Aging and the Human Immune System

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Given a finite lifetime, people hope to maximize its length and live all their years in good health. Maintenance of a vigorous and regulated immune system plays an important role toward that goal, since loss of immune function probably underlies the fact that infectious diseases are major causes of sickness and death in aged people [1,2]. In immunity as in other physiological functions, people vary greatly in the rate at which functional decline accompanies increasing chronological age [2]. As some individuals maintain vigor into very old age, it is hoped that more might do so if the principal features of immune system senescence were understood and addressed.

The immune system undergoes many changes in the aging process, as reflected in diminished T cell responses to recall antigens, decreased antibody formation in response to immunization, and increased autoantibody formation [2,3]. Generally, changes are more pronounced in T cell than in B cell function [4,5]. For some time these altered responses were believed to reflect an immunodeficiency state, but more current views regard them as reflecting dysregulation [1] or re-modeling [2] of the immune system. In evaluating these changes it is often difficult to identify effects of aging per se, because factors such as concomitant disease or poor nutrition can be responsible for altered immune function in elderly people [6]. To resolve this problem, criteria have been established for appropriate screening and selection of study populations in order to minimize effects of confounding factors in the study of aging [6].

While aspects of age-associated alterations in T cell and B cell function have been studied in both mice and humans for many years [summarized in several review articles in Vol 160 of *Immunological Reviews*, 1997], we will focus this brief review on recent findings in human subjects, and particularly on humoral immune responses.

Humoral response to foreign and self-antigens

One of the most consistent manifestations of immune system decline is reduced responsiveness to immunization. Elderly people have difficulties in mounting a protective response to protein, viral or bacterial vaccines, such as tetanus toxin, influenza or encephalitis virus, and *Salmonella* [3]. Recent studies consistent with that conclusion include trials with vaccines for *Neisseria meningitidis* serogroup C polysaccharide, a T cell-independent antigen [7]; pneumococcal polysaccharide [8]; and influenza virus [9]. Sera of elderly vaccine recipients in these trials showed lower bactericidal activity [7], lower opsonophagocytic activity [8], and/or lower concentrations of all antibodies [9]. In a trial of influenza A vaccination, antibodies were undetectable both before and after vaccination in 63 of 137 patients (mean age 82 years) in geriatric medical long-term care. In 25 patients there were detectable pre-vaccination titers but they failed to rise after immunization, and in only 49 patients did the titers rise after vaccination [9].

How these reduced humoral responses relate to morbidity and mortality in the aging population needs further study. Again, nutritional factors may greatly influence both serological conversion and clinical effectiveness following immunization [6,10]. Whether acting as a nutritional supplement or as an anti-oxidant, administration of 200 units/day of vitamin E for 4 months improved clinically relevant indices of immunity in healthy elderly subjects over 65 years of age [11]. People taking this supplement had a 65% increase in delayed-type hypersensitivity and an increase in antibody titer in response to hepatitis B and tetanus vaccines. The vitamin E supplementation affected neither antibody responses to diphtheria toxin, nor total levels of immunoglobulin, T cells, B cells or autoantibodies. Dietary supplementation with oils that modulate prostaglandin production can also increase immune responsiveness [12].

Over many years numerous investigators have reported, alongside the reduced responsiveness to foreign antigens, an increased frequency of both organ-specific and non-organ-specific autoantibodies associated with aging. Recent investigations have supported that conclusion, with identification of autoantibodies to gastrin associated with long *Helicobacter pylori* infection [13] and, in older diabetics, to glutamic acid dehydrogenase and IA-2, a marker for diagnosis and prognosis of type-1 diabetes [14]. IA-2, a member of the receptor-type protein tyrosine phosphatase family, is expressed in islet and brain tissue.

A difference in autoreactivity was observed in comparisons of healthy centenarians and non-selected elderly

people, in that sera from the centenarians did not have organ-specific Ig, such as anti-thyroglobulin autoantibodies, even though they sometimes had non-organ-specific autoantibodies [15]. Aging-related autoantibodies may be encoded either by unmutated or nearly unmutated V region gene segments, as are many natural autoantibodies [16], or by mutated V region segments. They are generally not pathogenic and occur without associated autoimmune disease, but they may be indicators of underlying dysregulation in the immune system.

Several mechanisms have been proposed to explain the increased frequency of autoantibodies in the elderly. One hypothesis is based on the function of the thymus. Asymmetric thymic involution may cause a clonal imbalance, with increases in autoantigen-specific helper/inducer T cells relative to the number of autoantigen-specific regulatory T cells [17]. This imbalance may, in turn, be related to a progressive increase in the number of B cell follicles present within the thymus [18]. Molecular mimicry by infectious agents is proposed as another mechanism that may trigger autoantibody formation. According to this hypothesis, an infectious agent may have antigens with some epitopes immunologically similar to host antigens, and these immunogens may induce antibodies that cross-react with the host antigens [19]. Still other mechanisms may lead to presentation of endogenous structures sufficiently different from normal 'self' that they stimulate immune responses. Long exposure to reactive oxygen species may alter DNA structure and increase its immunogenicity [20], just as chemical modifications of side chains can increase immunogenicity of certain proteins [21]. It is difficult to design a definitive test of the physiological importance of these models.

Searches for mechanisms underlying the changes in humoral responses to foreign and self-antigens also lead to questions concerning age-associated alterations in T cell and B cell repertoires and responsiveness, and the balance of cytokines formed upon antigen stimulation.

Changes in lymphocyte populations and T cell function

Measurements of total numbers of circulating lymphocytes in aging populations have yielded varying results. Some studies found a progressive decrease [22]. Krause et al. [23], however, found that young and old well-nourished women have similar numbers of circulating total T ($CD3^+$), T helper ($CD4^+$), and T cytotoxic ($CD8^+$) cells, and pointed out the need to consider nutritional status before measured changes are ascribed to aging. Earlier studies, cited in [3], showed little change in B cell numbers with aging.

When cell numbers do decrease, the loss could be from increased lymphocyte susceptibility to apoptosis, associated with an increase of Fas and Fas ligand in blood along with decreased expression of Bcl-2 and increased expression of Bax in $CD4^+$ and $CD8^+$ T cells [24]. Decreased cell numbers could also result from decreased production of new cells. The rate of production of new T cells is not precisely known. Although the thymus undergoes involution at a relatively early age, it can continue to contribute a diverse set of new T cells to the peripheral circulation, as shown in study populations up to 78 years of age [25,26].

Changes in T cell subpopulations and function in older people have been identified more consistently than changes in total cell numbers. For example, several investigators have reported an age-related increase in the fraction of activated/memory T cells relative to the fraction of naive T cells [2,27]. This shift was also seen in a study of age-related changes in tonsillar lymphocyte populations [28]. $CD45RA^+$ (naive) tonsillar T cells increased in number during the first two decades of life and gradually decreased thereafter, whereas $CD45RO^+$ (memory) T cells showed an opposite trend. CD40, a marker for mature B cells, did not change during aging, but $CD38^+$, a marker for B cells in a late maturation stage, declined dramatically up to the age of 65 as did the $CD5^+$ subpopulation of B cells.

Several investigators have reported the aging-related emergence of a T cell population with decreased or no expression of the co-stimulatory CD28 surface molecule [29]. The $CD4^+CD28^-$ T cells are long-lived, undergo clonal expansion *in vivo*, and react to autoantigens *in vitro*. They remain functional and produce high concentrations of interferon-gamma and interleukin-2, but CD28 loss is correlated with lack of CD40L expression, so that CD28- cells are not fully able to promote B cell differentiation and immunoglobulin secretion [30].

A consistent functional change associated with aging is impaired T cell proliferation on stimulation by mitogen or antibody-mediated receptor cross-linking [31]. Decreased proliferative responses *in vitro* may be related to the observation of an increase in the proportion of non-cycling T lymphocytes among circulating blood cells from elderly humans [32]. The increase in non-cycling cells was associated with G0/G1 and G1/S blocks in anti-CD3 activated T cells along with changes in proteins that regulate cell cycling. Several studies have also measured an age-related decrease in responsiveness to T cell receptor stimulation measured by changes in receptor-mediated signaling [4,33] and altered cytokine production [27].

Diminished responses of T cells can lead to decreased B cell activation, as reflected in expression of activation markers. For example, untreated B cells from elderly subjects had diminished expression of the B cell activation marker CD23 [34]. Although B cells from old and young persons expressed similar levels of CD23 in response to stimulation with PMA or IL-4, the older persons' B cells had a low induced expression of CD23 when they were incubated in culture together with T cells and anti-CD3 antibody. Thus, the low B cell activation was due to a low T

Ig = immunoglobulin

IL = interleukin

PMA = phorbol myristic acid

cell response rather than an intrinsic B cell defect. CD40L expression by T cells of the old subjects was impaired when measured after anti-CD3 stimulation but was the same as in cells of young donors after treatment with PMA, which activates cells directly via the protein kinase C pathway. The combined results indicate that a defect in T cell signaling, at a step or steps between the surface membrane and the PKC activation, leads to decreased CD40L expression and thus to decreased B cell activation.

All of these changes in T cell populations and functions could provide a basis for understanding both decreased cellular immune responses and dysregulation of B cell responses.

Is the immune repertoire altered?

The human V region repertoire of T cell receptors may be altered with age. Although monoclonal antibodies to TCR epitopes revealed little difference between old and young subjects in frequency of T cells bearing selected Vα and Vβ segments [35], several indications of clonal expansion, especially among $CD8^+$ cells, have been measured and may reflect a less diversified T cell repertoire in the elderly [36].

Human B cell repertoires have been measured by serology and molecular analysis. A stable repertoire of natural autoantibodies persists in elderly people [37]. At the molecular level, Xue et al. [38] found no differences between young and old in the average length or size range of CDR3 segments in the Ig VH chain and, focusing on the V_H5 family, no differences in D_H and J_H usage. Examining V_H6 family transcripts, Van Dijk-Hard et al. [39] found a lower mutation frequency in CDR3 regions of blood lymphocyte Ig mRNA in adults over 50 years of age, as compared with cDNA from adults aged 20–49.

A recent study compared Ig VH libraries from circulating B cells of old (over 65) and young (mean age 35) humans [40]. In the young adults, approximately two-thirds of the IgM-encoding VH cDNA clones had zero to three V_H mutations. There was much more variation among the elderly in the size of this low mutation fraction of clones, ranging from 22 to 85%. A set of highly mutated cDNA clones (>16 mutations), though small in number, was more prominent in the older subjects' libraries. In addition, V_H4 family expression was increased in older subjects, whereas V_H3 family expression dominated in young adults. Further study of two of the older subjects revealed that 90% of randomly chosen B cells analyzed by single cell reverse transcriptase-polymerase chain reaction had unmutated or nearly unmutated V_H gene segments, suggesting that naive B cells continue to be produced as in younger people and constituted a large fraction of circulating B cells. Whereas a stable autoantibody repertoire measured by immunoblotting suggests that the selection of developing naive B cells does not change with age [37], the shift in V_H gene segment usage, seen in both unmutated and mutated cDNA clones, raises the alternate possibility [40]. Further study is required to resolve this issue and to establish whether there are indeed characteristic B cell repertoire changes in aging.

Shifts in cytokine secretion and lymphocyte differentiation

Age-related decline in T cell proliferation and immune function may result from disruption in the balance of regulatory cytokines produced during an immune response. Th1 cells function to enhance mainly cellular immunity. Their cytokines, which are involved in the cellular defense, include IL-2, IFN-γ, IL-12 and IL-15. Th2 cells enhance humoral immunity. Their cytokines, which augment many antibody responses, include IL-4, IL-5, IL-6, IL-10 and IL-13. Balanced cytokine production is crucial for an optimal immune response.

The aging process is generally associated with a shift in the cytokine profile from a Th1 to a Th2 pattern. For example, most studies point to an aging-associated decrease in IL-2 secretion by T cells [4,5,41], and leukocytes from elderly subjects produce decreased amounts of sIL-2R, with changes in both the magnitude and kinetics of release [4,41]. Also, an increase in the production of IL-5, a Th2 profile cytokine, was observed in aged human mononuclear cells [42], and production of IL-10 – a cytokine known for its inhibitory effects on secretion of Th1 cytokines – was increased in human peripheral blood mononuclear cells stimulated with *Staphyloccocus entertoxin B* [31]. However, the picture may be more complex. In one study, T cells from healthy elderly humans yielded a low output of IL-4 (a Th2 cytokine) as well as IL-2 and IFN-γ (Th1 cytokines) when they were stimulated by anti-CD3 antibody plus PMA [27]. Furthermore, findings are not always consistent and functional consequences are not always clear. For example, Llorente et al. [43], seeking a correlation between autoantibody formation and IL-10 secretion, found neither increased IL-10 protein nor increased IL-10 gene expression in PBMC of elderly women, even from those who did produce autoantibodies. Furthermore, the production of autoantibodies was not inhibited *in vitro* after adding an anti-IL-10 monoclonal antibody to cell cultures. Secretion of IL-12, a key cytokine for the induction of Th1-type-response, was decreased after phytohemagglutinin or CD3 stimulation, but increased after *Staph. entertoxin B* stimulation [31]. Evaluation of cytokine measurements from different studies is difficult because of variations in study populations and conditions of *in vitro* cell stimulation.

PKC = protein kinase C
TCR = T cell receptor
VH = $V_H + D_H + J_H$

IFN = interferon
PBMC = peripheral blood mononuclear cells

Conclusions

Although it is not possible to conduct controlled experiments in humans as in mice, a great deal of information about aging-associated changes in the human immune system has been accumulated. Prominent among the findings are a decreased T cell responsiveness to a variety of signals; decreased antibody responses to foreign antigens in protein, bacterial and viral vaccines; and increased frequency of non-pathogenic autoantibody formation. However, people vary greatly in the relationship between immune system decline and chronological age. It has been, and remains, a challenge to determine which changes are truly due to aging rather than to factors such as poor nutrition or disease in older populations. Thus, selection of a study population is an important variable in research on human aging and immunity. It may be that strong nutritional support, providing supplements such as anti-oxidants or immunomodulators, as well as general macro- and micronutrient requirements, will sustain appropriate immune responses in a large fraction of older people. Current information raises many questions that require further study. Additional knowledge of mechanisms underlying a true aging-related decline may also point to a novel vaccine design or to agents that can boost appropriate responses.

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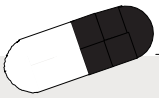
Capsule



High blood pressure and pregnancy

Hypertension is a common complication of pregnancy. An important clue to its underlying cause is provided by Geller et al., whose studies take them from patient to molecular causation to a plausible mechanism at atomic resolution. The authors identify a family with inherited early-onset hypertension that is exacerbated in pregnancy and show that the causative mutation lies in the gene encoding the mineralocorticoid receptor (MR), a protein that regulates salt reabsorption in the kidney. The mutation changes one amino acid in the hormone-binding domain, which causes MR to become constitutively activated. This aberrant activity is enhanced further by progesterone, a hormone that is produced at high levels in pregnancy and that normally acts as an MR antagonist. The inherited mutation appears to facilitate molecular interactions in MR that normally require binding of its natural ligands.

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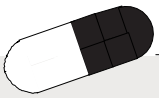
Capsule



A kinder cut of p73

In the brain of very young mammals, a vast oversupply of neurons is pruned back as the neuronal interconnections become increasingly refined. The pruning process relies on p53-promoted apoptosis. Pozniak et al. now find that the actions of p53 are counterbalanced by the actions of a truncated form of p73 lacking its transactivation domain. In its full-length form, p73 also promotes apoptosis, but its truncated form blocks apoptosis. The decision to produce truncated or full-length p73 is made at the point of transcription, which suggests a potential mechanism for a very rapid response to changing cell-death or cell-survival needs. A healthy supply of truncated p73, and thus cell survival, is promoted by the presence of nerve growth factor (NGF). Thus, p73, whose function depends on the particular isoform produced, is a mediator of the NCF cell-survival signal.

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