Preventing or reversing immunosenescence: can exercise be an immunotherapy?

There is now a strong body of evidence demonstrating that aging is accompanied by severe alterations in the immune system, a process known as immunosenescence. Among these changes are alterations in T-cell subpopulation size, cytokine secretion pattern, cell replicative capacity and antibody production, all of which culminate in a proinflammatory state called ‘inflammaging’ and a diminished capacity to respond to new antigens. These alterations are closely related to the increased mortality and morbidity rates observed in this population. However, the role of exercise on the prevention or treatment of immunosenescence is virtually unknown. Data gathered from the literature regarding the effects of physical activity on immune system aging are still limited and conflicting, with existing reports either advocating benefits or asserting a lack of evidence. Exercise as part of a healthy lifestyle has already been shown to provide long-term benefits with regard to cardiovascular, cognitive, psychosocial and other aspects of the elderly. If positive effects are also observed for immunosenescence, exercise could be a highly cost-effective measure to improve human quality of life compared with other strategies currently being pursued.

**KEYWORDS:** aging, cytomegalovirus, exercise, immunosenescence, inflammaging, lymphocyte, telomere

The progressive increase in life expectancy documented in the last decades represents a new burden on medical intervention as this increase is correlated with a higher prevalence of neoplasia and age-related diseases [1]. Furthermore, infections in the elderly are associated with higher morbidity and mortality rates compared with other age groups. According to Arnold et al. in 2011, the assurance of longevity and healthy aging occurs by maintaining the integrity of immunity [2]. However, this is not always possible because deleterious changes occur with aging in the composition, physiological function and competence of the immune system. The alterations that occur with aging that compromise the competence of the immune system are defined as immunosenescence. Comfort in 1979 defined senescence as the incapacity to maintain homeostasis under conditions of functional overload [3].

The etiology of immunosenescence is multifactorial and reflects the lifelong exposure to pathogenic agents and viral infections, contributing to increased early morbidity and mortality [4]. Of note are gastrointestinal infections, increased susceptibility of developing autoimmune diseases and cancer, and decreased response to vaccines [5,6]. These inflammatory and infectious processes, in turn, accelerate immunological exhaustion, particularly of the T-cell compartment of adaptive immunity [1], although the functionality of B cells [7] and innate immunity [8] are also affected to a lesser degree.

Many cell types are affected during immunosenescence, such as hematopoietic stem cells, lymphoid progenitors, mature lymphocytes of secondary lymphoid organs and peripheral blood [9]. The main feature of immunosenescence is the change in the cellular composition of the T-cell compartment, including a decrease in the number of naïve phenotype cells in association with an increase in the number of memory phenotype cells. Thymic involution is directly related to a reduction in precursor cell number and the decline of hematopoietic stem cell function. The innate immune system also suffers with aging from functional defects in APCs, an increased number of NK cells, and an increase in the inflammatory background. The alterations that compromise adaptive immunity include changes in some cell populations, decreases in the function of these cells, reduced telomere length and a higher apoptosis rate. Regarding the humoral immune response, a decrease in the B-cell population, deficiency in isotype switching and reduced ability of specific antibody production are observed [10,11]. Additionally, as pathogens can accelerate the changes caused by immunosenescence, latent CMV infections have been widely studied within this context [12].

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In this review, we describe the main changes that occur in the immunological system of elderly people, highlighting the main changes that occur in the T-cell compartment of adaptive immunity (Figure 1). Furthermore, we discuss the effects of exercising on the elderly immune system and its potential to prevent or reverse the consequences of immunosenescence.

**Innate immunity & immunosenescence**

Despite the limited number of studies addressing the innate immunity aspects of immunosenescence, some functional and phenotypic aspects do appear altered in the elderly. The functional and phenotypic changes in neutrophils, monocytes/macrophages, dendritic cells (DCs) and NK cells that have been described with aging are summarized in Table 1 [13–25]. Alterations, such as decrease in the antigen presentation capability [21], impairment of phagocyte function [17], altered cellular signaling [14] and cytokine release [25], likely result in the slowing of the host response to infections and the well-known increased susceptibility to infections of the elderly.

**Naive T cells & homeostatic proliferation**

One of the major causes of immunosenescence is the severe reduction of the naive T-cell compartment [26,27]. One of the mechanisms is the reduced capacity to generate lymphoid progenitors by functionally impaired hematopoietic stem cells due to a deficiency in the capacity to repair DNA damage [28]. Furthermore, thymic involution is another essential factor contributing to this decline. The thymus is completely developed at birth, but an involution process begins at puberty, in which functional tissue is replaced by fibrofatty tissue. This process persists throughout adulthood, with the thymus being completely involuted by 60 years of age [29,30]. The T-lymphocyte pool decreases dramatically (~80%) with thymic involution, thus affecting the capacity of the adaptive immune system to respond to new antigens. This decrease is observed in lymphoid organs and peripheral blood [31] and is more pronounced in the CD8+ than CD4+ subpopulation [32–34], suggesting that the latter is more likely to respond to yet-unknown mechanisms of survival [2].

Therefore, homeostasis of the T-lymphocyte subpopulation is dependent on a mechanism of self-regulation that consists of the homeostatic proliferation of peripheral naive T cells: the organism ‘senses the space’ left by the contracted T-cell compartment and attempts to restore homeostasis through the proliferation of peripheral naive T cells [35]. In this model, the pool of naive CD4+ T cells is maintained by homeostatic peripheral CD4+ T cell expansion, as demonstrated by a progressive reduction in the T-cell receptor (TCR) excisional circle content (TREC; a replicative cycle marker) with aging. Kilpatrick et al. analyzed the TREC content in two subpopulations of naive CD4+ T cells expressing/not expressing CD31 (which defines newly emigrated thymus CD4+ T cells [36]) in young and old individuals [37]. The authors showed a decrease in CD4+CD31+ naive T cells that was associated with a loss of thymic function and a reduction in the TREC content in the subpopulation of naive CD31+ cells in elderly individuals.

In humans, an increased proliferation of CD4+ T lymphocytes has been reported in individuals above 65 years of age and thymectomized children [38,39], and it is believed that the partial lymphopenia due to the loss of thymus function is responsible for the proliferative increase [33]. In newborns, peripheral T-cell proliferation appears to be responsible for 50% of the daily T-cell production, and this percentage is further elevated in adults [40]. IL-7 and IL-4 are essential for the survival of naive CD4+ T cells [41] and, although the exact mechanisms are not well understood, some *in vitro* studies in humans have concluded that IL-7 and other cytokines can stimulate T-cell replication without the loss of the naive phenotype [42,43]. In addition, IL-7 can at least partially reverse the reduction in thymopoiesis and thymic output, abbreviating the subsequent immune dysfunction. In this respect, pulmonary administration of IL-7, but not intravenous administration, resulted in a rapid distribution of the cytokine to the tissues of aged animals, promoting a significant increase of the intrathymic development of T cells [44].

As a consequence of homeostatic proliferation, the naive cells produced by the thymus have a long life cycle, remaining viable in a quiescent state in the peripheral blood [45]. However, it has been argued that the increased survival of naive T cells predisposes them to repeated/prolonged exposure to toxic environmental factors that can cause DNA damage (e.g., mutations) [2]. Therefore, homeostatic proliferation can accelerate cell senescence, leading to the shortening of telomeres, the main function of which is to protect the chromosomes ends, helping to maintain the integrity of the genome [46,47]. The telomere is synthesized at the end of DNA replication by...
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The enzyme telomerase, a reverse transcriptase composed of a protein component and an RNA molecule, which contains a template sequence complementary to more than a telomeric repetition and is, thus, capable of preventing progressive shortening of the DNA strand. However, maintenance of telomere length does not occur in human somatic cells because the gene that encodes telomerase is inactive in most cells. Thus, after successive cycles of cellular replication, telomere shortening results in inefficient protection of the chromosomes ends, initiating the process of cellular senescence that, upon reaching a critical point, can result in apoptotic cell death \([47,48]\). Telomere length can be used to assess the replicative history of cell populations \([49,50]\), and telomere shortening usually reflects the activity of the ‘mitotic watch’ by limiting the replicative capacity of somatic cells \([51]\).

This aging due to increased survival is also associated with a decreased repertoire of naive T cells and an expanded T-cell memory compartment, partially explaining the increased risk of infection and decreased efficacy of vaccination in the elderly \([52]\).

The role of apoptosis in immunosenescence remains to be clarified. Fas/FasL expression was reported to be increased in naive and...
memory CD4+ and CD8+ T lymphocytes in elderly individuals (65–95 years old), whereas the antiapoptotic molecule Bcl-2 was decreased compared with lymphocytes from young individuals (20–29 years old). However, a study on centenarians showed that the expression of Fas in memory lymphocytes was increased, although the expression of FasL was reduced [53]. Further studies are necessary to elucidate the role of apoptosis in immunosenescence.

### Naive T cells & functional alterations

The few studies that have addressed the function of residual naive T cells in the elderly point to considerable functional limitations with aging, including a reduced ability to produce IL-2 and to differentiate and expand into impaired effector cells, a decreased number of CD45RA–CD28+ T lymphocytes, telomere shortening and restriction of the of the TCR repertoire, when compared with the naive lymphocytes of young individuals [26,54,55]. Pfister et al. analyzed the impact of aging on naive T cells (CD4+ and CD8+) and found a significant decrease in CD45RA–CD28+ T cells in the elderly; however, the proliferative response remained unaffected [26]. Another report showed a decreased proliferative response to antigens, changes in surface molecule expression and intracellular signaling, and increased apoptosis rates [56]. Experimental studies have shown that prolonged survival in mice is associated with a high number of naive CD4+ T cells and a low number of memory CD8+ T cells, suggesting that the number of naive T cells could be used as an aging biomarker [57]. Thus, although further studies are required, it appears that disturbances in naive T-cell function are an important feature of immunosenescence.

### Memory cells & senescent cells

Many quantitative and qualitative changes occur in the memory cell compartment. As discussed above, parallel to the reduction in naive cells during aging, there is an accumulation of effector memory T cells [58]. The continuous antigenic stimulation and associated clonal expansion and differentiation of effector T cells lead to the appearance of senescent T cells, as identified by the expression of the surface receptors CD57 and KLRG1, absence of the expression of the costimulatory molecule CD28 and erosion of the telomeric region due to successive replicative cycles during immunological responses [59]. Telomere erosion is associated with increased resistance to apoptosis [60], allowing the

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### Table 1. Immunological changes associated with aging in innate immunity.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Parameter</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Membrane alterations: reduced levels of cholesterol, increased membrane fluidity and dysregulation of receptor recruitment to lipid rafts</td>
<td>[13,14]</td>
</tr>
<tr>
<td></td>
<td>Decreased receptor signaling functions: KPB, JAK, PI3K</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Preserved or decreased cell number</td>
<td>[15,16]</td>
</tr>
<tr>
<td></td>
<td>Decreased chemotaxis, opsonization, phagocytosis and free radical production</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td>Decreased signaling molecules expression: GM-CSF-R, TLR-4, fMLP-R, TREM-1</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>Preserved expression of adhesion molecules: CD11a/CD11c/CD11a/CD18/CD11b/CD18/CD14</td>
<td>[18]</td>
</tr>
<tr>
<td>Monocytes/</td>
<td>Increase in CD16+ (proinflammatory) subpopulation</td>
<td>[19]</td>
</tr>
<tr>
<td>macrophages</td>
<td>Dysregulation of TLR responses (diminished signaling of TLR-1/2)</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>Decreased in antigen presentation: phagocytic ability and free radical production</td>
<td>[21]</td>
</tr>
<tr>
<td>DC</td>
<td>Decreased in number (myeloid subpopulation)</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>Decreased in IL-12 production</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>Reduced proportion of pDC expressing TLR-7 or TLR-9</td>
<td>[23]</td>
</tr>
<tr>
<td>NK</td>
<td>Decreased function compensated by increased percentage and absolute cell number</td>
<td>[21,24]</td>
</tr>
<tr>
<td></td>
<td>Decreased in CD56bright (immunoregulatory) subpopulation</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Increased CD56dim (cytotoxic) subpopulation</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Preserved production IFN-γ</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Decreased in chemokine production</td>
<td>[25]</td>
</tr>
</tbody>
</table>

DC: Dentritic cell; fMLP-R: N-formyl-leucyl-phenylalanine receptor; GM-CSF-R: GM-CSF receptor; pDC: Plasmacytoid dendritic cell; TLR: Toll-like receptor; TREM: Triggering receptor expressed on myeloid cell.
accumulation of these senescent cells with high proinflammatory profiles in blood and tissues, and its contribution to many age-related diseases characterized by an inflammatory background.

In addition, changes in the pattern of cytokine secretion were detected in cultures of CD8+ senescent T lymphocytes (CD28–), including an increase in TNF-α and IL-6 and decrease in IFN-γ and IL-2 secretion, showing that CD28 is essential for the stabilization of many cytokines [63].

**Markers associated with immunosenescence**

Persistent CMV infection appears to be a factor involved in the process of immunosenescence. Although there is strong evidence that CMV is associated with the immune dysfunction of aging, the mechanisms underlying this association are not known. It is not clear whether CMV infection is a cause of immunosenescence or, inversely, the latter favors an increased susceptibility to CMV infection/reactivation [62]. In studies of experimental models, Nikolich-Zugich’s group showed that CMV infection causes marked changes in the CD8+ T cell pool, namely an increase in this pool and a distorted TCR repertoire diversity, due to expansion of the memory effector cell subpopulation concomitant to a reduced naive subpopulation. Moreover, the CD8+ response of mice infected with murine CMV to superinfection with other viruses was reduced. These authors conclude that CMV can accelerate the impairment of immune responses and the changes in the CD8+ pool that occur in mice during immunosenescence [62].

In latent/persistent infections, such as in CMV, the stimulation is periodic with cycles of viral dormancy and reactivation. Other studies by Nikolich-Zugich’s group suggested that the control of latent infections through specific memory, KLRG1+ and CD8+ T cells is preserved in the elderly and that this immuneactivation does not necessarily contribute to the development of immunosenescence, provided that these cells have been generated during adulthood and not in aged mice [63]. Accumulation of these memory–effector ‘senescent’ cells was not associated with their loss of function. It would be interesting to confirm these persistent viral experimental data in aged persistent human infections. On the other hand, in chronic active infections, such as latent CMV, HCV and HIV, there is continuous immune stimulation and probably a more rapid progression to immunosenescence [64,65].

In fact, some studies in aged humans showed that latent CMV infection characteristically induces the production of the proinflammatory mediators, most of which are involved in several age-related illnesses, such as cancer, cardiovascular diseases, Type 2 diabetes and rheumatoid arthritis [66]. In addition, a study demonstrated that CMV seropositivity was associated with a senescent phenotype, that is, a reduction in the frequency of naive T cells and the accumulation of CD45RA-re-expressing late-differentiated effector memory cells. However, the senescent phenotype was not observed in individuals predisposed to longevity, possibly because of a better control of the virus [67].

CMV infection can result in a skewed CD4+ and CD8+ T-lymphocyte repertoire in elderly individuals. Studies have shown that up to 50% of the CD4+ and CD8+ T lymphocytes can be committed to CMV antigens (i.e., pp65, the main structural protein of the virus and the immunodominant antigen) [59,68,69]. Therefore, a marker that can be used to describe the cell exhaustion caused by persistent infection is the loss of CD28 and its accumulation during aging, which correlate with many clinical outcomes, including the reduced capacity to control infectious processes.

Another marker is telomere length, as discussed above. Telomere length in CD8+CD28- and CD8+CD28- T cells was used to determine the replicative history of each subpopulation in healthy individuals and was significantly shorter in the CD8+CD28- T-cell subpopulation [70]. This finding is consistent with the replication history of these cells, presumably in response to repeated antigen exposure, and indicates that they are displaying a replicative senescence status [51]. These findings are in agreement with those of a previous study [71] showing that memory CD4+ T cells presented shorter telomere length than naive CD4+ T cells [70,71]. Indeed, telomere shortening has been used as a predictor of immunological incompetence in elderly individuals [61,72].

Cytokine secretion patterns may also serve as a marker to identify immunosenescence, as mentioned above for the CD8+CD28- senescent cells [61]. In addition, an *ex vivo* analysis of CD8+CD28- T lymphocytes showed increased expression of caspase-3 when compared with the CD8+CD28- T-cell subpopulation, suggesting a higher susceptibility of apoptosis in senescent lymphocytes [73]. However, the survival of terminally differentiated T cells is a controversial issue. A lack of significant differences in the
activation of caspase-8 and -3 in CD4+ and CD8+ memory effector T lymphocytes between young and older individuals has been reported, suggesting that these cells have developed apoptosis resistance [58]. The changes in the cytokine secretion pattern and the incapacity of these cells to respond appropriately to stimuli appear to be central events in immunological deficiency in the elderly, as represented by the higher risk of infections, autoimmunity and cancer [74,75].

**Inflammaging, fragility & other consequences**

Inflammaging is defined as low-grade chronic systemic inflammation established during physiological aging. Altered levels of proinflammatory cytokines (e.g., IL-6 and TNF-α), acute-phase reactants (C-reactive protein [CRP]), and decreases in IL-10 impair the maintenance of immunological homeostasis [76]. Inflammaging is considered a predictor of fragility and this condition is currently accepted as a pathogenic factor in the development of several, age-related diseases, such as cardiovascular disease [77], cancer [78], osteoporosis [79] and Alzheimer’s disease [80]. It was found that individuals over 60 years of age being treated with anti-TNF are less vulnerable to hospitalization with infectious complications compared with a group that had discontinued the therapy [81]. The progressive accumulation of TNF-α is also related to obesity, smoking, psychological stress and CMV infection in addition to aging [76,66].

However, the current notion that accumulation of senescent cells (concomitant to the reduction in the naïve cell pool) carries severe deleterious effects has been challenged. In studies of the very old population, it was verified that besides the reduction of naïve cells, the accumulation of late-differentiated effector memory cells was correlated with a prolonged survival of this population. This population was highly exposed to CMV; it was then reported that CMV-specific memory cells were relevant to the prolonged survival. Moreover, they showed that individuals who developed pure proinflammatory responses towards the CMV-specific peptides had prolonged survival compared with those who predominantly developed anti-inflammatory responses to these peptides. Thus, the immunosurveillance against CMV appears to be crucial to the longevity of these very old individuals [82].

Despite these findings, there is not a consensus on the definition of biomarkers of immunosenescence and death risk. In addition, it is not clear whether there is a correlation between the frail elderly and more frequent CMV reactivation or between higher titers of anti-CMV antibodies and shortened survival [83]. In a study of 2-year survival of an aged (>65 years) population, multiple logistic regression analysis revealed that only increased CRP levels and thymic function reduction (measured by the recently described sj/b-TREC ratio quantification method, which directly measures thymic-emigrant cells) were independently associated with increased mortality of healthy elderly [84].

Although several transversal studies suggest that persistent CMV infection is the main inducer of inflammaging [66], a longitudinal study found a lack of a role for CMV. In this study, 249 individuals with a mean age of 67.5 years old were followed for 10 years [76], reporting an increase in proinflammatory status over time (elevation of CRP, TNF-α, IL-6, IL-10 and IFN-γ) that was comparable between individuals seropositive and seronegative for CMV. Within this context, a longitudinal study conducted in a Swedish population of octo- and nonagenarians identified a set of immunological parameters associated with immune dysfunction during aging that forecasted early mortality [85]. These parameters were referred to as the immunological risk profile and comprised the accumulation of CD28+ T lymphocytes, a decreased CD4/CD8 ratio, seropositivity to CMV, the decreased proliferative capacity of T cells and a decreased number and functionality of B lymphocytes. Interestingly, another study described the increased proportion of a subset of cells expressing CD25 within the CD8+ memory cell compartment in the elderly. These CD8+CD25+ cells would represent CD8+ T cells in an initial phase of differentiation, presenting long telomeres and a polyclonal TCR repertoire, and are associated with a better function of the immune system in these individuals [2].

During aging, impairment of the gut-associated lymphoid tissue (GALT) capacity to efficiently synthesize strain-specific secretory IgA, together with the reduced efficiency of innate immune defenses, such as L-defensins, antimicrobial peptides and mucus secretion, may result in failure to control the resident microbiota, allowing an uncontrolled microbial growth on the enterocyte surface. In this context, enterocytes could engage the activation of inflammatory cytokines and chemokines, forcing DCs of the underlying GALT to drive the differentiation of effector Th1, Th2 and Th17 cells that induce a strong proinflammatory
response (Figure 2). Indeed, the proinflammatory state of the GALT may be a driving force behind the systemic inflammation (inflammaging) of the elderly [86].

**Tregs & immunosenescence**

There are scarce data regarding the ability of natural Treg cells to regulate/suppress immune responses with aging. Studies with a mouse model of aging showed significantly enhanced percentages of peripheral CD4^+^CD25^+^ Treg cells in aged mice and changes in the TCR repertoire and functionality of the CD4^+^CD25^+^ lymphocytes [87]. By contrast, in a single study in humans, an increase in age was associated with an augmented CD4^+^CD25^+^ lymphocyte number without changes in function when compared with young individuals [88].

**B cells & their alterations**

The impairment of immune protection against new antigenic stimuli and the decrease in the response to immunizations verified in elderly individuals can be associated with a decrease in antibody specificity, affinity and isotype switch with aging [89]. According to Ongrádi et al. quantitative changes include decreases in immunoglobulin levels and, qualitatively, decreased number and activity of B-cell populations and the antibody repertoire. The major consequence is an impaired capacity to mount strong humoral immune responses [90].

Another characteristic of immunosenescence of the B-cell compartment is the decreased bone marrow production of naive B cells, provoking an imbalance in the naive/mature B-cell ratio in the elderly, which, in turn, leads to the clonal expansion of some specific B cells and limitation of the repertoire diversity. A consequence of the deficiency in isotype switching is the accumulations of B IgM^+^ cells and the loss of IgG secretory cells. In addition, an increase in the IgD CD27^+^IgG^+^ subpopulation expressing reduced levels of CD40, CD80 and HLA-DR,
suggestive of exhausted memory cells, has been reported, indicating that these cells have a reduced capacity to present antigens [91].

Is exercise an immunotherapy for immunosenescence?

As discussed above, aging of the immune system, particularly the dysregulation of T-cell function, appears to be partly responsible for the comorbidities presented by the elderly population. These individuals are more susceptible to different infectious diseases, autoimmune diseases and cancer and respond less well to vaccination when compared with a young adult population. Although it is possible that exercise or lifestyle acts to prevent or treat immunosenescence, there is no clear answer to this question thus far.

Although the impact of exercise on the immune system is an area of extensive research, most studies have focused on the responses to acute exercise. Such studies have shown that the immune response to acute exercise is transient and variable, being influenced by a wide range of factors, such as the intensity, duration and mode of exercise, concentrations of hormones during exercise, and change in body temperature, blood flow, hydration status and body position (upright vs horizontal) [92,93]. Leukocytosis, granulocytosis, slight lymphocytosis and decreases in the proportion of T to B cells usually reflect changes in blood volume, demargination and tissue migration of the peripheral blood cells. Lymphocyte subsets show a decreased helper/suppressor cell ratio and an increase in NK cells. Prolonged exercise leads to a decrease in serum and salivary immunoglobulin levels [94,95]. Other studies showed that marathoners present with more airway infections 3–72 h after competition or even 2 weeks after competition [96–98]. However, few studies have addressed the immune response to exercise training in the long term, particularly in elderly people. The two sections below describe the few studies that have addressed this issue. The first describes interventional studies that found some benefits, and the second describes studies that did not. These data are summarized in Table 2.

Positive effects

Tests that evaluate proliferation and cytokine secretion in response to different stimuli are most commonly used to assess the competence of T-lymphocyte functions and the adaptive immune system. A transversal study that evaluated elderly individuals who practiced regular aerobic activity (60.5–67.1 years old) and those who were sedentary (62.3–69.3 years old) showed that regular aerobic activity was associated with a smaller increase in T-cell function, as demonstrated by a greater proliferative response and cytokine production (IL-2, IFN-γ and IL-4) to the mitogens phytohemagglutinin (PHA) and pokeweed [99]. Stimulation with phorbol myristate acetate and ionomycin also resulted in an increase in IFN-γ-producing CD4+ T cells and IL-2-producing CD8+ T cells in elderly individuals who walked regularly compared with sedentary elderly individuals [100]. An increase in the proportion of IL-2-producing T cells was also reported in a group of elderly women (62–86 years old) who underwent a 2-year intervention program of moderate physical activity when compared with a group of sedentary elderly women [101].

<table>
<thead>
<tr>
<th>Exercise type</th>
<th>Immunological parameters</th>
<th>Net immune effects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance</td>
<td>↑ Lymphocyte proliferation and cytokine production</td>
<td>Positive</td>
<td>[100,101]</td>
</tr>
<tr>
<td></td>
<td>↑ Costimulatory molecules on T lymphocytes</td>
<td>Positive</td>
<td>[102,104]</td>
</tr>
<tr>
<td></td>
<td>↑ DTH</td>
<td>Positive</td>
<td>[103]</td>
</tr>
<tr>
<td></td>
<td>↑ NK cells and phagocytic activity of neutrophils</td>
<td>Positive</td>
<td>[105]</td>
</tr>
<tr>
<td></td>
<td>↑ DCs and maturation</td>
<td>Positive</td>
<td>[106–109]</td>
</tr>
<tr>
<td></td>
<td>↓ Inflammatory background</td>
<td>Positive</td>
<td>[110–114,117]</td>
</tr>
<tr>
<td></td>
<td>Preserved telomere length in PBMC</td>
<td>Positive</td>
<td>[120,121]</td>
</tr>
<tr>
<td></td>
<td>↑ Antibody titer in response to influenza vaccination</td>
<td>Positive</td>
<td>[123–125]</td>
</tr>
<tr>
<td></td>
<td>↑ NK cell function, T-cell number and lymphocyte proliferation</td>
<td>Negative</td>
<td>[126–128]</td>
</tr>
<tr>
<td>Resistance</td>
<td>↑ PBMC subpopulations, cytokine production, lymphocyte proliferation</td>
<td>Negative</td>
<td>[129–132]</td>
</tr>
<tr>
<td></td>
<td>↑ DTH, NK cell cytotoxic activity; ↓ IL-6 serum concentration</td>
<td>Positive</td>
<td>[116]</td>
</tr>
</tbody>
</table>

DC: Dendritic cell; DTH: Delayed-type hypersensitivity; PBMC: Peripheral blood mononuclear cell.

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Table 2. Effects of chronic exercise on immunological parameters.
Another study showed an increase in CD25 expression by peripheral blood mononuclear cells stimulated with anti-CD3 in an elderly group who practiced moderate physical activity for more than 15 years when compared with a sedentary elderly group [102]. In this study, it was notable that, among the active elderly, a higher expression level of CD25 was correlated with more activity.

In most instances, mitogens were used in the experiments showing that the T lymphocytes of active elderly individuals responded to stimuli with greater proliferation and activation. This fact raises the question of whether physical activity could also have an impact on T-lymphocyte capacity when other physiological conditions were assayed, such as when specific microbial stimuli were used to induce such T-cell effector functions such as cytokine secretion and cytotoxicity. In this regard, Okutsu et al. used delayed-type hypersensitivity with purified protein derivative from Mycobacterium tuberculosis to evaluate the effect of 25 weeks of physical training on the Th1/Th2 response balance in the elderly [103]. The trained elderly presented an increased reactivity to the purified protein derivative and decreased IgG4 serum levels, with the latter being used as a marker for Th2 immune response. No changes in these parameters were found in the control sedentary group. Similar results were obtained by Shimizu et al. when evaluating the effects of a 6-month moderate physical training regimen on the expression of CD28 and the balance between CD4+IFN-γ+ T cells (Th1) and CD4+IL-4+ T cells (Th2) in elderly people [104]. Compared to sedentary individuals, the CD4+ T cells from the trained elderly presented increased CD28 and IFN-γ expression, although the percentage of CD4+IL-4+ T cells remained stable. These data support the hypothesis that regular physical activity favors in vivo Th1 immune responses in elderly people.

In addition to potentially inducing better adaptive immune responses, moderate physical activity appears to have a positive effect on the innate immune system. Yan et al. studied individuals who practiced aerobic physical activities twice weekly, for 1 h or more, for 3 years and verified that the number of NK cells increased significantly in active elderly individuals [105]. The phagocytic activity of neutrophils, which declines with aging, was also higher in an active elderly group than a sedentary elderly group.

Despite the key role of DCs in innate immunity and the subsequent adaptive immune responses, few studies have addressed the acute impact of different exercise intensities on DCs from young adults and athletes, and no studies have addressed the impact of regular physical activity on the elderly DC status. Sucháněk et al. showed that, after intense physical activity, young adults presented an increase in the number of peripheral blood DCs, both of myeloid and plasmacytoid origin [106]. Nickel et al. verified that the number of myeloid DCs increased after a marathon, whereas the plasmacytoid DCs decreased [107]. Chiang et al. demonstrated in mice that aerobic training was capable of modulating the development of DCs, which expressed higher levels of MHC class II molecules and IL-12 upon activation, suggesting that exercise training shifted DCs toward a more mature state [108]. Another experimental exercise protocol also showed that 5 weeks of running promoted an increase in murine DC numbers [109].

As discussed above, immunosenescence is accompanied by an increase in the inflammatory background known as inflammaging. Moderate physical activity (reaching 70–80% of the cardiac reserve) is associated with a lower percentage of peripheral blood monocytes and lower lipopolysaccharide-induced TNF-α production by these cells, including the CD14+CD16+ ‘inflammatory’ subpopulation [110,111]. In addition, the increase in aerobic physical activity performed by the elderly during their leisure time was associated with a decrease in serum levels of CRP, IL-6 and TNF-α and in the number of peripheral blood leucocytes [112–114]. Both the intensity and also the number of years over the lifetime that the activity had been performed appear to have a positive effect on the concentration of inflammatory markers, as individuals over 65 years with a history of many decades of physical activity presented a lower number of leukocytes and neutrophils and reduced concentrations of IL-6, IL-1, IL-1R antagonist and soluble TNF-R1 in comparison with sedentary individuals [115]. An 18-month period of progressive resistance training decreased serum IL-6 concentration in healthy 50–79-year-old men [116]. Ortega et al. studied women with fibromyalgia and demonstrated that a program of pool-aquatic exercise (8 months, twice-weekly 60-min sessions) resulted in diminished proinflammatory responses [117].

The effect of physical activity on the accumulation of memory T cells and the loss of the naive T-cell repertoire, which are typical of immunosenescence, was studied by Spielman et al. [118]. The T cells of 102 healthy men (18–61 years old)
were analyzed for senescent phenotype markers (KLRG1 and CD57) naive phenotype markers (CD28 and CD45RA), and a memory phenotype marker (CD45RO) expressed on the surface of CD4+ T cells and CD8+ T cells. Increase in age was found to be positively associated with an increase in the proportion of CD4+ and CD8+ senescent T cells (CD4+KLRG1+CD57+ and CD8+KLRG1+CD28-) and negatively associated with naive cells (KLRG1-/CD28+). One important measure of physical fitness is the maximal capacity of the body to transport and uptake oxygen during exercise of progressive intensity (maximal oxygen uptake [VO2 max]). VO2 max is assessed by an ergospyrometric test and is currently considered the gold standard of evaluating the maximal capacity of the cardiorespiratory system; indeed, it is the test most often used in athlete evaluation [119]. In Spielman’s study, VO2 max was inversely associated with senescent CD4+ and CD8+ T cells [118]. However, age was no longer associated with senescent or naive T cells when adjusted for VO2 max, whereas the inverse associations between VO2 max and T-cell subsets persisted after the adjustment for age. Collectively, these data showed that aerobic fitness is associated with a lower accumulation of senescent T cells, highlighting the beneficial effects of an active lifestyle on the aging of the immune system.

Studies that evaluated the effect of physical activity on telomere length in peripheral blood mononuclear cells of the elderly indicate that the telomere length is preserved in elderly individuals with a history of physical activity, either moderate or vigorous, and that this effect correlated with an improvement in VO2 max [120,121]. The mechanism that would be implicated with regard to this benefit is the increased activity of telomerase in active elderly when compared with sedentary individuals.

Each year, the influenza virus infection is responsible for high morbidity and mortality rates in the elderly population [122]. Although vaccination is the best preventive action, as stated earlier, the capacity to respond to immunizations is compromised in the elderly because of changes related to the humoral arm of the adaptive immune system. Data from two different studies by Kohut et al. suggest that moderate-to-vigorous exercise training in older adults may be associated with a greater mean fold increase in antibody titer in response to influenza immunization [123,124]. More recently, Woods et al. demonstrated increased seroprotection against influenza virus in elderly persons on a 10-month moderate aerobic activity program in comparison with elderly individuals who only participated in flexibility exercises [125].

No effect

Nieman et al. performed a transversal study in which they evaluated sedentary elderly women (67–85 years old) who were subjected to a 12-week moderate walking program or to flexibility exercises. Although an improvement in VO2 max of 12.6% was observed in the walking group, no effect was observed regarding such immunological parameters such as NK-cell function, T-cell number and lymphoproliferative response to PHA [126].

Two other studies with similar but slightly longer (6 and 12 months) interventional programs applied in sedentary individuals revealed similar results. There was an improvement in the VO2 max in the group performing moderate aerobic activity, but no effect on such immune parameters as lymphocyte subpopulations, proliferative responses and NK-cell activity [127,128].

Different protocols that investigated the effect of resistance exercise training (ranging from 6 weeks to 6 months) on the immunity of elderly subjects showed no changes in different aspects of peripheral blood mononuclear cell subpopulations, including their cell number, cytokine production and lymphocyte proliferation, as well as delayed-type hypersensitivity responses, compared with the pre-exercise levels [129–131].

The evaluation of a larger set of immunological parameters was performed by Raso et al. [132]. NK-cell cytotoxic activity, lymphoproliferative response to PHA and lymphocyte subpopulation determination (CD3, CD19, CD56, CD4 and CD8) and phenotype (CD25, CD28, CD45RA, CD45RO, CD69, CD95 and HLA-DR) were determined in elderly women subjected to a 12-month moderate resistance training program. Although the program resulted in increased muscle strength, no changes in the immunological parameters were observed compared with either a control group or the pre-exercise levels.

Conclusion & future perspective

There is now a strong body of evidence showing that aging is accompanied by severe alterations in the immune system, a process known as immunosenescence. Among these changes are alterations in T-cell subpopulation size, cytokine secretion pattern, cell replicative capacity and antibody production, all of which culminate in a proinflammatory state called inflammaging.
and diminished capacity to respond to new antigens. These alterations are closely related to the increased mortality and morbidity rates observed in this population. However, the role of exercise on the prevention or treatment of immunosenescence is virtually unknown.

In fact, physical activity may act as a stress agent on the human body, leading to adaptations at the tissue, cellular, molecular and systemic levels. Several studies show that physical activity can be an important factor for either preventing or treating cardiac and neurological diseases and diabetes [133–135]. With regard to the immune system, it has been reported that there is an increase in the recruitment of NK cells to peripheral blood during physical activity [136,137], which rapidly decreases after the cessation of activity [138]. Neutrophils are also increased during exercise, and the number remains elevated for several hours after activity cessation. In the adaptive immune system, the number of lymphocytes in circulation increases during exercise, then decreases to levels below those prior to exercise [139]. Other studies have shown that marathoners present with more airway infections 3–72 h after competition or even 2 weeks after competition [97,98].

Data gathered from the literature regarding the effects of physical activity on immune system aging are still limited and conflicting, with the existing reports either advocating benefits or asserting a lack of evidence. It is likely that the conflicting data may reflect the heterogeneity of study protocols, with different types, intensities and program lengths, and the distinct immunological parameters assayed. In addition, genetic and environmental factors can overcome the effect of exercise training on physical fitness. Exercise as part of a healthy lifestyle has already been shown to provide long-term benefits with regard to cardiovascular, cognitive, psychosocial and other aspects of the elderly. If positive effects are also observed for immunosenescence, exercise could be a highly cost-effective measure to improve human quality of life compared with the other strategies currently being pursued.

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### Executive summary

- There is now a strong body of evidence showing that aging is accompanied by severe alterations in the immune system, a process known as immunosenescence. Among these changes are alterations in T-cell subpopulation size, cytokine secretion pattern, cell replicative capacity and antibody production, all of which culminate in a proinflammatory state called inflammaging and diminished capacity to respond to new antigens. These alterations are closely related to the increased mortality and morbidity rates observed in this population.
- Although the impact of exercise on the immune system is an area of extensive research, most studies have focused on the responses to acute exercise, but only a few have addressed the immune response to exercise training in the long term, particularly in elderly people.
- Data gathered from the literature regarding the effects of physical activity on immune system aging are still limited and conflicting, with the existing reports either advocating benefits or asserting a lack of evidence. It is likely that the conflicting data may reflect the heterogeneity of study protocols, with different types, intensities and program lengths, and the distinct immunological parameters assayed.
- Exercise as part of a healthy lifestyle has already been shown to provide long-term benefits with regard to cardiovascular, cognitive, psychosocial and other aspects of the elderly. If positive effects are also observed for immunosenescence, exercise could be recommended as an ‘immunotherapy’, representing a highly cost-effective measure to improve human quality of life compared with the other strategies currently being pursued.

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Papers of special note have been highlighted as: (* of interest)


Preventing or reversing immunosenescence: can exercise be an immunotherapy?

Addresses the functionality of the immune system in the context of latent and chronic infections.


Addresses the functionality of the immune system in the context of latent and chronic infections.


Almanzar G, Schweiger S, Jenewein B et al. Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-cell repertoire, which may be the basis for an imbalance in the cytokine production profile in elderly persons. J. Virol. 79(6), 3675–3683 (2005).


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An important study that discusses the immunosurveillance against CMV and its role on the longevity of the very old.


Discusses the controversies of the interface between immunosenescence and CMV, in particular regarding their possible clinical implications.


Emphasizes the possible biomarkers of mortality, especially of the thymus function reduction.

Preventing or reversing immunosenescence: can exercise be an immunotherapy?


