Host Resistance and Immune Aging

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KEYWORDS

• Aging • Immunosenescence • Innate immunity • Inflammation • T cell • B cell

KEY POINTS

- Immunosenescence, describing age-associated changes in the immune system, generally results in impaired immune responses and contributes to the increased morbidity and mortality to infectious diseases and diminished vaccine responses found in older adults.
- A heightened pro-inflammatory environment, characterized by increased levels of proinflammatory and anti-inflammatory cytokines, acute phase reactants, and clotting factors, is found in older adults.
- Age-related chronic inflammation contributes to dysregulation of innate immune responses, potentially limiting or delaying further activation or contributing to inappropriate persistence of inflammation.
- B- and T-cell signal transduction and function in the adaptive immune system are both impaired in the context of aging. Chronic antigen stimulation throughout life, particularly in the control of cycles of cytomegalovirus reactivation, substantially diminishes the diversity of antigen receptors, particularly in the T-cell lineage.

INTRODUCTION

With age, immunologic function changes substantially, resulting in impaired responses to pathogens or vaccines. As a result, older adults are at increased risk for morbidity and mortality from infectious diseases and impaired responses to vaccination.[1] Clearly, nonimmunologic factors also contribute to these adverse outcomes; for example, age-related changes in chest wall mechanics and lung elasticity may affect respiratory mechanics and medications may affect cough—all potential contributors to respiratory infection risk.[2] However, it is evident that immunologic changes influence host defense against infection. The aging immune system is characterized by a variety

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of alterations that encompass developmental impairment, diminished signaling, and the effects of antigen exposure history on chronic inflammation and antigen receptor repertoire diversity—all of which contribute to defects in immune activation in response to pathogens or vaccines. However, the aged innate immune system also shows substantial inflammatory dysregulation with a paradoxical heightened proinflammatory environment; this may arise in part from endogenous stimuli linked to cellular damage. Here an overview of age-related changes in human host defense is provided, with an emphasis on consequences for outcomes to pathogens or vaccines in older adults.

CHANGES IN INNATE IMMUNITY WITH AGING

The innate immune system is the first line of defense in mounting a host resistance response to antigens; it is responsible for the earliest responses to pathogens or vaccines.[3,4] Innate immune responses are mediated by a network of cell types that include neutrophils, monocytes/macrophages, dendritic cells (DCs), natural killer (NK) cells, eosinophils, and basophils; endothelial and epithelial cells may also play roles in innate immunity.[4] Innate immune responses are closely linked to the activation of inflammatory processes, including phagocytosis, intracellular killing, pathogen-induced proinflammatory cytokine production, and upregulation of costimulatory proteins on antigen-presenting cells (APCs), such as DCs, monocytes, or macrophages. Such costimulatory protein expression provides additional signals facilitating T-cell activation and thus links innate to adaptive (ie, mediated by antigen receptors on B and T cells) immune responses.

Age-related Dysregulation of Inflammation

Several lines of evidence indicate that chronic inflammation is a characteristic of the aging immune system in humans. In particular, levels of proinflammatory cytokines (particularly interleukin-6 [IL]-6, also tumor necrosis factor -α [TNF-α], IL-1β, and others), acute phase reactants such as C-reactive protein, and clotting factors (including D-dimer) are generally elevated in older compared with young adults.[5–10] Moreover, such increases in cytokine production have been correlated with all-cause mortality in several studies.[11–13] Basal elevation of proinflammatory cytokines and other products may affect the ability of the aged immune system to respond to new pathogens or vaccines; in this regard, both proinflammatory and anti-inflammatory cytokine production may be augmented, resulting in more complex patterns of age-related inflammatory dysregulation.[14] The cause underlying this heightened proinflammatory state (termed Inflamm-Aging[15,16]) remains incompletely understood, but may in part reflect the consequences of cellular damage and endogenous activators of the innate immune system, as described in later discussion.

Neutrophils

Neutrophils are short-lived cells that are among the first to migrate in response to an infectious agent. For example, chemotaxis, describing movement toward a gradient of a stimulus (such as a chemokine or cytokine), appears impaired in neutrophils from older compared with young adults.[17–19] Moreover, phagocytosis of pathogens, such as *Streptococcus pneumoniae* as well as intracellular killing, both appeared impaired in neutrophils from older versus young individuals.[20,21] In addition, the generation of neutrophil extracellular traps (NETs), extracellular scaffolds of extruded chromatin containing antimicrobial peptides and proteases, is also diminished in neutrophils from older adults—further affecting pathogen capture and killing.[22] Several age-related signal transduction defects have been reported in neutrophils; for example, diminished accuracy of