Aging of the Immune System as a Prognostic Factor for Human Longevity

Accumulating data are documenting an inverse relationship between immune status, response to vaccination, health, and longevity, suggesting that the immune system becomes less effective with advancing age and that this is clinically relevant. The mechanisms and consequences of age-associated immune alterations, designated immunosenescence, are briefly reviewed here.

Human Longevity, Genetics, and Inflammation

Average life expectancy at birth of Homo sapiens did not exceed 40–45 years until a couple of centuries ago even in the most developed countries, although the survival of a small number of very old people even in “primitive” societies is well documented. However, aging of a large proportion of the population is a very recent phenomenon that emerged as a consequence of the reduction of infant mortality and improving medical care and environmental conditions (127). Infectious diseases have been a pervasive threat for survival throughout evolution; thus strong immune responses and inflammation in early life have played a major role in the survival of humans in the unforgiving environment that was common to our ancestors. Accordingly, we can assume that genes and gene variants associated with strong immune responses and inflammation have been positively selected, because they likely contributed to ensure survival to reproductive age. Indeed, studies on the evolution of the immune system indicate that stress responses, immunity, and inflammation are deeply interconnected and constitute an integrated network of defense capable of coping with most stressors, including microbial antigens (37, 79).

On this evolutionary background and on the basis of data collected in the last 15 years on centenarians and from longitudinal studies of free-living humans, two of the best models to study healthy aging and longevity in humans (34, 78), we argue that lifelong exposure to a “primitive” society is well documented. However, aging of a large proportion of the population is a very recent phenomenon that emerged as a consequence of the reduction of infant mortality and improving medical care and environmental conditions (127). Infectious diseases have been a pervasive threat for survival throughout evolution; thus strong immune responses and inflammation in early life have played a major role in the survival of humans in the unforgiving environment that was common to our ancestors. Accordingly, we can assume that genes and gene variants associated with strong immune responses and inflammation have been positively selected, because they likely contributed to ensure survival to reproductive age. Indeed, studies on the evolution of the immune system indicate that stress responses, immunity, and inflammation are deeply interconnected and constitute an integrated network of defense capable of coping with most stressors, including microbial antigens (37, 79).

On this evolutionary background and on the basis of data collected in the last 15 years on centenarians and from longitudinal studies of free-living humans, two of the best models to study healthy aging and longevity in humans (34, 78), we argue that lifelong exposure to a variety of infectious agents for a period much longer than previously encountered during human evolution (chronic antigenic load) is a major influence driving the aging of the immune system (33, 85). “Immunosenescence” is the term coined for the age-associated decreased immune competence that renders individuals more susceptible to disease and increases morbidity and mortality due to infectious disease in the elderly compared with the young (18, 42, 60, 85, 123). The nature of immunosenescence will be discussed in the next section. The main observed result at old age is a decrease in adaptive immunity and increased low-grade chronic inflammatory status, which has been referred to as inflamm-aging (32), a process that impacts on the internal milieu of the body by changing its composition over time (27) (change not only of the immune cells but also of their “microenvironment”). Within this perspective, chronic antigenic load and inflamm-aging are strong candidates as major driving forces of the rate of aging and of the pathogenesis of major age-related diseases (16, 17, 119). Inflamm-aging is the end result of such a process characterized by activation of macrophages and expansion of specific clones (megaclones) of T lymphocytes directed toward antigens of common viruses such as cytomegalovirus (CMV) or Epstein-Barr virus (EBV) (FIGURE 1; Refs. 31, 49, 81, 85, 116). All these phenomena have a strong genetic component, as shown by studies in old people and centenarians, which collectively established that the frequency of several variants (polymorphisms) of important genes involved in immune responses and inflammation are present at a different frequency in long-lived people compared with young subjects (FIGURE 1; Refs. 23, 41, 96, 97, 116). Within this scenario, the age-related changes in body composition (loss of muscle/bone mass and increase of fat mass) (84), insulin growth factor 1/insulin pathway (36), as well as inflammatory phenomena occurring in the central nervous system are also emerging as critical influences on the development of frailty and major age-related diseases (59, 121, 124).

The genetics of aging and longevity are quite unusual and have specific and unexpected peculiarities (15). First, for example, the same gene polymorphism can have different (beneficial or detrimental) effects at different ages, a phenomenon we proposed calling “complex allele timing” (15). Indeed, gene variants that are apparently neutral at young age show a greatly different biological role at old and very old age in terms of phenomena such as apoptosis, cell proliferation, and cell senescence. This is the case for a common polymorphism at codon 72 of the TP53 gene encoding p53,
a protein playing a crucial role in DNA repair, apoptosis, cell cycle arrest, and senescence. This substitution of arginine (Arg) for proline (Pro), located in the polyproline-rich domain, modulates cell growth arrest and activation of apoptosis and has been studied in relation to cancer biology and extreme longevity (113). The Arg variant is associated with a higher susceptibility to oxidative stress-induced apoptosis, whereas the Pro variant is associated with a higher tendency to cell cycle arrest and senescence. However, this applies only to cells from old donors in whom it becomes progressively more evident with age but is not seen in young donors’ cells (7). Second, an increased homozygosity, likely correlated with the profound age-related remodelling, has been found at several polymorphic sites in DNA from old people and centenarians (contrary to the accepted advantage of heterozygosity for survival at younger age) (10, 15). An example is the recent identification and characterization of a previously “anonymous” inter-Alu polymorphism associated with human longevity as a TG/CA microsatellite in the fourth intron of the YTHDF2 gene. Genotyping a total of 285 subjects of different ages (17-109 years) revealed that a significant increase of homozygosity was found in centenarians (10).

Recent methodological improvements have led to a better understanding of the genetic basis of immunosenescence. Using recombinant inbred mice, it is possible to detect quantitative trait loci (QTLs) that underlie age-related thymic involution. Approaches have been developed to enable higher resolution mapping of these QTLs and to carry out direct identification of candidate genes. It is likely that, given the complexity of immune system development, the number of cells involved in an immune response (and especially the changes in the immune system with aging), multiple genetic loci, and many genes will contribute to age-related changes in immunity (46). Furthermore, recent studies investigating the molecular mechanisms associated with thymic aging showed the necessity of taking biological variables such as gender and diet into account when studying the role of genomics in the molecular pathways responsible for thymic involution (62). The use of model organisms facilitates testing different hypotheses regarding the role of genetics in immune responses. Using several chromosome substitution lines of Drosophila melanogaster derived from a natural population, Lesser et al. (58) found significant genetic variation among lines in the immune response to E. coli, showing improvement, no change, or a decline with age. Overall, their data suggest that different loci contributed to variation in immune responses at each age, consistent with the mutation accumulation model of senescence. In mice, following LPS challenge, it was found that 500 genes were activated in macrophages from young and old individuals, but more than 150 were activated only in the old or only in the young (12).

Even if we still do not know how general these phenomena (complex allele timing and age-related increase of homozygosity) can be, it is reasonable to envisage that the genetics of longevity is likely much more complex than previously anticipated.

Centenarians are able to counteract the damaging effects of Inflamm-aging by activating a variety of anti-inflammatory networks, such as those involving interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), but still benefit from the action of immunity necessary to maintain health by resisting infectious disease (27, 114).

Thus centenarians are equipped with gene variants that allow them to optimize the balance between pro- and anti-inflammatory cytokines and other mediators involved in inflammation (11, 35). Indeed, genetic markers related to a pro-inflammatory phenotype associated with the major age-related diseases have been found to be underrepresented in centenarians, whereas those associated with anti-inflammatory activity are more highly represented in centenarians, confirming that the balancing of pro- and anti-inflammatory mechanisms during aging is largely under genetic control (114). Accordingly, it can be anticipated that a genetic propensity to produce excessive amounts of inflammatory factors associated with an insufficient anti-inflammatory response will play a major role in the development of frailty and age-related pathologies in later (post-reproductive) life, despite being protective in earlier (reproductive) life.
Immunosenescence and Inflamm-aging, by intimately changing the body microenvironment, have systemic effects on a variety of organs and systems and must be envisaged and conceptualized within a broad perspective, such as that proposed by Systems Biology, an approach that can help us to grasp its complexity and possibly to formulate rational anti-immunosenescence strategies (9, 106). To this end, an overview of the multiple facets of immunosenescence will be given in the next section on age-related changes in innate and adaptive immune functions.

First Line of Defense: Innate Immunity

Immunosenescence is the name given to the global age-associated immune dysfunctions (23, 33, 42, 51, 82). There are several hypotheses to explain the aging process; the same is true for immunosenescence (41, 85). Virtually all cells of the immune system can undergo immunosenescence, which can lead to the general erosion of the immune capacities. Different animal (4, 38) and in vitro models (75, 86) substantiate the existence of immunosenescence in humans. Although it has been generally accepted that some aspects of innate immunity are well preserved in aging (87, 100), cumulative evidence in the last decade supports the existence of age-associated changes in the cellular components of the innate immune system, including natural killer (NK) cells, phagocytes, and dendritic cells (DC), which are important in the increased susceptibility of elderly individuals to infectious diseases.

**NK cells**

NK cells are cytotoxic cells that play a significant role in innate defense against virally infected cells and possibly tumors, and recent studies support the hypothesis that high NK cytotoxicity associates with healthy aging and longevity, whereas low NK cytotoxicity associates with increased morbidity and mortality due to infections, atherosclerosis, and poor response to influenza vaccination (FIGURE 2; Refs. 8, 72, 99, 76). Inefficient signal transduction was found to be associated with decreased NK cell cytotoxicity in the aged (65, 99). For example, it has been shown that the CD94-NKG2A inhibitory signaling pathway is intact in NK cells from elderly individuals despite a decrease in CD94-NKG2A expression (63), suggesting an increased inhibitory signaling efficiency and decreased activating signaling at the cellular level. Moreover, the expression of killer-inhibitory receptors (KIR), which are more specific to NK cells, was shown to increase in aging (110). NK cells express a complex array of activating and inhibitory receptors, detailed knowledge of which is just now emerging, which is required to form a clear idea of the role of changes in NK cells in the elderly (8, 63, 99). So far, only one study has established the frequency of the KIR genes/pseudogenes and KIR genotypes in healthy aged and young people (in the Irish population). However, no significant associations between KIR gene expression and aging were found. It is hypothesized that alterations of KIR functions may increase susceptibility to infections or cancers, and thus a similar study needs to be performed in non-healthy, old individuals compared with healthy individuals (67).

Other aspects of NK cell function, such as the secretion of chemokines or interferon-γ (IFN-γ) in response to IL-2 are also decreased in the aged (66). NK cells have an important role in immuno-surveillance, and any alterations in their function will influence susceptibility to pathogens and the control of cancer development (77).

**Neutrophils**

The number and phagocytic capacity of neutrophils is well preserved in the elderly. However, certain other functional characteristics of neutrophils from elderly individuals, such as superoxide anion production, chemotaxis, and apoptosis in response to certain stimuli, are reduced (FIGURE 2; Ref. 40). It has been suggested that a decrease in signal transduction of certain receptors could be involved in the defective function of neutrophils with advancing age (30). In particular, the triggering of activating receptors such as Toll-like receptor-4 (TLR4), granulocyte macrophage colony...
stimulating factor (GM-CSF), and triggering receptor expressed on myeloid cell-1 results in a decreased response in elderly individuals associated with altered signal transduction and changes in the structure, dynamics, and function of lipid raft-dependent signaling in these cells (28, 107). Similarly, anti-apoptotic signals delivered by GM-CSF failed to rescue neutrophils from apoptosis in the elderly (29).

**Monocytes/macrophages**

The number of monocytes in peripheral blood does not change substantially with age, although there is a decreased number of macrophage precursors and bone marrow macrophages (90). In macrophages, phagocytosis, production of reactive oxygen species, chemotaxis, and response to TLR function are altered with aging (42, 90). A recent evaluation of TLR expression and function in monocytes from older adults concluded that TLR1/2 function is altered probably due to defects in signaling (FIGURE 2; Ref. 112). These consequences of aging on human TLR expression and function may impaire activation of the immune response and contribute to poorer vaccine responses and greater morbidity and mortality from infectious diseases in older adults. The reduction of class II major histocompatibility (MHC) expression is thought to be responsible for decreased antigen presentation by macrophages with age (44, 90, 117). The hyper-production of prostaglandin E2 by activated macrophages at least partly explains the reduced surface expression of class II MHC (90).

**Dendritic cells**

Dendritic cells (DC) are the major antigen-presenting cells (APC) responsible for initiating an adaptive immune response. It has been shown that DC retain their antigen presentation function with healthy aging (61), whereas DC from frail elderly people display changes in costimulatory molecules (FIGURE 2; Ref. 1). Moreover, aging is associated with a reduction in the number of DC derived from myeloid precursors (18), which also have a more mature phenotype and an impaired ability to produce IL-12 with age (17, 108). Other functions such as macrophagocytosis, endocytosis, response to chemokines, and cytokine secretion are impaired, probably as a consequence of decreased activation of the phosphoinositide-3 kinase pathway (2). Together, these data suggest that some age-associated immune dysfunctions can originate from impaired DC functions.

**Other cells**

Other cells participating in innate immunity also need further investigation to fully understand the role of each and the biological significance of any age-associated alterations. Natural killer T (NKT) cells that express a CD1d-restricted T-cell receptor (TCR) have a semi-invariant TCR using the Vα24Jα18 genes in humans and are therefore termed invariant NKT (iNKT) cells. These cells have been implicated in diverse immune reactions, ranging from self-tolerance and development of autoimmunity to responses to pathogens and tumors. Recent studies showed a reduced number of iNKT cells with aging (72, 89), suggesting their contribution to decreased protection against certain pathogens such as gram-negative bacteria (125).

**Lymphocyte Senescence**

**Longevity and lymphocytes: what we learned from longitudinal studies**

The OCTO and NONA immune longitudinal studies represent population studies of Swedish octo- and nonagenarians to establish predictive factors for longevity (123) in the context of functional and disability parameters also measured in these studies. The OCTO immune study identified an immune risk profile (IRP) predictive of subsequent mortality (FIGURE 3). The IRP was characterized by immune parameters consisting of high levels of CD8+ T cells, low levels of CD4+ T cells and CD19+ B cells, an inverted CD4-to-CD8 ratio, and poor proliferative response to concanavalin A (26). In the subsequent NONA study, the IRP included characteristics of immunosenescence, recognized as increased numbers of late differentiated memory and effector CD8+CD28– T cells and depleted numbers of naive cells that are able to recognize and combat new antigens (FIGURE 3; Ref. 121). Extensive analysis to search for associations between this IRP and various psychosocial parameters revealed that the IRP was associated only with evidence of persistent CMV infection, becoming prevalent in the very old (78, 121). Therefore, CMV seems to have a more insidious impact on the immune system than previously believed and also compared with other herpes viruses examined in these studies (78). The accumulation of large numbers of CMV-specific CD8+ T cells (122), as well as the finding that a majority of clonal expansions...
in the very old are associated with CMV, has provided additional support for the hypothesis that CMV contributes markedly to the development of an IRP and thus constitutes a good biomarker of immunosenescence in the elderly (81, 93).

The increase in circulating inflammatory mediators such as cytokines and acute phase proteins seems to contribute to the low-grade inflammation observed with aging. Age-related alterations in responses to stimulation also contribute to low-grade inflammation by changing the level of pro-inflammatory mediators such as TNF-α and IL-6. Because of their association with pathological cases and chronic diseases, inflammatory mediators can also act as biomarkers or risk factors for age-associated diseases and predictors of mortality (reviewed in Ref. 52). In the NONA immune study, the IRP was also examined in the context of low-grade inflammation (124). The IRP and low-grade inflammation were found to be major independent predictors of survival, an outcome that was not significantly affected by the individuals’ health status. The results suggest that the physiological aging processes of T-cell immunosenescence and low-grade inflammation are of crucial importance in late-life survival (124) and suggest a sequence of stages for IRP individuals that seems to begin in early life with CMV infection, followed by homeostatic T-cell changes with the generation of large CD8+CD28− effector cell expansions, a decrease in the number of CD4+ T cells, and eventually the development of an IRP (Figure 3). This is accompanied by a low-grade inflammatory process in very late life, supporting the hypothesis that immunosenescence is driven by a chronic antigen load, CMV in particular.

**T cells at the population level**

The progressively reduced number of naïve cells in the periphery with increasing age is associated with the thymic atrophy that occurs with aging. However, it is still debated whether thymic atrophy is responsible for reduced lymphopoiesis (21). Nevertheless, treating aged mice with IL-7 has been reported to increase thymic output, suggesting that intrathymic levels of IL-7 have a critical effect on the production of T cells (5). Old rhesus macaques also respond positively to this treatment, as shown by increased CD4+ and CD8+ T cells and a transient increase in the number of the naïve subset, suggesting that the same may be true of humans. IL-7-treated old monkeys responded significantly better to influenza vaccine than controls (4).

Although some T-cell functions are decreased with age, others are maintained or increased, the latter exemplified by the CMV-specific memory T-cell population, which can occupy a quarter or more of the whole T-cell repertoire (81, 82). These cells display the CD8+CD28−CCR7−CD45RA−KLRG1−CD57− phenotype of late-differentiated T cells (Table 1; Ref. 80). Nevertheless, some of these cells, which include the CMV-specific CD8+ T cells, still respond to certain stimuli (3). Recent results indicate that CMV antigens induce greater production of IFN-γ in CD4+ T cells in very old compared with young subjects. The comparative analysis of p65-specific responses in long-term carriers revealed that CD8+ and to a lesser degree CD4+ CMV-specific memory T cells do expand during life (115). It is likely that immune mediators such as cytokines may play a role in the maintenance of memory T-cell functionality and survival. IL-15 is known to promote CD8+ memory cell survival and expansion and was recently shown to induce CD28 downregulation (13). Although IL-15 can be considered as a factor associated with the accumulation of CD8+ T cells, it has been recently shown that the late-stage differentiated CD8+ population is the only one to turn over more slowly in the elderly compared with the young and therefore accumulate in the periphery (120). Globally, expansion of CMV-specific T cells does not favor the delivery of naïve T cells to the periphery (49). One putative intervention to restore a balanced T-cell subset distribution would be to deplete excess and possibly dysfunctional CMV-specific T cells but at the same time to maintain strict control of this potentially dangerous viral infection. Because CMV infection is asymptomatic in healthy individuals, it is difficult to know the time of first infection except in the case of CMV-seronegative patients receiving an organ from a

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### Table 1. Age-related changes in T- and B-cell markers and functions

<table>
<thead>
<tr>
<th>Decreased</th>
<th>Increased</th>
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<tr>
<td>CD28</td>
<td>KLRG1</td>
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<tr>
<td>CD27</td>
<td>ILT-2 (CD85j)</td>
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<td>ICOS</td>
<td>CD57</td>
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<tr>
<td>CCR7</td>
<td>CD49d</td>
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<tr>
<td>Proliferation with mitogens</td>
<td>KIR-positive T cells</td>
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<tr>
<td>IL-2 production</td>
<td>KLRF1</td>
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<tr>
<td>Telomere length</td>
<td>CD244</td>
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<tr>
<td>Telomerase activity</td>
<td>CD45RO+ T cells</td>
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<tr>
<td>Th1 response: IL-2, IFN-γ</td>
<td>Memory B cells</td>
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<tr>
<td>Delayed-type hypersensitivity</td>
<td>CMV-specific CD8+ T cells</td>
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<tr>
<td>TCR signal transduction</td>
<td>CMV-specific CD4+ T cells</td>
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<tr>
<td>Proteosome activity</td>
<td>DNA damage</td>
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<tr>
<td>Membrane fluidity</td>
<td>Anergic T cells</td>
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<tr>
<td>TCR repertoire</td>
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<td>CD45+ T cells</td>
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<tr>
<td>Cytoskeleton rearrangement</td>
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<td>Thymic output</td>
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<td>Efficient response after vaccination</td>
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<td>B-cell-derived antibody affinity</td>
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<td>B-cell casw with</td>
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<td>Antibody somatic recombination</td>
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<tr>
<td>Lymphopoiesis (B and T cells)</td>
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<tr>
<td>Naïve B cells</td>
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<tr>
<td>Generation of immature B cells</td>
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</table>

The decrease or increase in surface markers, subpopulation frequencies, functions, activities, and damages displayed are the most accepted. The corresponding citations can be found in the reference section. ICOS, inducible T-cell costimulator; CCR7, chemokine (C-C motif) receptor 7; KLRG1, killer cell lectin-like receptor subfamily G member 1; ILT-2, Ig-like transcript 2; KIR, killer cell Ig-like receptor; KLRF1, killer cell lectin-like receptor subfamily F, member 1.
CMV seropositive donor (95). One approach to better understand the role of CMV or other pathogens in remodeling the immune system is to assess the T-cell repertoire. We know from the OCTO/NONA longitudinal studies that the number of clonal expansions inversely correlates with remaining survival time (93). More studies are needed to clarify whether this is CMV-specific or a more general phenomenon occurring with aging.

**T-cell function, activation, and signaling at the cellular level**

Major functions known to decrease with age are IL-2 production and T-cell proliferation (Table 1; Ref. 60). This in vitro evidence would suggest an in vivo clonal expansion deficiency following antigen recognition partly explaining age-associated increased susceptibility to infections, auto-immune diseases, and cancers. Although T-cell receptor expression is maintained with age, other co-receptors such as the co-stimulatory molecule CD28 are lost (25) and would explain the lower activation levels (109). A full state of T-cell activation is achieved only when an immune synapse is formed, which facilitates the ligation of small numbers of T-cell receptors and other molecules (39). To this end, membrane microdomains called “rafts,” which are highly motile through the membrane, allow protein polarization at the site of the immune synapse (39, 103). Thus achieving the activation threshold is dependent on raft functions rather than purely dependent on the number of molecules expressed at the cellular level (22). However, a deficiency in raft functions would explain, at least in part, downstream signaling alterations such as those...
“Although an association between aging and cortisol levels is observed, the precise mechanism by which alterations in the neuroendocrine system can impact on immunity in aging is not clearly identified.”

**B-cell function and vaccination**

The age-associated immune dysfunctions described above may partly influence the efficiency of vaccination strategies in the elderly (74, 104). Although 70-90% of individuals <65 years old are efficiently protected after influenza vaccination, only 10-30% of frail elderly are protected (43). This is partly due to the fact that antibodies produced by old B cells are commonly of low affinity, providing less efficient protection compared with young individuals (Table 1; Ref. 56). The class switching and somatic recombination necessary for antibody production and diversity are both impaired in aged humans (38). B-cell lymphopoiesis is also reduced, which leads to an increase in the percentage of antigen-experienced cells compared with newly produced naïve B cells, parallel to the situation with T cells. There is an inappropriate differentiation of pre-B cells from pro-B cells, which is associated with the reduced generation of immature B cells (71). There is also evidence suggesting a shift in B-cell selection leading to increased frequencies of autoreactive cells with aging (48). This directly impacts on humoral immunity. Vaccination is the best prophylactic treatment for the aged population, and future research needs to take into account the characteristics of aged individuals for the design of new vaccines. One good example is the use of adjuvants in vaccine composition to increase its efficiency. In the next section, we will review some of the important extrinsic mediators of immunity that can be most easily targeted for use in the elderly for the prevention of immune senescence because they belong to the lifestyle rather than the pharmacological category.

**Extrinsic Influence on Immunity**

**Stress**

Although factors that initiate psychological and physical stress differ, the ways in which they impact the immune system are similar and include activation of the hypothalamic-pituitary-adrenal (HPA axis) and the sympathetic-adrenal-medullary (SAM) axis, both of which influence the immune system (128). Increased psychological stress in aging occurs in parallel with significant activation of the HPA axis (19, 64, 111). The persistent activation of the SAM axis in chronic stress responses and in depression impairs the immune response and contributes to the development and progression of some types of cancer (92). Stressed and depressed patients have reduced mitogen-stimulated lymphocyte proliferation, high levels of acute-phase proteins, IL-1, IL-6, and TNF-α. Both stress and depression are associated with decreased cytotoxic T cell and NK activities, which could affect immunosurveillance of tumors, and the events that modulate the development and the accumulation of somatic mutations and genomic instability (64, 92) altogether influencing longevity (118).

Although an association between aging and cortisol levels is observed, the precise mechanism by which alterations in the neuroendocrine system can impact on immunity in aging is not clearly identified. There is evidence suggesting that cortisol can act by increasing T-cell susceptibility to apoptosis as in the case of immunocompromised individuals (93). The glucocorticoid (GC) cascade is a putative candidate when its major role in suppressing the synthesis of pro-inflammatory cytokines by the innate arm following trauma is considered (83), and it may be useful for reducing age-associated low-grade inflammation.

**Sleep/physical activity**

Age-associated sleep dysregulation is a common phenomenon (6). Sleep-deprived rats display a number of physiological abnormalities, eventually leading to death. A loss of host defenses has been suggested based on the occurrence of sepsis in long-term sleep-deprived rats (24) as well as changes in immune mediators, including increased plasma levels of IL-1β (20), soluble tumor necrosis factor-α receptor 1 and IL-6 (98), and fluctuations in IFN-γ (20). Acute sleep loss also appears to be a potent stimulus of stress hormone release, including cortisol (69). Additionally, metabolic changes associated with sleep deprivation include hyperphagia, increased fasting blood glucose levels, and insulin resistance (101). This last parameter associated with high levels of markers of inflammation is well documented in elderly populations (73).

One of the most-utilized strategies to improve immunocompetence in older adults is through moderate physical activity (126). The immunomodulatory effects of exercise include a shift in the production of Thelper1 and Thelper 2 cytokines, enhanced NK cell and T-cell activity, and improved antibody responses (50). Moreover, physical activity may enhance immunity through the release of neuroendocrine factors (88). Additionally, exercise may enhance immunity through indirect effects on psychosocial variables such as depression and mood, thereby attenuating the negative influence of these
factors on immunocompetence. Human exercise intervention studies show a causal reduction in inflammatory markers, including C-reactive protein (14). Due to the many other beneficial health benefits associated with regular moderate exercise, recommendations to improve levels of physical activity are widely prescribed in the aging population (51).

Nutritional factors play a major role in the immune responses of healthy as well as immunocompromised individuals. Protein energy malnutrition is common in the elderly and may be an important factor in influencing diminished immune responses (45, 57, 68). Furthermore, infections (increasingly prevalent in the elderly), even when mild, can compromise nutritional status or lead to recompartmentalization of trace elements as part of the acute adaptive response. This can lead to a spiral of impaired immunity and exacerbated infections.

More recently, it was suggested that lipids are very important mediators of cellular functions (47, 102). Because cell membranes are primarily composed of phospholipids, fatty acids, and cholesterol and because these are the first elements in contact with free radicals, a change in the composition or quality of membrane lipids can influence cell fate. Eicosapentaenoic acid (EPA) infusion induced a dose-dependent decrease in neutrophil respiratory burst only in old individuals associated with a higher incorporation of EPA into plasma and mononuclear cells than in younger subjects (91). Defects in signaling associated with aging (FIGURE 4) have a common origin, i.e., the membrane. Changing the extrinsic lipid composition will directly influence intrinsic events because of the natural diffusion of lipid into cell membranes (42). Each lipid has a specific effect on cell functions, and the same lipid may have different effects depending on the individual's age (55, 91).

Although nutrition, immune function, and infection are clearly interrelated, it is no simple matter to quantify these relationships (70). Some agents used in intervention studies are listed in Table 2. Most of our current understanding relates to nutrient deficiency states and acute infections, and often investigations occur in hospitalized patient settings. Very few studies have been conducted on primary outcomes, such as infection/inflammation severity/resistance or quality of life end points. Although these are potentially highly relevant, the enormous redundancy and pleiotropy of the immune system makes it hard to predict the consequences at the organismal level.

Concluding Remarks
Immunosenescence is a complex phenomenon occurring as a consequence of incompletely understood multiple alterations in hemopoiesis, immune cell development and differentiation, and cell function. The adaptive immune system is particularly affected by thymic involution, reducing the generation of new T cells, and by the effects of long-term exposure of peripheral T cells to a variety of antigenic stimuli for a period much longer than that expected on the basis of the evolutionary history of H. sapiens. The combination of the accumulation of molecular and cellular defects at several levels of immune responses with such chronic antigenic load results in the paradoxical situation of an immune system that is concomitantly hyper-activated (Inflamm-aging) and defective. We suggest that a unifying hypothesis to explain these changes is to be found within the paradigm of retention or exacerbation of innate immunity coupled with dysregulation or dysfunction of adaptive immunity. Dissecting biomarkers used to distinguish healthy aging from age-associated pathologies or phenomena such as frailty, dementia, cancer, auto-immune diseases, and increased susceptibility to infections indicates that most of these are immune-related and are good indicators for survival/mortality. The above hypothesis requires rigorous testing in humans, from which the performance of longitudinal studies with detailed immunological and non-immunological follow-up and cause-of-death data are urgently required. In this context, available data

<table>
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<tr>
<th>Table 2. Attempts to restore immunity in the elderly</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Vitamin B6</td>
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<tr>
<td>Vitamin E</td>
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<tr>
<td>DHEA</td>
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<tr>
<td>Vitamin D</td>
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<tr>
<td>Zinc</td>
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<tr>
<td>Folate</td>
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<tr>
<td>PUFA</td>
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<tr>
<td>Probiotic</td>
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<td>(Bifidobacterium lactis HN019)</td>
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</table>

The different strategies to restore age-associated immune dysfunctions are shown (57, 70, 91, 102). An increase or activation of the pathway/process is represented by + and a decrease/inhibition by -. DHEA, dehydroepiandrosterone; PUFA, polyunsaturated fatty acids; PPAR-α, peroxisome proliferator-activated receptor alpha; NF-κB, nuclear factor-κ B; IFN-γ, interferon-γ.
suggest that the role of putatively asymptomatic infections, especially with CMV, in remodelling the immune system and influencing inflammatory status must be a prime consideration, together with the genetic background, to help explain inter-individual differential longevity. For intervention, because immune deficiencies are observed after several years and decades, the necessity for long-term studies rather than acute treatments must be recognized. The number of elderly people is increasing markedly, and their needs are growing rapidly. A better understanding of immune dysfunction will help prevent age-associated disorders and frailty, with the result that the frequency of disabled elderly people is decreased. Immunosenesence is currently a prognostic factor for human longevity, and thus a more sophisticated appreciation of immune dysfunction will contribute to increased quality of life of the elderly population.

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References

8. Bruunsgaard H, Pedersen AN, Schroll M, Skinhoj P, Pedersen E. Immunosenescence and influencing inflammatory status must be a prime consideration, together with the genetic background, to help explain inter-individual differential longevity. For intervention, because immune deficiencies are observed after several years and decades, the necessity for long-term studies rather than acute treatments must be recognized. The number of elderly people is increasing markedly, and their needs are growing rapidly. A better understanding of immune dysfunction will help prevent age-associated disorders and frailty, with the result that the frequency of disabled elderly people is decreased. Immunosenesence is currently a prognostic factor for human longevity, and thus a more sophisticated appreciation of immune dysfunction will contribute to increased quality of life of the elderly population.

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References

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References


49. Lahiri AK, Sinha DK. Reciprocal age related change in peripheral blood IFN-gamma-secreting Valpha24+Vbeta11+ NK cell numbers are decreased in cancer patients independent of tumor type or tumor load. Int J Cancer 116: 67–93, 2005.


