Update of skin immunosenescence in geriatric population

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Abstract

Increased life expectancy must be in line with good health and independence at the end of life. Elderly is a state when numerous factors change, including molecular, cellular, physiological, immunological, and psychosocial factors, directly causing functional impairment, inability to adapt and accumulation of various organ failures. As age advances, the immune system undergoes characteristic changes, usually resulting in decreased immune competence, termed immunosenescence. The alterations that happen in immunosenescence, including the abnormal elevation, decrease, and dysregulations of innate and adaptive immune responses, lead to more severe consequences of bacterial and viral infections, also autoimmune diseases and cancer in elderly.

Key words
Immunosenescence, innate immune system, adaptive immune system.

Introduction

Recent studies predicted that the steady increase of life expectancy in Europe, Canada, Japan, and England will allow many children born in 2000 to reach 100 years of life. The increase of life expectancy must coincide with an expectation of good health, and self-sufficient for the last part of life. Old age is a situation in which a number of factors (molecular, cellular, physiological, immunological, and psycho-social events) help to set up a scenario of “exhaustion of reserves”, that include an inability of functional adaptations and an accumulated deficits of many organs.

With advancing age, the immune system of animals and humans undergoes characteristic changes, usually resulting in decreased immune competence, termed immunosenescence. The alterations also affect the skin, the largest immunologically active organ of the body. The skin contains characteristic cell types of the immune system, such as macrophages, B lymphocytes, T lymphocytes, Langerhans cells, keratinocytes, and endothelial cells.

Immunosenescence involves age-associated restructuring changes of innate and adaptive immune functions. The alterations that happen in immunosenescence, including the abnormal elevation, decrease, and dysregulation of immune responses, lead to more severe consequences of bacterial and viral infections and reduced responses to vaccination. The role of age in the physiological changes of the immune system cannot be separated from the intrinsic changes, such as decreased DNA self-repair, and extrinsic changes, such as ultraviolet (UV) exposure. Skin that is chronically exposed to sunlight indicates immunological changes.

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There are three theories that explain the phenomena of immunosenescence:

1. Autoimmunity theory

Two age-related processes identified in causing autoimmune diseases are different rates of senescent cell accumulation in the immune system and target tissue/organ and heterogeneous accumulation of senescent cells in tissue/organ. Either happening simultaneously or separately, these two processes are the underlying cause of autoimmune diseases. Production of autoantibodies has been hypothesized to be secondary to thymus involution with a decline of naive T cells and the accumulation of clonal T cells. Furthermore, CD5+ B lymphocytes that increase in elderly population, produce autoantibodies that lead to the disequilibrium of mechanism controlling the immune response against self antigens.

2. Immunodeficiency theory

Old age consequently decreases body capability to modulate primary immune responses against the newly exposed antigens. The immune responses to the new antigens rely on the availability of naive T cells. When occurring together with age-related thymic involution and decreased reservoir of naive CD8+ T cell, the condition makes the elderly more prone to variety of infectious and non-infectious diseases.

3. Deregulation theory

Deregulation of immune system response also occurs in elderly. This condition is developed due to an age-associated disruption in the equilibrium of alternatively expressed isoforms for selected genes, implying that modification of mRNA processing may be a feature of human aging. Also, the downregulation of toll-like receptors (TLRs) and nod-like receptors (NLRs) may contribute to the lack of effective recognition of invading pathogens or the commensal flora.

Hematopoietic bone and thymus

The immune system cells are constantly renewed from hematopoietic stem cells (HSC). However, this ability decreases during senescence when the total amount of hematopoietic tissue decreases. As the thymus volume decreases, cortex and medulla of thymus are replaced with the adipose tissue.

Effect of aging in the immune system

Table 1 Immunosenescence of aging.

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
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| **Skin and Mucous**
  - Reduce cycle of replacement
  - Lower sweat production
  - Impaired barrier function
| **T Lymphocytes**
  - Decrease of CD4+ and CD8+ lymphocytes
  - Decrease of membrane receptor |
| **Dendritic cell**
  - Diminish ability to stimulate lymphocytes
  - Decrease presentation of antigen
  - Decrease chemotaxis
| **B Lymphocytes**
  - Decline lymphocyte number
  - Decrease in antibody production and IL-2 |
| **Natural killer**
  - Decrease cytotoxic capacity
  - Decrease secretion of IFN-γ
  - Diminish response to IL-2
| **Neutrophils**
  - Impaired chemotaxis and phagocytosis
  - Decrease superoxide anion production
  - Diminish activation of signal transduction
  - Decline of INF production
| **Macrophages**
  - Decrease of expression and function TLR
  - Decrease production of MHC II
  - Decrease production of TNF-α
| **Microglial Cells**
  - Increase of neurotoxic factors and neuronal degeneration
| **Adaptive Immunity**
  - Decrease of CD4+ and CD8+ lymphocytes
  - Decrease of membrane receptor
| **B Lymphocytes**
  - Decline lymphocyte number
  - Decrease in antibody production and IL-2
Innate immunity

Innate immune response constitutes the earliest response to pathogens. This response is non-specific and lack of immunological memory.\(^5\)

Skin and mucous membranes

Skin and mucous membranes are the first defense line of our body against pathogens. With aging, renewal of skin cells decreases, sweat production is reduced; there are changes at the structural level of epithelial cells, depletion of Langerhans and melanocyte cells, and subcutaneous tissue atrophy.\(^3\) Reduction of barriers in the epithelial layer of the skin, epidermal thinning, reduced quantity and movement of hair cells and mucous membranes, and decreased immunoglobulin (Ig)A also happen in aging skin.\(^1,3\) These changes lead to the impaired immunological defense of the skin.\(^1\) Alterations in skin immune system can increase the possibility to develop cutaneous infections, malignancies, and decreased or variable contact hypersensitivity reaction in elderly.\(^6\)

Dendritic cells and Langerhans cells

Dendritic cells are responsible for the first recognition of pathogens, processing and regulating both T and B lymphocytes, and also natural killer (NK) cells. Langerhans cells are the specific dendritic cell in the skin.\(^3\) The amount of Langerhans cell in skin decrease about 20% - 50% in elderly.\(^2,4\) Reduction of Langerhans cells is also identified in the epidermis of covered skin, e.g. buttocks.\(^2\) Decreased number and function of Langerhans cells along with the defect in cell-mediated immunity and cumulative exposure to UV radiation contribute significantly to the increase of malignancy risk in elderly.\(^6\)

Natural Killers (NK) cells

The NK cells are involved in the elimination of virus or tumor cells, also production of chemokines and cytokines that can activate other cellular components of innate and adaptive immunity.\(^3\) Recent studies pointed out that high NK cells cytotoxicity is associated with longevity and good health while low NK cells function is associated with an increase of morbidity and mortality. During senescence, reduction of important lymphokines for the lymphocyte activation, e.g. IL-2 also for the killing of the NK-resistant cell line occurs that leads to deficit of NK function, even when the numbers of NK cells are normal.\(^1\)

Macrophages

Macrophages can produce pro-inflammatory cytokines, including TNF-\(\alpha\), IL-1, IL-6, and IL-8. During senescence, precursors of macrophages decrease. In addition, the phagocytic function appears to be reduced, while the chemotaxis seems to be conserved.\(^1\)

Neutrophils

Although the numbers of neutrophils are preserved in elderly, the expression of CD16 Fc gamma receptor is reduced. Therefore, both the generation of superoxide mediated by the Fc receptor and the phagocytosis are impaired in elderly. The reduced response can cause Staphylococcus aureus infection that may lead to increased susceptibility to lung infection. Recently, several studies reported the alteration of the pathogen-mediated destruction of neutrophil extracellular traps (NETs). These studies confirmed the reasons of the increased incidence of infection in elderly.\(^1\)
Keratinocytes

Keratinocytes have the capacity to produce a variety of different cytokines, such as ILs, chemokines, TNFs, IFNs, growth factors (transforming growth factors), and suppressor factors (IL-10, IL-1 receptor antagonist, and a melanocyte-stimulating hormone [aMSH]), and play a well-established regulatory role in the immune and inflammatory reactions. In the absence of disturbances, keratinocytes release only low levels of these cytokines. They release considerable amounts when activated by UV, allergens, or infectious agents. Some of the cytokines have local effects, such as granulocyte-macrophage colony stimulating factor in the maturation of Langerhans cells, while others cause systemic effects, such as sunburn reactions (IL-1 and IL-6) or UV-induced immunosuppression (IL-10 and aMSH).

There are few reports regarding the influence of aging on epidermal cytokine production. Keratinocytes produce significantly less IL-1 in elderly humans and expression of human messenger RNA for the IL-1 receptor antagonist is increased, suggesting a marked decrease of overall IL-1 activity in older individuals. The relevance of these findings is not clear but a decrease of IL-1 activity could reduce the extent of the initial immune response. In contrast to these changes observed during biological aging, the IL-1 receptor antagonist is down regulated during photoaging, underlining the characteristic differences between these 2 forms of aging.

However, not all keratinocyte-derived cytokines are decreased during aging. Messenger RNA for transforming growth factor (TGF)-α and TGF-β are maintained at the same level.

Adaptive immunity

Adaptive immunity is slower than innate immunity but highly specific and permanent.

B Lymphocytes

In elderly population, B cell responses and antibody production are impaired that lead to reduced ability to respond effectively to virus and bacteria. The reduced function of B cells was thought due to lack of helper T function in T-dependent responses. On the other hand, there are B cells’ functions which are T-independent, such as response to polysaccharide (important for antibacterial protection) that seems to be inefficient too. In elderly, reduced level of IgM and IgD is also reported which relates to the transition from naive cells to B cells. On the contrary, the level of IgG and IgA increases.

T Lymphocytes

Regression of the thymus because of aging and chronic antigenic stimulation causes a decline in naive T cell output. This causes the increase of susceptibility to new infection, autoimmune disease, and cancer. CD8+ cells increase their number during senescence. In addition, naive T cells show multiple changes, including telomere shortening, reduced production of IL-2, and diminished ability to differentiate themselves into effector cells.

Cytokines

An increase of certain cytokines is a characteristic feature of several defined immunological reactions and alterations in older individuals. Therefore, it is worth being mentioned in the context of skin aging and the immune system.

Infection of Gram-negative bacteria on the skin, intestine, or lungs is a common cause of septic shock in the older population. In a murine
experimental model, reaction to lipopolysaccharide was 6 to 10 times more lethal in older mice (24 months) compared to young adult (12 months) or immature mice (2 months). This increase was due to excessive production of TNF-α and nitric oxide in aged mice. IL-6 level was also found to be increased in aged mice treated with lipopolysaccharide, whereas results for IL-1 were not consistent. IFN-γ level was moderately increased despite not significantly different from that in young mice. Because sensitivity to lipopolysaccharide is greater after stimulation with IFN-γ and aged mice contain a high proportion of IFN-7-releasing memory T cells, this moderately increased release of IFN-γ is postulated to be one of the reasons for the increased susceptibility to lipopolysaccharide.

Another mechanism suggested for cytokine dysregulation during aging is a decline in endogenous steroid hormones. Application of dehydro-3-epiandrosterone prevents an upregulation of IL-6 among elderly humans or aged mice and also leads to reversion of age-related increased levels of serum amyloid, serum IgG, and autoantibodies.

Effect of Immunosenescence

Infection A decrease and exhaustion of naive T lymphocytes, especially CD8+ T cells, could account for reduced competence to face new intracellular pathogens. Involution in thymus also contributes to the incidence of infection in elderly. Clinician is no stranger to infection in this population, such as primarily bacterial infection (pneumonia and urinary tract, skin and soft tissue infection), viral infection (reactivation of herpes zoster and increased morbidity and mortality due to influenza virus), also difficulty in detecting both active and inactive tuberculosis.

Cancer Studies of knockout mice have established a critical role for immune system in controlling spontaneous tumors. Mice that do not have 50% of IFN-γ or perforin, develop spontaneous lymphomas, lung adenocarcinoma, or sarcomas. Age-related cancers are predominantly carcinomas.

Autoimmune As the age advances, the alteration of the immune receptor signaling machinery underlies the higher incidence of autoimmune phenomena in the elderly, such as systemic lupus erythematosus.

Conclusion

Immunosenescence involves age-associated restructuring changes of innate and adaptive immune responses. The alterations that happen in immunosenescence include the abnormal elevation, decrease, and dysregulation of immune responses, leading to more severe consequences of bacterial and viral infections, autoimmune diseases, and cancer.

References


