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Stress and Immunological Aging

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Abstract

Immunological aging, which encompasses age-associated declines in the immune system (immunosenescence) and increases in inflammation (inflammaging), is associated with morbidity and mortality. A growing body of research suggests stress is one factor that may accelerate immunological aging. This article provides a brief overview of immunological aging, describes key biological pathways acting at multiple lifespan stages linking stress and immunological aging, and reviews recent innovative work characterizing associations between stress in several domains and immunological aging, as well as potential protective and risk factors. Important directions for future research include careful characterizations of the complexities of stress and rigorous measurement of immunological aging processes. Advancing knowledge of stress resilience and healthy immune aging may ultimately slow disease onset and extend healthspan.

Stress and Immunological Aging

Aging is characterized in part by immune deterioration. Dysregulation of the immune system, which provides mechanisms to combat infectious diseases, destroy cancer cells, and respond appropriately to vaccines, increases risk for morbidity and mortality. Stress, broadly conceptualized as exposure to difficult or challenging circumstances (stressors) and the psychological, behavioral, and physiological responses to such circumstances (stress responses) (also see [1]), has emerged as a major factor that may accelerate the rate at which the immune system ages. Older adults in particular may generate exaggerated immune responses to stress that further exacerbate an already weakened immune system due to aging [2, 3]. Chronic stress that is demanding, distressing, and ongoing, may have the most detrimental immune health effects.

This review article provides a brief overview of immunological aging, describes key biological pathways linking stress and immunological aging, and summarizes recent innovative work characterizing associations between stress and immunological aging as well as potential protective and risk factors (see Figure 1 for a conceptual overview). The review

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incorporates a lifespan perspective by focusing on stress experienced during and biological mediators acting at multiple developmental stages to influence immunological aging.

Immunological Aging

Normal aging is accompanied by declines in immunity, a process broadly referred to as *immunosenescence*, and increases in inflammation in the absence of infection, termed *inflammaging*. Hallmarks of immunosenescence include changes in the adaptive immune system, most prominently in the T cell compartment, responsible for protecting against pathogens residing inside cells or cells that have gone awry (e.g., cancer cells). Changes include decreases in naïve T cells and an accumulation of memory T cells, especially late differentiated senescent or near senescent CD8+ T cells that have shortened telomeres (i.e., protective caps on the ends of chromosomes that prevent deterioration) and that lose the costimulatory molecule CD28 and express maturation marker CD57 [4]. Cells of the innate immune system, such as neutrophils and natural killer (NK) cells that act as the first line of defense against invading pathogens, are also affected by increasing age [5]. Changes include defective activation and lower per-cell cytotoxicity. Inflammaging is characterized by age-related increases in circulating proinflammatory markers such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α) [6]. Immunosenescence and inflammaging are interrelated; for example, senescent T cells exhibit an inflammatory senescence-associated secretory phenotype (SASP) comprised of cytokines and chemokines that contribute to inflammaging [7]. Although age-related immune changes can be viewed from an evolutionary perspective as an adaptive remodeling [8], these changes are ultimately implicated in impaired vaccine response, greater susceptibility to infectious disease, and the development of age-related diseases (e.g., cardiovascular disease, cancer), disability, and death [4, 5, 9, 10].

Biological Pathways Linking Stress and Immunological Aging

Well-established mediators by which stress may influence immunological aging include disruptions in the hypothalamic-pituitary-adrenal (HPA) axis, specifically altered cortisol levels and glucocorticoid signaling [11]. Additionally, dysregulation of the HPA axis as indicated by greater intraindividual cortisol variability [12] is a newer mechanism for future research that may contribute to inflammaging in older adulthood [13]. HPA axis disruptions act across the lifespan, with emphases during higher-risk developmental periods such as early childhood or older adulthood when stress may disrupt ongoing neurobiological development or further exacerbate glucocorticoid impairment that accompanies normal aging. Infection with persistent viruses, particularly cytomegalovirus (CMV), is another pathway acting in early life and adulthood linking stress and immunological aging. Environmental stressors can increase the probability of CMV infection in childhood; once infected, psychological stress can reactive latent CMV in midlife and older adulthood that, in turn, may drive aspects of immunological aging and age-associated diseases [14–16].

Several other pathways linking stress and immunological aging are garnering interest in psychoneuroimmunology and aging biology. Mitochondria, the cells' "power plants" that generate energy and metabolic intermediaries needed for cellular function, are increasingly

recognized as important players in the stress-immune health link [17]. Circulating cell-free mitochondrial DNA (ccf-mtDNA) released in response to stress (C Trumpff *et al.*, unpublished) may act as damage-associated molecular patterns that trigger inflammaging in older adults [18]. Mitochondrial health likely acts across the lifespan to connect stress and immunological aging; however, older adulthood may be a particularly relevant developmental stage given age-related increases in ccf-mtDNA and accumulated defects that may compromise mitochondrial function. The gut microbiome is another pathway that may act primarily in older adulthood; aging is accompanied by increases in gut permeability (i.e., gut bacteria translocation into the outer area), as well as changes in microbial composition (i.e., less diversity), which is associated with inflammaging in older adults [19]. Moreover, new evidence in humans suggests stress can also increase gut permeability [20]. Epigenetic mechanisms reflected by changes in DNA methylation throughout the epigenome may also play a role in stress-immune aging connections across the lifespan; epigenetic clocks (i.e., molecular age algorithms based on DNA methylation levels) are associated with stress and T cell immunosenescence [21, 22].

Recent Innovative Work in Stress and Immunological Aging

The following sections describe key domains of recent inquiry into associations between stress and immunological aging as well as potential protective and risk factors.

Early Life Adversity

Stress that occurs early in development, in the form of abuse, neglect, separation from parents, or other adverse experience, may have particularly potent effects on immunological aging. Meta-analyses indicate early life adversity is associated with telomere shortening later in life [23, 24], and mitochondrial biology may play an important role in this association [25]. Early life adversity may also increase risk of CMV infection in childhood, which in turn drives T cell immunosenescence in young adulthood [26]. A lifespan approach may be especially useful in studying cumulative effects of stress on immunological aging, as well as identifying whether associations are driven by certain events, types of stressors, and related biological mediators acting in specific sensitive developmental periods [27, 28].

Environmental and Socioeconomic Factors in Adulthood

In adulthood, macro-level environmental and socioeconomic stressors relate to immunological aging. Higher perceived neighborhood problems (e.g., excessive noise, heavy traffic, lack of parks or playgrounds) are associated with shorter leukocyte telomere length in African American women, after controlling for individual-level risk factors [29]. Older adults with more socioeconomic resources, particularly with regard to finances and possessions, display less CD57 expression on NK cells [30]. Conversely, middle-aged adults with lower socioeconomic status display higher levels of T cell immunosenescence, due in part to impaired CMV control [31]. Molecular pathways, including increased gene transcription in immune cells responsible for proinflammatory, antiviral, and stress signaling, may connect socioeconomic stress to immunological aging in older adults [32].

Caregiving

Caregiving for a sick or disabled relative (e.g., spouse, child) is frequently examined in psychoneuroimmunology studies of chronic stress effects on immunity. High stress compared to low stress caregivers display lower mitochondrial health function and shifts in T cell composition characteristic of immunosenescence [33, 34]. Other research indicates associations between caregiving burden (but not caregiver status) and increased inflammaging (IL-6 and CRP) in older adults [35]. Associations between duration of caregiving and immunological aging have also been examined in longitudinal research; in older adult women, no significant associations were found between long-term caregiving patterns and leukocyte telomere length at the end of 8 years or changes in telomere length since baseline [36]. In terms of the innate immune system, neutrophil function was preserved in both young and old stressed caregivers, but those with higher psychological stress and other comorbidities displayed poorer neutrophil function [37]. Future research focusing on individual in addition to group differences in chronicity and levels of caregiving stress may further clarify links between chronic stress, age, and immunological aging processes.

Daily Stressors

Daily stressors, or routine challenges of everyday life such as work deadlines, family arguments, and providing care to others, may influence immunological aging. There is support for both the exposure (accumulation over time) and reactivity (heightened psychological and physiological responses) models of daily stress [38, 39]. However, daily stress research has focused exclusively on inflammatory markers (e.g., inflammaging), with one recent exception: greater accumulated daily stress appraisals over an 8-week period were associated with elevated gene expression of cellular senescence signal $p16^{INK4a}$ in middle-aged adults [40]. It remains unknown whether daily stressors in older adulthood influence other indicators or drivers of immunosenescence (e.g., accumulation of late-differentiated T cells or reactivation of latent viruses).

Interpersonal Stressors

Evidence from cross-sectional studies suggests that interpersonal stressors, including loneliness and low social support, are associated with shorter leukocyte telomere length, inflammaging, and T cell immunosenescence [41–44]. These effects may depend in part on CMV reactivation in midlife and older adulthood as well as parasympathetic function [44]. Importantly, interpersonal stressors may affect not only the individuals directly involved, but also other family members in the home exposed to such stress. Among children, greater negative mood reactivity to martial conflict was related to shorter leukocyte telomere length [45]. An important next step will be conducting longitudinal studies that assess how dynamics of interpersonal stressors in childhood and adulthood affect indicators of immunological aging even later in life.

Nonpharmacological Moderators of Resilience and Vulnerability

Health behaviors may attenuate stress effects on immunological aging, potentially acting concurrently in time and mainly in older adulthood. Exercise is one immune-restorative

behavior that may decrease stress and slow immunological aging in older adults [46], possibly by reducing proportions of senescent T cells and decreasing inflammaging [47]. Sleep is another restorative health behavior. Inadequate quantity or quality of sleep may exacerbate immunological aging, particularly in the context of stress [48, 49], by activating DNA damage and the proinflammatory SASP in older adults [50]. Lifestyle interventions such as calorie restriction have also been proposed to delay immunological aging. However, initial results in non-obese middle-aged and older adults suggest no clear evidence that long-term calorie restriction slows telomere shortening or T cell immunosenescence [51].

Psychosocial factors may buffer stress effects on immunological aging. Higher subjective and objective measures of social support/integration are associated with lower levels of inflammaging and an immune risk score based upon inflammatory markers and antibody titers for two herpesviruses, including CMV in middle-aged and older adults [52, 53]. Effective emotion regulation strategies and strength of ability to self-regulate may also protect against stressor exposure and reactivity and effects on immunological aging. These factors have yet to be examined in older adults. Identifying ways to effectively promote resilience in the face of stress and immunological aging continues to be an exciting future direction.

Conclusions and Future Directions

Current evidence indicates that stress is associated with immunological aging, including aspects of immunosenescence and inflammaging. Several areas for future direction also emerged from this review. First, defining and measuring “stress” is an ongoing area of investigation [1]. This review highlighted chronic and daily forms of stress in various domains (individual, interpersonal, broader socioeconomic contexts) experienced during different developmental periods (childhood, adulthood). However, individuals may experience several forms of stress simultaneously, and previous and ongoing stressors may influence subsequent stress experiences. Future work that incorporates these complexities into theorizing and research is warranted to determine which aspects of stress most strongly relate to different immunological aging processes.

Second, rigorous and replicable measurement of immunological aging parameters, as well as major drivers of immune aging (e.g., CMV), should be employed. Peripheral blood contains a mixture of several different immune cells and failure to account for the cell-type composition can lead to incorrect interpretations about immunological aging. As one example, unaccounted differences in cell-type composition may lead to pseudo-lengthening of telomeres, whereby measured telomere length appears longer, but only because of changes in the proportion of cells types being measured rather than actual lengthening of telomeres in any given cell type. Sorting cells prior to analyses or focusing on certain cell subsets (e.g., CD8+CD28−) could strengthen validity. Additionally, markers of immunological aging (and biological aging more broadly) may capture different aspects of the aging process; theory and previous research should help guide selection of relevant markers (or alternatively, construction of a composite or algorithm-based measure, see [54]).

Finally, advances in biomarker assays and increasing sophistication in research measurement and analysis provide support and motivation for well-powered studies of diverse samples that test complex models of stress and immunological aging, including links to clinically relevant health outcomes, as proposed in Figure 1. Longitudinal studies of stress, immunological aging, and biological mechanisms across different time scales and lifespan stages will be especially informative. Innovative inquiry into stress effects and the roles of protective factors and mediators in immunological aging may assist in slowing the onset of disease and extending healthspan – the portion of life spent in good health.

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*of special interest

**of outstanding interest

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Highlights

- Aging is accompanied by declines in immune function and increases in inflammation.
- Stress in several domains is associated with immunological aging.
- Biological pathways connecting stress and immunological aging are reviewed.
- Protective factors include health behaviors, intra- and inter-personal resources.
- Future work on stress resilience and healthy immune aging may extend healthspan.

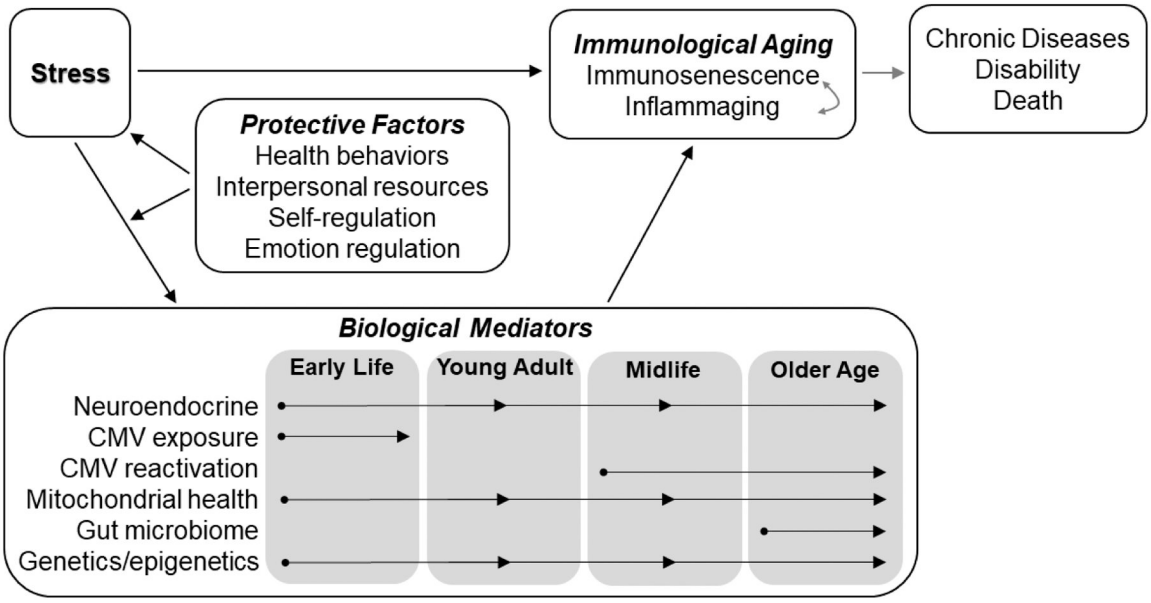

Figure 1.

Conceptual model depicting the focus of this review (particularly the associations shown in black arrows). Stress can influence immunological aging (and ultimately health outcomes) via biological mediators that may act at various lifespan stages, but several protective factors may moderate these associations.