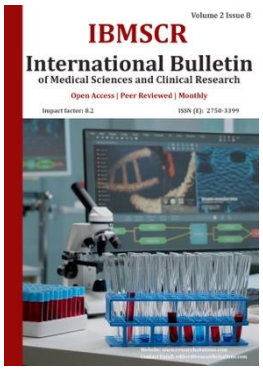

CHANGES IN LEUKOCYTES DURING AGING AND MECHANISMS OF IMMUNOSENENCE

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Abstract: Immunosenescence is a complex biological process that represents the functional and structural decline of the immune system associated with aging. This phenomenon significantly weakens the body's response to infections, tumors, and vaccines, leading to increased morbidity and mortality in the elderly [1]. Leukocytes, in particular lymphocytes and phagocytes, are the main elements of immunosenescence, and changes in their quality, quantity, and functional activity lead to age-related degradation of the entire immune system [2]. The stimulation of T lymphocytes by the thymus (thymocyte involution), the decrease in clonal diversification of B lymphocytes, as well as the transition of aged lymphocytes to a senescent state reduce the effectiveness of the immune response [3]. At the molecular level, immunosenescence is mediated by multiple mechanisms, including accumulation of DNA damage, telomere shortening, protein misfolding, mitochondrial dysfunction, and chronic secretion of inflammatory cytokines (inflamm-aging) [4]. Recent studies have shown that cytokines, proteins, and altered mitochondria secreted by immunosenescent cells contribute to the senescence of surrounding cells, further impairing the regenerative capacity of tissues [5]. This review provides a detailed overview of the phenotypic and functional changes in leukocytes during aging, the molecular signaling pathways that affect them, and the clinical significance of immunosenescence. In addition, current therapeutic approaches aimed at slowing or reversing age-related immune degradation, including senolytic drugs, immunomodulators, and lifestyle interventions, are discussed [6]. Understanding immunosenescence opens up prospects not only for strengthening immunity against pathogens and cancer, but also for preventing age-related diseases and increasing life expectancy [7].

Keywords: immunosenescence, leukocytes, aging, senescent cells, inflamm-aging, telomeres, immunity, lymphocytes, inflammation, immunosenescence

Research Objective

The main objective of this study is to systematically analyze the molecular, cellular and functional changes of leukocytes during the aging process, as well as the main mechanisms of immunosenescence, based on modern scientific data. The study also aims to study the clinical consequences of immune age-related degradation and the possibilities of preventing or slowing it.

Research Methods

Scientific articles, reviews and meta-analyses published between 2015 and 2025 were used in the preparation of the article. A comprehensive literature search was carried out in scientific databases such as PubMed, Scopus, Web of Science and Google Scholar. Keywords such as "immunosenescence", "leukocyte aging", "T-cell senescence", "inflamm-aging", "telomere shortening immunity" were used in the search. Selected articles were evaluated based on their methodological quality, impact factor of the published journal, and the reliability

of the research results. Methods of data systematization and analysis were used. Diagrams and tables were used to explain molecular mechanisms. Specific molecular pathways, cell types, and their interactions were analyzed separately in each section.

Introduction

The immune system is a complex network that protects the body from external and internal threats, such as pathogens, including viruses, bacteria, fungi, and tumors. Leukocytes (white blood cells), which constitute the main part of this system, include various cell types that provide innate and adaptive immunity [8]. Leukocytes include neutrophils, monocytes, macrophages, natural killer cells (NK cells), T lymphocytes, and B lymphocytes. With age, significant changes occur in the immune system, a process called immunosenescence. Immunosenescence is characterized not only by a decline in immunity, but also by its dysregulation, which leads to an increase in autoimmune reactions, chronic inflammation, and autoimmune diseases [9].

One of the main features of immunosenescence is the involution of the thymus. The thymus is the center of maturation of T lymphocytes, which, although it is most active during childhood, gradually atrophies with age. During adolescence, thymus activity decreases sharply, which leads to a decrease in the number and diversity of new naive T lymphocytes [10]. As a result, the T-cell immune response is weakened, which weakens the body's defense against new pathogens. Similar changes are observed in B lymphocytes: antibody diversification and affinity decrease, and the efficiency of memory B cells decreases [11]. Another important immunological phenomenon associated with aging is a state of chronic low-grade inflammation, called "inflamm-aging". In this case, the levels of cytokines that mediate inflammation, such as interleukin-6 (IL-6), the growth factor TNF-α, and C-reactive protein, are constantly increased in the blood and tissues [12]. Inflamm-aging is caused by inflammatory cytokines secreted by immunosenescent cells (SASP – Senescence-Associated Secretory Phenotype). SASP includes various cytokines, chemoattractants, proteases, and growth factors, which enhance the senescence of surrounding cells and reduce the regenerative capacity of tissues [13].

Changes in leukocytes during aging occur through a number of molecular mechanisms. These include the accumulation of DNA damage, telomere shortening, epigenetic changes, protein misfolding, and mitochondrial dysfunction [14]. Telomeres are repetitive DNA sequences located at the ends of chromosomes that shorten with each cell division. Once a certain threshold is reached, the cell cycle stops and the cell enters a state of senescence. Lymphocytes have low telomerase activity, so they rapidly lose telomere length, which limits their ability to proliferate [15].

Growth inhibitors such as p53 and p16INK4a, which are activated in response to DNA damage, also play an important role in immunosenescence. These proteins cause cell cycle arrest, which limits the immunogenic response of cells [16]. Mitochondrial dysfunction, in turn, leads to excessive production of reactive oxygen species (ROS), which in turn increases DNA and protein damage and activates inflammatory signals [17].

Recent studies have shown that immunosenescence is not only associated with immune decline, but also with various age-related diseases, including vascular diseases, neurodegenerative diseases, osteoporosis, and cancer [18]. Therefore, understanding

immunosenescence and studying its mechanisms is important not only for strengthening immunity, but also for increasing lifespan and preventing age-related diseases.

In this article, we will analyze in detail the changes in leukocytes during aging and the mechanisms of immunosenescence based on modern scientific data. The study also discusses modern therapeutic approaches aimed at studying the possibilities of slowing down or restoring immunosenescence.

Results

1. Changes in the number and composition of leukocytes

With aging, significant changes occur in the total number and composition of leukocytes. In general, the total number of leukocytes in peripheral blood may decrease slightly with age or remain stable, but the ratio of individual cell types changes [19]. For example, the total number of T lymphocytes, especially the number of naive T lymphocytes, is significantly reduced. The main reason for this is the involution of the thymus. Thymic activity peaks during adolescence and then gradually declines, as a result of which the production of new naive T lymphocytes is limited [20]. Therefore, in older people, there are more memory T lymphocytes, which represent immune memory, and fewer naive T lymphocytes. This significantly limits the body's ability to respond to new pathogens [21].

A similar trend is observed in B lymphocytes. In older individuals, the total number of B lymphocytes may decrease slightly, but more importantly, their functional properties change. Clonal diversification of B lymphocytes decreases, resulting in a decrease in the diversity and affinity of antibodies [22]. This leads to a weakening of the response to vaccines and a decrease in protection against acute infections. In addition, the production of autoimmune antibodies increases in older individuals, reflecting a dysregulation of the immune system [23].

Myeloid cells, such as neutrophils and monocytes, may remain relatively stable in number with age, but their functional activity decreases. For example, the phagocytic capacity, chemotaxis, and killing capacity of neutrophils are impaired [24]. The ability of monocyte-derived dendritic cells to present antigens is also reduced, which limits the activation of T lymphocytes [25].

2. Lymphocyte senescence

Senescent cells are cells that have stopped dividing permanently but are metabolically active. These cells display the SASF phenotype, i.e., secrete a variety of inflammatory cytokines, chemoattractants, and proteases [26]. Lymphocytes, especially T lymphocytes, frequently undergo senescence. This process is triggered by a variety of stress factors, including telomere shortening, DNA damage, and inflammation [27].

Senescent T lymphocytes typically lose expression of costimulatory molecules such as CD28. CD28 is an essential molecule required for full T lymphocyte activation, and its loss limits the ability of T lymphocytes to proliferate and produce cytokines [28]. In addition, senescent T lymphocytes express senescence markers such as KLRG-1 and CD57 [29]. These cells often produce proinflammatory cytokines such as interferon-gamma (IFN-γ) and TNF-α in high amounts, which contribute to inflamma-aging [30].

The accumulation of senescent lymphocytes leads not only to a decrease in immunity but also to a dysregulation of the immune system. For example, they lose the ability to control the immune response, which leads to chronic inflammation and tissue damage [31].

3. Molecular mechanisms

3.1. Telomere shortening and telomerase activity

Telomeres are repetitive DNA sequences (TTAGGG) located at the ends of chromosomes, which ensure the stability of chromosomes. Telomeres shorten slightly with each cell division, and when a certain threshold is reached, the cell enters a senescent state or undergoes apoptosis [32]. Lymphocytes, especially as they are rapidly proliferating cells, rapidly lose telomere length. The telomere length of lymphocytes in elderly individuals is significantly shorter than that of young individuals [33].

Telomerase is an enzyme responsible for maintaining or extending telomere length and is mainly active in embryonic cells and proliferating cells. Telomerase activity in lymphocytes is limited and increases only temporarily when stimulated by antigens [34]. However, in elderly individuals, telomerase activity in lymphocytes is lower than in young individuals, which further accelerates telomere shortening [35].

3.2. DNA damage and response pathways

DNA damage is a normal, ongoing process that can be caused by ionizing radiation, chemicals, or metabolic processes. The level of DNA damage increases with age because DNA repair mechanisms become less efficient [36]. In lymphocytes, DNA damage is particularly dangerous because they divide and multiply frequently. In response to DNA damage, the p53 pathway is activated. p53 is a growth inhibitor that causes cell cycle arrest and activates DNA repair mechanisms. If DNA damage is too extensive, p53 initiates apoptosis [37]. However, in most cases, lymphocytes are constantly exposed to low levels of DNA damage, which leads to their transition to a senescent state.

3.3. Epigenetic changes

Epigenetics is the study of non-heritable changes that regulate gene expression. With aging, lymphocytes undergo significant epigenetic changes. These include changes in the overall level of DNA methylation, histone modifications, and changes in chromatin organization [38].

For example, in T lymphocytes of older individuals, global DNA hypomethylation is observed, which leads to changes in gene expression. In particular, the methylation level of genes associated with inflammation decreases, which leads to their overexpression and increased inflamma-aging [39]. In addition, changes in the methylation level of genes regulating immunity lead to dysregulation of the immune system.

3.4. Mitochondrial dysfunction

Mitochondria are the energy production centers of the cell, which produce adenosine triphosphate (ATP). With age, the number and functional activity of mitochondria decrease, leading to a decrease in energy production [40]. In addition, mitochondrial dysfunction leads to an overproduction of reactive oxygen species (ROS).

ROS not only damage DNA and proteins but also activate inflammatory signals. In lymphocytes, mitochondrial dysfunction limits their ability to proliferate, move, and produce cytokines [41]. In addition, mitochondrial DNA (mtDNA) damage enhances the inflammatory response of the immune system, as mtDNA is recognized by intracellular pattern-recognition receptors (e.g., TLR9) and activates inflammatory signals [42].

4. Inflamm-aging and SASP

Inflamm-aging is a chronic low-grade inflammatory state associated with aging. In this case, the levels of cytokines that mediate inflammation in the blood and tissues, such as IL-6,

TNF-α and IL-1β, are constantly increased [43]. Inflamm-aging is caused by SASP secreted by immunosenescent cells.

SASP includes various cytokines (IL-6, IL-8, TNF-α), chemoattractants (MCP-1), growth factors (VEGF) and proteases (MMP) [44]. These substances not only enhance the senescence of surrounding cells, but also reduce the regenerative capacity of tissues. In addition, SASP leads to dysregulation of the immune system, which contributes to the development of autoimmune diseases and chronic inflammatory diseases [45].

5. Clinical consequences of immunosenescence

The clinical consequences of immunosenescence are very widespread. First, older people are at increased risk of infections, especially respiratory infections such as pneumonia, influenza and COVID-19 [46]. Second, they are more likely to develop cancer than younger people because the immune system loses its ability to effectively recognize and destroy immature cells [47]. Third, immunosenescence leads to a reduced response to vaccines, which reduces the effectiveness of vaccines in older people [48].

In addition, immunosenescence contributes to the development of age-related diseases, including vascular diseases, neurodegenerative diseases (such as Alzheimer's disease), and osteoporosis [49]. For example, inflamm-aging increases inflammation in the walls of blood vessels, which leads to the development of atherosclerosis. Similarly, inflammation in the central nervous system accelerates neurodegenerative processes [50].

Discussion

Immunosenescence is an integral part of aging, which is characterized by a functional and structural decline in the immune system. This process occurs through a number of molecular and cellular mechanisms, including telomere shortening, DNA damage, epigenetic changes, mitochondrial dysfunction, and inflamma-aging [51]. Leukocytes, particularly lymphocytes, are major carriers of immunosenescence, as changes in their number, composition, and functional activity contribute to the age-related degradation of the entire immune system [52].

Understanding immunosenescence opens up possibilities not only for understanding the decline of immunity, but also for preventing or slowing it. In recent years, various therapeutic approaches to immunosenescence have been developed. These include senolytic drugs, immunomodulators, telomerase enhancers, and lifestyle interventions [53].

Senolytic drugs are drugs that selectively kill senescent cells. For example, senolytic drugs such as dasatinib and quercetin can slow immunosenescence by inducing senescent cells to undergo apoptosis [54]. However, the long-term effects and safety of these drugs have not yet been fully studied.

Immunomodulators, such as the cytokines IL-7 or IL-2, attempt to reverse immunosenescence by stimulating the immune system [55]. For example, IL-7 can stimulate thymic function and increase the production of naive T lymphocytes. However, the clinical efficacy of these therapies has not yet been fully proven.

Another promising approach is to increase telomerase activity. Compounds that increase telomerase activity, such as TA-65, may slow immunosenescence by preserving telomere length [56]. However, overactivation of telomerase may increase the risk of cancer, as this enzyme is often active in young cells.

Lifestyle interventions, such as regular exercise, a healthy diet, and stress management, may play an important role in slowing immunosenescence [57]. For example, regular exercise increases telomerase activity, reduces inflammation, and improves immune function.

In conclusion, immunosenescence is a complex and multifaceted process, and understanding its mechanisms holds promise for enhancing immunity, preventing age-related diseases, and increasing lifespan. Future research should focus on developing safe and effective ways to slow or reverse immunosenescence.

Conclusion

Immunosenescence is a complex biological process that represents the functional and structural decline of the immune system associated with aging. This process is characterized by changes in the number, composition, and functional activity of leukocytes, especially lymphocytes. Due to thymus involution, the number of naive T lymphocytes decreases, which limits the body's ability to respond to new pathogens. The diversification and affinity of antibodies in B lymphocytes decreases, which leads to a weakening of the response to vaccines. The functional activity of myeloid cells, such as neutrophils and monocytes, also decreases.

Among the molecular mechanisms of immunosenescence, telomere shortening, DNA damage, epigenetic changes, mitochondrial dysfunction, and inflamma-aging are important. Telomere shortening limits the ability of lymphocytes to proliferate, DNA damage and epigenetic changes lead to altered gene expression, mitochondrial dysfunction leads to reduced energy production and overproduction of reactive oxygen species, and inflamma-aging causes a chronic low-grade inflammatory state.

The clinical consequences of immunosenescence are very serious, increasing the risk of infections, cancer, and age-related diseases in older people. In addition, immunosenescence leads to a weakened response to vaccines, which reduces the effectiveness of vaccines.

Various therapeutic approaches against immunosenescence are being developed, including senolytic drugs, immunomodulators, telomerase enhancers, and lifestyle interventions. However, the long-term effects and safety of these therapies have not yet been fully studied. Therefore, future research should focus on developing safe and effective methods to slow or reverse immunosenescence.

In conclusion, understanding immunosenescence opens up possibilities not only for understanding the decline of immunity, but also for preventing or slowing it. This opens up prospects not only for strengthening immunity, but also for preventing age-related diseases and increasing life expectancy.

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