THE IMMUNE CLOCK: HOW AGING REDUCES THE BODY'S DEFENSE AND HOW WE CAN SLOW IT DOWN

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ABSTRACT

Immunosenescence relates to the gradual decline in immune system function associated with aging. This process contributes to increased susceptibility to infections, lower vaccine response, and higher incidence of inflammatory and neoplastic diseases in the elderly. Among the main causative factors are quantitative and functional changes in T and B cells, the accumulation of senescent cells, chronic low-grade inflammation ("inflammaging") and imbalance in cytokine production. Advances in medicine have provided promising coping strategies. Among the emerging clinical methods are the use of senolytics (drugs that eliminate senescent cells), immune modulators, and therapies based on stem cells and microbiome. In addition, vaccine personalization for the elderly has been studied with a focus on increasing immune efficacy in this age group. At the same time, lifestyle interventions have a strong impact on attenuating immunosenescence. Regular physical exercise, especially moderate intensity, improves the immune response and reduces inflammatory markers. A balanced diet, rich in antioxidants, fiber, vitamins (such as A, C, D, E) and omega-3, also plays a central role in modulating immunity and protecting against immune aging. Therefore, the combination of innovative clinical approaches with healthy habits represents the most effective and sustainable strategy to mitigate the effects of immunosenescence and promote healthy aging.

Keywords: Immunosenescence. Healthy aging. Immunological interventions. Lifestyle and immunity.

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INTRODUCTION

Aging is a complex biological process, mediated by different factors and characterized by a gradual deterioration of physiological functions and an increase in sensitivity to diseases, whether infectious, chronic or neoplastic. Several organ systems are affected by aging, where the immune system stands out for its importance in maintaining homeostasis and defending against infectious agents and tumor cells. Immunosenescence, a term that refers to the aging of the immune system, is a phenomenon characterized by a series of structural and functional changes that compromise the body's ability to respond effectively to aggressions, leading to an increased susceptibility to infectious, autoimmune, and neoplastic diseases. The growing number of older adults worldwide makes understanding the mechanisms of immunosenescence and developing strategies to modulate this process a public health priority.

Immunosenescence is characterized by a series of alterations that include decreased production of T and B cells, alteration in the function of antigen-presenting cells, increased production of pro-inflammatory cytokines, and decreased response to vaccines, directly increasing the susceptibility of the elderly to various diseases, such as opportunistic infections, autoimmune diseases, and cancer, significantly compromising quality of life and longevity. Thus, immunosenescence not only increases susceptibility to diseases, but is also related to reduced life expectancy and quality of life in the elderly. Epidemiological studies have shown an inverse correlation between the functional status of the immune system and longevity. In addition, immunosenescence can contribute to the development of chronic diseases, such as atherosclerosis and type 2 diabetes mellitus, which are important determinants of mortality in the elderly. Understanding the molecular and cellular mechanisms underlying immunosenescence is critical for developing new strategies to promote healthy aging and increase life expectancy.

The molecular and cellular mechanisms underlying immunosenescence are complex and multifactorial. Thymic involution, characterized by decreased production of naïve T cells, is one of the main events associated with the aging of the immune system. In addition, cellular senescence, characterized by telomere shortening and the accumulation of DNA damage, contributes to T and B cell dysfunction. Epigenetic changes, such as DNA methylation and histone modifications, also play an important role in regulating the immune response during aging.

The clinical consequences of immunosenescence are diverse and wide-ranging. The decreased effectiveness of the immune response increases the susceptibility of older people to infections, such as pneumonia and influenza, which can lead to serious

complications and even death. In addition, immunosenescence is associated with a higher risk of developing autoimmune diseases, such as rheumatoid arthritis and Systemic Lupus Erythematosus, and neoplastic diseases, such as cancer. The reduced efficacy of vaccines in the elderly is also an important consequence of immunosenescence, compromising the prevention of infectious diseases.

In view of the complexity of immunosenescence and its significant implications for the health of the elderly population, we aim to review the molecular and cellular mechanisms underlying the immunosenescence process, its clinical consequences, and possible strategies to modulate the immune response in elderly individuals.

DISCUSSION

Immunosenescence leads to a gradual decrease in immune efficiency, affecting both innate and adaptive immunity, involving modifications in several components of the immune system, including reduced production of immune cells, alterations in cellular communication, and a chronic low-grade inflammatory state, known as "*inflammaging*"". In the following topics, we will explore in detail how these changes impact different aspects of the immune response and their implications for health throughout aging.

INVOLUTION OF THE THYMUS

The thymus is a primary lymphoid organ located in the upper mediastinum, playing a crucial role in the maturation of T lymphocytes, which are essential for the adaptive immune response. During childhood, the thymus reaches its maximum development, weighing between 30 and 40 grams at puberty. From this period on, a process of involution begins, characterized mainly by a decrease in the migration of naïve T lymphocytes to the periphery and by changes in the architecture and composition of the thymic microenvironment. These modifications include the increase in fat cells and the decrease and disorganization of the cortical and medullary regions of the thymus. This process plays an important role in immunosenescence, as the reduction in the production of naïve T lymphocytes results in a decrease in the repertoire of T cell receptor (TCR) clones in the periphery, limiting the adaptive immune response against new pathogens. Although in humans the number of naïve T lymphocytes remains close to the levels found in young individuals, thanks to the proliferation of naïve T lymphocytes in peripheral lymphoid structures, the immune response capacity is still impacted.

CELLULAR SENESCENCE

Since the early 1960s, studies have shown that senescent cells accumulate exponentially with increasing chronological age in various tissues. Early studies by Hayflick and Moorhead (1961) suggested a relationship between senescence and aging. Subsequent findings evidenced the presence of senescent cells *in vivo* and an increase in their number with age, corroborating the hypothesis that senescence itself can drive aging and is one of its main characteristics.

Cellular senescence also has deleterious effects, as it can hinder tissue repair and regeneration, contributing to the aging of tissues and the body. This is due to the accumulation of senescent cells, depletion of stem cell/progenitor compartments, and secretion of the senescence-associated secretory phenotype (SASP). Senescent cells have been observed in a variety of age-related diseases, such as atherosclerosis, diabetes, lung disease, and many others.

Although senescence is associated with aging, cells can undergo senescence regardless of the age of the organism due to different signs in addition to telomere shortening. Studies with transgenic mouse models have allowed the detection of senescent cells in different age-related pathologies and have made it possible to develop genetic or pharmacological strategies to demonstrate that selective elimination of senescent cells can prevent or delay age-related tissue dysfunction, prolonging lifespan and improving health.

Cellular senescence is a cellular program that acts as a double-edged sword, with beneficial and harmful effects on the health of the organism, and is considered an example of evolutionary antagonistic pleiotropy. Next, we will evaluate how the aging of the immune system affects each major cell group of the immune system and the cellular and molecular mechanisms involved.

Natural killer cells

Natural Killer (NK) cells are a type of lymphocyte that plays a crucial role in innate immunity. They are responsible for identifying and eliminating virus-infected cells, tumor cells, and foreign cells in the body, without the need for specific antigen recognition. NK cells have specific receptors, such as *killer immunoglobulin-like* (KIR) receptors, that allow them to detect target cells that do not express certain surface antigens. Under normal conditions, NK cells release granzymes and perforins, which are enzymes that induce apoptosis (programmed cell death) in target cells. In addition, they can secrete cytokines that help modulate the immune response, promoting the activation of other immune cells, such as T lymphocytes.

In aging, changes occur in the cellular microenvironment, including tissue composition and cytokine profile. These changes create a less favorable environment for NK cells, reducing their ability to proliferate and respond effectively to pathogens. The accumulation of senescent cells and the presence of chronic inflammation inhibit NK cell function, compromising immune surveillance.

For an optimal function of NKs, a balanced profile of cytokines (molecules essential for communication between immune cells) is necessary, however, in aging, there is an imbalance in their production, with an increase in pro-inflammatory cytokines (such as IL-6 and TNF-α) and a reduction in anti-inflammatory cytokines. This imbalance promotes a chronic inflammatory state, which can deregulate the function of NK cells, reducing their ability to recognize and eliminate infected or tumor cells, leaving the individual poorly susceptible to infectious and neoplastic diseases. Studies carried out by Sylwester (2005) will relate chronic infections of viruses of the *Herpesviridae family* with NK alteration, reducing the diversity and efficacy of the immune response.

Another aspect that negatively corroborates the proper functioning of NK cells is the HPA (hypothalamic-pituitary-adrenal) axis, which regulates the response to stress and the release of hormones such as cortisol. With aging, the regulation of this axis can become dysfunctional, resulting in elevated cortisol levels. Cortisol has immunosuppressive effects, including inhibition of NK cell activity. This impairs the ability of these cells to perform their cytotoxic and cytokine-producing functions, weakening the overall immune response.

T lymphocytes

T cells, or T lymphocytes, are essential components of the adaptive immune system. They play a crucial role in identifying and eliminating pathogen-infected cells, as well as regulating the immune response. There are different types of T cells, including helper T cells (CD4+) and cytotoxic T cells (CD8+), each with specific functions. CD4+ cells, also known as T *helper* cells, are vital for coordinating the immune response. They do not directly attack pathogens, but they help activate other immune cells. TCD4+ cells recognize antigens presented by molecules of the major histocompatibility complex class II (MHC II) in antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells.

Once activated, TCD4+ cells proliferate and secrete cytokines that orchestrate the immune response. For example, they can activate B cells, promoting the differentiation of these cells into antibody-producing plasma cells, which are essential for neutralizing pathogens. They also activate cytotoxic T cells (CD8+), increasing the effectiveness of

these cells in destroying infected and tumor cells, as well as recruiting macrophages, increasing the ability of these cells to phagocytize pathogens and damaged cells.

In turn, Follicular Helper T (FH T) cells are a specialized subset of CD4+ T cells that play a crucial role in the immune response by providing essential signals for proliferation, isotype switching, and somatic mutation of B cells in germinal centers. These cells are found in lymphoid organs and peripheral blood, and their function is vital for the production of immunoglobulins.

With aging, significant modifications occur in the phenotype and function of FH T cells, resulting in a decrease in the effectiveness of the immune response. These changes include loss of proliferative capacity, reduction in CD28 expression, and increased production of inflammatory cytokines such as IFN-γ. In addition, dysfunctional FH T cells have been linked to an increase in the prevalence of cancer, autoimmune diseases, and cardiovascular disease, conditions that are particularly common in the elderly. On the other hand, Regulatory Follicular T cells (FR T) perform opposite functions to FH T cells, regulating the immune response to prevent autoimmunity and excessive inflammation. Changes in the proportion of FH/T FR T cells are a relevant feature of aging, contributing to immunosenescence. Recent findings suggest that FH T cells and their subsets may be involved in atherosclerosis, cancer, and autoimmunity. Studies indicate that the change in FH T cell function with age can lead to an inadequate immune response to infections and vaccines, increasing the vulnerability of the elderly to infectious and malignant diseases.

CD8+ cells, also known as killer T cells, have the main function of eliminating cells infected by viruses and cancer cells. They recognize antigens presented by molecules of major histocompatibility complex class I (MHC I) in all nucleated cells of the body. In addition to their effector functions, T cells play a crucial role in maintaining immune system homeostasis. They help prevent autoimmune responses, where the immune system attacks healthy tissues in the body, through central and peripheral tolerance mechanisms. Regulatory T cells (T regs), a subgroup of TCD4+ cells, are essential to this process, suppressing excessive immune responses and maintaining self-tolerance.

With the impact of the immunosenescence of these cells, these defense mechanisms are affected through some mechanisms. Among them, we can highlight the decrease in the population of *naïve* T lymphocytes. Thymic involution reduces the production of new TCD4+ cells, resulting in a lower diversity of T cells, limiting the immune system's ability to respond to new antigens, and increasing vulnerability to infection. With aging, there is an increase in the number of memory TCD4+ cells due to chronic infections.

These memory cells replace *naïve* T cells, compromising their ability to respond to new pathogens.

To compensate for the lack of new TCD4+ cells, a compensatory proliferation of existing cells occurs. However, this homeostatic proliferation is not always sufficient to maintain an effective immune response, especially in the face of new immune challenges. Aging TCD4+ cells have a reduced ability to proliferate in response to antigenic stimuli, compromising the immune system's ability to mount an effective response against infections and tumors. The telomeres of TCD4+ cells age and become shorter, leading to replicative senescence. Short telomeres are an indicator of cellular aging and are associated with a reduction in the ability to divide

In addition, the increase in chronic inflammation, known as inflammaging, affects the function of TCD4+ cells. Inflammaging is characterized by the continuous production of pro-inflammatory cytokines, which can lead to dysregulation of the immune system and contribute to several age-related diseases.

Aging TCD8+ cells have a reduced ability to eliminate infected or cancerous cells. The effectiveness of cytotoxic function is essential for the elimination of virus-infected cells and tumor cells, and its reduction may increase susceptibility to these conditions. Like TCD4+ cells, TCD8+ cells also accumulate memory cells due to chronic infections. This accumulation may restrict responsiveness to new antigens, since the diversity of the T receptor repertoire is reduced.

Compensatory proliferation also occurs in TCD8+ cells to maintain the number of T cells. However, this homeostatic response may be inadequate to maintain effective immunosurveillance against new pathogens or neoplastic cells. The telomeres of TCD8+ cells also shorten with aging, leading to replicative senescence. Senescent TCD8+ cells are less effective at the immune response, contributing to the increased incidence of infections and cancer in elderly populations. Increased chronic inflammation also affects TCD8+ cells, impairing their function. Inflammaging is a feature of aging that exacerbates immune dysfunction, promoting an environment conducive to chronic and degenerative diseases. These cumulative changes in TCD4+ and TCD8+ cells contribute to immunosenescence by reducing the immune system's ability to protect against infections, autoimmune diseases, and cancer.

Macrophages

Macrophages are essential cells of the immune system, responsible for ingesting and destroying pathogens, dead cells, and cellular debris. However, with aging,

macrophages undergo a series of changes that impair their function and health. Studies show that aging leads to a decrease in phagocytosis, which is the ability of macrophages to engulf and destroy pathogens, and a reduction in immune resolution, which is the process of cessation of the inflammatory response after the pathogen has been eliminated, resulting in chronic inflammation.

Another significant change is the increase in markers associated with senescence, such as p16^INK4a and p21, which indicate a state of irreversible macrophage inactivation. These senescent macrophages not only lose their ability to fight infections, but they also begin to secrete inflammatory cytokines, contributing to inflammatory aging. The production of inflammatory cytokines, such as IL-6 and TNFα, is increased in aged macrophages, exacerbating systemic inflammation.

Autophagy, a cellular process of degradation and recycling of cellular components, is also reduced in aging macrophages. The decrease in autophagy leads to the accumulation of damaged cellular components and increased oxidative stress, which can cause damage to DNA and other cellular structures. In addition, the expression of Toll-like receptors (TLR), which are crucial for pathogen detection, is reduced in aging macrophages, further compromising immune responsiveness.

In addition, numerous studies have discovered intrinsic aging mechanisms in macrophages, harmful factors released by these immune cells, and the interaction with senescent mesenchymal cells, which together drive age-related bone loss. Bone marrow macrophages have recently been proposed to be responsible for megakaryocytic change during aging and overall maintenance of the hematopoietic niche. Studies on extraskeletal macrophages have shed light on possible mechanisms conserved within bone and highlighted the importance of these cells in systemic aging. New discoveries in this area are of utmost importance to fully understand the pathogenesis of osteoporosis in elderly individuals.

Neutrophils

Neutrophils are a group of leukocytes that are primarily functional against bacterial and fungal infections. Their main functions include phagocytosis, in which they encompass and destroy invading microorganisms; the release of digestive enzymes that help degrade pathogens; the production of cytokines that modulate the immune response; and the formation of NETs (*Neutrophil Extracellular Traps*), which capture and eliminate bacteria.

Recent studies indicate that neutrophils, as they age, have aberrant functions that may be associated with cellular senescence. These senescent neutrophils show a decrease

in phagocytosis capacity and cytokine production, as well as an increase in the production of reactive oxygen species (ROS), which can cause tissue damage. Studies have shown that prolonged exposure to inflammatory cytokines such as IL-6, TNF-α and IL-1β contributes significantly to these changes. These factors create a persistent inflammatory environment that leads to neutrophil dysfunction. In addition, epigenetic changes, such as DNA methylation, have been associated with decreased gene expression related to the immune response.

Host aging also significantly affects neutrophil function. Older people often have a compromised immune response, characterized by increased senescent neutrophils and a higher prevalence of chronic inflammation. This condition is associated with high levels of cytokines such as IL-6 and TNF-α, which perpetuate the inflammatory state. Other factors that lead to neutrophil senescence include oxidative stress, which is exacerbated by the continuous production of ROS, and failure of cellular repair mechanisms, which become less effective with age.

In this way, neutrophil immunosenescence compromises the immune response of the elderly, resulting in greater susceptibility to various pathologies. Among these pathologies are bacterial and fungal infections, due to the decrease in phagocytosis capacity and cytokine production, making the elderly more vulnerable to infections. Autoimmune diseases are also a concern, as immunosenescence can lead to a dysregulated immune response, increasing the risk of conditions such as lupus and rheumatoid arthritis. In addition, chronic inflammation and immunosenescence are associated with a higher risk of cancer, as the aging immune system is less effective at detecting and eliminating cancer cells. Cardiovascular diseases, such as atherosclerosis and myocardial infarction, are also more common due to chronic inflammation. Type 2 diabetes is another risk, since chronic inflammation and insulin resistance are associated with neutrophil senescence. Finally, neurodegenerative diseases like Alzheimer's and Parkinson's are also linked to chronic inflammation.

CYTOKINS

Cytokines play a central role in regulating immune responses, mediating communication between cells of the immune system and coordinating processes such as inflammation, cell proliferation, and response to pathogens. In the context of immunosenescence, the cytokine production profile undergoes significant changes, contributing to the decline in immune efficiency associated with aging. One of the main markers of this process is the increased production of pro-inflammatory cytokines, such as

IL-6, TNF-α and IL-1β, leading to the establishment of a chronic low-grade inflammatory state, known as *inflammaging*. This imbalance in cytokine signaling compromises the immune response, favoring the emergence of chronic diseases, recurrent infections, and reducing vaccine efficacy in the elderly. In the following topics, the mechanisms by which cytokines influence immunosenescence and their implications for health during aging will be discussed in detail.

Interleukin 11 (IL-11) is a pro-inflammatory and profibrotic cytokine of the IL-6 family, which has been identified as a key regulator in aging. Recent studies have shown that IL-11 is progressively upregulated in tissues with age, influencing an ERK-AMPK-mTORC1 axis that modulates aging pathologies at the cellular, tissue, and organic level. In addition, IL-11 has been linked to several aging-related diseases, such as cancer, fibrosis, and multimorbidities.

Interleukin-7 (IL-7) is a cytokine that is essential for T cell homeostasis and survival. It plays a crucial role in the development and maintenance of *naïve* T cells, which are important for the adaptive immune response. IL-7 is produced primarily by stromal cells of the bone marrow and thymus. Thus, IL-7 is particularly important during the maturation of T cells in the thymus. It provides survival signals that prevent apoptosis of developing T cells. In addition, IL-7 promotes the transition from double-positive T cells (CD4+CD8+) to CD4+ or CD8+ positive single T cells in the thymus, ensuring the formation of a diverse repertoire of *naïve* T cells. In the context of aging, IL-7 production may decrease, contributing to the reduction in the *naïve* T cell population seen in older adults. This can lead to immunosenescence, where the immune system's ability to respond to new antigens is compromised.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by a variety of cells, including macrophages, T lymphocytes, and endothelial cells, in response to infections and injury. It plays a central role in regulating the inflammatory and immune response. Unlike other inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), IL-6 has been identified as a useful and convenient marker of peripheral inflammation in older adults with various comorbidities. The authors noted that IL-6 concentration was a more consistent indicator of chronic inflammation than TNF-α and IL-1β. This may be due to the fact that IL-6 not only acts locally at the sites of infection and injury, but also exerts systemic effects by stimulating the production of acute phase proteins by the liver, such as C-reactive protein (CRP), which is widely used as a marker of inflammation.

Chronic inflammation, often evidenced by elevated levels of IL-6, is associated with a number of age-related diseases, such as cardiovascular disease, type 2 diabetes, neurodegenerative diseases (such as Alzheimer's and Parkinson's), and certain forms of cancer. The continued presence of IL-6 in the blood can contribute to the perpetuation of an inflammatory state that, in turn, aggravates these conditions. For example, in cardiovascular disease, IL-6 can promote atherogenesis, the formation of plaques on arterial walls, by inducing other inflammatory mediators and cell adhesion molecules.

POSSIBLE STRATEGIES TO SLOW DOWN IMMUNOSENESCENCE

Several therapeutic approaches have been explored with the aim of slowing down immunosenescence and mitigating its impacts on health. Strategies that involve nutritional interventions, regular physical exercise, stress management, use of bioactive compounds, pharmacological therapies, and even genetics show potential in preserving immune function throughout aging. In addition, advances in biotechnology and regenerative medicine open up new perspectives for more targeted and effective interventions.

Involution of the thymus

Regarding the problem of thymus involution, there are several models of regeneration of this organ that have been proposed involving a calorie-restricted diet, blockage in the production of sex hormones, treatment with pituitary hormones, growth factors and cytokines, which recover the function of thymic epithelial cells and thymocytes, and, consequently, thymic function. Some of these models are already being employed in clinical studies with human patients to investigate the role of these substances in thymic regeneration after infections, bone marrow transplantation, and during aging.

Treatment with growth hormone (GH) promoted an increase in thymic function and in the number of circulating naïve and total CD4+ T lymphocytes . In addition, some studies have shown that the joint administration of GH with highly active antiviral therapy (HAART) in lipodystrophic patients with HIV-1 improves the specific response of T lymphocytes to the virus.

In addition to pharmacological strategies, experimental models in tissue engineering, cell therapy, and gene therapy are being explored for the creation of a functional thymic tissue. Pioneering studies have demonstrated in *vitro* differentiation of T lymphocytes from human hematopoietic precursor cells in mouse thymic stromal co-culture systems in three-dimensional tantalum scaffolds (CellFoam). This observation favored the idea of constructing an in vitro organ, susceptible to transplantation, to replace the senescent

thymus. In this context, the identification of thymic epithelial precursor cells capable of originating the subtypes of TEC can be an important tool for the reestablishment of the thymic microstructure.

Telomere length

Regarding senescence, some cellular treatments have been proposed, such as those that demonstrated that hyperbaric oxygen therapy (HBOT) can increase telomere length and decrease immunosenescence in isolated blood cells. Repeated intermittent hyperoxic exposures, using HBOT-specific protocols, may induce regenerative effects that normally occur during hypoxia. The aim of the study was to evaluate whether HBOT affects telomere (TL) and senescent cell concentrations in a normal, non-pathological, aging adult population. The telomere length of helper T cells, cytotoxic T, natural killer, and B cells increased significantly by more than 20% after HBOT. The most significant change was seen in B cells, which increased in the 30th session. There was also a significant decrease in the number of senescent helper T cells and the percentages of cytotoxic senescent T cells also decreased considerably post-HBOT. Thus, the study indicates that HBOT can induce significant senolytic effects, including substantial increase in telomere length and elimination of senescent cells in aging populations.

Neutrophils

Regarding neutrophil senescence, cell-based therapies, especially those using human halogen mesenchymal stem cells (MSCs), have shown great promise in the treatment of neutrophil senescence. MSCs have immunomodulatory and tissue-repairing properties, and early clinical studies indicate that the administration of MSCs in frail older adults is feasible, safe, and potentially effective in improving signs and symptoms of frailty.

IGF-1

Insulin-like growth factor 1 (IGF-1), a growth hormone (GH) mediator, was later shown to induce the secretion of interleukin-7 (IL-7) in cultured primary human thymic epithelial cells. This finding suggests a crucial role of IGF-1 in regulating the immune system, particularly in the context of stress. Studies highlight that the GH/IGF-1 somatotropic axis is at the intersection between immunosenescence and frailty, suggesting that modulation of the GH/IGF-1 axis could be an effective strategy to combat the negative effects of stress on immune function, promoting better resilience to stress in the elderly.

Inhibition or modulation of cytokines

Inhibition of cytokines such as IL-11 has shown therapeutic promise in preclinical trials, with the ability to regenerate kidney cells, reduce hepatocyte death, and mitigate liver fibrosis. Recent studies highlight that IL-11 inhibition can lead to an improvement in health and longevity in animal models, with potential application in humans. Similarly, studies also suggest that IL-6 monitoring may offer a useful tool for the assessment of chronic inflammation in the elderly, allowing early and more targeted interventions, such as IL-6 modulation, which has shown potential in controlling chronic inflammation due to immunosenescence. On the other hand, the administration of exogenous IL-7 has been studied as a potential strategy to restore *naïve T cell function* in the elderly, improving the immune response and reducing susceptibility to infections and diseases.

Inhibition of the Rapamycin Target Pathway (mTOR)

Inhibition of the rapamycin target pathway (mTOR) has shown promising evidence in multi-species studies extending life expectancy and delaying the onset of age-related diseases. However, the application of these results in humans is still uncertain. A study conducted in 2014 evaluated whether the mTOR inhibitor RAD001 could improve immunosenescence in elderly volunteers, as measured by response to influenza vaccination. The results indicated that RAD001 increased vaccine response by about 20% and reduced programmed death receptor-1 (PD-1) expression in CD4 and CD8 T lymphocytes, suggesting potential benefits in immunosenescence.

Inhibition of mTOR is known to regulate crucial cellular processes such as cell growth, metabolism, and immune response. In mice, rapamycin extended lifespan and improved age-related conditions such as tendon stiffness, cardiac dysfunction, and cognitive decline. These effects are attributed to the regulation of autophagy, a process of eliminating damaged cellular components, and the modulation of inflammation. These findings indicate that RAD001 not only improved the immune response to vaccine antigens, but also reduced the percentage of CD4 and CD8 T lymphocytes expressing PD-1, a receptor that inhibits T cell signaling and is more highly expressed with age. These results suggest that inhibition of mTOR may have beneficial effects on immunosenescence in the elderly, potentially improving the health and quality of life of this population.

Lifestyle: diet and training influencing immunosenescence

Dietary components can directly affect inflammation, especially low-grade inflammation related to aging (*inflammaging*). Healthy diets, such as the Mediterranean diet,

are associated with lower concentrations of inflammatory mediators, such as C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), which are characteristic markers of this type of inflammation.

Among the components of a healthy diet, higher intake of whole grains, vegetables, fruits, nuts, and fish is associated with lower inflammation. These foods contain nutrients and bioactive compounds that can modulate inflammation and improve overall health. For example, the omega-3 fatty acids present in fish have anti-inflammatory properties, while the fiber present in whole grains can improve gut health and reduce systemic inflammation. In this context, a decrease in senescence in NK cells is observed, with diet being the main pivot. In this scenario, a diet rich in essential nutrients, such as vitamins (C and E), minerals (such as zinc), antioxidants, and omega-3 fatty acids, has been shown to be effective and fundamental for mitigating senescence. These nutrients protect immune cells against oxidative stress and support their functionality.

Anti-inflammatory diets, such as the Mediterranean diet, can reduce chronic inflammation and improve NK cell function (Novak & Mollen, 2015). Recent studies highlight the role of probiotics and polyphenols. Probiotics increase NK cell activity, while polyphenols, present in fruits, green tea, red wine, and dark chocolate, have antioxidant and anti-inflammatory properties, promoting a healthy cellular environment. Probiotic supplementation has been shown to significantly improve immune activity, even in the short term. Combined with diet, regular physical exercise, such as walking, light jogging, and resistance exercise, improves the cytotoxic activity of NK cells, helping them recognize and eliminate infected or tumor cells. It also promotes the production of cytokines that modulate the immune response while maintaining the functionality of NK cells in the elderly.

As a two-way street, the diet that can be a great ally in the fight against immunosenescence, when done with certain foods can cause *inflammaging* by promoting chronic inflammation in the body. Of these foods, those high in refined sugars, saturated and trans fats, and refined carbohydrates are known to increase levels of inflammatory cytokines, such as C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), leading to oxidative stress, insulin resistance, and gut dysbiosis, all factors that contribute to premature aging and chronic disease.

Another important point to be mentioned is protein-energy destruction (PEM), a nutritional condition that occurs when there is an inadequate intake of proteins and calories, resulting in multiple nutritional deficiencies. In elderly individuals, especially those over the age of 75, PEM is often associated with deficiencies in essential micronutrients such as vitamin D, zinc, and vitamin E. These deficiencies aggravate the condition of PEM and

contribute to increased frailty and susceptibility to infections. This frailty in the elderly is characterized by a reduction in strength, endurance, and physiological function, increasing vulnerability to adverse health outcomes. PEM is a determining factor in this syndrome, as it contributes to the loss of muscle mass (sarcopenia) and the impairment of the immune system. Deficiency of essential micronutrients, such as vitamin D, which is crucial for immune function and bone health, further aggravates this situation.

Elderly patients with PEM have a compromised immune response, making them more susceptible to infections. Fungal infections, for example, are often seen in these patients due to immunodeficiency. Vitamin E acts as an antioxidant that protects immune cells from oxidative damage, while zinc is essential for immune function and T cell production. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends that older adults with MEP receive an adequate intake of energy and protein, as well as nutritional supplementation when needed. The identification of EMP can be done through laboratory tests, such as the measurement of serum albumin, which is a marker of malnutrition. Treatment of PEM should include gradual replacement of nutrients orally or enterally, as needed, to improve nutritional status and reduce susceptibility to infections.

Furthermore, the emerging importance of dietary factors such as phytochemicals, probiotic bacteria, fatty acids, and micronutrients as possible modulators of immunosenescence and cellular senescence has been widely discussed in the scientific literature. These nutritional bioactive components have shown significant potential in modulating the immune response and inflammatory state, which makes them promising for nutrition-oriented therapeutic interventions during aging. Phytochemicals, found in vegetables, have anti-inflammatory and antioxidant properties that can help modulate the immune response and prevent cellular senescence. For example, studies indicate that polyphenols, present in fruits and vegetables, can reduce the production of pro-inflammatory cytokines, modulating the immune response in a beneficial way.

Probiotic bacteria also influence intestinal and systemic immunity, promoting a healthy gut environment that is crucial for immune function. They help maintain the integrity of the intestinal barrier, preventing the translocation of pathogens and modulating the production of inflammatory cytokines. Probiotics have been shown to improve the innate and adaptive immune response, which is especially important for the elderly population, whose immune function is often compromised.

Fatty acids, especially omega-3s, are also known for their anti-inflammatory effects, helping to reduce chronic inflammation associated with aging. Studies show that omega-3 fatty acids can decrease the production of inflammatory eicosanoids, such as

prostaglandins and leukotrienes, modulating the immune response in a positive way. In turn, micronutrients such as vitamin D and zinc are essential for immune function. Vitamin D acts as an immune modulator. The active form of vitamin D, 1,25-dihydroxy-vitamin D (1,25(OH)2D), interacts with the vitamin D receptor (VDR) present in almost all human cells, directly influencing the differentiation, proliferation, and apoptosis of immune cells, such as T lymphocytes. Studies suggest that vitamin D deficiency is associated with an increased risk of autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus.

Omega-3 fatty acids, especially EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), have anti-inflammatory properties. They modulate the immune response by reducing the production of pro-inflammatory cytokines and increasing anti-inflammatory ones, which may help decrease systemic inflammation and improve the immune response in chronic inflammatory conditions.

Zinc is crucial for immune cell development and function by participating in intracellular signaling and enzyme activity of T and B cells. Zinc deficiency can lead to a compromised immune response, increasing susceptibility to infections and autoimmune diseases. This trace element plays a vital role in maintaining the immune system, repairing tissues, and protecting against infection, and is especially important in old age. Zinc deficiency, which is quite prevalent among the elderly, is associated with a number of health problems, such as increased susceptibility to infections, decreased anti-tumor immunity, and attenuated response to vaccination. In addition, zinc deficiency is associated with accelerated aging and an increased risk of chronic diseases. Studies show that zinc supplementation can reduce inflammation, improve immune response, and promote successful aging, with better overall health and quality of life for seniors. An optimized zinc status can therefore be a determining factor in achieving a healthy and active old age.

Regarding the practice of physical exercise, numerous studies highlight its importance in modulating the immune system and reducing inflammatory markers in the elderly. The results demonstrated that both aerobic and resistance exercise were effective in increasing CD3+, CD4+, and CD8+ T cell counts, as well as increasing IL-10 levels and reducing IL-6 and TNF-α levels. However, the comparison between the two groups revealed that aerobic exercise had a more significant impact on modulating the immune system and reducing inflammatory mediators.

These findings are particularly relevant for the development of health intervention programs for older adults, since aerobic exercise can be considered a more effective strategy to improve immunity and reduce chronic inflammation associated with aging. The

reduction in the levels of inflammatory cytokines such as IL-6 and TNF-α and the increase in IL-10 can contribute to a better quality of life and greater longevity in the elderly population. In addition, the study highlights the need for personalized approaches in prescribing physical exercises for the elderly, taking into account their individual capabilities and health status. Implementing supervised aerobic exercise programs can therefore be a powerful tool in promoting healthy aging, preventing inflammatory diseases, and strengthening the immune system.

In summary, these studies offer solid evidence that aerobic exercise should be a priority in modulating the immune system and inflammatory markers in the elderly. These results provide a scientific basis for the adoption of physical exercise practices that aim to improve the immune health and quality of life of the elderly, highlighting the transformative potential of aerobic exercise in promoting healthier and more active aging. Complementing these findings, new studies examined the effects of a low-dose combined endurance and endurance training program on immune system modulation and systemic inflammation levels in older adults. To assess immune responses, the elderly underwent detailed analyses of T cells and their subpopulations (CD4+, CD8+, *naïve*, central, effector memory and T-EMRA cells) using flow cytometry. The results showed that the exercise program increased the participants' strength capacities and the ratio of CD4+/CD8+ T cells over time. There were also significant reductions in systemic levels of interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and vascular endothelial growth factor (VEGF). These findings suggest that even a short-term, low-intensity training program can provide significant benefits in modulating the immune system and reducing systemic inflammation in older adults. The simplicity and safety of the program make it a practical and affordable intervention, potentially beneficial for the immune health of the elderly.

The connection between both studies is evident: both demonstrate that the practice of physical exercise, whether aerobic, resistance or combined, has a significant impact on modulating the immune system and reducing inflammation in the elderly. While one study emphasizes the effectiveness of aerobic exercise in immune modulation, the other study highlights the benefits of a combined endurance and endurance program. Together, these studies suggest that adopting different types of physical exercise can be a powerful strategy to improve immune health and reduce chronic inflammation in the elderly, contributing to healthy and active aging.

Gut microbiota

Zinc plays a key role in maintaining the integrity of the gut microbiome. The deficiency of this mineral can favor the flowering of pathogenic taxa, increasing the risk of infections and other complications. In contrast, an adequate supply of zinc contributes to restoring the balance of the gut microbiome, promoting health and longevity.

Probiotics, live microorganisms that confer health benefits when ingested in adequate amounts, play a crucial role in gut homeostasis. They influence both the innate and adaptive immune response by promoting the production of antibodies and cytokines, which is essential for immune function. In this context, the inclusion of a diet rich in phytochemicals, probiotics, fatty acids, and micronutrients is an effective strategy to modulate immunosenescence and cellular senescence, contributing to the health and quality of life of the elderly.

The gut microbiota of older adults has distinct characteristics that can influence health and longevity. Studies indicate that the alpha diversity of microbial taxa, functional pathways, and metabolites is higher in the elderly compared to younger individuals. Still, the distances of beta diversity differ significantly throughout developmental stages, highlighting notable changes between older and younger adults. These variations include a relative increase in Akkermansia with aging, while *Faecalibacterium*, *Bacteroidaceae,* and *Lachnospiraceae* show significant reduction. In addition, the elderly have a decrease in metabolic potential related to carbohydrates and amino acid synthesis. However, there was greater potential for the production of short-chain fatty acids, such as butyrate, which exerts anti-inflammatory and immunomodulatory effects. These functional changes distinguish the gut microbiota of older adults from that of young adults.

Gut microbial diversity plays a crucial role in modulating the immune system, especially during aging. Changes in the microbiota can directly impact immunosenescence, since it is closely connected to immune function. Although the reduction in the ability to metabolize carbohydrates and synthesize amino acids compromises the immune status of the elderly, the increase in short-chain fatty acids and butyrate derivatives helps to mitigate the effects of immunosenescence, promoting a more balanced health.

CONCLUSION

Immunosenescence is a phenomenon that compromises the functioning of the immune system as a whole, affecting its cells and responses. This impairment includes innate immunity, which suffers from senescence by creating an unfavorable microenvironment for NK cells, reducing their effectiveness against tumor cells and,

consequently, favoring the development of neoplasms. At the same time, the aging of macrophages leads to the exacerbation of the inflammatory response mediated by pro-inflammatory cytokines, such as IL-6 and TNF-α, which can culminate in autoimmune diseases, such as rheumatoid arthritis. Aging, therefore, profoundly modifies the immune microenvironment, evidencing a vast field of studies to develop strategies that reduce the factors that compromise the well-being of aging human beings.

The discovery of several molecular pathways associated with aging and the characterization of the beneficial effects of calorie restriction (CR) have driven research on CR mimetics, drugs capable of replicating the effects of calorie restriction without the need to drastically reduce caloric intake. These mimetics have shown promise in promoting life expectancy and extending healthy life expectancy by modulating metabolic pathways and preventing inflammation.

Fortunately, therapeutic strategies to deal with aging-related conditions are advancing significantly. The use of mesenchymal stem cells (MSCs) is a notable example, considering their regenerative and anti-inflammatory properties. In the field of immunotherapy, innovative methods have gained prominence. Kim and Lee (2023) underlined the use of checkpoint inhibitors and adoptive T cells as effective tools to strengthen immunity in older adults. Senotherapy also presents itself as a promising approach, focusing on senolytics and senomorphs, which eliminate senescent cells or modulate their phenotypes.

It is worth noting that although considerable advances have been made, many studies related to the molecular and cellular mechanisms of immunosenescence are still in the early stages or awaiting conclusion. This limits the depth of knowledge available to support hypotheses or consolidate practical interventions. One of the factors that limits the consolidation of studies is the heterogeneity of immune responses in aging populations, which makes it difficult to generalize the results, since genetic, environmental, and lifestyle factors profoundly influence immune aging. Another relevant obstacle is the lack of robust longitudinal studies that track immunological changes over the course of aging in diverse populations, which restricts the understanding of how these changes develop over time. Added to this is the scarcity of clinical data proving the efficacy and safety of therapeutic interventions aimed at mitigating immunosenescence, such as immunotherapies or cell therapies. While some of these interventions have shown promising results, they are usually limited to preclinical studies or early clinical trials. Finally, ethical and economic aspects can also create impasses, especially regarding access to and feasibility of innovative therapies for broader populations. This combination of gaps in scientific knowledge and practical barriers highlights the need for more collaborative and diverse

research to support a more comprehensive and applicable understanding of immunosenescence.

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