The Immune System in the Elderly

III. Innate Immunity

Abstract

The capability to cope with infectious agents and cancer cells resides not only in adaptive immune responses against specific antigens, mediated by T and B lymphocytes clonally distributed, but also in natural immune reactions. These innate defence mechanisms include chemotaxis, phagocytosis, natural cytotoxicity, cell interactions, and soluble mediators or cytokines. However, specific and natural immune mechanisms are always closely linked and interconnected, providing the primary defense against pathogens. The Authors discuss the main changes observed with advancing age in granulocytes and natural killer (NK) cell activity, in the expression and function of adhesion molecules, and in the pattern of cytokine production. Since phagocytic function is the primary mechanism through which the immune system eliminates most extracellular pathogenic microorganisms, analysis of this function is of clinical importance. Neutrophils from aged subjects often exhibit a diminished phagocytic capacity, as well as a depressed respiratory burst, notwithstanding an activated state. The activity of NK cells during aging has been studied extensively and different results have been reported. The most consistent data indicate an increase in cells with high NK activity with advancing age. Cells from healthy centenarians can efficiently kill target cells. This finding seems to suggest that innate immunity and in particular NK cell activity, is not heavily deteriorated with age. Conversely, a low NK activity is a predictor of impending morbidity. Immunosenescence is associated with increased expression of several cell adhesion molecules (CAM) resulting in an augmented capacity to adhere. Finally, also the cytokine network, responsible for differentiation, proliferation, and survival of lymphoid cells, undergoes complex changes with age. The main findings are a Th1 to Th2 cytokine production shift and an increased production of proinflammatory cytokines, which could explain many aspects of age-associated pathological events, such as atherosclerosis and osteoporosis.
**Innate Immunity**

It is well known that the immune response declines with senescence and it is suggested that these changes render an individual susceptible to infection, autoimmune phenomena, and cancer. Bacterial and viral infections are a major cause of illness and death amongst aged subjects, and once infection is established, the elderly also have a diminished capacity to prevent its spread (1,2). The capability to cope with pathogens, cancer cells, and other threatening agents resides not only in specific immune mechanisms (T and B cells clonally distributed, capable of “specific” reactions with single epitopes of a given antigen), but also in an innate immune armamentarium. The “natural” defense mechanisms, collectively called “innate immunity,” include chemotaxis, phagocytosis, natural cytotoxicity (NK cell activity), cell-cell, and/or cell-matrix interactions, and production of soluble mediators (3,4). These are ancestral and basic immunodefense responses conserved throughout evolution (5).

**Granulocytes**

Because polymorphonuclear neutrophils (PMN) provide the primary cellular defense against bacterial or fungal infections, impaired phagocytic defence mechanisms may contribute to the increased susceptibility for infections in the elderly. Studies on polymorphonuclear neutrophil function in older persons have yielded conflicting results, but it is generally agreed that, like in other immune system components, there is a general decrease in functional activities (1). Normal or impaired phagocytosis, chemotaxis, degranulation, and nitroblue tetrazolium (NBT) reduction, and a relatively preserved or slightly diminished intracellular killing activity in PMN from the elderly compared to younger individuals have been documented (6–9). In subjects fulfilling the health admission criteria of the Senieur protocol (10,11), age does not affect phagocytosis frequency and index, superoxide production, and microbicidal activity against bacteria and yeasts. The chemotactic response to complement-derived chemotactic factors seems to be significantly impaired in elderly healthy subjects (12,13). Neutrophil adherence has been found to be higher or normal. A decreased chemotaxis, superoxide production, and lytic enzyme production after stimulation of PMN with the peptide fMet-Leu-Phe has been reported (14–20).

The flow cytometric analysis of cell surface marker expression in PMN displayed a higher level of CD15 and CD11b, but not of CD11a and CD11c in neutrophils in the elderly. CD15 mediates an increase in neutrophil adhesion with endothelial cells and platelets. The β2-integrin family of receptors (CD11a,b,c) is involved in cell-substrate adhesion, transduces signals from the extracellular matrix and regulates growth, gene expression, cellular differentiation, cell shape, and motility, as well as cytoskeleton architecture. The Fc and complement receptors mediate attachment and ingestion of particles coated with the corresponding ligands, and trigger phagocytosis, respiratory burst, and degranulation. A normal respiratory burst with a decreased phagocytic activity was observed in neutrophils from aged subjects and this could be explained as owing to differences in the intracellular activation mechanisms induced by receptors to C3bi (CD11b). Neutrophils in aged subjects showed a diminished Fc-mediated phagocytic capacity and an activated state as documented by an increased number of responding cells to oxidative burst, but with a normal type of response and expression of cell surface markers involved in adhesion mechanism: E-selectin ligand and β2-integrins. The differences in respiratory burst and phagocytic capacity could be owing to modifications in some but not other activation pathways (9).