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Review

Reduced dynamic range of antiviral innate immune responses in aging

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ABSTRACT

The worldwide population aged ≥ 65 years is increasing and the average life span is expected to increase another 10 years by 2050. This extended lifespan is associated with a progressive decline in immune function and a paradoxical state of low-grade, chronic inflammation that may contribute to susceptibility to viral infection, and reduced responses to vaccination. Here we review the effects of aging on innate immune responses to viral pathogens including elements of recognition, signaling, and production of inflammatory mediators. We specifically focus on age-related changes in key pattern recognition receptor signaling pathways, converging on altered cytokine responses, including a notable impairment of antiviral interferon responses. We highlight an emergent change in innate immunity that arises during aging – the dampening of the dynamic range of responses to multiple sources of stimulation – which may underlie reduced efficiency of immune responses in aging.

1. Introduction

A century of medical innovation has greatly reduced deaths from infectious disease and acute illness and dramatically increased life expectancy. The number of persons aged ≥ 65 years is expected to double in our current 20 year period to an estimated 74 million in the USA in 2030–973 million worldwide – and the average life span is expected to increase by another 10 years by 2050 (Colby and Ortman, 2014). It remains to be determined whether longevity has a natural limit or can continue to lengthen (Dong et al., 2016; Steenstrup et al., 2017). An extended lifespan, however, is associated with a progressive decline in immune function (immunosenescence) resulting in increased susceptibility to viral and bacterial infections and decreased response to vaccines with age (Carr et al., 2016; Shaw et al., 2013). Our new challenge will be to address such susceptibility and the growing burden of chronic and degenerative illness in aging – such as diabetes and Alzheimer's disease – and their attendant consequences to individuals and for public health and health-care costs.

The study of aging and longevity were launched more than a century ago by Élie Metchnikoff, who coined the word “gerontology”, although he is better known for the discovery of phagocytes and cell-mediated immunity for which he and Paul Erlich shared the Nobel prize in 1908 (Gordon, 2008). The complexity of distinct components that contribute to reduced health in aging necessitate a multifaceted approach to the investigation of immune deficiencies and the identification of targets for intervention. Recent advances in high-throughput and bioinformatics technology have allowed for increasingly detailed analyses of complex immunological interactions, facilitating the generation of a “systems-level” understanding of disease susceptibility (Furman and Davis, 2015; Peters et al., 2015; Whiting et al., 2015). Observed reduced responsiveness to immune stimulation in older individuals is associated with a paradoxical state of low-grade, chronic inflammation termed ‘inflamm-aging’ (Franceschi et al., 2000; Shaw et al., 2013). Particularly compelling are recent studies suggesting that chronic inflammation plays a critical role in susceptibility to infection and reduced responses to vaccination (Espeland et al., 2017; Hodes et al., 2016). There are promising findings regarding the benefits of metabolic interventions such as caloric restriction, metformin, and other anti-inflammatory regimens that highlight the central role of inflammation to longevity (Arai et al., 2015; Goldberg et al., 2015; Lanna et al., 2017; Mannick et al., 2014; Youm et al., 2015).

Here we focus on effects of aging on innate immune responses to viral pathogens including elements of recognition, signaling, and production of inflammatory mediators (Fig. 1) as well as emerging directions for future investigation. As viral clearance depends upon detection, systematic investigations of age-related changes in antiviral recognition and downstream signaling pathways are critical to our understanding of innate immune responses and potential therapeutic opportunities in aging. Notably, while specific cellular responses to viral recognition may differ in basal and induced levels, the overall result in aging leads to a reduced dynamic range of immune responses (Fig. 2).

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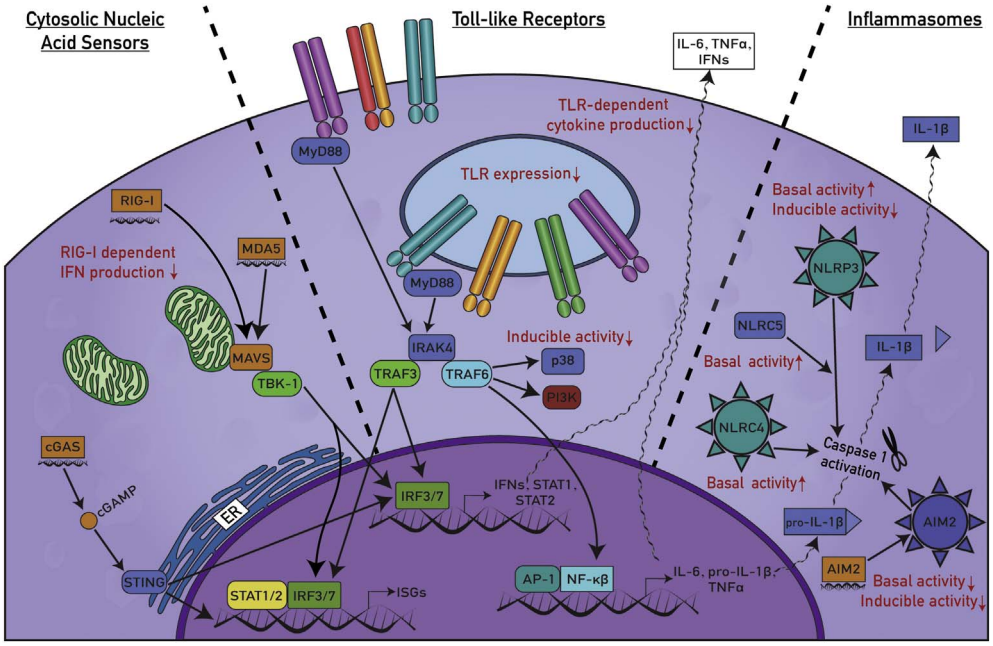

Fig. 1. Aging is associated with impaired pattern recognition and signaling. Pattern recognition receptors cytosolic nucleic acid sensors (RIG-I and cGAS), endosomal Toll-like receptors (TLRs), and inflammasomes recognize viral pathogens. Recognition by these receptors activates key signaling intermediates and transcription factors leading to the secretion of proinflammatory cytokines (*e.g.*, IL-6, TNFα), antiviral interferons (IFNs), and the expression of interferon-stimulated genes (ISGs) that serve key antiviral functions within the cell. Inflammasome activation in response to viral nucleic acids or virulence activity leads to caspase-1 activation and subsequent cleavage of pro-IL-1β into an active form that is then secreted. Basal expression of recognition receptors and both basal and induced signaling responses are altered in aging (red arrows).

2. Reduced toll-like receptor responses in aging

Innate immune cells comprised of several bone marrow-derived cell lineages including neutrophils (polymorphonuclear leukocytes, PMN), monocytes, macrophages, and both myeloid and plasmacytoid dendritic cells (mDC, pDC) exhibit multiple age-dependent phenotypes (Shaw et al., 2013). While the number of circulating PMN is maintained in older donors, many functions are markedly impaired such as recruitment, phagocytosis, release of cytokines and granules, and microbial activity (Tseng and Liu, 2014; Wessels et al., 2010). Older individuals exhibit a distinct hematopoietic stem cell population that is skewed towards myeloid cell differentiation (Pang and Iwasaki, 2011) which may contribute to altered viral susceptibility. They have preserved overall monocyte numbers but increased frequencies of non-classical (CD16 +) monocytes relative to younger individuals (Hearps et al., 2012). In addition, pDCs, specialized sensory DCs primarily involved in viral sensing and antiviral interferon (IFN) production, are decreased in frequency in older adults whereas other DC populations are preserved with age (Jing et al., 2009).

These 'first line' cells of immune defense surveil throughout the host and mediate recognition of pathogens using an evolutionarily conserved group of pathogen recognition receptors, of which the best characterized are the Toll-like receptors (TLRs). Both surface- and endosomally-expressed TLRs have been shown to be reduced in aging in monocytes (Nyugen et al., 2010; van Duin et al., 2007), macrophages (Kong et al., 2008), DCs (Panda et al., 2010) and PMN (Qian et al., 2014). Recognition of conserved pathogen features by TLRs triggers rapidly inducible cellular signaling cascades that result in the secretion of cytokines and the initiation of antiviral or antimicrobial transcriptional programs (Fig. 1).

TLR activation results in proinflammatory cytokine responses *via* NF-κB-dependent pathways and upregulation of Type I interferons and interferon-dependent genes (ISGs), thereby rapidly promoting a localized antiviral response and shaping subsequent adaptive T and B cell immune responses (Akira and Takeda, 2004; Kawai and Akira, 2007). Lower expression of TLRs leads to corresponding decreases in signaling and responses following the triggering of these pathways. Thus, PMN of older donors, which have reduced expression of TLR1, show reduced stimulation-induced upregulation of integrin activation markers CD11b and CD18, reduced production of the chemokine IL-8, and reduced rescue from apoptosis compared to younger donors (Qian et al., 2014). In monocytes, reduced production of cytokines after stimulation with TLR1/2 ligands in cells from older subjects is correlated with reduced responses to influenza vaccination (van Duin et al., 2007). Similar cytokine defects in cytokine production have been noted in murine macrophages in response to TLR2 and TLR4 stimulation (Boehmer et al., 2004; Boehmer et al., 2005). A notable exception is TLR5, which is increased on monocytes of older subjects, and as the sole TLR with a protein ligand (flagellin), may offer an opportunity for improved vaccine development for older patients (Qian et al., 2012; Taylor et al.,

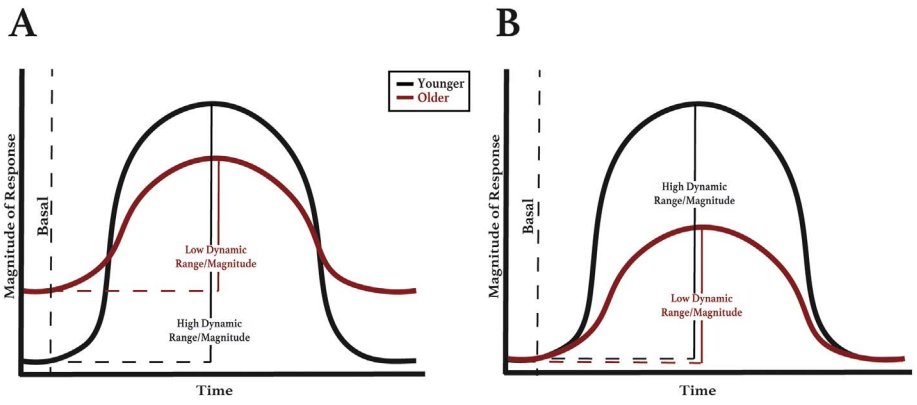

Fig. 2. Age-related alterations in immune responses. Cellular responses from older donors differ in two main manners, both of which result in a compressed dynamic range of responses.
(A) Elevated basal activity. Upon stimulation, the magnitude of the inducible response approaches that of younger subjects. Model A is consistent with many proinflammatory cytokine and inflammasome responses in older individuals.
(B) Equal basal activity. Upon stimulation, the magnitude of the inducible response is significantly reduced compared to younger individuals. Model B is consistent with impaired interferon responses observed in older individuals.

2011). Both classes of dendritic cells (mDC and pDC) from older donors show lower expression of TLRs globally and substantial decreases in cytokine production following TLR stimulation (Jing et al., 2009; Panda et al., 2010).

Downstream signaling following TLR recognition of ligand through signaling mediators such as myeloid differentiation primary response gene 88 (MyD88), p38 mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), and the phosphorylation capacity of signal transducer and activator of transcription (STAT)-1a is reduced in aging (Agrawal et al., 2007; van Duin et al., 2007). However, there is a paradoxical increase in basal activation of many components of the innate immune system with increased basal inflammatory cytokine production (Hearps et al., 2012) and a confounding decrease in inducible levels of cytokines on stimulation. Indeed, accompanying the impaired inducible TLR-mediated responses in cells from older individuals, the cells exhibit increased basal NF-κB nuclear localization and activation with age (Qian et al., 2012). Similarly, in the absence of infection kidneys of elderly rats exhibit a TLR7-dependent basal inflammatory pathway activated by endogenous small RNA ligands (Lee et al., 2017). These basal inflammatory responses with age result in a compressed dynamic range of proinflammatory cytokine responses to stimulation, an observation present across a range of age-related responses (Fig. 2A).

3. Cytosolic recognition of viruses in aging

Cytosolic nucleic acid sensing receptors and inflammasome activation are vital for viral recognition and subsequent initiation of immune responses to viral infection. Key recognition receptors include the cytoplasmic retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), cytosolic DNA sensors, and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that trigger inflammasome activation (Fig. 1). These receptors recognize viral nucleic acids and virulence activity-induced signals such as endogenous ligands associated with tissue damage (damage associated molecular patterns; DAMPs) (Brubaker et al., 2015; Kawai and Akira, 2007).

RIG-I like receptors are vital for the control of many major human viral pathogens, yet how RLR signaling is modulated in the context of aging is poorly understood. Recent studies of DCs detected lower levels of RIG-I from older human subjects (Qian et al., 2011) and monocytes from older subjects have significantly diminished IFN-α/β responses to RIG-I stimulation (Pillai et al., 2016). Interestingly, these same monocytes retain the ability to produce pro-inflammatory cytokines upon stimulation, suggesting that aging may lead to cell-intrinsic dysregulation specifically in the IFN arm of this response (Pillai et al., 2016). This is consistent with the studies of human PBMCs in which older PBMCs exhibit impaired IFN responses to 5′-ppp RNA transfection relative to younger controls 6 h after stimulation; although in this complex cell population responses were comparable after 24 h (Metcalf et al., 2015). As there is no evidence of altered basal IFN expression with age, impaired IFN induction is representative of a model of age-related reduced dynamic range distinct from that of TLR-mediated proinflammatory cytokine induction (Fig. 2B).

Inflammasome activation has been shown to be dysregulated in aging in murine models. In a pattern noted in human TLR responses, aged mice show increased inflammation and basal activation of the NLRP3 inflammasome despite impaired inducible NLRP3 activation in response to influenza infection (Bauernfeind et al., 2016; Stout-Delgado et al., 2012; Youm et al., 2013). Aging-linked impairment of inducible NLRP3 inflammasome activation is not as well-documented in human cells, in which IL-1β responses to NOD2 stimulation and influenza infection are preserved in older human monocytes and PBMCs (Pillai et al., 2016; Wang et al., 2016). In older human donors with hypertension, baseline NLRC4 and NLRC5 expression and inflammasome activation in the peripheral blood was increased, likely stemming from elevated nucleotide-derived metabolites in these donors and potentially contributing to the age-associated inflammation and hypertension (Furman et al., 2017). Indeed, while more work is needed to fully clarify cell-specific differences in the regulation of individual inflammasomes in aging, their baseline activation by endogenous ligands in older individuals occurs in both humans and mice and is an important facet of the inflamm-aging phenotype. Thus, the model of compressed dynamic range of responses is likely active for inflammasome responses as well (Fig. 2A).

Cytosolic dsDNA receptor AIM2 triggers the activation of the AIM2 inflammasome – important for the control of DNA virus infections – leading to caspase-1 activation and cleavage of pro-IL-1β into its active form (Guo et al., 2015). Human monocytes from older donors exhibit both reduced AIM2 expression and impaired caspase-1 activation upon poly(dA:dT) stimulation of AIM2, ultimately leading to decreased IL-1β secretion (Wang et al., 2016). A recent study has found that a family of dsDNA binding AIM2-like receptors (ALRs) are dispensable for IFN production downstream of cytosolic DNA sensing and that cGAS is the key sensor for this response (Gray et al., 2016). While it is not fully understood how aging alters cytosolic DNA sensing, a large overlap in signaling machinery between the DNA and RNA signaling pathways suggests the likelihood of similar cytokine production defects in both systems. This reduced dynamic range of inducible responses, which is observed in multiple contexts, is a striking feature of the aging innate immune response and has important consequences for response to infectious challenge.

4. Responses to viral infections in older individuals

Older populations (> 65 years of age) are the most vulnerable to severe viral illnesses including influenza A virus (IAV) infections, following which many succumb to pneumonia caused by secondary bacterial infections (Thompson et al., 2003). Similarly, aging remains the highest risk factor for severe infection with West Nile virus (WNV) (Gray and Webb, 2014; Montgomery, 2017; Montgomery and Murray, 2015; Yao and Montgomery, 2016). Age-related changes in innate immunity to many viruses remain to be fully explored, with a limited number of studies available to draw upon at present. However, pDCs from healthy older subjects secreted less IFN in response to IAV and to WNV (Jing et al., 2009; Qian et al., 2011). Notably, the age-related reductions in expression and inducible activation of TLR, RLR, and inflammasome recognition pathways as noted above will likely contribute to similar defects in viral infections, potentially resulting in impaired viral control and age-linked increases in susceptibility to IAV, WNV, and other viruses.

Monocytes from older human donors exhibit reduced RLR signaling and a significantly impaired type I IFN response to IAV infection *in vitro* despite preserved inflammatory cytokine production. This defect is associated with a marked reduction in the upregulation of antiviral interferon-stimulated genes and a corresponding increase in influenza viral RNA in the cells from older donors (Pillai et al., 2016). This is consistent with studies of pDCs and monocyte-derived DCs from older human donors showing impaired IFNα production in response to IAV (Canaday et al., 2010; Prakash et al., 2013; Sridharan et al., 2011). These age-related impairments in viral control may contribute to the increased susceptibility of older persons to IAV infection.

Murine studies also support an age-related increase in IAV susceptibility that has been linked to reduced numbers of alveolar macrophages and reduced phagocytosis of apoptotic neutrophils (Wong et al., 2017) which may contribute to impaired tissue repair and altered cytokine dynamics (Toapanta and Ross, 2009; Yin et al., 2014; Zhao et al., 2011). While certain murine models of aging have indicated elevations in type I IFN in the lung in response to IAV (Hernandez-Vargas et al., 2014), notably, many inbred mice lack functional copies of the interferon stimulated gene *Mx1* (Haller et al., 1980), which is necessary for IFN-mediated protection from the virus (Pillai et al., 2016). Thus, caution is warranted when extending the relevance of

these studies to older humans.

Studies of the effects of aging on infection with WNV in macrophages have demonstrated impaired DC-SIGN-induced reduction in the expression of TLR3 following infection with WNV *in vitro* (Kong et al., 2008). This impairment *via* the signal transducer and activator of transcription 1 (STAT1)-mediated pathway may be relevant for elevated cytokine production contributing to permeability of the blood-brain barrier and increased severity of WNV infection in older individuals (Hoffman et al., 2016; Kong et al., 2008). In DCs from older donors infected with WNV *in vitro*, reduced levels of pathogen recognition receptors RIG-I, and Toll-like receptors (TLRs) 3 and 7 were detected, with lower production of cytokines in response to infection with WNV (Qian et al., 2011). In particular, production of type I IFN was significantly lower in DCs from older donors compared to younger donors and diminished induction of late phase signaling responses, *e.g.* STAT1, IRF7, and IRF1, suggesting defective regulation of type I IFN induction (Qian et al., 2011). Murine models have identified critical roles for cytosolic receptors in control of WNV (Lazear and Diamond, 2015). Notably, the expression of TLR7 in older mice is lower upon WNV infection as compared to younger mice (Xie et al., 2015).

Herpes simplex virus 2 (HSV-2) infections in aged mice are associated with increased neutrophil-mediated liver damage in response to increased IL-17 secretion by NKT cells (Stout-Delgado et al., 2009). IFN production by pDCs is, in contrast, decreased in these older HSV-2 infected mice owing to impaired IRF7 upregulation upon viral infection, potentially further compromising antiviral immunity (Stout-Delgado et al., 2008). Respiratory syncytial virus (RSV) infection of aged mice is associated with delayed viral clearance, increased tissue damage, and impaired ISG upregulation consistent with impaired IFN responses (Boukhvalova et al., 2007; Wong et al., 2014; Zhao et al., 2011). A study focusing on respiratory immunity to a range of viruses including IAV, RSV, and SARS-CoV has suggested a shared mechanism whereby an age-linked increase in prostaglandin D_2 suppresses respiratory DC migration, ultimately compromising T cell responses to these viruses (Zhao et al., 2011).

Impaired type I IFN responses to both direct PRR stimulation and viral infection have been observed in a range of cell types in the context of aging, suggesting that conserved mechanisms underlie this recurrent defect. While IFNs are necessary for effective antiviral responses, aberrant IFN signaling *in vitro* and in murine models has been linked to accelerated cellular senescence and stem cell decline (Gough et al., 2012; Sato et al., 2009; Yu et al., 2015). Both the DNA damage response and mitochondrial dysfunction, which increase in aging, induce IFN production in a cGAS-dependent manner (Härtlova et al., 2015; West et al., 2015; Yu et al., 2015), and have been hypothesized to contribute to aging-associated phenotypes (Rübe et al., 2011; Sun et al., 2016; Vermeij et al., 2014). Thus, the reduced dynamic range of the IFN response observed in cells from older individuals may be an important adaptation to mitigate the caustic effects of chronic IFN production, favoring prolonged cell renewal at the cost of rapidly inducible antiviral immunity. Further systematic studies identifying the drivers of impaired IFN induction in the cells of older individuals will be critical for the development of a comprehensive understanding of how aging modulates antiviral immunity.

5. Conclusion and future directions

Even with recent progress in our understanding of antiviral immunity in aging, more studies will be needed to distinguish which *in vitro* deficits in viral sensing and control correspond to poorer *in vivo* outcomes. Regulatory intermediates that currently remain incompletely defined may soon illuminate interventions to improve immune responses. In particular, metabolic regulation and IFN responses as noted above, and immune elements needed to maintain a balance of pro-and anti-inflammatory processes represent ideal targets of study. In addition, many avenues of current investigation are beginning to clarify critical factors for healthy aging, such as individual genetic variants providing clues to determinants of successful longevity (Gopalan et al., 2017; McDaid et al., 2017; Mostafavi et al., 2016; Sebastiani et al., 2017), and the microbiome in maintaining health and longevity—as suggested by Metchnikoff a century ago (Gordon, 2008).

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