A Perspective on Cellular Immunity in the Elderly

Kristen V. Khanna and Richard B. Markham

From the Department of Molecular Microbiology and Immunology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland

The increased incidence of infection and malignancy in elderly individuals has prompted many studies that demonstrate that the aging immune system is impaired. Most of these studies have focused on the impairment of acquired immunity provided by lymphocytes. While defects in acquired humoral and T-cell-mediated immunity may exist, increased susceptibility to infection may result from defects in the constitutive functioning of macrophages and granulocytes. Recognition of the potential importance of defects in constitutive immunity in the elderly may provide new opportunities for therapeutic and prophylactic intervention in this population.

There is considerable epidemiological evidence that the incidence of both infections [1–4] and cancers [5, 6] increases with age. Efforts to characterize immune defects underlying this increased susceptibility of the aged have focused on readily measurable parameters of acquired immune function, particularly on deficits in T cell function. The critical role of macrophages and granulocytes in primary resistance to infection dictates a need to reevaluate the importance of defects in these cells in the elderly. A more comprehensive understanding of the basis for increased susceptibility to infection in elderly patients should permit the development of more effective strategies to diminish the impact of these defects.

Immune Defects in the Elderly

Reports of specific immune dysfunction in the elderly often conflict [7] or are described for a defined subset of elderly patients (e.g., males; patients over 65 or over 95 years of age; patients with chronic diseases; and hospitalized or institutionalized patients). Further complicating the issue are individual differences in the aging process that most likely correlate with changes in immunity. Several studies, however, have defined age-dependent alterations in immunity, including: (1) deficits in T cell function [7, 8], including defective generation of long-lasting memory responses after immunization [9]; (2) reduced generation of high-affinity antibodies [7, 10] in the face of elevated total antibody levels [11]; and (3) depressed lymphocyte numbers [10, 11]. Humoral immune defects are believed to be due in large part to age-related T cell dysfunction.

Most of the research on cell-mediated immunity in the elderly has used either human or murine systems to define in vitro and in vivo defects in T cell function. Miller [7] described decreased proliferative responses to T cell mitogens, which may be related to altered signal transduction pathways [12, 13] or to alterations in the production of [14, 15] and responsiveness to [16] IL-2. While numbers of both memory and naive T cells may be decreased in elderly subjects, the relative loss of naive T cells is greater, potentially reducing the ability of the host to respond to antigens not previously encountered [17, 18].

A Model for Deficient T-Cell Function

The intensively studied cell-mediated immune defects associated with HIV infection may provide a useful framework for understanding the association between T cell immune defects and susceptibility to infection. The ultimate loss of the essential T cell repertoire associated with HIV infection results in increased risk for certain malignancies and a range of opportunistic infections caused by bacteria, viruses, and parasites [19]. Susceptibility to such a broad range of pathogens is not typically observed in the elderly, however. Thus, the overwhelming T cell defects seen in AIDS patients are not likely to explain the disease patterns observed in aged individuals.

There is, however, a subset of infections shared by elderly and HIV-infected individuals, consisting primarily of infections with encapsulated bacteria and tuberculosis. In HIV-infected individuals these infections may be observed prior to the final collapse of T cell immunity that characterizes the onset of AIDS (fewer than 200 CD4+ T cells) [20]. Several studies have demonstrated defective macrophage function [19–22] and granulocyte function [22] in HIV-infected individuals prior to the onset of AIDS, and these defects may well explain the increased susceptibility to pyogenic bacterial pathogens observed in the HIV-infected, asymptomatic clinical setting. In fact, the susceptibility to this type of infection most closely resembles the susceptibility to bacterial infection observed in the elderly, although this has not been adequately addressed experimentally.
Constitutive Versus Acquired Immunity

Much of the battle between an infectious pathogen and its host occurs before the cells of acquired immunity enter the fray. Studies on aging and immunity have emphasized those parameters that are most easily measured, focusing primarily on parameters of acquired immunity such as cell number and phenotype, immunoglobulin levels, B and T cell proliferation to a variety of stimuli, and more recently, the apoptosis of T cells [7, 23]. While techniques to measure constitutive immune function have become more sophisticated, only limited study of this area has been undertaken in the elderly population.

This paucity of information in part reflects methodological problems in the study of constitutive immunity. For example, it is difficult to obtain enough monocytes or macrophages to perform many assays (roughly 2%–10% of peripheral blood mononuclear cells are monocytes), and granulocytes are extremely sensitive to handling. Tissue macrophages are difficult to obtain but may be the most relevant cells for studies of protective immunity to infection. Furthermore, the ability to extrapolate in vitro results to in vivo and clinical situations is questionable when cultured, adherent cells are used. For example, depending upon media and plating conditions, monocytes differentiate when they become adherent, thereby altering their functional abilities [24]. Some of these difficulties have been addressed in studies by Simms and D’Amico [25], who assessed adhesion molecule expression and its functional consequences with use of fluid-phase granulocytes.

Despite these difficulties, a body of evidence has accumulated indicating that the function of macrophages and granulocytes in the elderly is impaired. Granulocyte-macrophage colony stimulating factor (GM-CSF) is a regulator of granulopoiesis and of granulocyte and mononuclear phagocyte (MP) function. A comprehensive study of the effect of GM-CSF on priming of granulocytes from elderly subjects (aged 60–90 years) and young subjects (aged 20–25 years) showed that GM-CSF was unable to prime granulocytes from the elderly subjects for the activation of several parameters, including superoxide production, intracellular calcium flux, antibody-dependent cellular cytotoxicity, and intracellular killing mechanisms [26]. These processes are critical at the earliest phases of infection and thereby influence susceptibility to infection rather than the immune response mounted to an established infection.

Significantly more macrophages from elderly individuals than from young individuals are required to elicit optimal T cell responses to a mitogen [27]. Decreased responses to pneumococcal vaccine in aged mice have been attributed to a macrophage defect [28], and macrophages from aged BALB/c mice produced 50% less hydrogen peroxide than those from young mice in response to stimulation with bacterial products [29].

Organ-specific defects in MP function have also been described. The clonal growth of alveolar macrophages from aged (12- and 24-month old) mice has been shown to be significantly lower than that of alveolar macrophages from young (4-month old) mice [30], a fact that is interesting in light of the well-established increased incidence of pneumonia in the elderly [2, 4]. On the other hand, growth of bone marrow–derived adherent cells did not differ between the aged and young groups [30], suggesting a compartmentalization of this MP defect.

The secretion of IL-8, which recruits MP, appears to be dysfunctional in the elderly. Clark and Peterson [31] have found that spontaneous production of IL-8 is decreased in elderly men. An interesting finding is that the monocytes from these same men produced more IL-8 than those from the younger controls when the cells were stimulated with bacterial lipopolysaccharide. The overproduction of IL-8 in elderly men may be detrimental, leading to an overly zealous proinflammatory cascade. The recruitment of massive numbers of immune cells to the lungs, for example, could result in increased pulmonary inflammation, which may well increase morbidity and mortality among elderly patients.

With regard to the number of absolute immune cells in the elderly, it appears that the number of MPs is similar to that in young subjects. However, as suggested above, production of certain cytokines, including IL-1, TNF-α, IL-6, and IL-8, may in fact be upregulated [10, 31]. The link between these upregulated activities and the functional immune deficiencies observed in the elderly is unclear, but it is reasonable to expect that any sort of cytokine dysregulation may interfere with the ability of the host to respond to a specific infectious challenge.

In addition to cytokine dysregulation, hormonal imbalances in the elderly may also affect functioning of the constitutive immune response. A reciprocal relationship has been demonstrated to exist between levels of certain hormones and macrophage function. Dehydroepiandrosterone (DHEA) and DHEA-sulfate are the primary androgens secreted by the adrenal gland, and a decline in DHEA levels is associated with aging. Macrophages are the only cells known to synthesize DHEA-sulfatase, which cleaves the sulfate group from DHEA-sulfate, making the biologically active product DHEA. In addition, it is believed that DHEA may have a direct effect on macrophage function and thereby an indirect effect on cytokine-secretion patterns among lymphocytes. Khorram and colleagues [32] evaluated nine healthy men (mean age, 63 years) with low circulating levels of DHEA who participated in a DHEA-replacement study. While lymphocyte numbers remained unchanged, monocyte numbers increased significantly in the DHEA recipients, as did the production of insulin-like growth factor, which has immune-enhancing activity.

Intervention for Deficiencies in Constitutive Immunity

Whether defective immune responses arise at the level of constitutive or acquired immunity, enhancement of acquired immune defenses through vaccination can only be beneficial. If antigen processing is defective, however, elicitation of optimal responses to vaccines may be problematic. Addressing the vac-
cination problem at the level of the antigen-presenting cell may offer some solutions to the infections of the elderly.

Sambhara and colleagues [33] have found that influenza antigens delivered with immunostimulatory complexes result in a potent protective response in aged mice. Furthermore, the aged mice receiving the adjuvant-associated vaccine had a faster recovery from illness than mice receiving the current influenza vaccine.

Deficiencies in micronutrients, which are common in the elderly (and often found in HIV-infected individuals), may also contribute to the defects in constitutive immunity. Given the high prevalence of zinc deficiency in the elderly [34], it is interesting that such deficiencies have been associated with an increased risk of bacterial infections in HIV-infected individuals [35]. Other micronutrients with identified roles in the proper functioning of phagocytic cells include selenium [36] and vitamin E [36–38]. Protein deficiency has been associated with decreased lymphocyte proliferation, reduced cytokine release, and lower antibody responses to certain vaccines [39].

Conclusion

Many different types of immune defects in elderly individuals and in experimental animals have been identified. The previous focus on defects in cell-mediated immune responses provided a possible explanation for the increased risk of cancer, viral infections, and infections with intracellular bacterial pathogens, such as *Mycobacterium tuberculosis*. The pronounced susceptibility to extracellular bacterial infections, such as with *Streptococcus pneumoniae*, is less readily explained by T cell deficits. The more recent demonstrations of abnormalities in the function of macrophages and granulocytes might explain the increased susceptibility to both intracellular and extracellular pathogens.

Although increased immunization efforts should provide some compensation for whatever deficits may exist in phagocytic cell function in the elderly, therapy specifically targeted at phagocytic cells, including the use of adjuvants with immunizations and nutritional supplementation, offers the opportunity to enhance further the ability of these hosts to resist infectious challenges.

References

23. Phelouzat MA, Arbogast A, Laforge T, Quadri RA, Proust JJ. Age-related decreased susceptibility to extracellular bacterial infections, such as with *Streptococcus pneumoniae*, is less readily explained by T cell deficits. The more recent demonstrations of abnormalities in the function of macrophages and granulocytes might explain the increased susceptibility to both intracellular and extracellular pathogens.
24. Although increased immunization efforts should provide some compensation for whatever deficits may exist in phagocytic cell function in the elderly, therapy specifically targeted at phagocytic cells, including the use of adjuvants with immunizations and nutritional supplementation, offers the opportunity to enhance further the ability of these hosts to resist infectious challenges.