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Aging, sex, inflammation, frailty, and CMV and HIV Infections

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Abstract

Aging is characterized by significant immune remodeling at both cellular and molecular levels, also known as immunosenescence. Older adults often manifest a chronic low-grade inflammatory phenotype. These age-related immune system changes have increasingly been recognized not only to lead to immune functional decline and increased vulnerability to infections, but also to play an important role in many chronic conditions such as frailty in older adults. In addition to sex as an important biological factor, chronic viral infections including that by human immunodeficiency virus (HIV) and cytomegalovirus (CMV) are all known to have major impact on the aging immune system. This article provides an overview of our current understanding of aging immunity, sex, inflammation, frailty, and HIV and CMV infections.

Keywords

Aging; Immunosenescence; Sex; CLIP; Frailty; HIV; CMV

1. Introduction

The immune system undergoes significant changes with aging, collectively termed as immunosenescence by some. For example, aging is associated with thymus involution, contraction of the immune repertoire, decrease in the number and proportion of naïve lymphocytes, accumulation of memory and senescent lymphocytes, as well as T cell clonal expansion and loss of expression of costimulatory molecular CD28 [1–3]. Meanwhile, aging is associated with the development of a chronic low-grade inflammatory phenotype (CLIP) [4,5] or inflammaging [6,7]. Such complex immune remodeling constitutes a hallmark of aging [8]. The clinical impact of immunological aging is profound, particularly the immune functional decline leading to increased vulnerability to infections as well as CLIP that is

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believed to contribute to many chronic conditions in older adults. In this article, we will briefly review the relationships among aging immunity, sex, inflammation, frailty, and HIV and CMV infections, and what is known about how these relationships are affected by sex.

2. Impact of sex on aging immunity

Recently, sex has increasingly been recognized as an important biological factor with significant impact on the aging immune system. For instance, a number of studies have shown that older males have more accumulation of memory and senescent $CD8^+$ T cells and lower $CD4^+$:$CD8^+$ T-cell ratio than their female aged peers (reviewed in [9,10]). Brown and colleagues demonstrated the impact of sex on naïve and senescent T-cell redistribution in response to acute maximal exercise, with significant interaction between sex and training status even in young athletes [11]. A large study conducted by Piasecka, et al. in healthy individuals showed a role of sex in shaping immune responses to microbial challenges [12]. Klein and colleagues have shown that following vaccination, female mice mounted greater antibody responses to influenza vaccines, and generated more effective protection against influenza virus challenge, than male mice [13], directly linking sex to immunity against a specific pathogen that disproportionally causes high morbidity and mortality in elderly humans. Data from a human study have also shown an immunosuppressive role for testosterone in the response to influenza vaccination [14]. Taken together, these studies provide emerging evidence supportive of a significant impact of sex on aging immunity.

3. Aging and chronic low-grade inflammatory phenotype (CLIP)

Aging is often accompanied by CLIP, which is characterized by low-grade, systemic, persistent, and smoldering chronic inflammation, marked by 2–4-fold higher circulating levels of multiple inflammatory mediators. The profound clinical implications of CLIP are best demonstrated by its association with the development of almost all age-related chronic conditions including frailty (see below), cardiovascular disease, neurodegenerative diseases, and metabolic dysfunctions [7]. Taking cardiovascular disease as an example, CLIP is considered as a key driver in the initiation and progression of atherosclerosis/atherothrombosis as well as plaque formation and rupture, the central pathophysiological processes that are dynamic and progressive leading to clinically acute and severe cardiovascular disease, such as myocardial infarction and stroke, as well as post-acute myocardial remodeling with dilatation and wall thinning [15]. High serum levels of inflammatory markers such as C-reactive protein (CRP) are considered not only as CVD risk factors but also predictors for disease progression; CRP is now routinely monitored in clinical practice [16].

While etiologies and underlying mechanisms for CLIP remain to be further delineated, they are likely multi-factorial. Distinguished from acute inflammation which is a time-limited response to incident infection or injury, CLIP is likely secondary to chronic antigenic stress caused by persistent viral infection, such as CMV and its reactivation (see below), as well as harmful microbial products from gut dysbiosis. Another potentially important etiology is cellular senescence as senescent cells can survive and accumulate in the circulation and in the tissues through the body. These senescent cells, which no longer proliferate or perform

normal physiological function, secrete a variety of pro-inflammatory mediators, reflecting what has been termed the senescence-associated secretary phenotype (SASP) [17,18], leading to the development and worsening of CLIP. Other factors have also been considered as significant contributors to CLIP, including smoking, decreased production of sex steroids, and accumulation of adipose tissue.

4. Frailty, aging immunity, and HIV infection

Frailty is widely recognized as an important and common geriatric syndrome characterized by decreased physiological reserve and involving multiple physiologic systems and increased vulnerability to serious adverse health outcomes including falls, disability, and mortality [19–22]. According to the most commonly utilized criteria, frailty as a phenotype is defined by the presence of three or more of the following clinical and functional characteristics: weakness (measured by grip strength), low physical activity, slowed motor performance (measured by walking speed), exhaustion, and unintentional weight loss [19]. While frailty has been studied most extensively in the general HIV-uninfected (HIV-) geriatric population, it has also been recognized as a common and important syndrome in the HIV-infected (HIV+) aging population. This is because after the introduction of highly effective combined anti-retroviral therapy (cART), life expectancy for HIV+ persons has increased dramatically and age-related chronic conditions such as frailty have become major health concerns [23,24].

In the general HIV− geriatric population, a large and growing number of reports have provided supportive evidence for a role of immunosenescence, particularly CLIP, in the pathogenesis of frailty. While a comprehensive review of this body of literature is beyond the scope of this article, several lines of scientific evidence deserve emphasis here. *i*) Direct associations between frailty and higher molecular mediators of CLIP (e.g., IL-6, CRP and others) [25–27] and immune activation (e.g., neopterin) [28], with the latter suggesting the involvement of immune activation, upstream of CLIP, in frailty; *ii*) Direct associations between frailty and higher counts of circulating immune cells, or the cellular components of CLIP, e.g., total leukocytes and their subpopulations including neutrophils and monocytes [26,29]. Among T lymphocyte subsets, frailty is associated with higher counts of $CD8^+CD28^-$ T lymphocytes and $CCR5^+$ T lymphocytes, the latter having a type-1 pro-inflammatory phenotype [30–32]; *iii*) inverse associations of circulating IL-6 levels with hemoglobin concentration and serum insulin-like growth factor-1 (IGF-1) levels in frail older adults, but not in non-frail older adults; low hemoglobin and IGF-1 levels were each independently associated with frailty, as well [25,33,34]. In addition, increased WBC counts were inversely associated with decreased IGF-1 levels [35]; *iv*) frail older adults had lower cell proliferation and higher IL-6 production by peripheral blood mononuclear cells (PBMCs) upon stimulation with lipopolysaccharide (LPS) compared to age-, sex-, and race-matched non-frail controls, [36], supporting a link between immunosenescence and frailty. In similar studies, PBMCs from frail individuals demonstrated significantly higher expression of a number of stress-responsive inflammatory pathway genes upon LPS stimulation compared to matched non-frail individuals [37], and constitutive monocytic expression of CXCL-10, a potent pro-inflammatory chemokine, was highly correlated with elevation in serum IL-6 levels in frailty [38]; and *v*) in community-dwelling HIV− older

adults over 70 years of age, frailty was associated with significantly lower strain-specific antibody responses to influenza vaccine as well as lower clinical protection against influenza infection [39], indicating an adverse impact of frailty on immunity against influenza in the elderly.

It should be noted that the above studies all have reported associations with frailty; the studies are cross-sectional and thus cannot indicate causality. In general, there is a severe paucity of longitudinal data on frailty and particularly on factors that may precede its onset. Nevertheless, the available data, in the aggregate, suggest that CLIP may contribute to frailty directly, or indirectly through other intermediary pathophysiological processes, and that activation of inflammatory pathways is an important part of the immune senescent dysregulation that leads to CLIP and frailty [40]. In other words, taken together these lines of evidence suggest that immunosenescence, particularly CLIP and its upstream immune and inflammatory pathway activation, may contribute to the development of frailty, and frailty may in turn adversely impact immunity, e.g., immunity against influenza.

Substantial evidence supportive of a role of CLIP in the pathogenesis of frailty has also emerged in the HIV+ aging population, as reviewed elsewhere [21,41]. Recent data from two large cohort studies of HIV infection, the Multicenter AIDS Cohort Study (MACS) in men who have sex with men and the AIDS Linked to the Intravenous Experience (ALIVE) study in people with a history of injection drug use, deserve a brief discussion. Consistent with the data reported in the general HIV− geriatrics population, results from the MACS demonstrated an association of frailty with higher concentrations of serological inflammatory markers [42] as well as with higher concentrations of IL-6 and CRP, greater proportions of lymphocytes with the senescent T cell phenotype, and lower circulating levels of free testosterone and dehydroepiandrosterone [43]. The described high level of immune activation was beyond that due to treated HIV infection [44]. Similarly, data from the ALIVE study demonstrated a significant association between frailty and CLIP [45]. Of note, CLIP encompasses many molecular mediators, likely forming a complex and interactive network. In fact, analyses of five CLIP mediators measured in the ALIVE study at baseline demonstrate that while soluble TNF-α receptors I and II levels were highly associated with IL-6 levels [46], levels of neopterin, an upstream immune activation mediator, was associated only with levels of soluble TNF-α receptors I and II levels, not with those of more distal and downstream inflammatory mediators IL-6 and CRP [47], suggesting potential a network of upstream vs downstream or proximal vs distal CLIP mediators in HIV infection with therapeutic implications.

5. CMV, aging immunity, and HIV infection

It is possible that the additional immune activation associated with frailty, above that associated with treated HIV infection, is related to immune responsiveness to CMV infection. CMV, which is highly prevalent in the general HIV− geriatric population and almost universal among HIV+ aging persons, may cause clonal T-cell expansion, leading to immune activation and adverse health outcomes [48–51]. The potentially important impact of CMV on aging immunity is further supported by the fact that it is the target for a very large proportion of circulating T cells in HIV− people, often more than 10% of cells and

sometimes 30–40% [52–54], and in HIV+ people [55]. Some studies have found a direct association between positive CMV serology and frailty or functional decline in the elderly [56,57], but others did not find such association [58,59]. In the MACS cohort, we observed broad and diverse CMV-specific $CD4^+$ and $CD8^+$ T responses in both HIV− and HIV+ men [55}. Moreover, in this cohort a greater IL-2 response by CD4 T cells exposed in vitro to a panel of overlapping peptides spanning 19 CMV open reading frames significantly predicted onset of frailty over 9 years of follow-up of HIV− men who were initially not frail [60].

One daunting challenge is that a positive anti-CMV IgG serology, the current diagnostic paradigm for CMV infection, is an imprecise measure that merely indicates prior exposure to the virus, not necessarily a chronic (persistent) infection and certainly not the nature and scale of either the infection or the immune response to it. Therefore, several recent studies have investigated the cellular immune response to CMV and the direct detection of CMV itself. We found, in an elderly population, that defining chronic CMV infection by detection of CMV DNA in peripheral blood monocytes, rather than by positive CMV serology, led to a much stronger association of CMV infection with higher frequencies of $CD8^+$ T cells specific for CMV (as defined by binding to a tetramer containing a peptide derived from CMV pp65 (NLV)) and with immune activation (as measured by serum neopterin levels) [51,61]. Subsequent longitudinal analysis in older women with chronic CMV infection further demonstrated that higher serum IL-6 levels and higher proportions of CMV pp65 (NLV)-specific $CD8^+$ T cells at a given study visit were associated with the presence of CMV DNA in monocytes as assessed by nested PCR [62]. Although highly sensitive, nested PCR is a qualitative assay. Digital droplet PCR (ddPCR) allows accurate quantification of low numbers of target DNA copies, which was evaluated to quantify CMV copies in semen as well as in the PBMCs from HIV+ male participants [63,64]. Parry and colleagues also applied ddPCR to evaluate CMV viral load in the peripheral monocytes and reported its age-related increase among healthy older adults [65]. However, further studies are needed to validate these findings and the utility of ddPCR in diagnosing chronic CMV infection and measuring CMV viral load. In addition, there are no longitudinal studies using ddPCR, and also no studies of the effect of sex on presence of CMV DNA in monocytes or other blood cells, because most studies using ddPCR thus far have been done in predominantly or exclusively male populations.

Another challenge is the technical limitation of commonly used tetramer, pentamer or dextramer analyses, allowing the detection of CMV-specific T cells to only one viral epitope at a time. Considering that human CMV is a very large virus that can produce hundreds of epitopes, at least, CMV-specific T cell responses detected through these analyses likely represent only a tiny proportion of T-cell immunity against CMV. Indeed, as described above, we observed broad and diverse CMV-specific $CD4^+$ and $CD8^+$ T responses upon *ex vivo* stimulation with CMV peptide pools in the MACS [55,60]. In the latter study, the finding that a strong CD4 T-cell IL-2 response to CMV antigens predicted development of frailty depended on analyzing the total CD4 cell IL-2 response across 19 CMV open reading frames, and was not observed when responses to just one or two CMV proteins or peptides were assessed, as is commonly done [60]. This was because of the extreme diversity of the individual T-cell responses to CMV.

Given the rarity of overt CMV replication in immunocompetent older individuals, it is possible that very low and restricted T-cell responses may be sufficient to protect from CMV disease. This raises the hypothesis that broad and strong T-cell responses against CMV observed in older adults represent excessive and detrimental immune reactivity, with significant adverse impact on aging immunity, leading to immunosenescence and CLIP. While CMV-induced T-cell clonal expansion likely contributes to immune repertoire restriction and T-cell immunosenescence, this hypothesis certainly deserves further investigation. In this connection, there is evidence that the immune response to CMV may enhance protective immune responses to other infections in young but not old individuals [66].

In fact, there are many similarities between the differences between young and old hosts and CMV-uninfected and -infected hosts, raising the possibility of confounding of age and CMV infection in cross-sectional studies, especially in view of the well-documented observation that the prevalence of CMV infection increases with age. For example, it has been found that higher levels of effectormemory RA T cells, seen in both older populations compared with younger, and CMV+ populations compared with CMV-, were more strongly associated with CMV seropositivity than with age [67–72]. Of note, Pera et al recently reported that differences in variables associated with aging, such as percent of $CD28^{-}$ $CD8^{+}$ T cells and serum CRP concentration, were far less pronounced between young and old CMV-seronegative people than they were between young and old CMV-seropositive people, and between young CMV-seronegative and young CMV-seropositive people [73]. Sex differences did not contribute significantly to these findings. It was hypothesized that CMV-activated CD4 T cells could account for much of the association between CMV infection and atherosclerosis [73,74]. Recently, in a longitudinal study following elderly adults for up to 2.5 years, Reed et al [75] reported that CMV-seropositivity did not alter the trajectories of late-differentiated ($CD8^{+}CD28^{-}$) T cells. The levels of these cells were significantly correlated with perceived stress in people with low, but not high, titers of antibody to CMV [76].

There is, however, evidence that the immune response to CMV differs by sex. Villacres et al reported that females had greater CMV-induced secretion of IFN-χ and IL-2 than males [77]. Di Benedetto et al demonstrated that serum levels of IL-1β differed significantly by CMV serostatus only in males, and serum levels of sTNFR differed significantly by sex (lower in females) only in CMV-seronegative individuals [78]. Puissant-Lubrano et al reported that CMV seropositivity was associated with lower numbers of circulating plasmacytoid dendritic cells with age, but with little effect of sex [79].

6. Concluding remarks

Substantial evidence indicates that a number of factors have major impact on aging immunity, including sex as a major intrinsic biological factor, and extrinsic and environment factors such as chronic CMV and HIV infections. It is generally established that aging immunity includes immune functional decline leading to increased susceptibility to infections in older adults, particularly those who are frail. Recent data support the notion that immunosenescence, particularly CLIP, contributes to the development of many age-

related chronic conditions. However, it remains challenging to distinguish the direct effect of CLIP from other potential etiologic mechanisms. To this end, further investigations into mechanisms by which those intrinsic and extrinsic factors impact aging immunity as well as into the origin and regulation of immunosenescence itself, and how it is affected by sex, are urgently needed. Longitudinal studies are particularly needed to distinguish between the effects of aging and those of chronic CMV infection; nearly all of the available data on this question are from cross-sectional studies. Interventional studies with anti-CMV treatments would also be highly beneficial. These studies will no doubt help move the field of aging immunity forward and ultimately improve the human healthspan.

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Highlights:

1. Immunosenescence refers to immune system changes during aging
2. Chronic low-grade inflammatory phenotype (CLIP) is a feature of immunosenescence (84)
3. Emerging data suggest sex as an important factor influencing immunosenescence
4. Immunosenescence affects susceptibility to infection, chronic disease, and frailty (85)
5. Chronic CMV infection contributes to immunosenescence in aging and HIV infection (83)