memory T cell populations revealed a more modest 3–5 fold decrease in diversity that may still be sufficient for adequate adaptive immune responses [101]. This last study was notable for analyzing multiple replicate libraries from purified T cell subsets and employed nonparametric statistical methods designed to address some of the challenges in measuring the immense potential range of T cell diversity from relatively limited sample amounts [102]. It should be noted that CMV status of analyzed participants was unknown in the study showing a greater contraction in repertoire [100] and that CMV-seropositive subjects were excluded from the second study [101]. It seems likely that the effects of oligoclonal CMV-specific T cell expansion, if present, would result in substantial contraction in TCR diversity.

In addition to age-related decreases in T cell generation, developmental and signaling alterations are found in cells from older adults which contribute to functional deficits. For example, one of the most reliable age-related findings in the human T cell compartment is the loss of CD28 expression on CD8 T cells [103]. CD28 interacts with cell-associated costimulatory protein ligands such as CD80 and CD86 on APCs to provide a crucial second

signal for T cell activation (in conjunction with TCR recognition by peptide bound to host MHC proteins on APCs); the loss of CD28 expression in CD8 T cells is associated with alterations in T cell activation in older individuals, and early studies indicated that reconstitution of CD28 expression in CD8+ CD28− human T cells restored IL-2 production [104]. In addition to loss of CD28, CD8 T cells express other markers of exhaustion, replicative senescence, or terminal differentiation in the context of aging (such as PD-1, CD57, or KLRG1) that limit the response to pathogens or vaccines [105–107].

In contrast to aged mice, fewer studies have addressed signaling deficits in human T cells. However, in CD4 T cells from older, compared to young adults, alterations in signaling have been found in naïve cells, where an increase in Dual Specific Phosphatase (DUSP)-6 protein expression was linked to a decline in expression of a specific micro RNA (miR-181a)—resulting in decreased phosphorylation of the Extracellular Signal Regulated Kinase (ERK), a member of the Mitogen Activated Protein (MAP) Kinase family transducing TCR signals [108]. In memory CD4 T cells from older adults, increased gene expression of another MAP Kinase phosphatase, DUSP4, also resulted in impaired ERK signaling [109]. In addition to alterations in signal transduction resulting in impaired TCR-dependent activation, recent studies have reported that the senescence phenotype (characterized by features such as inhibited telomerase expression and decreased proliferation and TCR signaling) in both CD8 effector memory and CD4 T cells (which lack CD28 expression) is strongly associated with aberrant signaling via the p38 MAP kinase; notably, p38 inhibition appeared to reverse the senescence phenotype [110, 111]. Taken together, these findings provide evidence for both diminished activation (as in the ERK pathway) and inappropriate dysregulation (for p38) of signal transduction in T cells from older adults—mirroring the dysregulation and decreased responsiveness in the aged innate immune system.

B Cell Aging

Like T cells, the B cell lineage generates a highly diverse repertoire of rearranged antigen receptor genes, and there is evidence from analyses of Complementarity Determining Region 3 (CDR3) in the Ig heavy chain variable region that diversity in bulk populations of B cells is substantially reduced with age and with changes in functional status such as the geriatric syndrome of frailty [112]; chronic infection with EBV (which specifically infects B cells) or CMV influences B cell repertoire, which may also be altered by the presence of non-malignant oligoclonal B cell expansion [112, 113]. It should be noted, however, that some studies have shown relative preservation of diversity in tonsillar B cells [114]. Current use of next generation sequencing in purified B cell populations has also revealed evidence for age-related repertoire changes, although challenges remain in incorporating subject heterogeneity and variation into the analyses of the enormous amount of sequence information from studies of relatively few individuals [115].

Mature B cells express a rearranged immunoglobulin antigen receptor on their cell surface, and may undergo differentiation to plasma cells secreting immunoglobulin of the same specificity in defense against extracellular pathogens. Because many B cell functions are dependent on T cell help, the effects of aging on the B cell lineage reflect both B cell intrinsic changes and those resulting from altered T-B cell interactions; an example of this

would be impaired antibody response to influenza vaccine linked to impaired induction of antibody-producing plasmablasts [116]. However, intrinsic B cell defects have been found in expression of activation induced cytidine deaminase (AID), a protein that is essential for heavy chain class switching, in which the constant region exon (denoting the isotype and correlated with function, such as a μ constant region exon for IgM, γ1 constant region for IgG1and so on) encoding an expressed immunoglobulin (Ig) heavy chain "switches" to a different exon, with deletion of the original exon and intervening DNA. AID is also required for another B cell-specific process: somatic hypermutation, in which the variable region of an expressed Ig gene in mature B cells found in germinal centers of secondary lymphoid organs such as lymph nodes undergoes further mutation to enhance its affinity for a given antigen. The age-related impairment of AID expression was associated with a decreased proportion of B cells that had undergone class switching and with impaired influenza vaccine antibody responses [117, 118]. Decreased AID expression was linked to decreased levels of the E47 transcription factor that regulates AID, and to upregulation in expression of specific microRNA species [118, 119]. Notably, memory B cells from older adults were found to have increased gene expression of TNF-α, and the extent of basal TNF-α mRNA was negatively correlated with proliferative responses [120]. Finally, a history of CMV infection may also influence B cell function; individuals with a positive CMV serology had increased intracellular levels of TNF-α in B cells and diminished AID gene expression and switched memory B cell levels [121]. These findings in B cells reflect the dysregulated inflammatory responses found in cells of the innate immune system discussed above, as well as the effects of CMV on T cell function in older adults. A summary of age-associated alterations in B and T cell function is depicted in Figure 2.

SYSTEMS ANALYSIS OF IMMUNE AGING

Several studies have employed global analyses of cytokine production or gene expression to understand age-related alterations in immune response. In general, these studies have shown that immunologic challenge in older adults results in impaired responses when compared to young adults, but with evidence for dysregulated or delayed responses. Such a delayed and diminished gene expression signature of cytokine production in response to TLR4, TLR7/8, and Retinoid acid-Inducible Gene-1 (RIG-I, a cytoplasmic innate immune PRR RNA helicase that senses RNA, particularly in the setting of viral infection) was found in analyses of human PBMCs from older, compared to young adults [122]. Transcriptomic analyses of PBMCs before and after influenza vaccination revealed altered kinetics for early induction of interferon-stimulated genes and for a day 7 post-vaccine plasma cell gene expression signature associated with a successful vaccine antibody response [123]. These studies also revealed age-related dysregulation of innate immune signaling pathways and a mitochondrial biogenesis gene expression signature that was associated with vaccine response in young and older adults, suggesting an intriguing link between metabolic activity and vaccine response. Other studies of influenza vaccination in older adults showed that pre-vaccine expression of apoptosis pathways was also correlated with vaccine response [124]. These studies have excluded neutrophils, which are not found in the PBMC compartment, but a recent study of neutrophil gene expression in patients with hemorrhagic shock revealed an impaired innate immune response in older, compared to young adults [125]. Notably, older

adults showed persistent gene expression signatures reflecting both inflammation and immunosuppressive states (such as impaired expression of antigen presentation or co-stimulatory proteins) at later timepoints when neutrophils from young adults had trended toward baseline—consistent with an emerging theme of impaired but dysregulated (and frequently delayed) response in the aged immune system.

FUTURE DIRECTIONS

Understanding the biology of altered immune response in the context of aging has obvious clinical impact, and future studies should incorporate the intrinsic heterogeneity in human cohorts (extending beyond gender and race to comorbid medical conditions, medication use, smoking, alcohol use and other factors). In particular, the immunologic basis of alterations in functional status in older adults, such as frailty, remains incompletely understood. Examples of additional complexity include age-associated epigenetic effects, such as changes in methylation status, that strongly correlate with age and mortality [126, 127]. Finally, studies of age-related changes in the intestinal microbiome are in early stages [128], but it seems clear that engagement of innate and adaptive immunity by commensal organisms will influence immune responses to pathogens or vaccines. Integrating such complexity and heterogeneity into studies of the aging immune system will be challenging, particularly for large data sets arising from transcriptomic, microbiome, or other analyses, but will be essential to provide increasingly detailed insights for translation to pathways for therapeutic modulation and improvement of health in older adults.

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Synopsis

Aging of the human immune system results in impaired responses to pathogens or vaccines. In the innate immune system, which mediates the earliest pro-inflammatory responses to immunologic challenge, processes ranging from Toll-like Receptor function to Neutrophil Extracellular Trap formation are generally impaired in older adults. However, examples of enhanced inflammation with age, such as in TLR function, are also present, reflecting tissue context or cellular activation state. This inflammatory dysregulation is reflected in the age-associated increase in plasma cytokine, acute phase reactants, and clotting factors, termed “Inflamm-aging”, that likely results from contributions from immunologic and non-immunologic cells, the response to cellular damage, and the presence of endogenous damage-associated ligands activating the innate immune system. In the adaptive immune system, T and B cell subsets and function are altered with age, with examples of both impaired signaling and inappropriate activation, and shifts toward antigen experienced cells at the expense of naïve cells in both lineages. The control of cytomegalovirus infection, particularly in the T lineage, plays a dominant role in the differentiation of the T cell compartment and in the diversity of antigen receptors available to respond to pathogens or vaccines.

Key Points

- Immunosenescence, describing age-associated changes in the immune system, generally results in impaired immune responses, and contributes to the increased morbidity and mortality to infectious diseases and diminished vaccine responses found in older adults.
- A heightened pro-inflammatory environment, characterized by increased levels of pro- and anti-inflammatory cytokines, acute phase reactants, and clotting factors, is found in older adults.
- Age-related chronic inflammation contributes to dysregulation of innate immune responses, potentially limiting or delaying further activation or contributing to inappropriate persistence of inflammation.
- B and T cell signal transduction and function in the adaptive immune system are both impaired in the context of aging. Chronic antigen stimulation throughout life, particularly in the control of cycles of cytomegalovirus reactivation, substantially diminishes the diversity of antigen receptors, particularly in the T cell lineage.

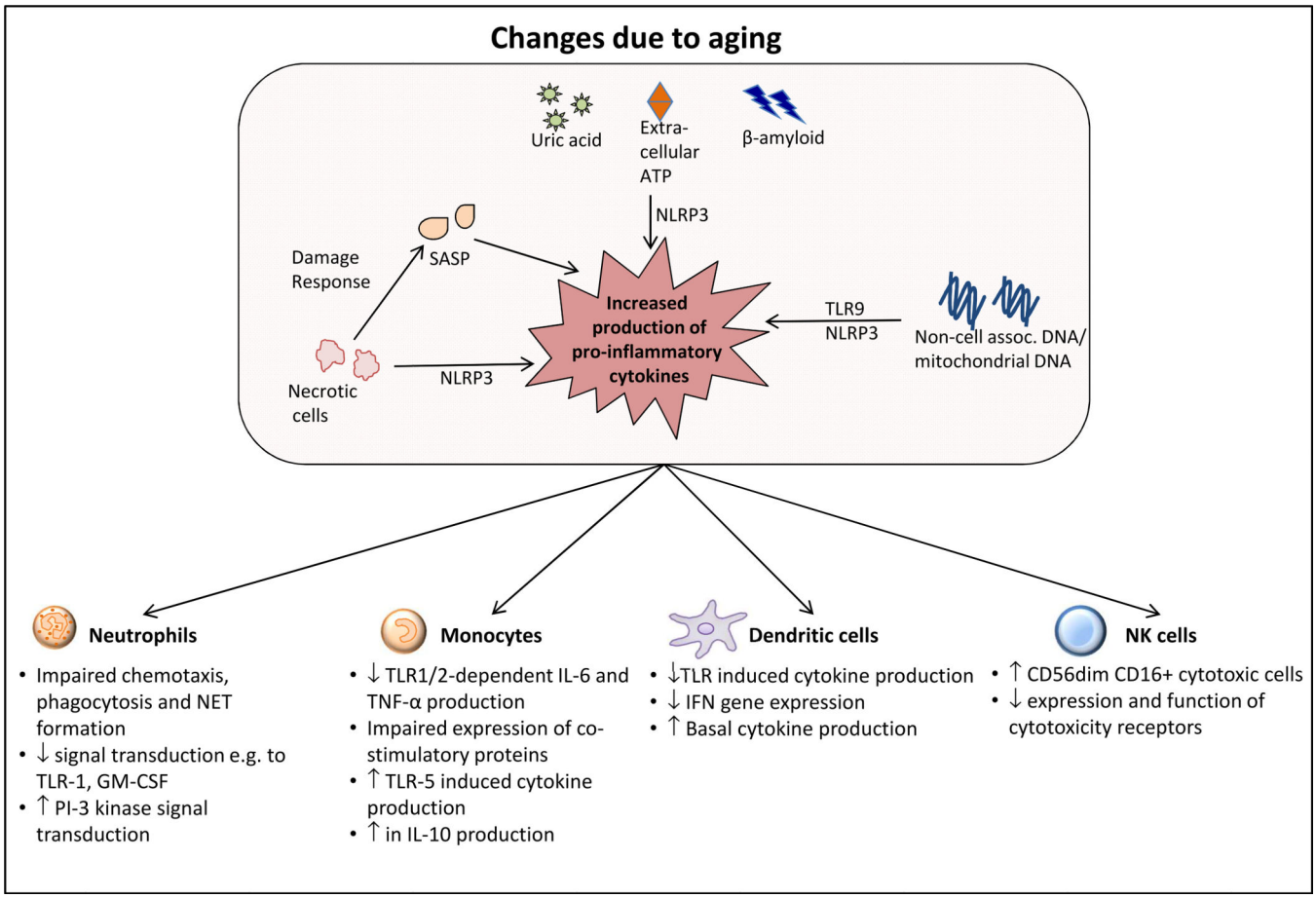

Figure 1.

Age-associated alterations in the innate immune system. Contributing factors to a heighted basal pro-inflammatory state, and dysregulated responses in individual cell lineages are summarized. Abbreviations: TLR Toll-like Receptor; NLRP3 NOD-like Receptor Protein 3; SASP Senescence-Associated Secretory Phenotype; NET neutrophil extracellular traps; TNF-α tumor necrosis factor-α; IL interleukin. See text for details.

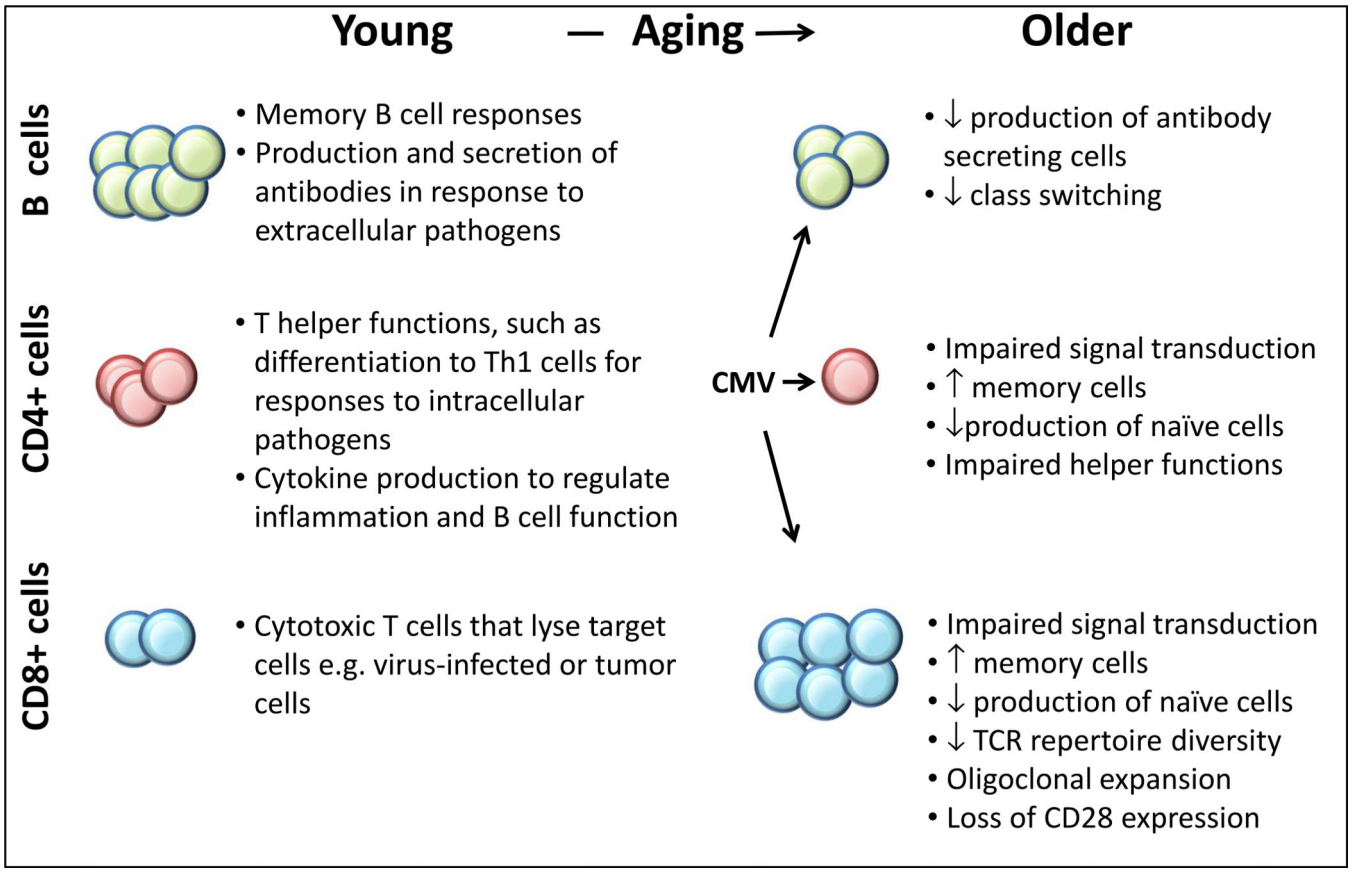

Figure 2.

Age-associated alterations in the adaptive immune system. Contrasts in function in B and T cells in young and older adults are summarized. Abbreviations: TCR T-cell Receptor; CMV Cytomegalovirus.