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EDITORIALS

Some immunological changes in elderly subjects

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ABSTRACT

Age-related alteration in normal immunologic functions has been observed. The deterioration in immune function in elderly subjects is due not only to aging, but also to the presence of chronic disease. The aging of the immune system, referred to as immunosenescence, is associated with a dramatic reduction in responsiveness as well as functional dysregulation.

Age-associated changes are evident in both B and T lymphocytes and, at higher organizational levels, in the thymus, marrow and lymphoid follicles (evident especially by failure of germinal center formation).

Data in the literature reviewed in this paper suggest that both innate (natural) and adaptive (acquired) immune responses decline with advancing age. Previous studies have revealed a reduction in total NK cell numbers in association with aging. Most immunologic activities show a decline with age (e.g., primary delayed type hypersensitivity skin reactions), some show an increase (e.g., autoreactive immunity), and a few show no significant change or only a minimal change (e.g., Arthus type hypersensitivity). This deterioration of immune function with advancing age contributes to the increased incidence of morbidity and mortality from infectious disease and possibly to autoimmunity and cancer among elderly. The main purpose for the types of studies described is to develop strategies to stimulate B- and T-cell development in the elderly. Despite these advances numerous questions remain.

The present review summarizes a selection of data related to some immunological changes in elderly subjects.

Key words: immunology, aging, cellular senescence

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Aging of organisms is among the most complex processes currently known. Of the various physiologic processes in our body, that of the immune system appears to be one of the most vulnerable (1). Longitudinal studies are defining progressive alterations to the immune system associated with increased mortality in the very elderly. It is therefore not surprisingly that increased attention has been given to the nature of age-related alteration in immune functions, especially since it is becoming apparent that altered immune functions contribute to many major acute and chronic diseases of the elderly. These modifications linearly progressed with age suggesting that the immune system does not escape the aging process (2-4).

Current hypotheses on the problem of physiological aging of organisms generally fall into one of two categories. The first category invokes alterations in gene expression that are either programmed or that are modulated by non-mutational changes in DNA structure, the second invokes extrinsic and intrinsic factors that damage intracellular molecules. There is evidence that cells accumulate damage over a lifetime what induces a gradual reduction of growth rate and impairment of functions of the cells.

Immunosenescence is defined as the state of dysregulated immune function that contributes to the increased susceptibility to infection, cancer and autoimmune diseases observed in all organisms, including humans. The contribution of the immune system to healthy aging and longevity is still an open question. Although the immune system exhibits profound age-related changes, it has been suggested that old individuals frequently do retain some capacity to produce fully functional new T cells. The maintenance of immunity has to be balanced with appropriate controls to prevent non-specific inflammation and immunopathology, which it is thought are major problems in aging. Immunosenescence is the state of dysregulated immune function that contributes to the increased susceptibility of the elderly to infection and possibly, to autoimmune disease and cancer. Chronic illness probably contributes to further dysregulation of control of the immune response (5-7).

Reactive oxygen species (ROS) produced endogenously as a consequence of normal cellular metabolism or derived from external sources result in severe damage of cellular components that lead to degenerative processes and subsequently to aging. Cells contain a number of antioxidant defenses to reduce fluctuations of intracellular ROS. However, the levels of produced ROS often exceed the cell's intrinsic antioxidant capacity and lead to a condition known as oxidative stress. Several studies have shown that both oxidative stress and inflammation are linked and that the immune system is also involved in this age-related process. More specifically, the oxygen stress related to immune system dysfunction seems to have a key role in senescence, in agreement with the oxidation/inflammation theory of aging (8).

Recent studies have shown that there are no differences in terms of aging in endothelial adherence. Therefore, specific PMN cell functions studied in laboratory setting tend to not demonstrate significant aging changes. It appears that PMN cells from older individuals are more sensitive to the levels of CM-CSF, IFN-g, and growth hormone than are PMN cells from younger adults. The phagocytosis of aged PMN by macrophages strongly correlates with the incidence of apoptosis in the PMN. Statistically significant differences were found between the young and middle-aged group and the healthy or ill elderly groups for the percent phagocytic PMNs. Overproduction of ROS may be associated with the development of atherosclerosis and impaired efficacy in response to patogens as a consequence of inefficient cell

signaling caused by impaired membrane fluidity due to high lipid levels. Major alterations of PMN cell functions, including impaired phagocytosis, have been identified in aged subjects with chronic bronchitis and in patients with poorly controlled diabetes.

The elucidation of the age-related alterations in immune functions is of great importance in light of the rising susceptibility of the elderly to infections, the likelihood that immunosenescence might also contribute to the age-related rise in cancer and the role autoantibodies and immune complexes might play in general physical deterioration of aging individuals throught their participation in subclinical chronic tissue damage. Studies on potentiation of immunologic activities of aging individuals are increasing (9-13).

Macrophages perform several functions, from phagocytosis and killing to cytokine production that regulates the activation of other cells of the innate immune response to priming an acquired immune response or turning it off. The observed age-associated dysfunction of macrophages is the result of their functional adaptation to the age-associated change in tissue environments. Changes in macrophage function may contribute significantly to decreased clearance of microorganisms and decreased responsiveness of the adaptive immune system. The non-specific immune response of macrophages instead of decreasing, may increase. Evidence of impaired tumor cytotoxicity has been described in elderly humans, which was linked to decreased levels of reactive oxygen and nitrogen intermediates. A study on monocyte activity in humans, although of limited sample size demonstrated impaired lysis of 2 different tumor cell lines by monocytes from elderly subjects, with diminished IL-1 levels and ROS generation (14-17).

Thymic involution commences at the time of puberty because of increases in sex steroid and decreases in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) production. Receptors for these hormones are widely distributed on thymocytes and thymic stromal cells. Since the involutions of the thymus, which occurs at about the time of sexual maturity, precedes the age-related decline in T cell-dependent immune responses, thymic involution has been suspected to be responsible for the decline. Thymus involution is associated with atrophic changes in its stromal cells that synthesis thymic differentiation factors. Given the difficulty of finding (or defining) naïve cells in the elderly, and given the well-know phenomenon of thymic involution, one focus of attention for researchers interested in immunosenescence must be the thymus itself. Rejuvenating the thymus to the size and cellularity seen during early life and restoring thymic output, may be an attractive avenue to explore. In addition, changes in bone marrow stem cells have also been described that are distinct from thymic changes (18-21).

It is well documented that both the T-lymphocyte and B-lymphocyte compartments of the adaptive immune system deteriorate progressively with advancing age. Lymphocyte homeostasis encompasses a continuum of processes that together determine the production, turnover, composition, and representation of lymphocyte pools.

One characteristic of the aging immune system is that lymphocyte production in the bone marrow and the thymus is reduced, but why this decline occurs has not been fully elucidated. Recent studies have showed that intrinsic changes in hematopoietic precursors that affect their proliferative potential are one factor that contribute to the age-related decline in B- and T-cell production.

Immunosenescence is a process that primarily affects the T cell compartiment of the immune system. In humans, the number of circulating T cells has been reported either to decrease progressively after adulthood or remain the same. Qualitative changes with age are also evident. At the membrane level, two observations support the view that surface receptors change with age-one indicating loss, and the other an emergence of new receptors. The loss is reflected by the decrease in the surface density of Th1 antigens with age. Intracellular changes have also been detected. At the cytoplasmic level, both morphologic and functional changes have been observed. At the nuclear level, an increase in the loss of

chromosomes in T cells has been observed with age, the loss of X and Y chromosomes being the most prevalent. Not only T-helper and cytotoxic cell activation at the single cell level change with aging, but the frequency and behaviour of regulatory T cells is attracting increased attention once more, also in the context of aging. Aging is associated with changes in the CD4+ T-cell compartment. Defective CD4+ T-cells responses correlate with and probably contribute to reduced antibody responses seen in aged subjects. T-cell help is diminished in senescence, and T-cell-mediated suppression is increased. Therefore, deficits in humoral immunity have often been regarded as reflective of alterations in T-cell function. In aging, there is decreased naïve CD8+ T cells whereas memory CD8+ T cells are increased, under the influence of Cytomegalovirus (CMV).

Changes in B cells are much less clear but appear to have some similarities to age-related changes in T cells. Advancing age is accompanied by profound changes in B-cell generation and, consequently, homeostasis. The total number of B cells does not change appreciable with age, the size of certain subpopulations may change as indicated by the increase in circulating levels of IgG and IgA. Qualitative changes also appear to be occurring in B cells with age. Though alterations in B lymphocytes are apparent, the dramatic decline in humoral and cell-mediated responses is predominantly the consequence of senescent T cells. This is reflected by the inability of old B cells to respond to T cell-dependent antigens, even in the presence of young T cells. An age-related alteration could also be occurring at the intracellular level, for B cells of old subjects (22-29).

Natural killer (NK) cells represent the best model to describe innate and adaptative immune response in aging. NK cell cytotoxicity decreases in aging as well as interferon-gamma (IFN-γ) production. Natural killer (NK) cells are cytotoxic lymphocytes that lack CD3 and express variable levels of CD16, CD56 and CD57. In recent years NK cells have been categorized into two major groups based on the level of CD56 expression. This phenotypic classification correlates with functional activity as $CD56^{bright}$ NK cells are the major cytokine producing subset whereas $CD56^{dim}$ NK cells exhibit greater cytotoxic activity.

Recent studies have revealed a reduction in total NK cell numbers in association with aging. Low NK cell function relates to the development of severe infections, which may be fatal, in elderly subjects. As this population plays a central role in cytokine secretion during the innate immune response this decline may contribute to impaired immune regulation in elderly individuals. NK cells also interact with T cells, altering subsequent cytokine expression of both NK cells and T cells, and the magnitude of shifts in costimulation can alter the Th1 or Th2 quality of the T cell response. These activated NK cells are now called lymphokine-activated killer (LAK) cells, which can lyse cell lines that are resistant to NK cell lysis. Several recent reviews have summarized extensive studies on changes in T cell function with aging. The age-related decline in T cell function is preceded by involution of the thymus gland (cortex involutes much more than the medulla), with dramatic declines in thymic hormone levels.

The deterioration of the immune system with aging, which leads to an increased morbidity and mortality from infections, appears to be related to decreases in specific lymphocyte functions. The main questions to be addressed in this context are the reasons for dysfunctionality of T cells in the elderly and what to do to improve T cell function. There is a decrease in lymphocyte chemotaxis.

Among immune functions, a decline in T-cell functions during aging predominates. Humoral immunity is highly compromised with the onset of old age. In several studies, B cells were shown to differ functionally in senescence. Age-related alteration in normal immunologic functions has been observed.

How we can define naïve cells in the elderly? Naïve cells in the elderly have undergone considerable division and may be considered aged cells despite being phenotypically naïve. It was reported that naïve and central memory (TCM) CD8+ T cells are decreased in aging, whereas the CD45RA- effector memory (TEM) and CD45RA+ effector

memory (TEMRA) CD8+ T cells are increased. As this population plays a central role in cytokine secretion during the innate immune response this decline may contribute to impaired immune regulation in elderly individuals (e.g., decreased level of IL-6 or increased level of IL-10 might better control inflammatory responses and cancer development).

Age-associated alterations on a per-cell basis contribute to immunosenescence, as illustrated by altered signal transduction pathways. Age-related changes in the cell membrane and specifically impacting on lipid rafts may help to explain the severe impairment of CD4+ T cell signaling observed in aging. The functional changes associated with endothelial senescence may be involved in human aging and age-related vascular disorders. (30-40).

Neuroendocrine factors and stress hormones have also hypothesized to contribute to the immunosenescence and decreased macrophage function. This and other age-related defects may be exacerbated by changes in the lymphopoietic support potential of the bone marrow and thymic microenvironment as well as by age-induced fluctuations in the production of various endocrine hormones. There is a considerable literature showing that endocrine hormones have a significant effect on B and T-cell development. Particular attention with regard to the latter point has focused on changes in the production of sex steroids, growth hormone, and insulin-like growth factor-1 (41-43).

In aging, there is an increased production of TNF-α. However, the pro-inflammatory cytokine gene polymorphisms for IL-2, IL-6, IFN-γ did not differ significantly between elderly and controls, but differences were observed for IL-10, TGF-β and TNF-α genes, supporting a role of HLA and cytokine genes in successful aging. The function of chemokines in promoting and modulating leukocyte migration is essential for a prompt and efficacious inflammatory response and in host defence against infections. The overexpression of IL-1α specifically characterizes endothelial senescence. No modulation of this cytokine was observed in endothelial quiescence and in senescent or progeric human fibroblasts. The expression of IL-1β and IL-1ra was found not to be affected by senescence (44).

Apotosis is associated with cellular depletion and suppression of inflammatory response. The expression of L-selectin on polymorphonuclear neutrophils (PMN) decreases as the cell ages in the circulation and that these older PMN have more fragmented DNA and show morphological features of apoptosis.

The alterations in naïve and CD8+ T memory cells in aging may be due to their differential sensitivity to apoptosis. It was also observed that the increased apoptosis in aged naïve and central memory (TCM) CD8+ T cells was associated with increased cleavage of both caspase-8 and caspase-3 as compared to young subjects. This kind of increased apoptosis of naïve and central memory T cells may contribute to T cell immunodeficiency associated with human aging. Abnormal phagocytosis of apoptotic body and failure to generate anti-inflammatory response by dendritic cells (DCs) may explain the paradoxical increased inflammation associated with human aging. The study of the susceptibility to apoptosis, telomere length, turnover and clonal composition of the regulatory population, reported that CD4+CD25+ T-regulatory cells (T-regs) are generated continuously, most likely by differentiation of CD4+ T-cells in the presence of regulatory cues. Senescence observed in cultured cells is irreversible and is accompanied by enhanced p53 activity (p53 can initiate apoptosis), thereby, eliminating damaged cells. The recent findings clearly suggest that an enhanced p53 activity leads to a higher rate of apoptosis and cell cycle arrest (p53 plays a central role in organismal aging).

There is a growing body of evidence indicating that age-associated defects in non-T cells contribute to the waning of immune responses. The complex process of immune activation is dependent on the close participation of T cells and antigen-presenting cells (APCs). APCs are responsible for uptake, processing and presentation of antigen in association with distinct major histocompatibility complex epitopes to antigen receptors on T cells. APCs in elderly individuals produce elevated levels of IL-10, which has anti-inflammatory proprieties. The elderly are able to generate larger number of DCs from peripheral blood mononuclear cells and that these cells have a phenotype and

antigen presentation capacity to a tetanus toxoid-specific T cell line similar to those of DCs from younger subjects. The ability of DCs to differentiate after interaction with T cells may be impaired with aging or chronic illness, and this circumstance may be related to the observation that production of GM-CSF, a key DC growth factor has been found to be diminished in the elderly (45-48).

There is very little change in the quantity of antibodies people produce, of any isotype, with age. However, there is a change in the quality of the antibody response. Older people produce fewer antibodies that are specific for the activating pathogen or vaccine. At the same time, the number of nonspecific antibodies increases. Quite often these antibodies have self reactivity (e.g., anti-dsDNA). The appearance of these antibodies is not associated with pathogenic autoimmune disease, although it is true that the incidence of some autoimmune diseases increases with age. Both primary and secondary antibody responses to vaccination have been impaired, the degree of impairment being greater when T cell involvement is required to drive the antibody response (usually related to the complexity of the antigen). The specificity and efficacy of antibodies produced in older individuals are lower than those produced in younger individuals.

Most immunologic activities show a decline with age (e.g. delayed type hypersensitivity skin reactions, some show an increase (e.g. autoreactive immunity), and a few show no significant change or only a minimal change (e.g. Arthus type hypersensitivity). The existence of positive and negative correlations between age and most cell- most antibody-mediated immunologic indices underscores the complexity of the mechanisms responsible for the changes and suggests that those mechanisms which regulate immune responses are highly susceptible to aging.

Aging is associated with a paradox of increased autoimmunity, yet also with a state of immunodeficiency, with an increased frequency of infections and cancer.

Knowing that the thymus is the source of T cell differentiation-promoting factors, it would seem obvious that thymic factors would be used extensively to restore immunologic activities of the aged. Various compounds have been employed in enhancing nonimmunologic and immunologic cellular activities. The concepts on the mechanisms and dynamic contributing to peripheral tolerance by CD4+CD25+ T-regs, have important implications for the design of therapeutic strategies involving generation and use of CD4+CD25+ T-regs in autoimmune and inflammatory diseases. Interestingly, the mitochondrial oxidant production can be lowered by reducing food intake. It is thought that this is accomplished primarily by lowering oxidative stress and tissue damage by ROS (49-52).

Concluding remarks

It would appear that age-related alterations in immune functions are due to changes in the parenchyma and stromal immune cells and in their milieu.

Since their changes are closely linked to the involution and atrophy of the thymus, an understanding of thymic changes could be a key to understanding immunosenescence.

Improving our understanding of immune aging is a necessary step towards identifying ways to ameliorate and treat the underlying causes of immunosenescence.

Aging is associated with a paradox of immunodeficiency and inflammation (an evidence of hyperactive immune system).

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