Immunosenescence and Inflamm-aging

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Abstract

Immunosenescence is the alteration of the immune system due to aging process which affects both innate and adaptive immunity. The major changes in innate immunity are decreased functions of surface barriers and innate immune cells. Several aspects of adaptive immunity are also altered, particularly naïve B cells, naïve T cells and $CD8^+$ T cells. Consequently, the elderly are prone to certain infections, cancer, and autoimmune diseases. Interestingly, there is a term, "inflamm-aging," which refers to the chronic low-grade systemic inflammation caused by the activation of the aging immune system. Inflamm-aging is characterized by increased serum levels of pro-inflammatory cytokines and other inflammatory biomarkers. This condition is linked to some chronic diseases, including atherosclerosis, diabetes, Alzheimer's disease, as well as osteoporosis, and most importantly increases mortality risk in the elderly. Therefore, immunosenescence and inflamm-aging represent a significant challenge to the global health since the world is entering the aging society.

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Introduction

Aging society is a current global concern since aged population is increasing. From the United Nations World Population Healthy Ageing Report 2013, the percentage of older people (age 60 and more) are rising from 9.2% in 1990 to 11.7% in 2013, and it has been estimated that by 2050 the world older population will reach 21.1%.[1] Older people have higher risks to develop many diseases such as diabetes, hypertension, heart diseases, infectious diseases, cancer, and autoimmune diseases than younger people. Also, the severity and complications of these conditions increase with age, while the prevention and treatment of such diseases in older persons are more difficult than those in younger ones. There are several factors that contribute to these findings and immunosenescence, which is the age-associated decline of the immune system, is believed to be one of the contributing factors. The main function of the immune system is to protect the body from any harmful insults, including infections, and cancer. Therefore, the deterioration of the aging immune system can make the elderly's body susceptible to such insults. Moreover, several studies have shown that there is an increased level of chronic inflammation in older people, which is termed "inflamm-aging" and this condition may lead to the increased morbidity and mortality in older individuals.[2] Thus, immunosenescence and inflamm-aging have recently gained more attention from many researchers and physicians around the world.

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Overview of the immune system and immune response

The immune system primarily functions to protect the body from foreign substances. Interestingly, the balance between activation and suppression of the immune system is critical to the overall health of the body. For example, if the immune system functions excessively, hypersensitivity will occur leading to allergic and autoimmune diseases. On the other hand, if the immune system is defective, immunodeficiency will develop resulting in infectious diseases and cancer. The immune system consists of several cell types and mediators that work collectively as a complex system. It can be divided according to its functions into two parts: innate and adaptive immunity.[3,4]

Innate immunity is the first line of defense against foreign substances and can function immediately. It can eliminate the harmful insults within minutes or hours after encountering them. However, it has no memory. That is, it will respond in the same way even if the same substance re-enters the body. Innate immunity consists of three components:

1. Surface barriers, e.g., skin, mucosa, chemicals on the surface area, normal microbiota, sneezing, coughing, urination, and defecation;
2. Cellular components, e.g., neutrophils, monocytes, macrophages, NK cells, eosinophils, basophils, mast cells, and dendritic cells;
3. Humoral components, e.g., complements, antimicrobial peptides, and cytokines.

Adaptive immunity differs from innate immunity in several ways. First, adaptive immunity is highly specific to each foreign substance or antigen. Second, it usually takes several days or weeks for the adaptive immunity to fully respond to new foreign substance because the adaptive immune cells need to be activated, proliferate and differentiate into effector cells to function. This type of response is called primary immune response. Third, adaptive immunity has memory. If it encounters the same antigen again, the response will be much faster, higher, and better than the primary immune response. This type of response is, therefore, called secondary immune response. Adaptive immunity is composed of two arms:

1. Humoral immunity, e.g., antibodies which are produced by B lymphocytes and plasma cells;
2. Cell-mediated immunity, e.g., T lymphocytes which can be subdivided into several groups: $CD4^+$ T lymphocytes or helper T cells (T_H), $CD8^+$ T lymphocytes or cytotoxic T cells (CTLs), and regulatory T cells (Treg).

Despite the fact that the immune system is divided into innate and adaptive immunity, both arms need to work together to protect the body from any foreign substances or harmful insults. That is, when foreign substances such as bacteria invade body surface barrier, innate immune cells (e.g., macrophages) will engulf the bacteria and release certain mediators such as cytokines, chemokines, or vasoactive mediators, to recruit more innate immune cells (e.g., neutrophils) and other soluble proteins (e.g., complements) from the blood circulation to the infection site. This inflammatory process helps the body fight against infection at an early stage. At the same time, dendritic cells will uptake and process the bacteria and migrate via lymphatic vessels to peripheral lymphoid organs (e.g., regional lymph nodes) where adaptive immune cells reside. To activate adaptive immunity, dendritic cells then present the bacterial peptides to prime specific T lymphocytes. Activated T lymphocytes will proliferate and differentiate into effector T cells and some of the T cells will help to activate specific B lymphocytes to become plasma cells and produce antibodies. Subsequently, the effector T cells and antibodies will travel the circulation to the infection site and help the innate immune cells to eliminate the infection. Once the infection is cleared, the immune response will return to its resting stage. However, some of the activated T and B lymphocytes will differentiate into memory cells, which can survive for a long time, to protect the body against the same bacteria if they invade the body again in the future.

Immunosenescence

In general, the term "immunosenescence" refers to the alteration (especially the deterioration) of the immune response due to aging process. Recently, Graham Pawelec has proposed a more stringent definition of immunosenescence as "a state defined by robust measures of immune parameters (biomarkers) that are different in younger and older individuals and which have been associated with a clearly detrimental clinical outcome (e.g. mortality, frailty, poor response to vaccination, etc.)."[5] Nonetheless, immunosenescence may also include the decline of the immune response due to chronic activation of the immune system by chronic infections (e.g., human immunodeficiency virus (HIV) infection, cytomegalovirus (CMV) infection), or certain chronic diseases, cancer, and transplantation. The latter condition of immunosenescence is sometimes called "premature immunosenescence."[6] This review article mainly focuses on the alteration of the immune response due to aging process.

There are several lines of evidence demonstrating that immunosenescence increases risks of several infections, cancer, autoimmune disorders, and other chronic diseases (e.g., atherosclerosis, diabetes) in older people. In addition, immunosenescence has been shown to reduce immune response to vaccination in the elderly.[7] A longitudinal cohort study in older Swedish population shows that healthy elderly with "immune risk phenotype (IRP)," which includes $CD4^+$ T cells:$CD8^+$ T cells ratio < 1, poor mitogen-activated T cell response, increased terminally differentiated CTLs, decreased B cell numbers, and seropositive to CMV, have higher morbidity and mortality rates compared to other healthy older populations.[8] The incidence of sepsis significantly increases in older people compared to younger ones and the mortality rate of sepsis also increases with age.[9] A randomized double-blind placebo-controlled trial on the efficacy of influenza vaccine in the elderly shows that the vaccine provides only 50% efficacy in elderly subjects.[10] Moreover, the rate of admission and the length of stay from influenza in Americans over 65 still increase even with extensive influenza vaccination campaigns in the United States.[11]

Regarding the etiology of immunosenescence, three theories have been proposed.[7]

1. The autoimmune theory: It is believed that the immune system ability to discriminate between self *vs* non-self diminishes with age. This results in the destruction of self-tissues leading to autoimmunity and, ultimately, autoimmune diseases.
2. The immune deficiency theory: It is proposed that aging process reduces the capability of the immune system to detect and eliminate foreign substances which leads to infections and cancer.
3. The immune dysregulation theory: Aging of the immune system may cause the malfunction of its components, thereby generating uncontrollable immune response and tissue destruction.

Overall, the exact mechanisms that cause immunosenescence are still unclear; however, some of the established mechanisms include thymic involution (discussed later in T cell section) and

cellular telomere erosion from genetic factors, environmental factors, and chronic viral infection.[12] In term of chronic viral infection, CMV is considered the most important virus that induces immunosenescence because it latently infects majority of the world's population, particularly the older ones.[13] To control this latent CMV infection, the immune system needs to utilize significant amount of resource which leads to prolonged increased CMV-specific $CD8^+$ T cell clones, a phenomenon called "memory inflation."[14] These CMV-specific $CD8^+$ T cell populations then compete with other T cell populations causing the decrease in T-cell receptor (TCR) diversity, therefore increasing the elderly's susceptibility to other types of infection.[15] Memory inflation is also linked to increased systemic pro-inflammatory cytokine levels and inflamm-aging as discussed later in this review.[16]

Additionally, long-term activation of the immune system, chronic stress, and malnutrition, particularly in micronutrients, are believed to contribute to immunosenescence.[7] For example, in older individuals energy deprivation of T cells from the lack of substrates, including glucose, accelerates T cells to express senescent phenotype, such as reduced proliferation and telomerase activity.[17,18] Interestingly, age-related changes in the composition of lipid rafts, a plasma membrane area crucial for intracellular signaling, impair functions of neutrophils and T lymphocytes.[19] Moreover, gut microbiota, which are important in intestinal immune development, are different between young and old people and associated with diet and health of the elderly.[20]

Furthermore, the age-related alterations of secondary lymphoid organ structure and its microenvironment (e.g., lymph node size reduction, the loss of T and B cell segregation, the reduced area and function of follicular dendritic cells, the impairment of T cell diapedesis through high endothelial venules, and the change in interleukin (IL)-7 microenvironment due to decreased and altered fibroblastic reticular cells)[21-23] probably play an important role in immunosenescence.[15,24]

Nonetheless, not all evidence points to negative health effects of immunosenescence. Some researchers speculate that immunosenescence is a protective mechanism in the elderly. It is rather an aging adaptation of the immune system. For example, thymic involution may occur as a result of the need to conserve energy in older individuals since the possibility of encountering new pathogens decreases with age. Thus, instead of spending limited resource on developing new naive T lymphocytes which requires higher energy consumption, the body shifts to maintaining memory T lymphocytes which consumes much less energy. Also, the dampened functions of several immune cells might prevent further damage resulting from a dysregulated immune response in the aged population.[17]

Immunosenescence and Innate Immunity

Surface barriers

The protective capabilities of surface barriers decline with age. These changes are, for example, reduced skin turnover rate, skin atrophy, decreased functions of sebaceous and sweat glands, and reduced number of Langerhans cells, which are skin dendritic cells.[25]

Neutrophils

The number of neutrophils remains unchanged, but their life span at the site of infection decreases due to their inability to respond to granulocyte-macrophage colony stimulating factor (GM-CSF).[26] Their phagocytic activity and intracellular killing by reactive oxygen species (ROS) production diminish.[27,28] These impaired functions of neutrophils probably result from the decreased expression of Fc-gamma-receptor III (CD16). Neutrophils from aged mice demonstrate decreased neutrophil extracellular traps (NETs) formation in response to methicillin-resistant *Staphylococcus aureus* infection.[29] Also, their chemotaxis, the ability of neutrophils to migrate to the site of infection, reduces.[30] The impaired functions of neutrophils may be due to epigenetic change from the influence of chronic low-grade inflammation in older people.[31]

Monocytes/Macrophages

In general, the number of monocytes remains unchanged in the elderly; however, changes occur in the proportion of their subpopulations.[32,33] Some studies show that Toll-like receptor (TLR)-induced cytokine production and costimulatory molecule expression are impaired.[34,35] The reduced cytokine production in macrophages is likely caused by the shortening of telomeres.[36] In addition, macrophages produce lower ROS and their phagocytic function decreases.[37,38] Notably, the lower ROS production can be viewed as desirable for the elderly subjects because it reduces tissue injury from free radicals. On the other hand, the decrease in phagocytic activity, specifically on apoptotic cells, may be a contributing factor to inflamm-aging as discussed later.[39]

NK cells

It is well-established that the number of NK cells in aged population increases.[40,41] Interestingly, NK cell subsets are altered, including decreased immature $CD56^{bright}$ NK cells, increased mature $CD56^{dim}$ NK cells, and increased dysfunctional $CD56^-$ NK cells.[42] Regarding their functions, NK cells exhibit reduced proliferation, cytotoxicity and cytokine production.[6] Moreover, the expression level of activating receptors on NK cell surface decreases.[43]

Dendritic cells

The number of dendritic cells in the elderly usually remains unchanged except in some subsets. For instance, the numbers of Langerhans cells at the skin[25] and plasmacytoid dendritic cells[44] decrease

with age. Dendritic cell functions such as phagocytosis,[45] and TLR-associated reactivity[46] tend to decrease, while plasmacytoid dendritic cells secrete lower levels of type I interferons.[47] In addition, dendritic cells lose their ability to prime T cells due to the impairment in cross-presentation, maturation, migration, costimulatory molecule expression, and cytokine secretion.[15] However, some studies have demonstrated that dendritic cells in aged subjects secrete higher levels of pro-inflammatory cytokines such as IL-6, and tumor necrosis factor (TNF) and exhibit elevated responses against self-antigen.[48,49]

Immunosenescence and adaptive immunity

T lymphocytes

Thymic involution is the main factor affecting T cells in the elderly since the thymus is the primary lymphoid organ where immature T cells develop into mature T cells. It has been estimated that thymic involution begins at the age of 9 months and by the age of 50 years only thymic remnant remains.[50] Hematopoietic stem cells in older persons also have a tendency to develop into myeloid precursor rather than lymphoid precursor.[51,52] Accordingly, older individuals have decreased number of T lymphocytes, particularly naïve T cells, whereas the number of memory T cells rises with age because T lymphocytes are more likely to be activated and differentiated by antigens.[12] There is also an increase in a specific group of T lymphocytes named "virtual memory $CD8^+$ T cells" which are believed to be activated by self-antigens or microbiota in the body but cannot fully proliferate in response to cognate antigens.[51,53] Intriguingly, $CD4^+$ T cells are less likely to be affected by age as compared to $CD8^+$ T cells. For example, the number of naïve $CD8^+$ T cells usually decreases, while there is an increase in dysfunctional terminally differentiated $CD8^+CD28^-CD57^+$ CTLs, thus reversing $CD4^+$ T cells:$CD8^+$ T cells ratio to < 1 in the elderly.[6,54,55] Moreover, TCR diversity decreases in aged population. One possibility as mentioned earlier is that certain infections, notably CMV, can induce the proliferation of T cell clones specific to such infections, thereby replacing other T cell clones and reducing TCR diversity in the body.[56] In term of the functions, the memory T cells that develop during older age respond to antigens much less effectively than do the memory T cells that develop during younger age.[57] Immunological synapse and signaling pathway are also less effective.[12] Furthermore, T cell trafficking,[58] CTL response, and T_H1 response are less efficient in the elderly[51] while T_H2 response is elevated.[16] Notably, the T_H17:Treg ratio rises which might explain how old people are more susceptible to autoimmune diseases.[59]

B lymphocytes

The number of B lymphocytes, specifically naïve B cells, decreases with age, while the proportion of memory B cells increases. Consequently, B cell receptor (BCR) diversity reduces similar to what occurs in T cells.[60,61] Their ability to produce antibodies against new antigens decreases and the affinity of these newly produced antibodies are typically low.[62,63] In addition, these antibodies demonstrate low opsonizing capability (ability to induce phagocytosis).[64] Autoantibodies are also more prevalent in older people than younger ones.[65] The germinal centers in the elderly are smaller and contain fewer IgM-producing cells.[66] Recently, a new B cell subset called "aging-associated B cells (ABCs)" has been discovered in mice with old age and humans. The differentiation of ABCs is under the control of transcriptional factor T-bet upon the ligation of BCR, TLR7, and interferon-gamma receptor. ABCs mainly react to nucleic acid-containing antigens, including viruses and self-antigens, through their TLR binding. Their main functions may include clearing viral infections and self-debris. Interestingly, the ABCs accumulate with age and may play a role in autoimmunity because they produce autoantibodies.[67,68]

Inflamm-aging

Inflamm-aging is a term used for low-grade chronic systemic inflammation without apparent causes. This condition is characterized by elevated serum levels of pro-inflammatory cytokines, including IL-1, IL-6, and TNF, as well as inflammatory biomarkers such as C-reactive protein. However, there are no clear definitions of either which levels or which combinations of these molecules are considered as inflamm-aging. In addition, the sources of these cytokines and biomarkers remain unclear. Possible sources are adipose tissue, activated white blood cells, and other cell types with senescence-associated secretory phenotype (SASP).[15] Originally, inflamm-aging is believed to be the consequence of immunosenescence; nevertheless, the current notion is that both conditions can influence each other.[17]

Importantly, inflamm-aging plays a role in morbidity and mortality in aged population.[2] Inflamm-aging-associated diseases are generally diseases that are related to inflammation, e.g., atherosclerosis, diabetes mellitus, Alzheimer's disease, cancer, and osteoporosis.[16,69] Chronic inflammation leads to atherosclerotic plaque formation through participation of several immune cells, particularly macrophages, and can induce systemic insulin resistance and glucose intolerance.[70,71] Chronic inflammation also contributes to cancer development through SASP-altered microenvironment.[72] However, more vigorous studies are still needed to substantiate the complex association between inflamm-aging and these diseases.

The cause of inflamm-aging is still uncertain; nonetheless, several mechanisms inducing inflamm-aging have been proposed.[16,17,69,72-74] First, immunosenescence is believed to be one of the main causes of inflamm-aging. Both genetic and environmental factors play a role in this process. One compelling evidence is chronic infections, such as CMV, HIV, and Ebstein-Barr virus. As mentioned earlier, CMV can induce the phenomenon called "memory inflation" and this condition leads to increased pro-inflammatory cytokine production from the activated T lymphocytes.[14,15] Another interesting evidence comes from the recent findings that innate immunity has certain levels of memory, termed "trained immunity or innate memory."[17] This trained immunity, mostly studied in macrophages and NK cells, increases levels of pro-inflammatory cytokines and protection against subsequent infections regardless of the type of previous infection. This innate memory is probably caused by the changes in epigenetics and energy pathway of the activated innate immune cells.[75]

Second, senescent cells with SASP are probably the main producer of pro-inflammatory cytokines in inflamm-aging.[72] SASP arises from cellular senescence process which is generally induced by DNA damage, telomere shortening, oxidative stress, protein misfolding, chemicals, and radiation. SASP demonstrates cell cycle arrest, but it is metabolically active and secretes numerous inflammatory mediators, including pro-inflammatory cytokines and chemokines.[76] Intriguingly, SASP can also accelerate cellular senescence of nearby cells through its secreted mediators.[77]

Third, another proposed mechanism of inflamm-aging is the accumulation of damaged self-macromolecules released from injured and dead cells over time due to mitochondrial dysfunction, external stimuli, insufficient clearance mechanisms, and inadequate autophagy.[69,78] These damaged molecules possess damage-associated molecular patterns (DAMPs) which can activate innate immunity by binding pattern recognition receptors (PRRs). The activation of PRRs, particularly through inflammasomes, induces pro-inflammatory cytokine production.

Fourth, similar to DAMPs, pathogen-associated molecular patterns (PAMPs) produced by gut microbiota can activate PRRs and inflammasomes, thereby increasing pro-inflammatory cytokine secretion. This condition worsens in the elderly because of age-associated degeneration of gastrointestinal epithelium and dysbiosis of gut microbiota.[20,72,79]

Fifth, microRNAs (miRs), small non-coding RNAs which regulate gene expression, are believed to play a role in inflamm-aging.[16,72] Since many miRs regulate NF-kB pathway which is a major signaling pathway in inflammatory response, alteration of certain miRs could affect inflammation. Interestingly, some miRs are classified as senescence-associated miRs (SA-miRs), while some are classified as inflammation-associated miRs (Inflamma-miRs).[80] Moreover, one study demonstrates that miR-146a-deficient mice have a phenotype similar to inflamm-aging.[81] Lastly, because adipocytes in obese people secrete pro-inflammatory cytokines and obesity correlates with age, especially in Western countries, obesity-induced inflammation is considered an important mechanism of inflamm-aging.[16,72,82,83]

Chronic inflammation often leads to tissue destruction and diseases. However, some researchers propose that controlled low-grade chronic inflammation is a protective mechanism in the older individuals.[17,69] This concept is thought-provoking particularly in the context of trained immunity which gives the body preparedness against other types of infections.[75] Interestingly, some healthy aged individuals also have certain levels of pro-inflammatory cytokines indicating some degrees of chronic inflammation.[84] Thus, other factors such as anti-inflammatory cytokines (e.g., IL-10) may play an important role in balancing these conditions (inflamm-aging *vs* anti-inflamm-aging).[85] In fact, inflamm-aging has been shown to be associated with high levels of both pro- and anti-inflammatory biomarkers and its impact on morbidity and mortality in the elderly may rely on the balance between these two types of inflammatory mediators.[86]

Possible Interventions

Since immunosenescence and inflamm-aging have been generally associated with poor health outcomes in aged population, many researchers are trying to develop either preventive or therapeutic measures to modify these conditions. For instance, by adding an adjuvant to a subunit vaccine against herpes zoster, the efficacy of this vaccine in the 70-year-old and older age group becomes very similar to that in the younger ones.[87] Some medications, such as metformin, and rapamycin, have been shown to decelerate aging process.[15,88] Nevertheless, the mechanisms by which these drugs alter this process, and the overall health benefit of these drugs are still uncertain. Mechanistically, the modulations of cytokines (e.g., IL-7, and anti- *vs* pro-inflammatory cytokines), signaling pathways (e.g., NF-kB, mTOR), and microRNAs also hold promising prospects.[16,21,69] In addition, lifestyle modifications (e.g., diet, exercise) are encouraging, such as caloric restriction, Mediterranean diets, foods with zinc, polyphenols, and omega-3 fatty acids.[69,72,74] Interestingly, gut microbiota modification through dietary intervention is also plausible.[72]

Conclusion

Immunosenescence and inflamm-aging are the age-associated alterations of the immune system, which

affect both innate and adaptive immunity. These chronic conditions lead to an increase in morbidity and mortality in the elderly from several diseases, for examples, infectious diseases, cancer, atherosclerosis, diabetes, and autoimmune diseases. However, new concepts have emerged that these immune alterations may be an aging adaptation of the body and actually beneficial to older individuals. Since aging society is becoming a global health concern, understanding the causes and underlying mechanisms of these two conditions are crucial and may shed light on how to develop new therapeutic and preventive measures to improve the health and quality of life of the aged population in the future.

Take home messages

- Immunosenescence and inflamm-aging are now considered a double-edged sword. They can be either detrimental or beneficial to the body depending on an individual's circumstances.
- The mechanisms underlying these conditions are still unclear and a better understanding of these processes will help to develop new measures to enhance the health of aged population.

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Conflict of Interest

None to declare.

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