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Impact of aging on viral infections

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Abstract

Older people are more susceptible to a variety of viral infections, including those that induce respiratory disease, resulting in higher morbidity and mortality than younger people. Aging impacts both innate and adaptive arms of the immune system to impair control of viral infections. This review will summarize key findings on how aging impacts immunity to viral infection.

Keywords

Aging; viral infection; immunity

Introduction

The number of people aged over 65 is rapidly rising in most western countries. In 2008, more than 12% of the US population were 65 years or older, and this percentage is expected to increase greatly in the next 20 years [1]. The health care cost is larger for older people than young people as a result of the increased susceptibility to infectious diseases and reduced immune responses to vaccination with aging. For example, older people exhibit a higher mortality rate to influenza viral infection compared to younger people [2]. Therefore, it is important to understand the impact of aging on the immune system. In this review, we discuss the how aging impairs immunity with a focus on viral infections. In addition, we will review the potential strategies to enhance immunity in older people.

Overview of the impact of aging on human immune system

The immune system is comprised of innate and adaptive arms, and both are involved in control of viral infections [3]. Altered response to influenza viral infection have important consequences since failure to control this infection can lead to bacterial super-infection [4] and exacerbations of cardiovascular diseases [5]. Aging may impact both the innate and adaptive immune system to impair control of viral infections. Over the years, there has been a greater focus on how aging impacts the adaptive immune system with less known regarding the innate system.

Impact of aging on adaptive immunity

Adaptive immunity is important for combating viral infection, in part by generating antigen specific immunity, leading to the development of protective immunologic memory. Aging induces a multitude of effects on adaptive immunity, which we will briefly review here.

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1) Humoral immunity and aging—Aging causes both qualitative and quantitative changes in humoral immunity. Somatic hypermutation (SHM) is a key process for antibody generation and diversity. Aging impact this process at multiple levels. For example, B-cell germinal centers within the spleen and tonsils of aged individuals exhibit preserved SHM [6]. However, in the circulating B-cell pool as well as germinal centers of Peyer's patches, SHM decreases with age [7]. Additionally, E47 is a transcription factor encoded by E2A and regulates many B cell functions. The activation-induced cytidine deaminase (AID) induces class switch recombination (CSR) and Ig somatic hypermutation. Both of these components of humoral immunity are affected by aging as B cells isolated from peripheral blood of older human subjects have decreased expression of E47 and AID [8]. These alterations have also been associated with a decrease in the proportion of B cells that have undergone CSR [8]. In sum, aging impairs antibody generation by B cells at several levels to reduce humoral immunity.

Regarding the cellular composition of B cells, both the number and proportion of peripheral B-cells decrease with age. Absolute number of naïve B-cell numbers in peripheral blood is not altered although the representative proportion of these cells increases with age. This is likely a consequence of decreased total number of IgM memory B cells [8,9]. Overall, aging impacts the B-cell pool with memory B-cells exhibiting reduced numbers while naïve B-cell pool size remains preserved.

Bacterial super-infection is a complicating factor, which worsens morbidity and mortality after respiratory viral infections, including influenza [10]. On a functional level, aging impairs the ability to generate protective antibodies in response to both vaccination, e.g., against pneumococcal antigens and in response to pneumococcal infection [11,12]. This may be a result of a reduction in IgM memory B cell number and also in the function of these cells. Murine studies have shown that antibodies generated from aged mice are less protective to bacterial infection compared to antibodies generated in young mice [13]. However, these studies have not yet been translated to humans.

2) Aging and T-cell function—Antigen-specific B cells require interactions with $CD4^+$ T cells for subsequent expansion and differentiation and generation of T-cell dependent antibodies. Studies using T-cell receptor transgenic mice have shed important insights on the intrinsic defects of $CD4^+$ T cells with aging. These studies have shown that aged $CD4^+$ T cells have a reduced ability to form functional immunological synapses upon stimulation with peptide pulsed antigen presenting cells (APC) than young T cells [14]. This leads to defective T-cell receptor activation and poorer IL-2 production with aging, which impairs expansion of these cells and the generation of Th1 $CD4^+$ effector T-cells. As these cells are important for antiviral immunity, age induced-defects in these cells may be involved in defective viral control with aging. Aged $CD4^+$ T-cells also exhibit an impaired ability to provide help to B-cells to induce T-dependent antibody responses, which may also contribute to impaired viral control in aged hosts [15].

T-cell thymic output is reduced with aging [16]. As a result, there is reduced number of naïve $CD4^+$ T-cells accompanied with an accumulation of memory $CD4^+$ T-cells, likely the result of environmental exposures or homeostatic proliferation. The reduced naïve $CD4^+$ T-cell pool exhibit a restricted TCR repertoire, which may impair the ability of these cells to respond to a *de novo* viral infection. $CD8^+$ T-cells, which are critical to kill virally infected cells, also manifest a reduction in naïve T-cell numbers, and also exhibit restricted TCR repertoire [17]. Experimental studies suggest that this restricted repertoire may impair control of influenza or herpes simplex viral infection [18]. $CD8^+$ T-cells also exhibit impaired T-cell costimulation, for example the upregulation of CD28 and the production of

cytotoxic molecules such as granzyme B, which may also impair the ability to kill virally infected cells.

$CD4^+CD25^+$ regulatory T cells are important for maintaining immunological tolerance to self-antigens. These cells may also serve to resolve inflammation. Studies in mice have demonstrated increased number of regulatory T cells with aging [19]. It is not clear why aging leads to an accumulation of these T-regs. However, age-increased T regs numbers have been implicated in impaired eradication of tumors in aging mice [20]. It is not yet clear whether increased numbers of T-regs with aging impacts control of viral infection.

Aging and innate immunity

Most of the studies described above indicate that aging impairs adaptive immunity. How aging impacts innate immunity, which serves as the first line of control against pathogen invasion, is less well studied. Plasmacytoid dendritic cells (pDCs) are key cellular responders of viral infection [21]. They are the most potent type I interferon (IFN) producing cells and this action initiates several host responses, such as activating natural killer cells, which aids in viral clearance. pDCs detect the presence of viral infection by sensing components of viruses by toll like receptor (TLR) 7–9 signaling within the endosomes. This signaling pathway induces the upregulation of several signal adaptors, including IFN regulatory factor (IRF) 3, 5 and 7, which leads to increased gene expression of the type I IFNs.

There have been several studies that have documented that aging impairs pDCs to produce type I IFNs, either in response to TLR 7 or 9 ligands, such as single stranded RNA or CpG sequences or in response to viruses, such as cytomegalovirus or herpes simplex virus [22]. Our prior work demonstrated that this defect with aging was critical for an impaired ability to clear herpes viruses in aging mice [23]. We found that aging led to an impaired ability to upregulate IRF-7 upon TLR9 stimulation and that age-increased oxidative stress was partly responsible for the impaired type I IFN responses with aging [23].

Other experimental studies have found that aging can impair certain components of TLR responses in macrophages and conventional dendritic cells (DCs), in particular the production of proinflammatory cytokines and upregulation of costimulatory molecules, although there have been other studies that have found that TLR responses in these cells are preserved or even enhanced [24].

We recently found that an imbalanced innate cytokine response induced lethal immune pathology during viral infection using experimental models of herpes viral infection, including HSV and CMV, in mice [23,25]. Specifically, we found that aging leads to rapid exaggerated IL-17 responses, which induces neutrophil recruitment into the liver and subsequent lethal liver injury. This response was coupled to impaired type I IFN responses by pDCs, which impairs viral control. We speculate that the increased viral load directly or indirectly activates NKT-cells to produce IL-17 in aged hosts during viral infection. Our work also found that aged NKT-cells exhibit elevated IL-17 responses to direct viral stimulation *in vitro* than young cells [25]. If our work is translated to humans, it will suggest that specific anti-inflammatory therapies may be beneficial in older people infected with influenza viral infections.

Specific examples of viral infection with aging

1. HIV—It has been almost 30 years since the human immunodeficiency virus (HIV) was first discovered. The portion of older HIV-infected patients has greatly increased since then. With the introduction of highly active antiretroviral therapy (HAART) in 1996, HIV

infection is now considered to be a treatable chronic disease. Many patients who were infected in their youth are now in their 6^{th} decade or older. Thus, understanding how aging and HIV infection interact will be of increasing biomedical importance.

Clinically, older HIV-infected individuals display a more rapid progression to acquired immunodeficiency syndrome (AIDS) as well as a greater rate of mortality than young patients. They are also more susceptible to the adverse effects of antiretroviral therapies even though surprisingly their ability to control viral levels is better than the younger patients [26,27].

Immunological alterations in older HIV-infected people include inversion of the normal CD4:CD8 T cell ratio, decreased number of naïve T cells, telomere shortening in $CD4^+$ and $CD8^+$ T cells, lower T cell proliferation and altered cytokine profiles (e.g. lower IL-2 production while higher IFN gamma production) [28]. It is possible that the progression of chronic HIV infection accelerates the effects of aging on immunity, an area that warrants further investigation.

2. Influenza virus—Novel H1N1 influenza pandemic has spread around the world since 2009. In sharp contrast to the seasonal influenza virus, in which 90% of annual deaths occur in individuals over age 64, the majority of deaths with the H1N1 occur in people aged of 20–49 years [29,30]. The increased burden of disease found in younger population compared to the older population may be explained by the presence of preexisting cross-protective antibodies against the current H1N1 strain. Those antibodies may have been generated in older people after exposure to related H1N1 strain present in 1950s [31].

Innate immune responses play a role in protecting the host from the bacterial secondary infection after influenza virus exposure. Furthermore, TLR responses in DCs may predict the efficacy of influenza vaccination. In particular, the production of TNF-α, IL-6 and or IL-12 p40 in human DCs was substantially decreased in the older than the younger in response to TLR1/2, TLR2/6, TLR3, TLR5 and TLR8 stimulation [32]. These defects were associated with the impaired surface and intracellular expression of TLR proteins and TLR related genes. Also, this study revealed that the cytokine production without TLR stimulation was elevated in the cells from the older compared to younger people, which may explain why older cells exhibit impaired cytokine production upon TLR engagement. Importantly, defects in cytokine production after TLR activation are strongly associated with poor antibody response to influenza immunization [32]. A murine study found altered inflammatory cytokine responses to influenza viral infection with impaired IL-12 responses with aging coupled to increased TNF-α [33]. This may reflect dysregulated innate responses to infection with aging, although it has not been addressed mechanistically.

Aging impairs adaptive T-cell immunity to influenza viral infection. Prior work has shown that $CD8^+$ T-cell viral reactive IFN-γ responses and virus specific cytolytic activity decrease with aging. An impaired expansion of the $CD8^+$ T cells was also noted in the same study [34]. These cellular defects in $CD8^+$ T-cell responses with aging may contribute to the known impaired efficacy of influenza vaccinations in older people.

3. West Nile viral infection—Clinical studies have shown that older people are more susceptible to West Nile Viral (WNV) infection, a flavivirus. The disease is spread via mosquito bites, although most infections are asymptomatic, some patients exhibit flu like symptoms and others present with meningitis or encephalitis [35]. Regarding adaptive immunity to WNV with aging, a murine study revealed that there are T cell defects in the age-related vulnerability to west nile virus (WNV). Specifically, T cells from the aged mice display defects in cytokine (such as IFN-γ and TNF-α) and lytic granule production. These

cells are also unable to generate multifunctional anti-WNV effector T cells within the brain. This suggests that both qualitative and quantitative impairment with age in effector T cell immunity in the brain lead to increased susceptibility to the virus infection [36]. Despite these findings in the mouse, a human study found that memory T cell responses in patients with WNV infections were age-independent despite differences in $CD8^+$ T cell effector expansion after the primary response to the virus [37]. It is not yet clear how aging alters innate responses to WNV.

4. CMV infection—Cytomegalovirus is a beta herpes virus, which exhibit latency within the host. The interaction between the host and the virus during the initial exposure to the virus and during the period of latency may influence the T-cell pool. In particular, CMV infection can lead to the accumulation of memory T-cells and a skewing of the naïve T-cell repertoire [38]. CMV infection induces a series of changes in T cells including telomere shortening, which may impair the ability of these T-cells to subsequently divide [39]. In addition, aged $CD8^+$ effector memory T cells exhibit a defective upregulation of costimulatory molecules, e.g., CD28 along with increased upregulation of natural killer related genes KLRG1 [40]. Functionally, these cells have decreased proliferative capacity with a resistance towards apoptosis. Moreover, CMV infection is associated with higher systemic levels of inflammatory mediators such as TNF-α [41] and IL-8 [42]. These effects may further exaggerate the influence of aging on T-cell responses.

Although CMV infection is clinically silent in most immune competent hosts, a prior history of CMV infection has clinical consequences as it contributes to the immune risk profile. This profile consists of a number of immunological measurements including inversion of $CD4^+$ and $CD8^+$ T-cell numbers, poor proliferation response of T-cells, low B cell numbers, reduced number of naïve T-cells, CMV seropositivity and presence of CMV reactive T-cells. This profile of immunological measurements has been associated with increased mortality in observational longitudinal studies of people in the 8^{th} and 9^{th} decade [43].

Strategies to improve immunity in older people

There are various approaches to improve immune responses with age. First, there are vaccine approaches to protect older people from infection. One strategy is to use adjuvants. Adjuvants increase the ability of APCs to prime antigen specific T cells, partly, by stimulating innate receptors such as TLRs. For example, Poly I:C (a TLR3 agonist) is shown to be effective in enhancing the $CD4^+$ T cell help in aged mice [44], although this approach has yet to be applied to protection from viral infection.

Aging induces thymic involution leading to reduced production of naïve T-cells. Hence, strategies to prevent thymic atrophy with age or increasing T-cell output hold potential in counteracting the impact of age on the immune system. Administration of thymic growth factors including keratinocyte growth factor (KGF), IL-7 and ghrelin may increase thymic output to counter the effects of aging on thymic involution. KGF acts by enhancing IL-7 production within the thymus, by binding to KGF receptors on thymic epithelial cells [45,46]. IL-7 increases thymic output of T-cells allowing for the maintenance of long-lived memory T cells, following vaccination [47]. Hence, there may be pharmacological approaches to counter age-induced thymic atrophy, which may improve T cell memory responses and increase vaccine efficacy in older people.

Another promising strategy is to prevent age-induced telomere shorting with age. This approach is based on the observation that telomere shortening with aging is associated with overall decreased replicative potential and function of T lymphocytes. Telomerase activation elongates telomere and is associated with T cell activation, which could increase the ability

of the cell to divide. For example, treatment of $CD8^+$ T cells from HIV-infected individuals with TAT-2 (a small molecular telomerase activator) has the dual effects of increasing tolemerase activity as well as enhancement of a variety of antiviral effector functions including antigen specific cytotoxicity and IFN-γ production [48]. This approach may prevent telomerase shortening with age and possibly improve anti-viral T-cell responses.

Conclusion

Aging impacts several components of the immune system including innate and adaptive immunity. Understanding the mechanisms by which aging alters immunity may lead to novel therapies to improve immunity with aging, in particular the ability to clear viral infection. The development of such novel therapies are urgently needed as the number of older people in our society continues to rise, with increasing disease burden from viral infections.

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