Targets of Immune Regeneration in Rheumatoid Arthritis

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CME Activity

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Abstract

Many of the aging-related morbidities, including cancer, cardiovascular disease, neurodegenerative disease, and infectious susceptibility, are linked to a decline in immune competence with a concomitant rise in proinflammatory immunity, placing the process of immune aging at the center of aging biology. Immune aging affects individuals older than 50 years and is accelerated in patients with the autoimmune disease rheumatoid arthritis. Immune aging results in a marked decline in protective immune responses and a parallel increase in tissue inflammatory responses. By studying immune cells in patients with rheumatoid arthritis, several of the molecular underpinnings of the immune aging process have been delineated, such as the loss of telomeres and inefficiencies in the repair of damaged DNA. Aging T cells display a series of abnormalities, including the unopposed up-regulation of cytoplasmic phosphatases and the loss of glycolytic competence, that alter their response to stimulating signals and undermine their longevity. Understanding the connection between accelerated immune aging and autoimmunity remains an area of active research. With increasing knowledge of the molecular pathways that cause immunosenescence, therapeutic interventions can be designed to slow or halt the seemingly inevitable deterioration of protective immunity with aging.

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One of the megatrends affecting the global population is a redistribution of age strata, with a declining frequency of children younger than 5 years and an increasing frequency of adults older than 65 years. Advancing age is the key risk factor for cancer, cardiovascular disease, type 2 diabetes, and degenerative diseases of the musculoskeletal and nervous systems. The rise in morbidities in the elderly imposes an enormous

burden on essentially all societies. The ability to slow the pace of aging or even reverse aging-related organ decline would have a major societal impact and would affect all fields of medicine. Progress has been hampered by the lack of understanding of the molecular pathways that lead to the aging phenotype. There is general agreement that the aging process is complex and multifactorial, but a much better understanding is needed before the aging-associated decline in organ function can be turned into a modifiable condition. As a first step, it seems more conceivable to prevent aging-related loss than to regain lost function. To make advances toward that goal, appropriate model systems are needed. The aging process needs to be quantified and monitored over time. The immune system seems particularly vulnerable to aging-related decline, manifesting with the inability to fight malignancy and infection and instead inducing a state of chronic smoldering inflammation. Immune cells are easily accessible in humans, and failure of immune protection is measurable in human cohorts. Thus, advancing the understanding of how the immune system ages may fill an important knowledge gap and may provide unique opportunities to counteract aging-related functional decline.

Much has been learned about the immune aging process through disease states that are associated with acceleration of aging. Best studied is premature immune aging in patients with the autoimmune syndrome rheumatoid arthritis (RA).[1] Individuals affected by RA, on average, advance the immune senescence process by approximately 20 to 30 years.[2] In healthy individuals, age-induced loss of immunocompetence becomes obvious after age 50 years and manifests with a progressive increase in the risk of viral reactivation (eg, herpes zoster), a steady decrease in anticancer immunity, and a dimensional increase in the risk of cardiovascular disease.[3] In patients with RA, markers of immune aging, such as loss of telomeric sequences in immune cells, appear during middle age, are present in untreated patients, and often do not correlate with the activity of the disease process itself.[1] Molecular insights into the immune aging process have also come from studies of individuals affected by progeroid syndromes, rare monogenic disorders that cause features of progressive aging early in life.[4] Several causative genes have now been identified, and they fall into 2 crude categories, including genes coding for DNA repair molecules and genes contributing to the structure of the nuclear envelope.[5] Progeria syndromes have focused attention on the following processes: genome instability, telomere attrition, prematurity of cellular senescence, and defective stem cell homeostasis. Diseases such as RA in which the aging process seems accelerated provide valuable tools to probe the molecular pathways underlying the aging phenotype and its functional consequences and provide an opportunity to explore novel therapeutic interventions to fight the functional loss of immune protection in aging humans.

CHRONOLOGICAL AND BIOLOGICAL AGE

Modern medicine has allocated considerable resources to defining risk factors for diseases, but none of these risk factors comes close to progressing in age. Crossing the age barrier of 50 years renders individuals susceptible to a myriad of pathologic conditions, including cardiovascular diseases, cancer, and musculoskeletal diseases.[2] So far, aging is seen as a linear process that happens to a similar extent to everyone.[6] Recent research has clarified that individuals age differently.[7] Even the aging processes within the organs of an individual are happening at different speeds.[8] Therefore, it is important not only to determine the calendar age of an individual but also to assess the biological age and the aging status of the organs as well.

The most accessible biological aging parameter in cells is their telomeric length.[9] Telomeres are the natural ends of chromosomes, protecting the integrity of chromosomal DNA and avoiding replicative loss of vital information at chromosomal ends.[10] Replicative loss of DNA ends is caused by the functional properties of DNA polymerase, which cannot replicate to the very end of the chromosome.[11] Therefore, every proliferation cycle is linked to a loss of approximately 100 bp of telomeric DNA.[12] Telomeres are a distinct DNA substructure consisting of multiple repeats of TTAGGG. Following an initial double-stranded telomeric part, which can be replicated by conventional DNA polymerase, the telomere ends in a 3′ single-stranded overhang. This overhang can be replicated only by telomerase, an enzyme

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