CHAPTER

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The Immunity in Elderly

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INTRODUCTION

There is an increasing awareness that many chronic infections and diseases impact on the immune system. The immune system is a very dynamic network, consisting of various innate and adaptive cells and indirect messaging mediated by soluble factors. The changes in immune profiles translate into obvious signs of immunological aging that are more profound in diseases. In the current decades, there is an increase in the aged population across the world. According to the WHO, the proportion of old individuals (age > 60 years) will rise to 22% of the world population.[57] In this context, it is very important to improve our knowledge of aging and its associated diseases to fight with the burden of diseases and to promote healthy aging.

BASICS OF IMMUNITY

Immunity is the state of protection, against any substance that is recognized as foreign by the body. The immune system is composed of two major subdivisions, the innate or nonspecific immune system and the acquired or specific immune system (Figure 1).

Innate Immunity- Innate or nonspecific immunity is a primary defense mechanism against invading organisms, involves barriers that keep harmful materials from entering the body. It is a key element of the immune response including several cellular components such as macrophages, natural killer (NK) cells, and neutrophils, which provide rapid first-line defense against pathogens.

Acquired or adaptive Immunity- Acquired immunity is immunity that develops with exposure to various antigens, specific to that antigen and acts as a second line of defense and its response can be antibody mediated (humoral), cell mediated (cellular), or both. Active Immunity- Active immunity is induced after contact with foreign antigens (eg, microorganism or their products). This contact may consist of clinical or subclinical infection, immunization or transplantation of foreign cells. In all these instances the host actively produces antibodies. However, protection is delayed until antibody production reaches an effective level. Passive Immunity- Passive immunity is achieved by administration of preformed antibodies. It provides prompt protection against certain viruses (eg, HBV) in non immunized individuals but does not provide long-lasting protection.

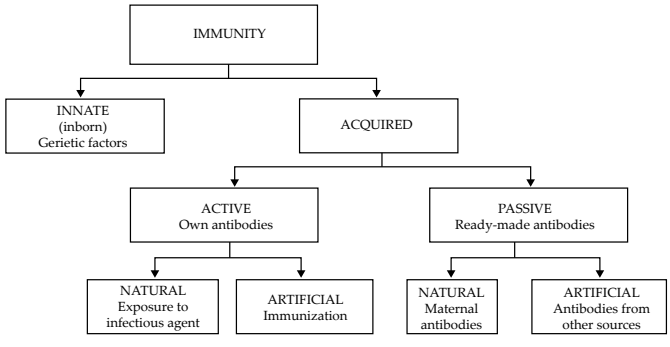

Fig. 1: Schematic presentation of the immune system (Source: http://futuresurgeon0607.blogspot.com/)

Cell-mediated Immunity- It is the type of immunity that functions in defense against fungi, parasites, bacteria, and viruses inside host system and against tissue transplants, with highly specialized cells that circulate in the blood and available in local tissue site.

Humoral Immunity- This is the component of the immune system that involves antibodies secreted by B cells and circulates as soluble proteins in blood.

Cells in the Immune System- All cells of the immune system originate from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid and a lymphoid progenitor cells. These progenitor cells subsequently give rise to the myeloid cells (monocytes, macrophages, dendritic cells, megakaryocyte and granulocytes) and lymphoid cells (T cells, B cells and natural killer (NK) cells) respectively. These cells make up the cellular components of the innate (non-specific) and adaptive (specific) immune systems (Figure 2).

IMMUNOSENESCENCE

The term 'immunosenescence' is used to describe loss of immune functions in elderly people (age > 65 years). Though it involves both the innate and adaptive immune system,[2] the important contributor is the changes observed in adaptive immunity, including T and B lymphocytes. The antigen-specific immunity is impaired with aging partly due to alterations in the innate immunity. Although its mechanisms are not very clear, it has been associated with increased susceptibility to diseases, infections and poor response to treatments and vaccination.[1] The ability of maintaining receptor diversity is reduced with aging and this is paralleled by the reduction in the number of circulating naïve T-cells (CD45RA+CCR7+CD28+CD27+).[3,4] This can be explained by the phenomenon of involution of the thymus, where T-cell maturation occurs. This is associated with increased number of memory cells due to pathogens encountered during the course of life.[5] Another hypothesis to explain immunosenescence partly is the telomere length. The telomere shortening primarily identified in highly differentiated effector memory CD8+ T cells, most of which are CD28− T cells.[6] The loss of telomeric repeats is associated with loss of proliferative capacity and

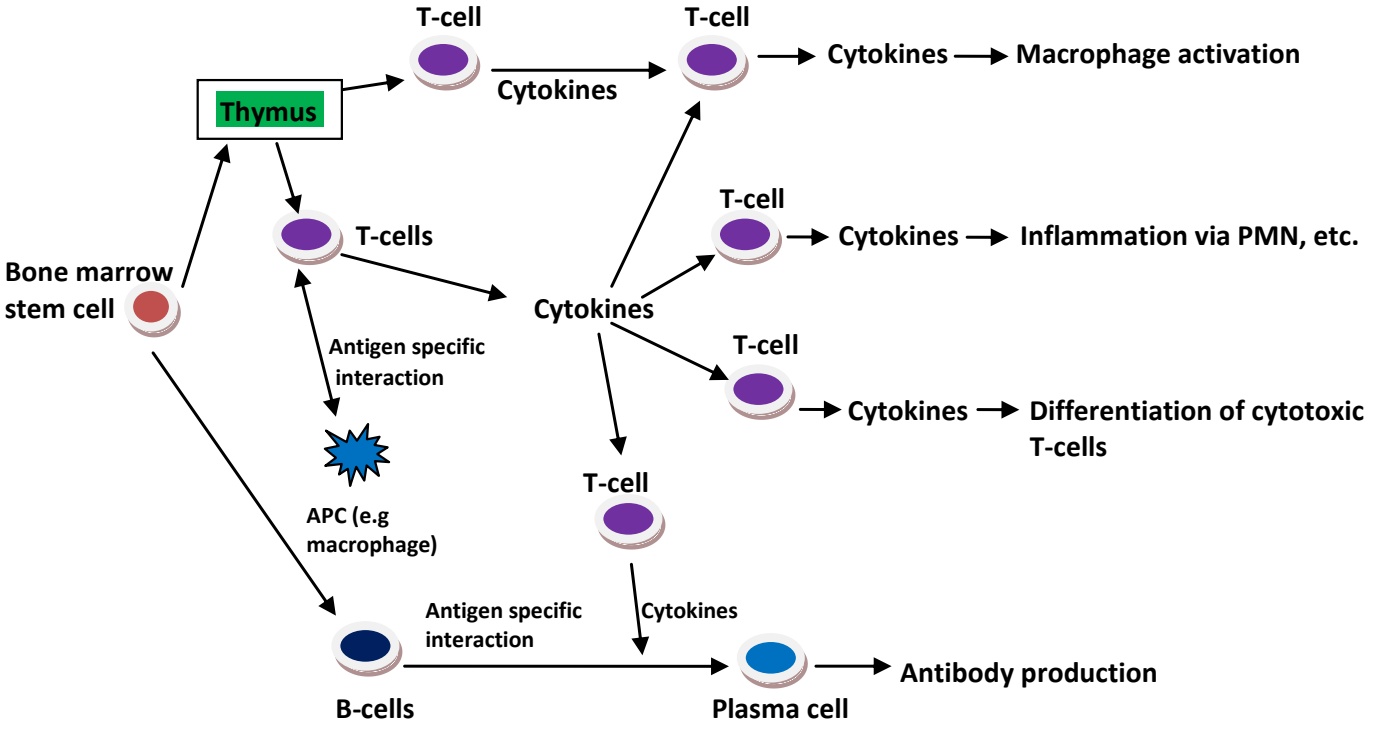

Fig. 2: Schematic diagram of the cellular interactions in the immune response. APC: Antigen presenting cell

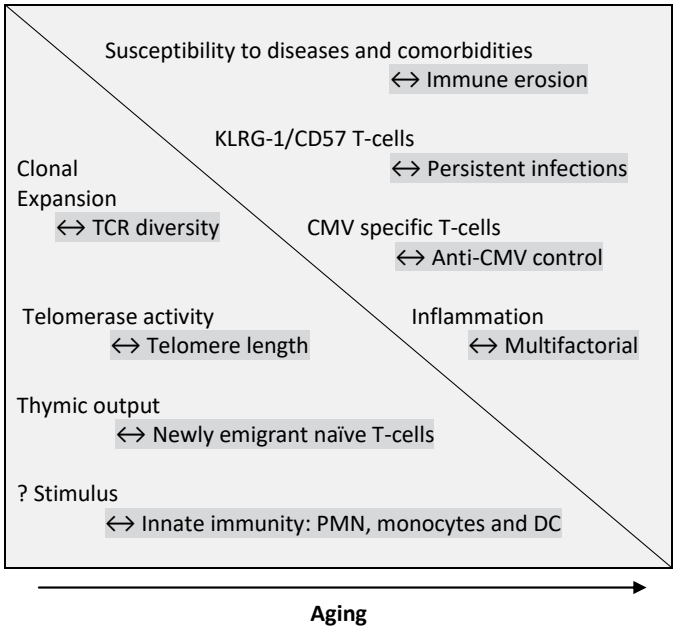

Fig. 3: The components of immunosenescence: The items depicted on left side show decline with age, while items on the right show upregulation with age. ? Unknown; CMV: Cytomegalovirus; DC: Dendritic cell; PMN: Polymorphonuclear neutrophil; TCR: T-cell receptor

replicative senescence. Despite this evidence the telomere length is not the shortest in the highly differentiated T cells,[7] suggesting a more complex relationship between telomeres and senescence.

INNATE IMMUNITY IN AGING

The cells of the innate immune system, like neutrophils, monocytes/macrophages and dendritic cells undergo changes with aging that lead to impaired immune function. With aging, monocytes increased in numbers.[8] Defective Toll-like receptor (TLR) function has been studied in monocytes, where the production of IL-6 and TNF-α reduced when induced by TLR1/2.[9] Aging has a general suppressive effect on dendritic cell function. Neutrophils show reduced functions, like slowed response to chemotaxis, phagocytosis, generation of superoxide, alterations in signal transduction and membrane lipid rafts with aging.[10] This age-related decline in neutrophil functions is explained partly by the decreased Fc-γ receptor expression.[11] Some events associated with signaling and activation may also interfere with neutrophil functions. For example, the dehydroepiandrosterone sulfate (DHES) levels are highly reduced with aging (adrenopause) that could highly impact neutrophil activation. The DHES increases superoxide generation by neutrophils via a PKC-β/p47(phox) pathway[12] that suggests altered antibactericidal effect due to modulation of neutrophil activity.

T AND B CELLS IN AGING

There are several memory subsets in the CD4 and CD8 compartments. Based on surface markers used to distinguish these, there are central memory ($CCR7^+CD45RA^-CD45RO^+CD28^+CD27^+$), effector memory ($CCR7^-CD45RA^-CD45RO^+CD28^{+/-}CD27^{+/-}$) and late differentiated ($CCR7^-CD45RA^+CD45RO^{low}CD28^-CD27^-$) cells. The frequency of $CD28^-$ T cells, which is often associated to aging of the immune system, encompass both the effector memory and T-effector memory re-expressing CD45RA (TEMRA) cells and discrepancies exists between CD4 and CD8 T cells.[13] Some markers are associated with lack of functionality of T cells. CD57 and KLRG-1 are associated with lack of proliferative response and are considered as markers of replicative senescence. These cells lack expression of costimulatory molecules like CD28 and CD27. A majority of the expanded cells are

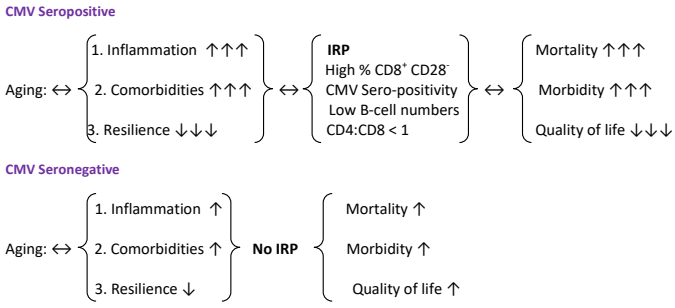

Fig. 4: The Impact of cytomegalovirus infection on immunity and health. With aging there is an elevated proinflammatory profile that is enhanced by CMV infection. Associated co morbidities and poor resilience will add up to the existing condition and may lead individuals to be at risk later in life, as suggested by the IRP. This will be reflected into different mortality, morbidity and quality of life grades. +: Present; +++: Very high; --- : Very low; CMV: Cytomegalovirus; IRP: Immune Risk Profile. Source: Aging Health @2013 Future Medicine Ltd.

expressing CD57, KLRG-1 or both suggesting antigen-specific T-cell expansion leads to an increased proportion of replicative senescent cells. Both the number and the function of B cells are reduced with aging. The senescent B cells also exhibit increased production of low-affinity antibodies due to decreased isotype switching from IgG to IgM antibodies.[16] These lead to increased susceptibility to diseases, reduced responses to vaccination and increased incidence of cancer in aged populations.[14,15] Reductions in B-cell lymphopoiesis in old age could contribute to reduce tumor immunosurveillance. So it appears that loss of B-cell diversity is strongly associated with poor health rather than age.[17]

IMMUNITY IN AGE-RELATED DISEASES

To understand the relationship between diseases in the elderly and the immune system the following diseases are discussed below:

INFECTIOUS DISEASES

The aged immune system is not as efficient in recognizing and eliminating new invaders or in preventing their spread. Age-associated alterations in systemic immunity contribute to the increased incidence and severity of infectious diseases in elderly.[18] The organisms such as bacteria, viruses, fungi or parasites often encounter less resistance after invading the elderly. CMV is asymptomatic in most individuals and only in rare cases CMV disease develops.[19] The prevalence for CMV varies from 45 to 100% according to age, location and hygiene conditions. CMV prevalence is lower in Europe/USA and higher in Africa/Asia but significant differences exist within large countries.[19] In aged people CMV specific $CD8^+$ T cells increased and circulating naive T cells are decreased. The risk of influenza-related death increases exponentially after 65 years.[20] CMV and influenza per se is not directly inducing death, but the events associated with these diseases are detrimental, especially in elderly with poor resilience (Figure 4).

The lifelong exposure to pathogens leads to a relative increase in the proportion of memory T cells. The most observable phenotypic and functional changes are seen in the subsets of $CD8^+$ T-cell. The continuous stimulation of memory cells by specific persistent antigens like CMV leads to their progressive exhaustion characterized by the loss of costimulatory molecules (CD28 and CD27), shortening of telomeres and terminal differentiation ($CD45RA^+CD57^+$). The presence of CMV and CMV-specific T cells hinders the response to co-infections such as EBV.[21] The accumulation of these virus-specific $CD8^+$ T cells compromises immune function and restricts the overall immune repertoire in elderly. CMV infection has been associated with the Immune Risk Profile (IRP), a cluster of parameters predicting mortality in the elderly. Apart from CMV seropositivity, increased numbers of $CD8^+CD28^-$ T cells, an inverted CD4:CD8 ratio (<1) and low B-cell counts are part of the IRP.[22] $CD8^+CD28^-$ T cells also exhibit suppressor activities which may alter antigen presentation and changes in dendritic cell function with aging.[23] In contrast the $CD4^+$ T cells are less affected by replicative senescence. The memory $CD4^+$ T-cell response is impaired with aging.[24] Overall, $CD8^+$, $CD4^+$ and putative antigen presenting cell (APC) changes with an altered interaction between these cells lead to reduced vaccine efficacy.

ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) is an age-related neurological disorder that leads to progressive dementia. AD is histopathologically characterized by extracellular amyloid plaques formed by amyloid-β (Aβ) peptide and by intracellular neurofibrillary tangles. The inflammation resulting from deposits of highly aggregated Aβ fibrils plays an important role in the pathogenesis of AD.[25] In the brain, microglia express MHC class I and II molecules after activation by neurodegeneration or ischemia.[26] By contrast, microglia activation in the brain of AD patients is caused by Aβ and the activated microglia cluster at sites of Aβ deposition.[27] The microglia from elderly donors show changes in their cytoplasmic structure, leading to functional defects and development of AD in the elderly, but it still remains unknown how the activation of microglia is influenced by age and senescence.[27]

CARDIOVASCULAR DISEASES

There are several types of cardiovascular diseases associated with aging. The higher prevalence of coronary disease, hypertension, diabetes, ventricular hypertrophy, fibrosis and senescence of cardiac cells lead to events that may predict more severe cardiac failure with aging.[28,29] The atherosclerotic plaques are composed of activated helper T cells, γ/δ T cells, macrophages, smooth muscle cells and $CD1a^+$ dendritic cells, whereas B cells and NK cells are absent.[30] These cells induce a proinflammatory milieu that contributes sustained inflammation and the development of the lesions. Innate cells like neutrophils participate in the development of ischemic stroke. $CD4^+$ T cells modulate immune response by secreting type-2 cytokines (IL-4 and IL-10) or type-1 cytokines (IL-12, IFN-γ and TNF-α). The majority of the T cells present in atherosclerotic plaques are memory cells lacking CD28 expression. These cells have a poor proliferative capacity but a higher proinflammatory/cytotoxic (IFN-γ

and TNF-α) profile that sustain local inflammation and disease progression.[13]

CANCER

The incidence of cancer increases with advancing age.[31] This is due to the cumulative events such as exposure to carcinogens, mutations and reduced immune functions. In healthy elderly people, the killing, proliferative and response of NK cells to triggering are reduced.[32,33] The reduced killing may be due to the altered perforin release and interaction at the immunological synapse site of the target cells.[34] This mechanism can explain why elderly individuals are more susceptible to cancers. The immune-compromised individuals (e.g., HIV patients) are more susceptible to non-Hodgkin's lymphoma (NHL) and cervical cancer.[35] The tumor induced local inflammation suppresses the adaptive immune system favoring tumor development.[36] The elderly people are less susceptible to acute lymphoblastic leukemia (ALL) due to reduced thymopoiesis and more susceptible to chronic lymphocytic leukemia (CLL) due to immunosenescence. Moreover tumors often express Fas ligand which induces apoptosis of T cells through Fas receptor. Therefore elevation of Fas receptor with aging contributes tumor growth.

DIABETES

Type 2 diabetes has become an epidemic especially in the elderly[37] with the majority in the 45–64 years.[38] With aging the body composition is changed such as sarcopenia and fat accumulation.[38] The reduced muscle bulk with lack of motility (sedentary lifestyle) leads to decrease energy expenditure favoring fat accumulation. Other risk factors are insufficient exercise, smoking, alcohol, weight gain and an unbalanced diet.[39] There is a strong link between inflammation, diabetes and metabolic syndrome. The study of Hjelmesæth et al strongly suggests that CMV infection and the associated events can initiate/accelerate the onset of diabetes.[40] CMV seropositivity is associated with glucose regulation in elderly.[41] Therefore diabetes and metabolic syndrome influence immunosenescence.

INFLAMMATION & AGING

Inflammation in aging is often referred to as low-grade inflammation.[42] A set of proinflammatory mediators such as RANTES, MIP-1α, MCP-1, CRP, IL-6, IL-8 and TNF-α have been identified in aging. Among these, CRP, IL-6 and TNF-α are often associated with comorbidities such as cardiovascular diseases, atherosclerosis, dementia and diabetes. These association studies did not enable to predict disease onset in the elderly at the inflammatory level. Furthermore, studies have shown that higher levels of proinflammatory molecules are not always associated with poor health, since centenarians show higher IL-6 levels.[43] This suggests that inflammation in aging is probably a sign of unsuccessful aging associated with diseases.

REVERSING IMMUNITY

Many strategies such as caloric restriction, hormone therapy, cytokine therapy or stem cell approaches have been demonstrated to restore immunity in animal models, but may prove difficult to perform in humans due to lack of consensus.[44] The following approaches are employed to reverse the immunity in elderly with justified manner.

NUTRITIONAL INTERVENTION

Some vitamins and mineral supplementation can help in augmenting immunity, such as vitamin A helps to maintain the epithelial integrity of the respiratory and gastrointestinal tracts, thereby reduces the risk of influenza and gastrointestinal infection; vitamin D enhances activation of Toll like receptors (TLRs) and increases cathelicide production, which contributes to the destruction of intracellular organism. Zinc has a role in helping phagocytosis, and maintenance of the complement cascade. While malnutrition has detrimental effect on immunity, caloric restriction has positive effect on T cell function. So a balanced diet approach would be justified.[45,46]

EXERCISE AND LIFESTYLE MODIFICATION

Moderate exercise helps to maintain the physical functions and cardiovascular fitness improves the T helper immune responses. Smoking and alcohol consumption should be stopped and lipid profile should be within normal range to maintain a healthy immune system.

Vaccinations: Vaccinations are a reliable and cost-effective method for prevention of infections. The elderly people not able to respond optimally to vaccination due to reduced thymic output of naive T cells, increasing memory T cells but their progressive replicative senescence,[47] and imbalance between pro- and anti-inflammatory cytokines. Apart from changes in T cells a latent CMV infection and physical frailty also impact on the outcome of vaccinations. Physical frailty such as slow walking speed, low physical activity and weight loss have been associated with reduced antibody response to vaccination and post vaccination influenza infection.[48] The strategies to improve the effectiveness of vaccines in elderly individuals include:

a. Using adjuvant: TLR-4 agonist, glucopyranosyl lipid adjuvant stable emulsion, improves the antigen-presenting capacity of dendritic cells by improving T-cell immune response by increasing the production of proinflammatory cytokines when added to influenza split-virus vaccine.[49]

b. Broadening the cross-reactivity of strains: The use of MF59 adjuvenated vaccine offers a broader range of protection for multiple strains.[50]

c. Changing the route of administration: Intradermal injection improves immunogenicity in elderly individuals.[51]

Reversing thymic involution and increasing thymopoiesis

Eexogenous administration of keratinocyte growth factor induces the production of IL-7 on thymic epithelial cells, thereby increasing thymic output in murine models.[52,53] By in vivo administration of FGF-7, the senescence-associated gene Ink4a can be repressed in involuted thymus to generate T-cell progenitors.[52] The T-cell functions can be restored by promoting 4–1BB, or blocking PD-1 and supplementing with cytokine cocktails. Blockade of 4–1BB highly reduces the production of key cytokines such as IFN-γ and TNF-α.[54] Cytokines play a pivotal role in T-cell survival, homeostasis and activation. Recent study

showed that IL-15 preferentially promote proliferation of $CD28^{null}$ $CD4^{+}$ T cells over the $CD28^{+}CD4^{+}$ T cells. IL-15 also enhances the cytotoxic activity in a short-term manner by increasing IFN-γ, granzyme B and perforin production.[55] Further studies are necessary to understand the impact of different cytokine cocktails on other T-cell subsets and not only on $CD28^{null}$ T cells.[56]

CONCLUSION

Immunesenescence is a major challenge against active ageing which is the major determinant for susceptibility to diseases and may also be a cornerstone in sustaining chronic conditions due to the associated proinflammatory profile. Notably the putative alterations in T- and B-cell interaction are still poorly understood in pathological situations and in subclinical condition like age-associated low-grade inflammation. The Immunosenescence has the direct effect on development of frequent and severe infection, which further increases morbidity, disability and death in elderly population. Overwhelming detrimental effect of weaning immunity precipitates aggressive malignancy in them. Thymic rejuvenation is attractive, but still requires cautious interpretation. Vaccination is an effective measure but efficacy decreased with advancing ageing, which mandates discovery of new and augmented vaccination strategy. Lifestyle modification, nutritional supplementation, caloric restriction but avoiding malnutrition through balanced diet may be employed to augment immunity in elderly. Telomerase based approach and gene therapy could be the future prospects.

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