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Immune Senescence: Known Knowns And Unknown Unknowns

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The elderly have increased susceptibility to infectious diseases and a decreased response to vaccination. A large body of data suggests this is a result of age-related functional changes and dysregulation of the immune system, termed ‘immunosenescence’, that result in serious clinical consequences such as increased infections, cancers and autoimmune diseases. Particularly well studied is the reduced immunity against influenza virus, as influenza directly or indirectly contributes to the leading causes of global mortality, particularly in older adults. Increased human longevity represents major social and medical challenges, many of which are influenced by an altered immune system. In this volume, leading investigators review both our established understanding of immune changes in aging as well as new horizons for investigation.

IMMUNOSENECENT CHANGES WE KNOW

A chronic generalized pro-inflammatory milieu reigns in aging, termed ‘inflammaging’, characterized by elevated cytokine levels and reduced inflammatory responses (PAWELEC et al)[1]. In innate immune responses, TSENG and LIU review well documented age related decreases in neutrophil (PMN) phagocytosis and clearance of pathogens, chemotaxis, free radical production, and apoptosis. These functions are elicited by receptor-ligand interactions, suggesting that the reduced functionality of neutrophils with aging results from alterations in signaling pathways downstream of receptors (FULOP et al). Key pathogen receptors, the toll-like receptors (TLRs) have been shown to be reduced in aging monocytes, dendritic cells (DCs), and PMN (ZAPATA and SHAW)[1]. In older adults, an age-related decrease in TLR-1/TLR-2 mediated cytokine production was associated with decreased TLR-1 surface expression. A decline in TLR-induced expression of the CD80 costimulatory molecule, and a diminished level of TLR-induced secretion of inflammatory cytokines in DCs from older subjects correlates with a reduced influenza-specific antibody response [1].

Natural killer (NK) cells show changes in subset frequencies in aging as well as cytolytic function (SOLANA et al). In adaptive immunity, highly differentiated memory T cells accumulate in aged humans with a concomitant shrinkage of repertoire diversity for naïve T cells, likely due to persistent antigenic stimulation and the pro-inflammatory environment (KARED et al). A decline in the frequency of influenza specific CD4+ memory T-cells, and in decreased cytolytic properties of CD8+ effector and effector memory cells contribute to

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inefficient response to influenza vaccine in older subjects (KARED et al). In aging B cells, studies describe decreases in class switch recombination (CSR), the process that generates protective antibodies and memory B cells; decreases in the expression of the enzyme, activation-induced cytidine deaminase (AID), the transcription factor E47, which contributes to AID regulation; decreases in the percentage of switched memory B cells (CD19+CD27+IgD-) before and after vaccination as compared with younger individuals, as well as increases in serum/B cell TNF-α (FRASCA and BLOOMBERG). Weakened T cell help, and decreased B cell and cytotoxic T cell responses (HAQ and MCELHANEY), and an imbalance in effector memory T cell pool and regulatory responses culminate in unproductive priming and recall responses to vaccines in the elderly and consequently, vaccination responses are greatly reduced in older donors (HAQ and MCELHANEY, POLAND et al). The mechanisms that underlie the observed deficiencies in immunity in aging are incompletely defined but include signaling pathways (FULOP et al), and responses to chronic viral stimulation (KARED et al).

NEW KNOWNS IN ALTERED IMMUNITY IN AGING

Recent studies have demonstrated that there is host genetic variation related to aging and the genetic determinants of immunosenescence offer insight into the effect of aging and could transform development of novel approaches to overcoming aging defects (RUAN et al, POLAND et al). Variants in inflammation-related genes can control the balance between pro- and anti-inflammatory networks. The genetic background of immune-related genes, such as the highly polymorphic human leucocyte antigen (HLA) and natural killer (NK) cell immunoglobulin-like receptors (KIRs) genes, are associated with successful aging and longevity (RUAN et al). A high frequency of pro-inflammatory polymorphisms or haplotypes in these inflammation-related genes will increase the susceptibility to age-related diseases (RUAN et al, POLAND et al).

There is measurable and successive age-dependent decline in hematopoietic stem cell (HSC) activity from adulthood to old age in various organs, including intestine and muscle and the blood forming system with skewing of HSCs (GEIGER et al). Aged HSCs differ in both their self renewal and differentiation ability (GEIGER et al). This age-associated decline in HSC function is driven by both intrinsic and extrinsic factors and leads to a decline in the regenerative capacity that may limit lifespan (GEIGER et al). This may contribute to the age-related alteration in balance of classical (CD14+ CD16+) and alternatively-activated (CD14dim CD16-) monocytes, which is a likely source for altered inflammatory responses [2,3].

In addition, there is increasing appreciation that our simplistic view of neutrophils must be expanded, to now include neutrophil extracellular DNA traps (NETs) which immobilize bacteria, and an appreciation that neutrophils can participate in the resolution of infection and inflammation. Neutrophil subsets with either pro- or anti- inflammatory properties actively orchestrate host defense and resolution of inflammation (TSENG and LIU, FULOP et al). The NLRP3 inflammasome, a key cytoplasmic pathogen recognition system, has recently been shown to share age-related increased activation (FULOP et al, OLIVIERI et al)[1].

NK cell subsets are altered in aging with loss of CD56bright cells and expansion of CD56dimCD57+ long-lived NK cells, perhaps related to persistent viral stimulation, or reduced telomere length in aging (SOLANA et al). In T cells the role of thymic involution has recently been considered less important for the decrease in naïve T cells with aging as was originally thought in favor of homeostatic proliferation (Qi et al). Furthermore, beside the phenotypic changes in T cells, it is increasingly appreciated that their remaining functional abilities are not exclusively phenotype-dependent but intrinsic to the aging process by alteration of the feed-forward and feedback signaling machinery of T cells (FULOP et al). In addition, the role of the major mTOR metabolic pathway was highlighted in altered T cell functions with aging. Many changes in B cells in aging are evident either in their phenotypes or in their functions (FRASCA and BLOOMBERG).

In the clinical realm, abundant new studies address improvements in strategies to improve effective vaccination responses in the elderly, with a particular focus on novel vaccine and adjuvant development for the elderly. Notably, the pneumococcal vaccine, where older adults produce similar concentrations of antibodies as younger subjects, but with markedly lower potency and opsonic capacity (POLAND et al), new vaccine formulations such as recombinant HA-flagellin (TLR5 agonist) fusion proteins (VAX128), live attenuated influenza vaccine (LIAV), virosomal vaccines and virus-like particle (VLP) vaccines, and novel vaccination delivery such as targeting nasal mucosa, or skin vaccines (HAQ and MCELHANEY, POLAND et al). Importantly, numerous adjuvants to enhance responses in the elderly are under investigation including MF59, a microfluidized oil-in-water emulsion containing squalene that stimulates inflammatory cells and establishes an immunostimulatory environment conducive for APC proliferation and presentation as well as antibody production; Adjuvant system 03 (AS03), contains α-tocopherol, squalene and polysorbate 80 is another oil-in-water emulsion (HAQ and MCELHANEY, POLAND et al).

Particular urgency is noted for understanding the important parallels in the arena of immune activation from chronic viral infection between HIV patients and aged individuals (ZAPATA and SHAW). With advances in Antiretroviral Therapy (ART), the HIV-infected population in the developed world will increase which will have profound effects on clinical HIV care (ZAPATA and SHAW). Further, the exact cause of neurodegenerative diseases such as the dementia of Alzheimer's disease is still not known and the current paradigm that neuroinflammation plays a crucial role is questioned here. A new view is put forward stating that based on histopathological observations in human brain, the ability of senescent microglia to provide neuroprotection deteriorates as brains get older and that such CNS specific immune senescence is a major factor contributing to the development of aging-related neurodegenerative diseases, notably Alzheimer's disease (STREIT and XUE).

Several recent studies reveal mechanisms of age-related changes in immunity, highlighting an appreciation of alterations in lipid rafts in PMN and T cells (FULOP et al), constitutive activation of phosphoinositide 3-kinase leading to inaccurate migration and directional chemotaxis (TSENG and LIU), and alterations in gene expression as a result of polymorphisms (RUAN et al, POLAND et al). We have begun to appreciate the fundamental role for microRNAs (miRNAs) in regulating immune responses, and modulation during aging. Aging-associated miRNAs are largely negative regulators of the

immune response and target central nodes of aging-associated networks, in particular, NF-κB, the downstream effector of TLR signals that leads to induction of proinflammatory responses (OLIVIERI et al). Further, an increased appreciation of the role of autophagy in determining lifespan (CUERVO and MACIAN) and genetic correction of the age-dependent decline of autophagy in liver prevents the functional decline of this organ in old rodents. Autophagy can be boosted by interventions such as caloric restriction, or treatment with rapamycin, resveratrol, spermidine or metformin and these lead to increased lifespan (CUERVO and MACIAN), identifying important area for further studies to understand how increased autophagy leads to overall organismal function improvement.

TOWARDS THE UNKNOWNS

The complexity of the immune response is not the result of isolated events, single proteins, chemicals, enzymes, or even individual cell types but the coordinated result of interacting cell types, tissues, alterations in gene regulation and expression, signaling pathways, and biological networks (POLAND et al). Immunosenescence can be viewed as the response of the immune system to a lifetime's surveillance and efforts against pathogens and persistent intrinsic and extrinsic challenges. These include chronic disease states such as diabetes, obesity, and atherosclerosis, nutritional status, genetic background, and environmental conditions. The combined, synergistic efforts that lead to immunity and over time to immunosenescence require a systems level approach to define (POLAND et al). Notably, studies of healthy older subjects may be relevant to surviving other health complications, and investigation of deficiencies in aging may in fact reveal adaptive strategies for successful survival. Recent theories of aging -- including evidence that caloric restriction enhances longevity -- suggest paradoxically that reduction in anabolic processes may be beneficial to survival. But during acute infection, such reduction can lead to inappropriate immune responses and increased tissue destruction. Successful aging reflects a complex balance between lifespan extension and effective immune responses. Thus, immunosenescence may be viewed not only as detrimental but also as adaptive and therefore contributing to survival in an ever changing homeostatic environment.

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