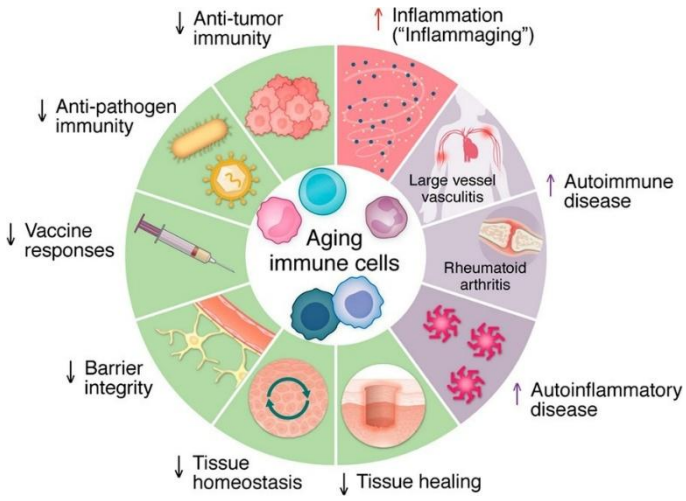
Why Autoimmunity Rises later in Life Aging Immune Cells may Explain

A recent Review published synthesized how immune aging contributes to immune dysregulation, functional decline, and autoimmunity.

Human health span and life expectancy have markedly increased over the past century. This increased lifespan presents various biomedical and societal challenges. The immune system is profoundly susceptible to aging, as it is continuously exposed to internal and external stressors. Recent studies reveal an aging inflection point around age 50, with the spleen and lymph nodes among immune organs showing the earliest molecular signatures.

Meanwhile, epidemiological data suggest that most of the 19 most prevalent autoimmune diseases have an onset after age 50, with type 1 diabetes a major childhood and adolescent exception. That aging T cells become less effective against tumors and pathogens but gain pathogenic potential in autoimmune disorders has prompted research into the effects of aging on T cell resilience, function, and effector programming. In the Review, the authors summarized recent developments demonstrating the role of immune aging in immune dysregulation, functional decline, and autoimmunity.



Study

The continual need for new immune cells is a major driver of immune aging. Studies suggest that lymphocyte pools remain relatively stable throughout adulthood, indicating their constant replenishment. Around 70 million naïve B cells, 65 million naïve CD4+ T cells, 17 million naïve CD8+ T cells, about 600 million memory T cells across the CD4+ and CD8+ compartments, and 60 million memory B cells are generated daily, highlighting the proliferative burden. Conversely, myeloid cells have even more pronounced replication-induced aging, as they have shorter lifespans than lymphocytes.

Meeting the high demand for monocytes and neutrophils warrants extensive proliferation of hematopoietic stem cells (HSCs). The clonal expansion of HSCs increases with age, and these cells also develop an age-associated myeloid lineage bias. HSC mutations that increase proliferation, self-renewal, bypass senescence, or promote inflammatory resilience drive clonal expansions, which are recognized clinically as clonal hematopoiesis of indeterminate potential.

Immune system decentralization is one of the hallmarks of immune aging, in which B and T cells occupy non-classical anatomical niches after leaving their primary tissue. For example, tertiary lymphoid structures are perivascular clusters of B and T cells that form outside of the spleen, bone marrow, and lymph nodes. These structures are a hallmark of some autoimmune diseases, particularly in periaortic tissue in giant cell arteritis (GCA), and occur in the synovium of a subset of patients with rheumatoid arthritis (RA), usually those with more severe disease.

In addition to immune cells, aging also reshapes the extracellular matrix, stromal niches, tissue architecture, and chemokine milieus. Thymic involution is an example of the pro-aging immune environment. The loss of thymic epithelial cells with age leads to a marked decline in naïve T cell output and the contraction of the T cell repertoire. This process highlights how tissue aging shapes the diversity and number of immune cells available throughout the lifespan.

Importantly, the Review emphasizes that T cell aging is not uniform. Naïve CD8+ T cells decline markedly with age, whereas naïve CD4+ T cells are more resilient and remain diverse. Memory T cell aging is also highly context-dependent, shaped by antigen specificity, exposure history, and lineage-intrinsic programs. This heterogeneity helps explain why some T cell pools remain functionally robust, whereas others shift toward states skewed toward innate-like, inflammatory, or senescent phenotypes.

Results

RA typically becomes clinically overt in the second half of life. Early studies of cluster of differentiation 4 (CD4+) T cells from RA patients identified an accelerated immune-aging phenotype: Age-inappropriate telomere erosion, contraction of clonal diversity, and premature loss of CD28 expression. Pathogenic effector functions arise in aged T cells not just from damage accumulation, but because aging reshapes the intracellular organelle communication and coordination.

Specifically, organelle stress and organelle crosstalk breakdown reprogram T cells toward tissue-destructive states. These T cells are driven into maladaptive activation loops, which perpetuate chronic inflammation. Further, CD4+ T cells in RA exhibit impaired mitochondrial health due to defective mitochondrial DNA (mtDNA) repair; although the essential repair machinery is produced in the nucleus, these cells fail to import it into mitochondria.

mtDNA fragments that escape into the cytosol and extracellular space act as damage-associated molecular patterns (DAMPs), triggering inflammation and amplifying immune activation. Given the defective mtDNA repair in CD4+ T cells in RA, mitochondrial adenosine triphosphate (ATP) synthesis sharply decreases, disrupting the tricarboxylic acid cycle activity. Moreover, CD4+ T cells in RA exhibit lower levels of late-cycle metabolites and higher levels of early-cycle intermediates.

Excess acetyl coenzyme A drives post-translational modifications, and hyperacetylation of cytoskeletal proteins results in mispositioning of organelles and altered cell morphology. These deficits render CD4+ T cells highly tissue-invasive and mobile in RA. Mitochondria-lysosome crosstalk is disrupted in CD4+ T cells in RA, and AMP-activated protein kinase (AMPK) fails to localize to lysosomes, leaving mechanistic target of rapamycin complex 1 (mTORC1) poorly restrained.

Consequently, mTORC1 uncouples from ATP status, enabling T cells to proliferate and grow despite bioenergetic stress. This hyperactivation of mTORC1 in energy-deficient cells contributes to their evasion of immune response-limiting mechanisms. Overall, impaired mitochondrial resilience leads to maladaptive remodeling, ultimately resulting in the release of DAMPs from T cells. These defects, associated with accelerated immune aging in RA, reprogram T cells toward pathogenic states.

The Review also highlights GCA as a contrasting model of aging-related autoimmunity. Unlike RA, which reflects accelerated immune aging in T cells, GCA may involve stalled or delayed immune aging, in which stem-like CD4+ T cells retain youthful proliferative capacity while aging arterial tissue accumulates neoantigens. This mismatch between immune and tissue aging may help explain why GCA occurs almost exclusively after age 50, with a median diagnostic age near 75.

In GCA, stem-like CD4+ T cells have been identified in aortic tissue, where they can reside within tertiary lymphoid structures near the vasa vasorum. These cells preserve self-renewal and responsiveness uncommon in advanced age, allowing them to generate differentiated effector T cells that infiltrate aging, neoantigen-rich vascular tissue. This paradox suggests that autoimmune disease in older adults may arise not only from immune decline, but also from discordant aging between immune cells and peripheral tissues.

Conclusion

Aging causes progressive erosion of immune integrity through metabolic stress, stem cell exhaustion, organelle dysfunction, and reduced lymphocyte stemness. As tolerance mechanisms attenuate, B and T cells adopt more innate-like features, elevating vulnerability to autoimmunity. Concurrently, aging lymph nodes, vasculature, and bone marrow disrupt immune coordination. Collectively, this creates conditions for inflammaging and autoimmunity.

The authors suggest that future therapeutic strategies should aim to restore metabolic resilience, improve organelle communication, preserve lymphocyte stemness, enhance mitochondrial repair, temper persistent mTOR signaling, and correct maladaptive endoplasmic reticulum stress. Understanding mechanisms of delayed immune aging could also guide approaches to rejuvenate immune function, strengthen vaccine responsiveness, and prevent age-associated autoimmunity.

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