Impact of aging on the immune system

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Abstract
Organismal aging is a complex multifactorial process influenced by various factors such as biological clock, gene expression, cellular senescence, oxidative stress, immune system, nutrition and metabolism, and lifestyle. The immune system plays a crucial role in the human body, maintaining normal immunity, defending against invasion of pathogenic microorganisms, maintaining homeostasis of the internal environment, and other functions. Research to date has found that the immune system weakens during the human body’s aging process, resulting in a series of diseases. The aging of the immune system is the inevitable result of the body’s aging, but it is also the fundamental cause of aging. As the body ages, the immune system gradually declines, and the decline of the immune system is associated with a decrease in the number of lymphocytes, a reduction in the activity of immune cells, and an increase in the inflammatory response, which makes the elderly more susceptible to infections and certain specific diseases. This phenomenon not only affects the quality of life of older people but also places a heavy burden on society. Understanding the effects of aging on the immune system is, therefore, important for improving the health of older adults. This paper focuses on the relationship between aging and the immune system.

Keywords: Aging Immune system, Immune cells

Contexts
The immune system of the aging organism undergoes various changes that increase susceptibility to infections and, to some extent, contribute to the development of chronic inflammation and related diseases. With age, the cellular components of the immune system are reduced, including lymphocytes, natural killer cells, and dendritic cells. Throughout this process, the efficiency of the immune response is significantly reduced due to the inability of lymphocytes to recognize and attack pathogens effectively. The aging body’s immune system favors a pro-inflammatory response. It can damage tissues and increase the risk of heart disease, arthritis, and cognitive decline. In addition, the aging body’s immune system has a reduced ability to present antigens, and dendritic cells have a reduced ability to present antigens, which prevents the immune system from effectively recognizing and attacking pathogens. The aging body’s immune system has a reduced ability to monitor cancer cells, which may lead to an increased risk of cancer and a higher incidence of cancer in the elderly.

1. Effects of aging on immune organs

1.1 Central immune organs thymus and bone marrow

1.1.1 Effects of aging on the thymus gland
The thymus, an essential organ of the immune system, undergoes many changes during aging. Structurally, the thymus atrophies with age. This is mainly reflected in a decrease in thymic tissue and the number and density of thymocytes. In addition, the weight of the thymus decreases due to apoptosis and a reduction of thymic lymphocytes. This series of changes leads to a decrease in immune function. Functionally, the aging thymus is characterized by a decline in the number and position of T-lymphocytes, the main product of the thymus, and during aging, the thymus fails to promote the differentiation of immature lymphocytes, which is manifested by an increase in the number of immature lymphocytes in the thymus and in the peripheral blood\textsuperscript{[1]}. As a result of the decrease in the number and function of T-lymphocytes, the immune response is compromised, as evidenced by a reduction of the body’s response to pathogens and a decrease in the ability to clear already present pathogens.

1.1.2 Effects of aging on bone marrow
Aging has an effect on bone marrow cytokine secretion, where the expression levels of some cytokines are elevated, such as interleukin-1β and tumor necrosis factor-α, but interleukin-6 and transforming growth factor-β are decreased. However, the abnormal expression of these cytokines may lead to abnormal inflammatory responses and immune responses, thus affecting the immune function of the bone marrow. During aging, immune cells in the bone marrow also undergo senescence. On the one hand, the number of immune cells decreases with age, leading to a decline in immune response-ability; on the other hand, the
subpopulation of immune cells also changes, such as a dysregulation of the balance of CD8+ cells and CD4+ cells, and a decline in the expression of MHC class I molecules[2]. This, in turn, affects the ability of immune cells to recognize and respond, making them more susceptible to diseases such as infections and cancer.

1.2 Peripheral lymph nodes and spleen

1.2.1 Effects of aging on lymph nodes

The number of lymph node decreases with age, and it has been found that this may be related to apoptosis of lymph node cells and atrophy of lymphoid follicles. Many cytokines and gene expression changes are essential in lymph node aging. For example, cytokines related to inflammatory response (e.g., IL-1, IL-6, etc.) and gene expression related to apoptosis (e.g., Bax, Bcl-2, etc.) are changed[3]. These changes affect the survival and function of lymph node cells and, thus, the efficiency of the immune response.

1.2.2 Effects of aging on the spleen

The spleen is one of the main gathering places for lymphocytes, and the number of lymphocytes in the spleen decreases as the body ages. This change affects the ability of lymphocytes to proliferate, differentiate, and produce antibodies, thereby reducing the efficiency of the immune response. In addition, there is an increase in the spleen’s autoreactive T and B cells, leading to an increased autoimmune response and causing autoimmune diseases. However, the spleen produces more inflammatory factors, such as IL-1 and IL-6, during aging, leading to an increased inflammatory response[4]. This change disrupts the body’s immune balance and leads to tissue damage and disease. During the aging process, the spleen’s uptake and secretion of cytokines can become dysregulated. Some cytokines, such as IL-1 and IL-6, will increase, while the secretion of other cytokines, such as IL-4 and IL-10, will decrease. This change leads to abnormalities in the activation and differentiation of immune cells, thus affecting the efficiency of the immune response[5].

2. Impact of aging on the innate immune system

2.1 Corresponding changes in macrophages

When pathogens invade the body, the innate immune system plays a role, and phagocytes, mainly macrophages, recognize and engulf pathogens and mobilize NADPH exosomes and mitochondria to release large amounts of reactive oxygen species (ROS) into phagocytic vesicles to achieve the killing and elimination of pathogens[6]. During this process, macrophages must balance ROS production and elimination to achieve pathogen clearance while preventing ROS from causing damage and senescence. Hippo kinase Mst1/2 senses intracellular ROS and recruits to the vicinity of ROS-releasing organelles and is activated, further activating and stabilizing the key antioxidant transcription factor, Nrf2, to achieve Macrophages can kill pathogens and, at the same time, can themselves resist oxidative damage and senescence, which is an important mechanism. A novel antioxidant and anti-aging signaling in macrophage participation in host defense was revealed, elucidating the critical means by which Mst1/2 is involved in regulating macrophage maintenance of oxidative stress homeostasis for pathogen clearance while avoiding ROS-induced self-injury and cellular senescence[7].

2.2 Corresponding changes in NK cells

With the redistribution of NK cell subpopulations as senescence proceeds, the expression of activating receptors decreases, and cytotoxicity is reduced. Based on the relative density of CD56 surface expression, NK cells can be divided into two phenotypically and functionally distinct subpopulations, CD56dim and CD56bright. With aging, CD56bright immature NK cells, which mainly secrete cytokines, gradually decline, thus affecting the signaling and recruitment of other immune cells; meanwhile, CD56dim mature NK cells, which particularly have a killing function, continue to increase and begin to express CD57, but with a reduced proliferative responsiveness to cytokines such as IL-2[8]. It has been shown that aging has varying degrees of influence on the signaling pathways involved in natural or CD16-dependent NK cytotoxicity and the reason for the decline in NK cell lysing activity in the elderly may be related to the decreased ability of NK cells to release inositol triphosphate after interacting with the target cells as well as the delayed hydrolysis of lipoyl alcohol 4,5 diphosphate[9].

3. Impact of aging on the adaptive immune system

3.1 Corresponding changes in T cells

The most striking change with age is a smaller initial T-cell pool and a larger memory T-cell pool, leading to decreased available TCRs. The main reasons are thymic degeneration, impaired homeostatic proliferation of initial T cells, and T cell depletion. In the elderly, the extreme differentiation of memory T cells results in no longer expressing co-stimulatory molecules such as CD28 and CD27, which results in T cell senescence or depletion. Both senescent and depleted T cells show molecular features of aging (e.g., mitochondrial dysfunction and epigenetic remodeling). In addition, T-cell senescence
can show signs of DNA damage and short telomeres and activate signaling pathways associated with senescence. Senescence is accompanied by the accumulation of dysfunctional, terminally differentiated T cells. T-cell immune responses are limited by the appearance of a senescent or exhausted T-cell phenotype due to prolonged antigenic stimulation or chronic viral infections. Although both senescent and depleted T cells are defective in TCR-triggered proliferation, they differ in molecular signaling and secretory phenotypes. Senescent T cells secrete large amounts of pro-inflammatory factors (e.g., TNF and osteocalcin) associated with a senescence-associated secretory phenotype (SASP). Senescent T cells have senescence characteristics, including low telomerase activity and short telomeres, signs of DNA damage, anti-apoptosis, and β-galactosidase activity. Human CD4+ T cells and CD8+ T cells differ in their sensitivity to senescence, with CD8+ T cells acquiring an immunosenescent phenotype more rapidly.[10]

### 3.2 Corresponding changes in B cells

With aging, the antibodies produced by the organism change from foreign antigens to self-antigens, the antibody isotype changes from IgG to IgM, and the affinity of the antibodies changed from high to low. It is hypothesized that these changes are related to the germline gene coding library changes and the decrease in Ig somatic mutations. As the study progressed, some contradictory phenomena were observed, such as increased antibody levels in serum and low peripheral B-cell counts. The increase in total serum antibody levels can be explained by the following mechanisms: an increase in the number of B cells and plasma cells in the organs rather than in the peripheral blood; an increase in the lifespan of B cells and plasma cells in the germinal centers; and an increase in the production of Ig by individual cells.[11] The germinal center is essential for T cell-dependent and high-affinity antibody production. It was found that old rats have a significantly lower response in the germinal center and a relative lack of somatic mutations. Signal transduction between T and B cells is also crucial for antibody production by B cells.[12]

### Concluding remarks

With the aging of the body, the structure and function of the immune system change, mainly focusing on the decline of the external antigenic stimulus response, the hyper-response to its antigenic immune response, and the dysregulation of autoimmune monitoring. However, the development of the physiological deterioration of the immune system to the critical point of pathologic aging. Therefore, it is essential to prevent aging and to develop drugs that can delay or reverse the aging of the immune system to increase the resistance of the elderly to infection. Explore medicines that modulate the function of the immune system to reduce the risk of autoimmune diseases and cancer in older adults. Conduct occasional studies on community-based interventions to explore the feasibility of slowing down aging by improving lifestyle habits and increasing exercise. To study the relationship between immunity and nutrition and develop nutritional supplements for the elderly to enhance their immune function. Provide scientific dietary advice to the elderly to maintain their health and part of the immune system.

### Reference: