

Does Innate Immunity Get Old?

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Abstract Innate immune cells are the first to be triggered after infection and represent the first line of defense against pathogens. Molecular mechanisms underlying innate cell recognition and effector functions have been extensively investigated; however, less is known on how these features might be influenced by the aging process. In particular, although alterations in phenotype and functions of different innate cells have been found in aged donors, it is still unclear how aging globally affects innate signatures. It has been proposed that accumulation of a lifetime exposure to environmental factors may trigger an increased production of proinflammatory cytokines and other molecules leading to a chronic inflammatory state known as “inflamm-aging.” However, the exact mechanisms of “inflamm-aging” have not been yet characterized. In this chapter, we try to discuss the main alterations occurring during aging in innate cells, such as granulocytes, antigen-presenting cells (macrophages and dendritic cells) or Natural Killer cells and explain the “inflamm-aging” process.

1 Introduction

The mammalian immune response to infection is mediated by two arms, the innate and the adaptive immune system. Innate immune cells are a first-line defense against pathogens and respond to infection regardless of previous exposure, since they apparently do not exhibit memory of prior activation. In contrast, adaptive immune cells display immunologic memory that has two basic characteristics, antigen specificity and an amplified response upon subsequent exposure. However, this distinction is rather artificial since the innate and the adaptive immune systems cooperate with each other and some adaptive features are shared by innate cells.

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Innate immunity is mediated by multiple cell types such as antigen presenting cells (macrophages, dendritic cells, DC) granulocytes (neutrophils, eosinophils and basophils), Natural Killer (NK) cells, and by several soluble factors such as proinflammatory cytokines, type I interferons (IFN), and acute phase proteins. The primary physical and functional protection against pathogens is represented by dynamic barriers comprising the skin and the epithelial linings of the gastrointestinal, respiratory, and urogenital systems. These barriers prevent entry and colonization of potential pathogens. Epithelial cells express pattern recognition receptors (PRR) capable of responding to pathogen-associated molecular patterns (PAMP). Upon PAMP recognition, these cells secrete several types of antibacterial peptides, such as defensins, cathelicidins, and dermicidins, which together with other bactericidal and bacteriostatic substances control the bacterial load on epithelial surfaces. If epithelial damage occurs, macrophages are one of the first players to fight the pathogen. Macrophages express a broad variety of PRR such as Toll-like receptors (TLR), NOD-like receptors (NLR), or C-type lectin receptors (CLR), which are able to sense the threat by responding to PAMP as well as to danger signals released from damaged tissue [1]. The signals elicited by the engagement of such receptors are crucial for an effective inflammatory response and are generally targeted by adjuvants during vaccination. Macrophages phagocytose the invading organisms, initiate an inflammatory response that recruits neutrophils and NK cells, and facilitate the maturation, differentiation, and migration of DC. DC are the main antigen-presenting cell (APC) population and may proceed to initiate an adaptive immune response that contributes to eliminating the invading pathogens and provides memory in the recall response. Although most studies in humans and mice have focused on the analysis of the severe deterioration of adaptive immunity with age, recent literature has demonstrated that aging also has an impact on innate immunity, thus probably contributing to the overall declining function of the immune system [2–4]. Indeed, in the elderly, there is a reduction in the ability to resist infectious diseases and to generate protective immune responses, which might imply possible defects in barriers or in PAMP recognition. Notably, although several intrinsic functions of innate cells such as macrophages or neutrophils seem to be compromised during aging, elderly individuals display increased production of proinflammatory cytokines and other molecules, such as acute phase proteins and coagulation factors. This chronic inflammatory state is known as “inflamm-aging” [5]. The exact mechanisms of “inflamm-aging” have not been yet characterized. As we discuss in more detail in the next paragraphs, other cell types, such as stromal cells, may represent an important *in vivo* source of proinflammatory mediators [6]. In this chapter, we review the impact of aging on the innate immune system in particular focusing on its cellular components such as granulocytes, APC and NK cells and describe the “inflamm-aging” process.

2 Granulocytes and Resistance to Pathogen Infections in the Elderly

Granulocytes are involved in the earliest responses to microbial and parasitic infections, and their bactericidal ability relies on the generation of reactive oxygen and nitrogen species and the release of degradative enzymes and antimicrobial peptides. Indirect evidence implies that granulocyte function might be compromised by aging, as suggested by increased morbidity and mortality related to bacterial infections in the elderly [7]. Only limited data exist on age-associated changes in eosinophil and basophil function in humans, mostly suggesting a trend toward decreased degranulation [8] and production of superoxide anions [9]. Conversely, several reports indicate that the effect of age on neutrophil function might be broader. Despite their short half-life (8–12 h), neutrophils are key players in immune reactions. They directly eliminate pathogens and significantly contribute to tissue destruction during inflammation [10]. Indeed, individuals with neutrophil dysfunction or neutropenia undergo recurrent bacterial and fungal infections [11]. Similar to macrophages, neutrophils are activated by compounds that bind to receptors recognizing PAMP, such as formyl-methionyl-leucyl-phenylalanine (fMLP), endotoxins, and other TLR ligands, or by cytokines such as granulocyte monocyte-colony stimulating factor (GM-CSF), IL-15, or IL-18. Stimulation by proinflammatory cytokines or bacterial products extends neutrophil life span at sites of inflammation by survival signals and activates their effector functions. In murine models, several functions of neutrophils isolated from aged mice after *Candida albicans* injection seemed to be unaffected compared with young mice, including respiratory burst, exocytosis, chemotaxis, and phagocytic activity [12]. The ability of aged mice to fight infections is controversially debated. Aged C57BL/6 mice displayed lower capacity to kill *C. albicans* in vivo compared to young mice, while resistance to *Streptococcus pneumoniae* infection was not altered by age in the same mouse strain [12]. Human neutrophils appear to be impaired in several functions including chemotaxis, phagocytosis of microbes, and generation of superoxide in response to stimulation by bacterial factors such as LPS, fMLP, TREM-1, or opsonized bacteria, even in healthy elderly subjects [13, 14]. Moreover, aged neutrophils displayed an impaired responsiveness to GM-CSF survival signals [15], with implications not only for the ability of old adults to clear infections but also for the resolution of inflammation itself. In fact, if the number of apoptotic neutrophils at the inflamed site exceeds the capacity of macrophages to clear the dead cells, they could progress to secondary necrosis, leading to persistence of inflammation. Many of the defects in human neutrophil function have been associated with changes of the cell membrane and/or with proximal events in receptor signaling [13]. Alterations of lipid raft function have been reported in neutrophils from the elderly. SHP1 is quickly displaced from lipid rafts after GM-CSF stimulation in neutrophils from young donors, thus enabling fast and optimal neutrophil activation, whereas it is constantly present in neutrophils from old donors, thus possibly contributing to the decreased GM-CSF effects on neutrophils

from the elderly [16]. At the same time, activating receptors such as TREM-1 and TLR4 show reduced recruitment to lipid rafts in neutrophils of aging donors, which leads to reduction of their signaling function [14, 17]. This impairment in downstream signaling events observed after ligation of TREM-1 and the receptor for GM-CSF could also have an impact on several crucial neutrophil functions such as superoxide generation or chemotaxis. In spite of all the data indicating altered neutrophil function in aged individuals, further studies are required to clarify how these alterations might influence the efficacy of immune responses in old age, and possibly identify potential targets for intervention.

3 Dendritic Cells and Antigen Presentation in the Elderly

APC are key components of the immune system initiating the activation of T-cell-mediated adaptive immune responses against pathogens or tumors. DC, the main APC in mice and men, are derived from bone marrow progenitors that differentiate in peripheral tissues, and then acquire the capacity to process and present antigens. In case of infections, they are activated by PAMP or danger signals through their PPR at the site of inflammation and undergo maturation. Mature DC migrate to secondary lymphoid organs where they present antigens to CD8⁺ and CD4⁺ T cells in the context of MHC class I or class II molecules, respectively, and initiate an adaptive immune response. Mature DC express high levels of MHC class I and class II, adhesion and costimulatory molecules, as well as some chemokine receptors [18]. Only a very limited number of studies on the impact of aging on human DC can be found in the literature. The capacity of DC to present antigen to T cells was reported to be similar in healthy elderly and in young individuals [19]. More recently, it has been shown that DC from frail elderly individuals induced less T-cell proliferation and expressed lower levels of costimulatory molecules and IL-12. In addition, IL-10 is elevated in elderly individuals, and this can suppress DC maturation [20].

DC derived from aged mice apparently showed normal TLR expression and ability to prime immune responses [21]. However, aging-related alterations have been detected in the two main DC subsets, myeloid DC (mDC) (including Langerhans cells and interstitial DC) and plasmacytoid DC (pDC). pDC are lymphoid in origin and morphologically similar to plasma B cells and secrete high levels of type I IFN and IL-12 especially in response to viruses [22]. In contrast to mouse, human mDC do not express TLR7 (recognizing single-stranded RNA) and TLR9 (recognizing unmethylated CpG sequences), which are conversely present on pDC. TLR9 activation by CpG-A or during infection with Herpes simplex virus-2 (HSV-2), a pathogen known to activate TLR9 [23], resulted in lower IFN- α levels in aged murine pDC compared to young ones [24]. In this study, transfer of pDC from young mice, but not from old ones, into HSV-2-infected old mice induced strong IFN- α responses and viral clearance, suggesting that pDC from old mice displayed altered IFN- α response [24]. Also in humans IFN- α production

was found to be reduced in elderly individuals [25]. Defective TLR responses of pDC might contribute to the higher susceptibility of the elderly to viral infections.

Another interesting alteration found in the elderly concerns antigen processing. Cellular protein degradation is used to generate peptides for MHC presentation to T cells. Generation of peptides for antigen presentation overlaps with autophagy, a pathway that delivers cytoplasmic constituents for lysosomal degradation. However, in addition to delivering cytosolic material for MHC class II loading, it was recently shown that macroautophagy also regulates intracellular antigen processing for MHC class I presentation, as well as antigen packaging for optimal cross-presentation [26]. Interestingly, autophagy declines with aging [27] and this phenomenon may therefore have important consequences on several aspects of antigen processing/presentation in DC and therefore on the quality and magnitude of T-cell responses. Altogether, these data indicate that DC changes may contribute to the immune alterations of the elderly and enhancing their function may compensate for at least some of the age-related changes in the T-cell compartment.

4 Senescent Macrophages and the Paradox of “Inflamm-Aging”

Macrophages are phagocytic cells, which function as pathogen sensors and play an important role in the initiation of inflammatory responses, elimination of pathogens, antigen presentation, activation of the adaptive immune response, and wound healing. Similar to other innate cells, macrophages have the ability to recognize PAMP and the endogenous signals released from damaged tissue through their PRR [1]. Several age-associated alterations in macrophage functions have been reported. Decreased expression of MHC class II molecules and defective antigen presentation have been described both in human and mouse macrophages in the elderly [28, 29]. Similar to neutrophils, various signaling pathways were found to be altered in macrophages from aged individuals, such as reduction in total levels of the mitogen-activated kinases (MAPKs), p38 and Jun N-terminal kinase (JNK), and the nuclear levels of NF- κ B [30, 31]. Macrophage alterations in IFN- γ signaling, which is crucial for resistance to intracellular pathogens, have also been reported. Indeed, in spite of normal levels of IFN- γ receptor expression, macrophages from aged mice displayed lower levels of total as well as activated STAT-1 α , which is downstream of IFN- γ signaling, as compared to young mice [32]. Moreover, signal transduction genes involved in the TLR-signaling pathway, such as MyD88, were downregulated in macrophages from aged mice [33]. In line with these signaling defects, LPS-stimulated macrophages from aged mice expressed lower levels of proinflammatory chemokines, cytokines (TNF, IL-1 β , and IL-6), and their receptors [30, 31, 33, 34]. Although data available on LPS-mediated cytokine responses by human monocytes in the elderly were partially conflicting, a recent study reported an age-associated reduction in TNF and IL-6 production in human monocytes after stimulation with agonists of the TLR1/2 heterodimer. This impairment of monocyte activation was associated with a decrease in surface

expression of TLR1, but not TLR2 [35]. Not only expression of inflammatory cytokines but also upregulation of costimulatory protein, such as CD80, was defective on TLR-activated monocytes in the elderly. This defect in TLR-induced CD80 expression strongly correlated with reduced protective antibody response to influenza immunization, as it frequently occurs in old individuals [36].

The evidence for age-associated defects in TLR-induced expression of cytokines as well as of costimulatory molecules in human and mouse macrophages appears to contrast with the observation of a proinflammatory milieu in old individuals. Indeed, as already mentioned in the introduction, elderly individuals are characterized by higher circulating levels of proinflammatory cytokines and other markers such as C-reactive protein. This phenomenon has been termed “inflamm-aging” [5]. One emblematic example is IL-6. The plasma levels of IL-6 are low or undetectable in most young people and start to increase at about 50–60 years of age. IL-6 plasma levels continue to increase with age, until the extreme limit of human life, and high levels of IL-6 are found in a high percentage of centenarians [5, 37]. In these subjects, other proteins, such as acute phase proteins, lipoprotein A, fibrinogen, and other coagulation factors, are similarly increased. In line with these results observed in humans, *in vivo* stimulation with LPS or other bacterial products induces higher expression of these inflammatory markers in aged versus young mice [38, 39]. This apparent paradox of defects in TLR function on APC and increased proinflammatory cytokine levels in the context of aging can be reconciled by the observation that inflammatory cytokines can also be produced by other tissue cells such as adipocytes, muscle, endothelial, or stromal cells. In this regard, it was shown that senescent fibroblasts and epithelial cells display a marked proinflammatory phenotype, secreting significant levels of IL-6 and IL-8 [40]. Elevated cytokine levels produced by such cells may render APC refractory to further stimulation by TLR ligands or other PAMP and therefore impair effective T-cell priming. Finally, since proinflammatory cytokine production by monocytes/macrophages is modulated by both adipokines [41] and adrenal hormones [42], whose circulating levels are altered with age, “inflamm-aging” might likely be the result of a complex interplay of immunologic, hormonal, and neuroendocrine factors *in vivo*.

5 NK Cells and NK Cell Receptors During Aging: NK Cell “Reprogramming” of Oligoclonal Senescent T Cells?

NK cells are innate lymphocytes capable of recognizing and killing target cells and producing immunoregulatory cytokines (especially IFN- γ and TNF), and chemokines (MIP-1 family members and RANTES). Together with other members of the innate system, NK cells are crucial for the initial control of many viral and bacterial pathogens. Similar to other innate cells such as granulocytes or macrophages, NK cells can be activated via cytokines such as IL-15, IL-12, IL-18,

or type I IFN, via the receptor for the constant fraction of the antibody (Fc γ RIII or CD16) or via multiple activating receptors. Most of these receptors were originally discovered in NK cells and are called “NK receptors.” Many of them, however, are also expressed by other cell types, including T cells and myeloid lineage cells, where their functions are usually less well characterized. The recognition strategies used by NK cells are various. Some activating receptors can detect PAMP (e.g., murine Ly49H, which recognizes the ligand m157 encoded by the murine cytomegalovirus, MCMV) or self-proteins whose expression is upregulated in transformed or infected cells, similar to danger signals (e.g. NKG2D). Moreover, NK cells are endowed with inhibitory receptors specific for MHC class I molecules, such as the Killer Ig-like receptors (KIR) in humans and the C-type lectin Ly49 family in mice. Once engaged by their cognate MHC ligand, the inhibitory receptors recruit SRC homology 2 (SH2)-domain-containing protein tyrosine phosphatases such as SHP1 and SHP2 and these events lead to inhibition of NK cell activation [43]. In contrast to T- and B-cell responses to antigen, the innate NK cell response to pathogens was generally believed to be immediate. However, recent studies have challenged this concept [44, 45]. Indeed, it has been shown that NK cells, which have been primed by cytokines or viral antigens, can display memory-like properties during recall responses and primed NK cells were detectable up to 70 days after infection. Like memory T cells, “memory” NK cells were shown to be self-renewing, long-lived, and could mount a secondary response after viral challenge [46]. Together with these pioneer studies on memory, many other reports have enlightened the complexity of NK cell differentiation history, which is in line with their long-lasting life. Indeed, NK cells that leave the bone marrow are not effector ready to kill but can still undergo different steps of maturation, which can be distinguished according to the expression of CD27 and CD11b in mice [47]. In humans, others and we have shown that three major NK cell subsets can be identified according to the expression of CD56 and CD62L, CD94 or CD57: CD56^{bright} CD62L⁺ (CD57⁻ CD94^{high}) cells, CD56^{dim} CD62L⁺ (mainly CD57⁻ CD94^{high}), and CD56^{dim} CD62L⁻ (mainly CD57⁺ CD94^{low}) NK cell subsets [48–52]. CD56^{bright} NK cells represent a more immature step of NK cell differentiation and display longer telomeres than CD56^{dim} CD62L⁻ cells, while CD56^{dim} CD62L⁺ cells display intermediate telomere length between CD56^{bright} and CD56^{dim} CD62L⁻ NK cells. After cytokine priming in vitro and in vivo, CD56^{bright} give rise to CD56^{dim} CD62L⁻ cells, acquire the expression of cytolytic granules and KIR, and gain the ability to respond to activating receptor stimulation [49, 53–55]. Therefore, CD56^{dim} CD62L⁻ KIR⁺ CD94^{low} CD57⁺ NK cells appear to be enriched in terminally differentiated cells. In parallel with the accumulation of memory T cells and decrease of naive T cells, frequencies of terminally differentiated CD56^{dim} CD62L⁻ or CD57⁺ NK cells increased with aging, while CD56^{bright} and CD56^{dim} CD62L⁺ or CD57⁻ NK cells decreased [49, 56–58]. It has been reported that the absolute total numbers of NK cells (CD3⁻ CD56⁺ cells) are increased in old individuals [57]. This increase was mostly due to the accumulation of CD56^{dim} NK cells, while absolute numbers of CD56^{bright} NK cells decreased with age [56, 57]. These data suggest that terminally differentiated CD56^{dim}, especially CD62L⁻ CD57⁺ NK cells, might have an

extended life span in the elderly; in addition, generation of new NK cells is partially compromised in the elderly. Accumulation of terminally differentiated NK cells during aging might explain the controversial findings available in the literature concerning NK cell cytotoxicity in the elderly [57–61]. Indeed, NK cell cytotoxicity depends on the expression of several markers (self-MHC-specific inhibitory receptors, NKG2A) which defines different NK cell subsets. Since the distribution of NK cell subsets changes with age, homogenous NK cell subsets should be compared in young and old donors in order to drive definitive conclusions. Similarly, it has been observed that IL-2-induced proliferation, production of IFN- γ , and chemokines were decreased in NK cells from aged individuals [56, 57, 62]. Since the ability to proliferate and produce IFN- γ after cytokine stimulation is a typical property of CD56^{bright} NK cells as well as of CD56^{dim} CD62L⁺ or CD57⁺ NK cells, reduced NK cell cytokine production, and proliferation in the elderly might not be due to an intrinsic NK cell defect, but rather to decreased frequencies of certain subsets during aging [49, 57].

As previously mentioned, inhibitory MHC-specific receptors of the KIR as well as of the Ly49, CD94-NKG2A, and LIR families are in some cases expressed also by T cells, especially CD8⁺ T cells. Two patterns of receptor expression can be observed, depending on the receptors studied. Some receptors, such as CD94/NKG2A, are expressed after activation by most T cells, whereas others, such as KIR and Ly49 receptors, are expressed only sporadically on T cells [45]. In infected mice, only a small percentage of LCMV-specific effector cells express Ly49 receptors, and this percentage does not change significantly in the memory population [63]. In one study, it was shown that CD8⁺ T cells upregulated Ly49 expression after autoantigen stimulation in vivo [64]. In humans, a substantial population of memory CD28^{null} CD8⁺ T cells expressing KIR, as well as several other NK receptors (NKR) such as CD16, CD56, CD57, CD161, or CD94/NKG2A, accumulated with age [65]. This “NK cell reprogramming” of oligoclonal senescent T cells may be a compensatory adaptation to maintain immune competence despite CD28 loss and overall contraction in TCR diversity with aging [66]. However, by acquiring a new set of NKR and KIR, senescent T cells may evade conventional tolerance mechanisms in the aging host. Indeed, it has been shown that these senescent NKR/KIR⁺ T cells found ideal stimulatory conditions in inflammatory microenvironment and CD8⁺ or CD4⁺ NKR/KIR⁺ T cells were enriched in several autoimmune diseases such as rheumatoid arthritis [67]. Moreover, KIR engagement on T cells led to the activation of antiapoptotic signals, suggesting that KIR may directly contribute to the persistence of senescent T lymphocytes [68, 69].

6 Perspectives

In this chapter, we have tried to review the numerous studies addressing alteration occurring in the innate immune compartment during aging. Many of these studies suggest that numbers, distribution and selective functions of certain innate cells are

altered in aged mice or in humans. Although some intrinsic cell defects have been reported, many of the impaired responses seem to be dependent on the host environment or on the different composition of innate cells in the elderly. Therefore, further investigation on innate cell differentiation history as well as on the possible extrinsic factors influencing innate cell functions and differentiation would be important to understand the possible aberrations in the innate immune system of the elderly and to define interventional therapeutic tools.

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