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Neuroendocrine and viral correlates of premature immunosenescence

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Aging continuously remodels the immune system, a process known as immunosenescence. Here, we review evidence of premature immunosenescence in younger individuals under conditions of chronic psychological stress, chronic inflammation, or exposure to certain persistent viral infections. Chronic stress may accelerate various features of immunosenescence by activating key allostatic systems, notably the hypothalamic–pituitary–adrenal axis and increased cortisol levels. Chronic stress is associated with thymic involution, blunted T cell proliferation, increased serum proinflammatory markers, and shorter telomere lengths. Human cytomegalovirus (CMV) infection has been implicated in accelerating immunosenescence by shrinking the T cell receptor repertoire and causing clonal expansion of senescent $CD8^+CD28^-$ T cells with a proinflammatory profile. These factors increase inflammation associated with aging, or "inflammaging," particularly as it relates to etiology of several age-related diseases and increased mortality. Patients with rheumatoid arthritis have been shown to have several signatures of premature immunosenescence, including expansion of senescent T cells associated with cognitive impairment. We end by speculating that bipolar disorder can be considered as a model of accelerated aging because it has been associated with shortened telomeres, higher CMV IgG titers, and expansion of senescent and regulatory T cells.

Keywords: aging; immunosenescence; cytomegalovirus; lymphocytes; glucocorticoids; psychological stress

Introduction

Aging is a continuous, slow process that compromises the normal functioning of various organs and systems in both qualitative and quantitative terms. Over the last few decades, a growing body of literature has reported that aging remodels the immune system, a process known as immunosenescence. Human immunosenescence includes changes in cellular and molecular components of both innate and adaptive immune responses, frequently leading to overall poor immunity. However, not all components of the immune system age in the same way, at the same speed, or in the same direction.[1]

In the past, there was a general assumption that all immunological functions decreased during aging, but current knowledge clearly indicates that compensatory increases also occur over time. For instance, regarding innate immunity, most studies report increasing peripheral counts of natural killer (NK) cells in contrast to impaired cytotoxic function during aging.[2] Although previous studies reported increased innate functions of macrophages against pathogens in mice, such as chemotaxis, phagocytosis, and superoxide anion production,[3] studies of human monocytes and macrophages suggest that there is an age-associated impairment in these functions.[4] Decreased neutrophil functions, including impaired chemotaxis, intracellular bacterial killing, phagocytosis, and neutrophil extracellular trap formation, have been observed in both aging mice and humans.[4] Studies of antigen presenting cells generally show impaired functions with aging.[4] Interestingly, the increase in some innate functions reported in mice can be mediated by stress mediators, including glucocorticoids, noradrenaline, and eHSP72.[5,6] In addition, a low-grade inflammatory status has been observed during aging and was characterized by higher plasma levels of

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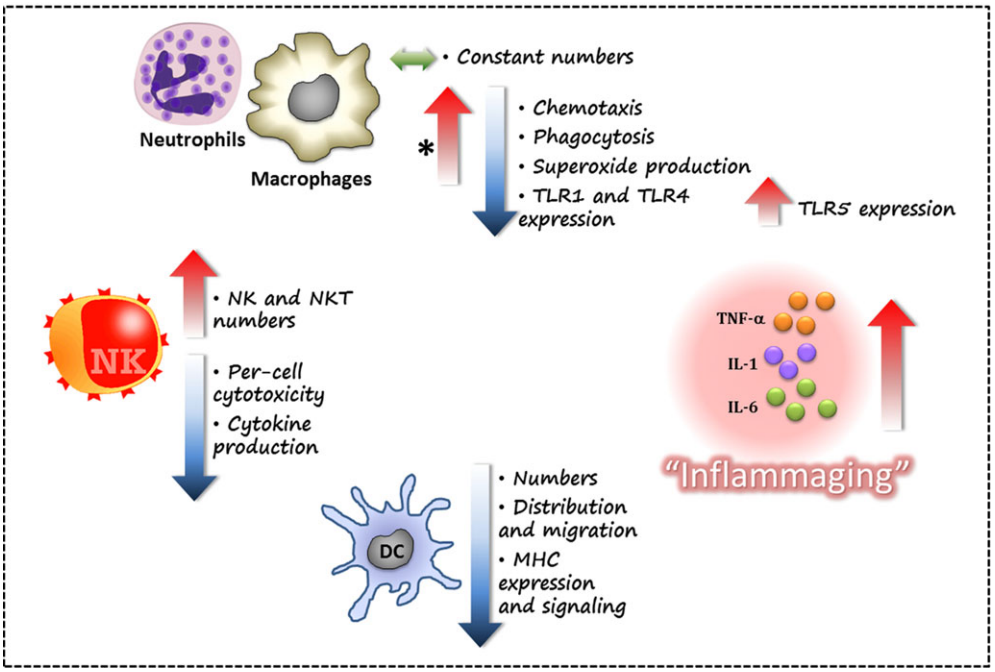

Figure 1. Senescence of the innate immune system. Aging continuously remodels the innate immune system, leading to important phenotypical and functional changes. Although constant numbers have been observed for neutrophils and macrophages, compensatory increases in natural killer (NK) cells and NK T cells have been reported. Although previous studies with mice reported increased innate functions of macrophages against pathogens, such as chemotaxis, phagocytosis, and superoxide anion production, studies of human monocytes and macrophages suggest that there is an age-associated impairment in these functions. In addition, several functional activities are impaired among innate immune cells, including reduced expression of Toll-like receptors (TLRs) by macrophages as well as low expression of major histocompatibility complex (MHC) by dendritic cells (DCs). Inflammaging, a concept of the aging innate system, is associated with a low-grade increase in proinflammatory cytokines and acute-phase reactants. The asterisk indicates changes reported in mice only.

proinflammatory cytokines (TNF-α, IL-6, IL-1), acute-phase proteins (C-reactive protein), and soluble IL-2 receptors.[7,8] This phenomenon was termed *inflammaging* and has repeatedly been associated with increased morbidity and mortality during aging. Figure 1 summarizes current concepts related to aging of the innate immune system, highlighting human senescence.

In addition to innate immunity, the adaptive immune system (i.e., B and T cells) is particularly targeted and remodeled during aging (Fig. 2). Peripheral T cells develop key phenotypical and functional changes during aging even though the total size of the T cell pool remains roughly the same as one ages. Mammalian aging is associated with progressive thymic involution (3% per year) and, consequently, reduced thymic export of naive T cells ($CD45RA^+$).[9] In parallel, possibly as a compensatory mechanism, there is an age-related expansion of memory T cells ($CD45RO^+$). In addition, there is an age-related reduction of T cell proliferation, defects in intracellular signaling, impaired cytotoxicity, expansion of late-differentiated or senescent T cells ($CD28^-$), reduced NK T (NKT) cells, changes in cytokine production, and profound shrinkage of the T cell receptor (TCR) repertoire.[1,10] Strikingly, after 65 years of age, there is contraction of 99% of the TCR diversity, drastically limiting the recognition of new antigens by T cells. Indeed, although the antibody responses to recall antigens are preserved during aging, the humoral responses to new antigens, dependent on T cell help, are impaired in older adults. During aging, there is a benign $CD8^+$ T cell clonal expansion specific to persistent viral infections, further contributing to a diminished repertoire.[1]

Of clinical importance, human immunosenescence has been implicated with an age-related

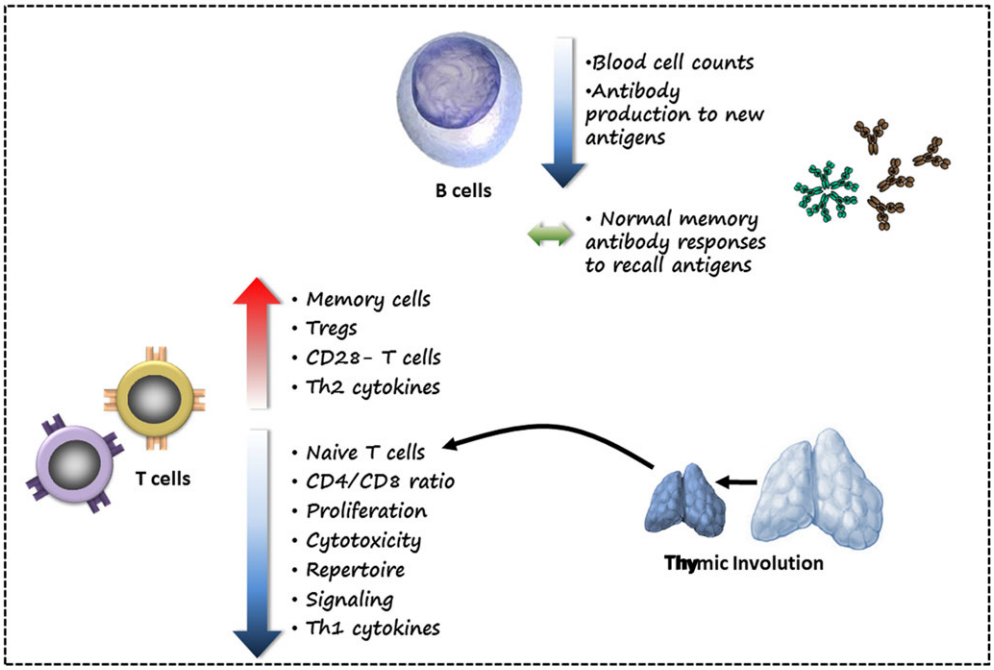

Figure 2. Senescence of the adaptive immune system. The adaptive immune system is particularly targeted and remodeled during aging. Age-related thymic involution is associated with important phenotypical cellular changes, including a drop in naive (CD45RA) cells and an accumulation of memory (CD45RO) T cells in the circulation. Expansion of regulatory T (T_{reg}) cells and senescence-related ($CD28^-$) T cells are observed during aging in contrast to reduced functional responses, such as impaired T cell proliferation, cytotoxicity, and lower production of T_H1-type cytokines. Antibody production to new antigens is significantly impaired during aging, a phenomenon associated with impaired T cell help. In contrast, normal memory antibody responses to recall antigens are observed during aging.

increase in susceptibility to infectious diseases, neoplasias, metabolic diseases, psychiatric disorders (major depression, bipolar disorder (BD)), cardiovascular disease, neurodegeneration, cognitive impairment, arthritis, type II diabetes, osteoporosis, and frailty.[8] The increasing age-related morbidity, however, is not evenly distributed and seems to be influenced by other immune-modulating factors. Indeed, the speed of an individual's biological clock depends on the important interaction between genetic inheritance and environmental factors.

In addition to occurring during normal aging, premature immunosenescence may also occur in younger individuals. Here, we review evidence that neuroendocrine hormones elicited by psychosocial stress, chronic inflammation (as observed in arthritis and some psychiatric disorders), and certain persistent viral infections may lead to premature human immunosenescence and earlier onset of many age-related diseases. We also speculate that BD, because of several features that resemble aging, might be considered as a model for accelerated aging.

Psychosocial stress leads to premature immunosenescence

Several findings from studies published in the last decade have indicated that human aging is normally associated with increasing psychological morbidity (distress) and stress-related physiological changes. Indeed, we have previously shown that strictly healthy elderly subjects were more stressed, anxious, and depressed than young adults.[11] The healthy older adults had higher cortisol (45%) but lower dehydroepiandrosterone (DHEA, 54%) levels (as measured in saliva) compared to young adults,[11] suggesting a neuroendocrine imbalance of the hypothalamic–pituitary–adrenal (HPA) axis. Increased cortisol levels were associated with a reduction in naive T cell numbers and reduced

T cell proliferation during healthy aging.[12] These neuroendocrine changes may contribute to immunosenescence owing to the fact that all leukocytes express glucocorticoid receptors and are therefore responsive to neuroendocrine products.

Because these neuroendocrine changes may result in enhanced exposure of lymphoid cells to the deleterious actions of high levels of glucocorticoids, it follows that altered neuroendocrine functions could underlie several features of immunosenescence.[13] Indeed, changes in both innate and adaptive immune responses during aging are also similarly reported during chronic glucocorticoid exposure.[13] Furthermore, the immunosenescence described during healthy aging is found to occur at a similar magnitude following chronic stress or glucocorticoid exposure.[13] Indeed, during aging, stress conditions, and chronic glucocorticoid exposure, the following changes are all similarly found: thymic involution and a related drop in naive T cell export from the thymus, increased memory and regulatory T (T_{reg}) cells, a T_H1 to T_H2 cytokine shift, reduced cell-mediated immunity (e.g., blunted T cell proliferation), restricted TCR$\alpha\beta$ repertoire in $CD4^+$ and $CD8^+$ T cells, increased serum proinflammatory markers (inflammaging), and shorter telomere lengths.[13]

Superimposing chronic stress on aging has been associated with premature immunosenescence and further activation of the HPA axis.[14] Elderly caregivers of spouses with dementia represent a model to study the superimposed (and detrimental) effects of chronic psychological stress on immunosenescence. Caregiving for the first-grade elderly relative with dementia is a demanding task associated with increased stress, anxiety, depression, and notably suppressed immune functions.[15] A longitudinal study showed that caregivers had an increased mortality rate (>63%) compared to nonstressed controls.[16] In other studies, chronically stressed individuals (including older adults) frequently reported poor immune responses, especially those functions associated with the adaptive immune system (reviewed in Ref. 17). These associations may be explained by accelerated aging of several lymphoid organs and key immunological functions.[18] Caregiving for a chronically ill partner (stroke or dementia) is associated with increased susceptibility to upper respiratory infections, including influenza,[19] and reduced immune responses to pneumococcal pneumonia vaccines.[20] Elderly caregivers of Alzheimer's disease patients have been shown to have impaired T cell proliferation,[14] reduced NK cell activity,[21] and reduced IL-2 production,[14] in contrast to higher TNF-α, IL-10,[22] and IL-6 levels.[23] The psychological stress may lead to an increased proinflammatory profile owing to upregulation of key transcriptional factors involved in triggering inflammation. Previous studies have reported that exposure of young adults to acute psychosocial stress induced significant upregulation of NF-κB in peripheral blood mononuclear cells (PBMCs).[24] Similarly, cells of chronically stressed elders showed increased expression of NF-κB compared to nonstressed controls.[25] Stressed elderly people may thus be at risk for the development of stress-related pathologies because of detrimental additive effects of stress on the aged immune system. Indeed, higher plasma levels of proinflammatory cytokines (e.g., TNF-α, IL-1, and IL-6) observed in stressed elderly individuals are, importantly, related to increased morbidity and mortality during aging.[26] In addition, chronic psychological stress has been correlated with increased oxidative stress, reduced telomerase activity, and shorter telomere length, further indicating accelerated cell senescence, which could be implicated with reduced longevity.[27]

Taken together, these data indicate that stress-related factors, notably cortisol and DHEA, are important pacemakers of immunosenescence. Recent studies also indicate that some chronic persistent viral infections may be considered another source of premature immunosenescence, as discussed further below.

Cytomegalovirus as a driving force of accelerated T cell aging

Human cytomegalovirus (CMV) is a ubiquitous β-herpesvirus associated with an increased age-related prevalence, ranging from 40% (18–24 years old) to over 90% (75–80 years old).[28] In most cases, the CMV promotes a latent asymptomatic infection; but it has also been associated with chronic infection—conditions including atherosclerosis, autoimmune disorders, periodontitis, and inflammatory bowel disease.[29,30] CMV can promptly reactivate from latency when immunity is suppressed, indicating that constant immune surveillance is necessary to prevent viral reactivation. During aging, subclinical CMV reactivation has been associated with

increased CMV IgG titers. Psychological stress (as observed in healthy elderly subjects) has been identified as an important factor that may drive CMV reactivation, representing a potential mechanism linking stress, immunity, and aging.

Recent studies on aging have indicated that CMV is importantly involved with several signatures of accelerated immunosenescence. Of note, CMV has been associated with reduced T cell repertoire, reduced B cell numbers, and increased plasma IL-6 levels.[31] Importantly, CMV plays a pivotal role in driving expansion of late-differentiated $CD8^+CD28^-$ T cell numbers during aging, an expansion known as "memory inflation."[1] CD28 is the main costimulatory receptor expressed by T cells,[32] and its expression is necessary for full T cell activation and proliferation after stimulation; loss of CD28 expression on T cells has a major impact on their function.[33] It is believed that $CD8^+$ T cells downregulate CD28 expression after several rounds of proliferation (i.e., replicative senescence); $CD8^+CD28^-$ T cells are resistant to apoptosis, have short telomeres, and proliferate poorly.[34,35] Peripheral T cells lacking CD28 include effector-memory and terminally differentiated memory cells re-expressing CD45RA (TEMRA), which may contribute to inflammaging by secreting large amounts of IFN-γ, TNF-α, IL-1β, and IL-6 upon stimulation.[1]

There is a price to be paid for the constant immune surveillance necessary to keep the CMV infection under control. In elderly individuals, as many as 50% of $CD8^+$ and 30% of $CD4^+$ T cells are CMV specific, at the expense of a highly diversified naive/memory T cell repertoire.[36] In an example of a clinical consequence of such a reduction in the T cell repertoire, the impaired vaccine responses observed in the elderly have been related to an increased CMV-specific $CD8^+$ T cell clonally expanded pool and a concomitant decrease in naive T cell diversity.[37] Conversely, very old individuals exhibited smaller T cell responses to CMV and showed a loss of certain T cell clonotypes that can respond to the virus.[38] Therefore, survival into very old age is accompanied by an immune system less engaged in dealing with persistent viral infections.

CMV has been associated with an increased risk of developing important age-related diseases, including cardiovascular disease[39] and type II diabetes.[40] Previous Swedish longitudinal OCTO and NONA studies have identified CMV seropositivity as part of an immune risk profile associated with increased mortality and characterized by an inverted CD4/CD8 ratio owing to accumulation of $CD8^+CD28^-$ T cells.[41] We have recently investigated the role of herpesvirus infections and cognitive and functional states as predictors of the inverted CD4/CD8 ratio in healthy older adults (mean age: 67 years).[42] Elderly subjects identified with an inverted CD4/CD8 ratio were found to have increased CMV serology (but not an increased serology for another herpesvirus, Epstein–Barr virus) and poor cognitive and functional states.[42] Interestingly, increased CMV IgG titers alone contributed to an eightfold higher chance of inverting the CD4/CD8 T cell ratio. We also observed in work in progress expansion of $CD8^+CD28^-$ T cell populations in parallel with very low expression of helper T cell canonical transcription factors T-bet (T_H1), GATA3 (T_H2), and RORγt (T_H17), but not T_{reg} cell–associated FoxP3 in older adults with an inverted CD4/CD8 cell ratio (Ornagui *et al.*, unpublished data). These preliminary data further suggest that an immune profile previously identified in very old subjects also exists in hexagenerians.[43] A previous longitudinal study indicated that CMV^+ American older adults have a greater incidence of frailty and increased risk of 5-year mortality compared to CMV-seronegative subjects.[44]

Overall, these data highlight the role of CMV in accelerating immunosenescence by shrinking the TCR repertoire and clonally expanding $CD8^+CD28^-$ T cell numbers with a proinflammatory profile. We next investigated whether chronic inflammatory conditions are associated with premature immunosenescence. We follow that by a more speculative discussion of bipolar disease and chronic low-level inflammation.

Chronic inflammation and premature aging

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease with signatures of premature immunosenescence.[45] We recently reported several accelerating aging signatures in peripheral lymphocyte subsets in adults with controlled RA.[46] These alterations included a significant drop in $CD3^-CD19^+$ B cells (–41%), expansion of $CD4^+$ $CD25^+FoxP3^+$ regulatory T cells (73%), as well as senescent $CD4^+CD28^-$ (81%) and $CD8^+CD28^-$ (38%) T cells.[46] Several studies have reported a

contributing role of $CD28^-$ T cells in the pathogenesis and extra-articular manifestations of RA, including impaired cognitive performance. We recently reported that RA patients with lower scores in cognitive tasks had greater numbers of $CD8^+CD28^-$ T cells than age-matched controls.[46] As previously discussed, CD28 is lost after replicative senescence, but this loss can also occur under proinflammatory conditions, such as in the presence of TNF-α.[47] $CD4^+CD28^-$ T cell clones from RA patients are consistently autoreactive, produce large amounts of IFN-γ, and express killer immunoglobulin receptors, which are known signatures of premature immunosenescence.[48] Furthermore, supporting a model of premature senescence, previous studies have investigated T cell β-chain sequences in $CD4^+$ T cells of RA patients and found a 10-fold contraction in T cell diversity/repertoire.[48]

An important marker of cellular senescence is the length of telomeres, which are sequences located at the chromosome end that progressively erode with each division cell cycle. In RA, telomere shortening has been observed in both hematopoietic progenitor cells (HPCs) and in peripheral lymphocytes.[49,50] The HPCs of young adults (20–30 years old) with RA had telomeres shortened to the same magnitude as found in healthy adults of 50–60 years of age.[49] In accordance, $CD4^+$ T cells of patients with RA showed reduced median length telomere compared to healthy controls.[50] In addition, a previous study with a large cohort of RA patients indicated that telomere attrition occurred independently of disease severity and duration.[51] Telomere shortening may occur as a consequence of homeostatic proliferation or deficiency of telomerase activity, the enzyme responsible for the maintenance of the telomeric structure.[52] T lymphocytes, unlike other cells, are capable of reactivating telomerase, increasing their life span.[48] However, in RA the telomerase activity seems to be insufficient for maintaining the longevity of T cells.[52]

In addition, RA has been related to the early development of common conditions of aging, such as osteoporosis[53] and cardiovascular diseases.[45] Proinflammatory cytokines, mainly TNF-α, are involved in modulating the balance between bone-forming and bone-resorbing mechanisms. The increased vascular injury is mainly owing to the action of proinflammatory cytokines in combination with cytotoxic T cells targeting the vascular endothelium.[45] Furthermore, the expansion of $CD28^-$ T cell numbers was correlated with vascular damage observed in these patients.[54] Taken together, these data demonstrate that RA is a disorder characterized by premature aging of the immune system and early onset of common age-related diseases.

BD: a possible model of accelerated aging

BD has been recently hypothesized to be an accelerated aging disorder.[55] BD is characteristically a cyclic disease with alternate depressive mood and manic mood episodes. Owing to its biphasic nature, BD was considered a chronic stressor that results in several detrimental stress-related effects, including neurological and immunological changes, that resemble those found during healthy aging. Indeed, there are several characteristics shared by BD and aging. For example, BD and aging present with many neurological alterations, at both structural and functional levels. Among these alterations are brain atrophy, gray matter reductions in areas such as the prefrontal cortex, and increases in the size of the amygdala.[56] Neuropathological studies indicate neuroplasticity and connectivity deficits. In addition, cognitive impairment is also characteristic of both aging and BD. Of note, verbal working memory, response inhibition, sustained attention, psychomotor speed, abstraction, and set shifting are the cognitive domains and functions with marked impairments in BD.[57] Both functional and neuroanatomical changes worsen with BD disease progression and the number of different episodes.[58] Concomitantly, lower levels of neurotrophins, especially brain-derived neurotrophic factor (BDNF), have been reported for both BD and aging. While healthy aging is associated with a normal reduction in BDNF levels, in BD individuals these levels have been shown to be influenced by age and by length of illness.[59]

Similar to aging, BD has been associated with an important immune imbalance toward low-grade inflammation.[60,61] While the underlying mechanisms involved with the low-grade inflammatory status are largely unknown, expansion of peripheral-activated T cells, low T_{reg} cell numbers, and activation of intracellular signaling cascades (i.e., MAPKs, NF-κB) have been reported in BD patients.[62–64] The occurrence of low-grade inflammation in BD might be considered a form of premature inflammaging, as it has been associated with

comorbidities normally found in older adults, such as cardiovascular disease, functional impairment, and poor cognition.[65]

Another feature shared by aging and BD is premature cellular immunosenescence. Recently, a significant expansion of $CD8^+CD28^-$ T cell numbers in parallel with shortened telomere length in PBMCs were observed in type I bipolar patients compared to healthy controls.[63,66] Interestingly, patients also were shown to have higher anti-CMV IgG levels compared to healthy controls,[66] and the shortened telomere length was inversely correlated with CMV serology.[66] Therefore, we speculate that increased allostatic load in BD may lead to higher CMV reactivation, expansion of senescent $CD8^+CD28^-$ T cells, and telomere shortening. In addition, CMV may drive a systemic proinflammatory state in BD by inducing production of prostaglandin E2 in human fibroblasts, along with the major CMV envelope glycoprotein (gB) upregulating the expression of NF-κB, a key transcription factor for proinflammatory genes.[67] Therefore, the CMV infection may be a driving force in the process of early immunosenescence in BD. Future studies should address the clinical significance of these findings in a prospective setting.

Similarly to major depression, neuroendocrine alterations have been reported in BD. A recent meta-analysis reported increased morning cortisol levels in BD patients compared to controls, indicating altered basal HPA axis activity.[68] Similarly, Dettenborn *et al.* reported that unipolar depressed patients present with higher levels of hair cortisol than healthy controls.[69] Conversely, a recent study by Wieck *et al.* demonstrated that BD patients were hyporesponsive to acute stress exposure, with blunted cortisol secretion compared to healthy controls, indicating impairment in HPA axis regulation.[64] Interestingly, the functional impairment of the HPA axis was associated with exaggerated inflammatory responses. Similarly, patients with major depression or posttraumatic stress disorder and individuals exposed to childhood emotional abuse had blunted stress responses and higher circulating inflammatory mediators compared to healthy, nondepressed individuals.[70,71] A previous meta-analysis revealed that clinical severity in depression was related to blunted cortisol levels in response to stress.[72] Similar findings were observed in patients with burnout syndrome, associated with chronic stress, describing important inverse correlations between clinical severity and blunted salivary cortisol levels in response to acute stress exposure.[73] Taken together, the several age-related changes reported in BD suggest that this psychiatric disorder may be considered to be a new model of accelerated aging. This new understanding brings insight to novel therapy approaches, including the use of anti-inflammatory medications and stress-management interventions. Indeed, nonsteroidal anti-inflammatory drugs and monoclonal antibodies targeting inflammatory cytokines have been proven useful in treating major depressive disorder.[74]

Conclusions and future perspectives

Premature immunosenescence may occur in young subjects, especially under conditions of chronic stress, such as that which occurs in BD or RA patients and during certain persistent viral infections (e.g., CMV). The clinical consequences are the early onset of several age-related diseases and increased mortality.

Immunosenescence includes remodeling changes in cellular distribution and functional aspects of the immune system. T cells are particularly targeted during aging, and several changes in T cell subsets have been observed, notably, expansion of late-differentiated senescent $CD28^-$ T cells and shrinkage of the TCR repertoire. These changes have been associated with increased CMV serology and increased numbers of CMV-specific T cells with a senescent phenotype. Another key feature of immunosenescence is inflammaging, which is associated with chronic low-grade inflammation, age-related diseases, and increased mortality during aging. Healthy elderly subjects, in the absence of any clinical condition, were found to be psychologically stressed and had higher levels of stress mediators (cortisol) as compared to healthy young adults.[11] Glucocorticoids have many immunoregulatory properties, and immune changes reported during aging are also similarly reported during chronic glucocorticoid exposure.[13] Chronically stressed elders show many features of accelerated adaptive and innate immune senescence, indicating the superimposing impact of stress during aging. Furthermore, patients with RA had several signatures of premature immunosenescence, including expansion of senescent T cells, which are associated

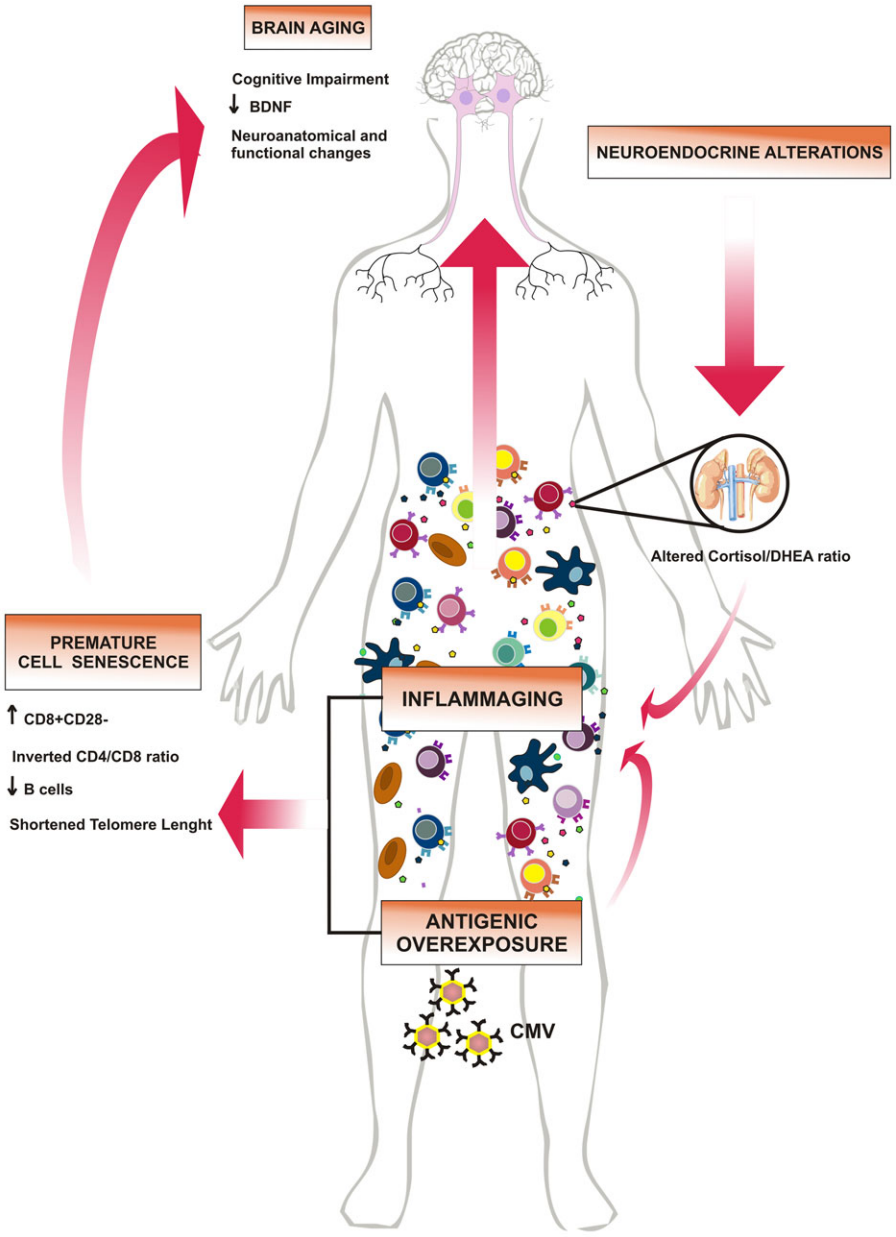

Figure 3. Major biological changes supporting premature senescence in bipolar disorder, rheumatoid arthritis, and chronic stress. A neuroendocrine imbalance promoted by psychosocial stress (i.e., increased cortisol/DHEA ratio), chronic inflammation (as observed in arthritis and bipolar disease), and cytomegalovirus (CMV) infection may lead to premature immunosenescence and earlier onset of many age-related diseases. Arrows indicate potential underlying causal relationships of premature senescence.

with marked cognitive impairment.[45,46] Because of many of its clinical features—association with shortened telomeres, higher CMV IgG titers, and expansion of senescent and regulatory T cells—BD might be considered as a model of accelerated aging. Figure 3 shows major biological changes similarly observed in BD, RA, and chronic stress, indicating features of premature senescence.

The immune system is plastic and thus can be modified during aging. It may be possible to

attenuate and potentially reverse many features of immunosenescence via stress-management therapies, improved health-related behaviors, and hormone-replacement therapies.[75] Furthermore, low-cost practices, including moderate regular exercise and micronutrient and antioxidant supplementation, may also be beneficial for aging healthily by attenuating the effects of immunosenescence.[6] Finally, interventions aimed at attenuating inflammation and preventing CMV reactivation may be of great value for promoting health aging.

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Conflicts of interest

The authors declare no conflicts of interest.

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