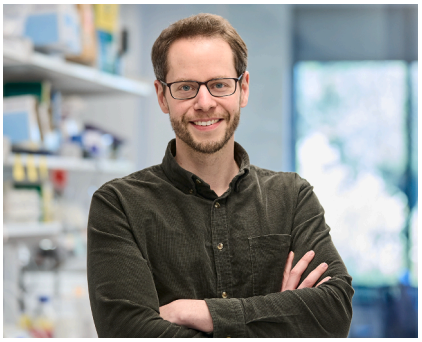
Immunity

CellPress

Voices

Aging and immunity

Time marches endlessly on … but what does that mean for the immune system? Here, investigators discuss how aging impacts the immune response and how immune cells can shape the aging process, with broader implications for modifying immunity to improve not only longevity but also health span.



Christoph A. Thaiss
Arc Institute, Stanford University

Sensing immune shifts

In the opening line of his visionary 1956 lecture "Mind and Matter," physicist Erwin Schrödinger declared, "The world is a construct of our sensations, perceptions, memories." Two major sensory systems underlie this construct: exteroception, which perceives the physical and chemical environment, and interoception, which senses the body's internal milieu. Signals from immune cells significantly broaden the interoceptive landscape. For example, cytokines released in response to microbial detection activate receptors on sensory neurons, relaying signals to the brain that coordinate adaptive responses.

While exteroceptive function declines with age—often mitigated in our daily lives by devices such as glasses or hearing aids—much less is known about how interoception ages. Immune cell function undergoes profound changes across the lifespan: bone marrow output shifts toward a myeloid bias, memory and senescent T cells accumulate, autoantibody production rises, and inflammatory cytokines increase systemically. Yet our understanding of how these immunological shifts are sensed, processed, or interpreted by the brain remains limited.

Large-scale proteomic studies have identified aging signatures in both the immune system and the brain as strong predictors of health span and longevity. This convergence raises a compelling question: can properties of the aging immune system reveal mechanisms underlying brain aging and its profound consequences for age-associated disease?

Nearly 7 decades after Schrödinger's lecture, the concept of sensation has expanded beyond the traditional senses. Now, the immune system emerges as a critical conduit in brain-body communication. Understanding how immune aging shapes neural perception could open new pathways to counteract age-related disease and cognitive decline.

Ye Tian
Chinese Academy of Sciences

A systemic mitochondrial view

Mitochondrial metabolism and stress signals influence T cell activation, macrophage polarization, inflammasome activity, and hematopoietic stem cell fate. Age-associated mitochondrial decline plays a role in weakened immune responses and chronic inflammation, which are key aspects of immunosenescence and inflammaging. However, this view tells only part of the full story.

For too long, mitochondrial aging has been viewed as a cell-intrinsic problem within immune cells. What remains underappreciated is that mitochondria also serve as systemic signaling organelles, transmitting stress signals that influence immune responses across different tissues. Mitokines, redox signals, and mitochondrial DNA released from mitochondria can affect distant immune compartments, yet these cross-organ communications are rarely included in current models of immune aging.

Neuronal mitochondria serve as a central yet often overlooked hub in this network. Mitochondrial stress in specific neuronal populations can influence peripheral immunity by affecting neurotransmitters, neuropeptides, and calcium signaling. Chronic immune activation, in turn, damages neuronal mitochondrial integrity, creating self-perpetuating neuro-immune aging loops. This decline in neuronal mitochondrial signaling could signal a critical turning point in age-related immune decline, especially when overall system coordination weakens despite the cellular machinery remaining largely intact.

This bidirectional mitochondrial signaling acts as a higher-level regulator of immune resilience, similar to neuroendocrine control.

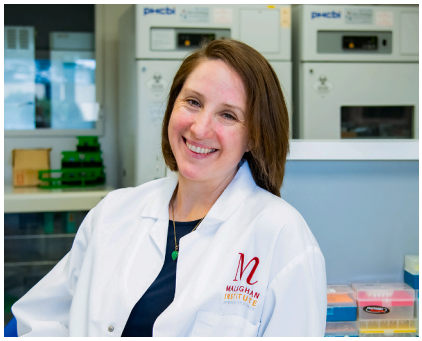
Adopting a systemic mitochondrial perspective will change how we understand and intervene in immune aging, shifting the focus from isolated cellular defects to the coordination of networks that maintain resilience.

Daniel A. Winer
Buck Institute for Research on Aging; Toronto General Hospital Research Institute

Modeling aging in space

To understand processes that may contribute to immune system aging, it is useful to apply a range of models, including models of rapid aging. One such approach is to study the immune system during spaceflight, or with spaceflight analog devices, such as simulated microgravity or simulated cosmic radiation. Spaceflight induces many features of aging on the immune system. Studies have described increases in inflammatory mediators—such as IL-1, IL-6, IL-8, TNF, some chemokines, and growth factors—in flight or immediately post-flight. These features are similar to the low-grade chronic inflammaging seen during aging. Moreover, like aging, spaceflight boosts some myeloid cell numbers, and myeloid cells often show defects in phagocytosis or antigen presentation. The adaptive immune system is also compromised in both aging and spaceflight models. T cells show reduced activation to stimulation and features of exhaustion. Cumulatively, immune changes from spaceflight and aging lead to increased risk of viral reactivation.

Going forward, it will be important to tease out shared mechanisms of immune system aging in these spaceflight models. Some of these emerging pathways include those linked to hallmarks of aging, such as mitochondrial dysfunction, oxidative stress, genome instability, altered telomere dynamics, deregulation of nutrient-sensing pathways, altered microbiome, and intercellular communication. From studies in simulated microgravity and spaceflight, other key pathways are emerging, such as in cytoskeleton or with ion channels, with potential relevance in aging. By keeping our eyes toward the stars, we will learn more about aging processes on Earth and facilitate future travel in space.



Michelle Linterman
Malaghan Institute of Medical Research

Humoral immunity to vaccines

Average human life expectancy has more than doubled in the last century. This impressive gain in years reflects the culmination of many interventions enabling children to survive their first 5 years of life: sanitation, clean water, antibiotics, and safe, effective vaccines that limit mortality from infectious disease. The global shift to longer lives has created a new challenge: to increase health span in the later years of life. Innovative approaches to vaccine formulation, development, and dosing will be important in limiting the morbidity and mortality associated with infectious disease in older people.

Upon vaccination, older adults tend to generate lower titer antibody responses and fewer memory B cells, culminating in impaired protective humoral immunity against infections. Mechanistically, this poorer age-associated humoral response is caused by altered germinal center reactions that are slower to start, smaller in magnitude, and of poorer quality than those found in younger adults. The germinal center is a collaborative cellular network, with stromal cells bringing antigen-specific T and B cells together in secondary lymphoid organs. In aging, changes in stromal cell biology, T cell localization and function, and the B cell receptor repertoire all contribute to suboptimal germinal center responses. However, we now appreciate that these changes are malleable, and germinal centers can be boosted in older individuals. The wealth of recent discoveries on aging immunity, germinal centers, and vaccines is a strong foundation for a new era of precision vaccinology that aims to boost germinal centers in aging and support health across our lifespan.

Adrian Liston
University of Cambridge

T cell decay or adaptation?

There are a multitude of T cell changes associated with aging. Homeostatic proliferation substitutes for thymic production, restricting the repertoire. Populations shift toward an inflammatory Th1 bias, with enrichment of exhausted and senescent cells. At the cellular level, we see reduced function, metabolic alterations, and epigenetic shifts. While some of these phenotypes may result from external environmental factors of the limited cohorts studied to date, others are likely to be intrinsic to biological aging. Further, it is probable that these changes contribute, at least in part, to the immunological pathologies of aging individuals, including vaccine failure, immunodeficiency, and chronic inflammation.

Unanswered within the T cell aging field is the degree to which these changes are degenerative versus adaptive. Under the degenerative model, corrective systems have only been selected to maintain integrity throughout the reproductive lifespan, with survival extension causing entropic decay of system integrity. The alternative is one where the human body has evolved, to an extent, an immune reprogramming for old age. Under this adaptive model, the observed changes are part of an advantageous shift that leverages accumulated antigenic experience and minimizes potential adverse effects of youthful immune exuberance. An adaptive basis for T cell aging would necessitate the existence of an immunological chronometer and instructive signals to drive reprogramming. These pathways could potentially be subverted when adaptive aging becomes maladaptive. In this way, the distinction between degeneration and adaptation is not merely philosophical; understanding why T cells change with age would shed light on promising therapeutic approaches.

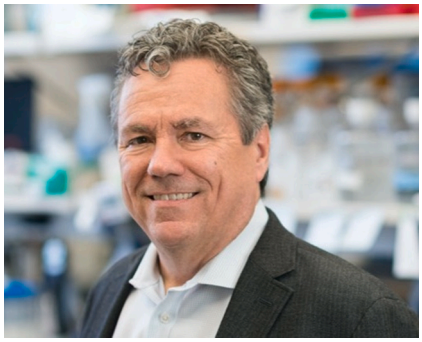
Corina Amor
Cold Spring Harbor Laboratory

Tailoring immunotherapy

Modulation of the immune system holds immense therapeutic potential across a wide range of diseases. In recent decades, we have seen significant advances with the development of immune checkpoint blockade and chimeric antigen receptor (CAR) T cells. While initially developed for oncology, immune-based cell therapies are being expanded to additional indications such as autoimmunity and fibrosis. Because many of these diseases, including cancer, are significantly more prevalent in individuals over the age of 50, we need an improved resolution of how host age impacts both disease progression and immunotherapy outcomes.

While there is a general appreciation that aging impacts the immune system (affecting the frequency and functionality of certain immune populations), it remains less clear how aging immune cells impact the susceptibility, onset, and progression of specific diseases and/or alter microenvironment immunity and susceptibility to disease. Inherent epigenetic and metabolic differences between young and old CAR T cells seem to affect their phenotype and long-term persistence, but we need a clearer view of how these therapies are influenced by age.

Understanding how aging modulates both endogenous and adoptive immunity would enable age-tailored immunotherapy approaches to select optimal immune populations and target proteins, reinvigorate senescent immune populations, or counteract the senescent non-immune microenvironment with engineered receptors, ultimately maximizing the efficacy and safety of these therapies across all age groups.



Scott W. Lowe
Memorial Sloan Kettering Cancer Center

Redefining senescence

Cellular senescence represents a biologically potent cell state with broad implications for cancer and aging. Initially defined as a program of durable proliferative arrest, senescence is now recognized as a dynamic and heterogeneous process that can exert both beneficial and deleterious effects on tissue biology. Hence, while transient senescent states can promote wound repair or suppress tumorigenesis, senescent-cell persistence fuels fibrosis, immune suppression, and a pro-tumorigenic microenvironment. This duality underscores a central challenge: distinguishing adaptive from pathogenic senescence and developing strategies to selectively target the latter.

Senescent-like states are heterogeneous and frequently overlap with other context-specific cellular phenotypes, complicating their classification. The canonical definition of senescence emerged from *in vitro* systems, yet it is increasingly evident that tissue- and environment-specific cues critically shape senescent programs *in vivo*. These complexities have hindered the field's ability to define the process unambiguously. Advances in single-cell and spatial profiling are now revealing a continuum of transcriptional, epigenetic, and functional senescent-like states with context-dependent roles in disease. These approaches also illuminate how senescent cells interact with their microenvironment, modulate immune responses, and contribute to chronic disease.

Looking ahead, the field must transition from definitions to interventions. Developing robust biomarkers, elucidating the determinants of senescent cell persistence, and designing strategies that selectively eliminate pathogenic states remain major challenges. Yet the potential rewards are substantial: senescence biology offers a therapeutic entry point across oncology, fibrosis, regenerative medicine, and aging. By integrating mechanistic insight with translational rigor, targeting senescence could transform both cancer therapy and healthy aging.

Guang-Hui Liu
Chinese Academy of Sciences

The immune system as the master conductor

Aging manifests differently in each organ, yet a common thread connecting them all is the progressive dysfunction of the immune system. But is immunosenescence a passive follower or an active conductor of the body's aging symphony? Growing evidence points to the latter. The immune system's unique position—circulating throughout the body and interacting with every tissue—makes it a central regulator, if not a driver, of systemic aging.

The critical hurdle in understanding the influence of this conductor is its inherent complexity: the asynchronous aging of immune cells. Immune subsets and the individual cells within them exhibit profound heterogeneity and display non-linear, emergent properties arising from their exposures. Traditional approaches fall short of meaningfully resolving this cacophony. The path forward requires a multi-omics, systems-level decoding, fueled by artificial intelligence (AI). By integrating layers of biological data, AI can cut through the noise to identify the critical leverage points—the specific cell states, signaling pathways, and metabolite fluxes—that orchestrate the transition from health to frailty.

This is not just an academic exercise. Pinpointing these master regulatory nodes opens the door to targeted interventions. Can we recalibrate the immune conductor to slow the entire aging process? The convergence of systems immunology and AI offers an unprecedented chance to move from observing aging to reprogramming its tempo, ultimately fostering a healthier old age for the global population.

DECLARATION OF INTERESTS

C.A. is listed as the inventor of several patent applications (62/800,188; 63/174,277; 63/209,941; 63/209,940; 63/209,915; 63/209,924; 17/426,728; 3,128,368; 20748891.7; 2020216486; 63/510,997) related to senolytic CAR T cells. M.A.L. receives funding from GSK for work outside of this piece. D.A.W. is a cofounder of Cosmica Biosciences, a company that studies altered biological aging in spaceflight exposures. D.A.W. has patent applications related to this topic: "Methods for Simulating Inflammatory Aging, Cardiac Dysfunction, Neural Dysfunction, and Changes Associated with Spaceflight in Cells and Organoids, and Methods for Identifying and using Compounds Useful for Treatment of Cellular Changes Associated with Inflammatory Aging, Cardiac Dysfunction, Neural Dysfunction, and Spaceflight" (PCT/US2024/042658, WO 2025/038925).