explained

At What Age Does the Immune System Weaken?

After decades of combatting daily assaults, aging immune cells spark a whirlwind of change that drastically affects human health.

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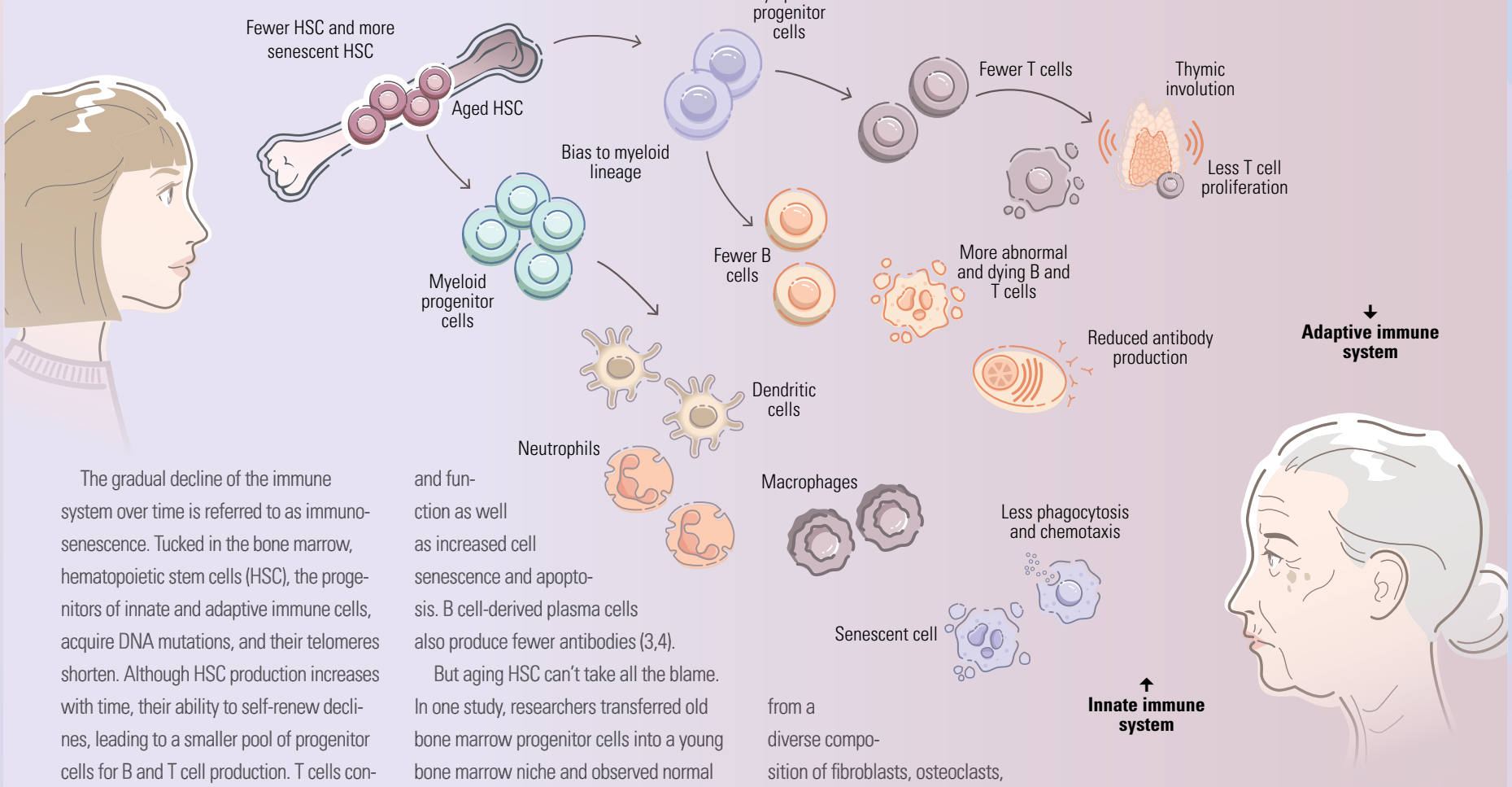
Aging is inevitable, and much like our faces begin to acquire lines, our skin loosens, and our hair grays, immune cells inside our bodies also age. There is no magic number where a set biological timer goes off and the immune system suddenly declines, but researchers have found rapid epigenomic changes in the immune system at two key timepoints. The first occurs around the late 30s to early 40s in both men and women but doesn't drastically affect immune function. Around the sixth decade of life, the second set of changes occurs slightly earlier in men than women and sparks dramatic functional changes (1,2).

What happens to the immune system with age?



The gradual decline of the immune system over time is referred to as immunosenescence. Tucked in the bone marrow, hematopoietic stem cells (HSC), the progenitors of innate and adaptive immune cells, acquire DNA mutations, and their telomeres shorten. Although HSC production increases with time, their ability to self-renew declines, leading to a smaller pool of progenitor cells for B and T cell production. T cells continue their maturation in the thymus, but this organ gradually shrinks with increasing age, further decreasing T cell output and clonal diversity. Mutations in HSC progenitors also lead to defects in differentiated lymphocytes, culminating in less B and T cell proliferation and function as well as increased cell senescence and apoptosis. B cell-derived plasma cells also produce fewer antibodies (3,4).

But aging HSC can't take all the blame. In one study, researchers transferred old bone marrow progenitor cells into a young bone marrow niche and observed normal numbers of circulating pre-B cells in mice, suggesting that the tissue microenvironment plays a significant role in immune cell aging (5). Indeed, the aging bone marrow tissue has a higher percentage of senescent mesenchymal stem cells. It gradually shifts from a diverse composition of fibroblasts, osteoclasts, megakaryocytes, chondrocytes, and stem cells to mainly adipocytes, replacing once red bone marrow with yellow fat cells. Cumulatively, these changes inhibit HSC function and skew HSC differentiation to favor myeloid over lymphoid cell production.

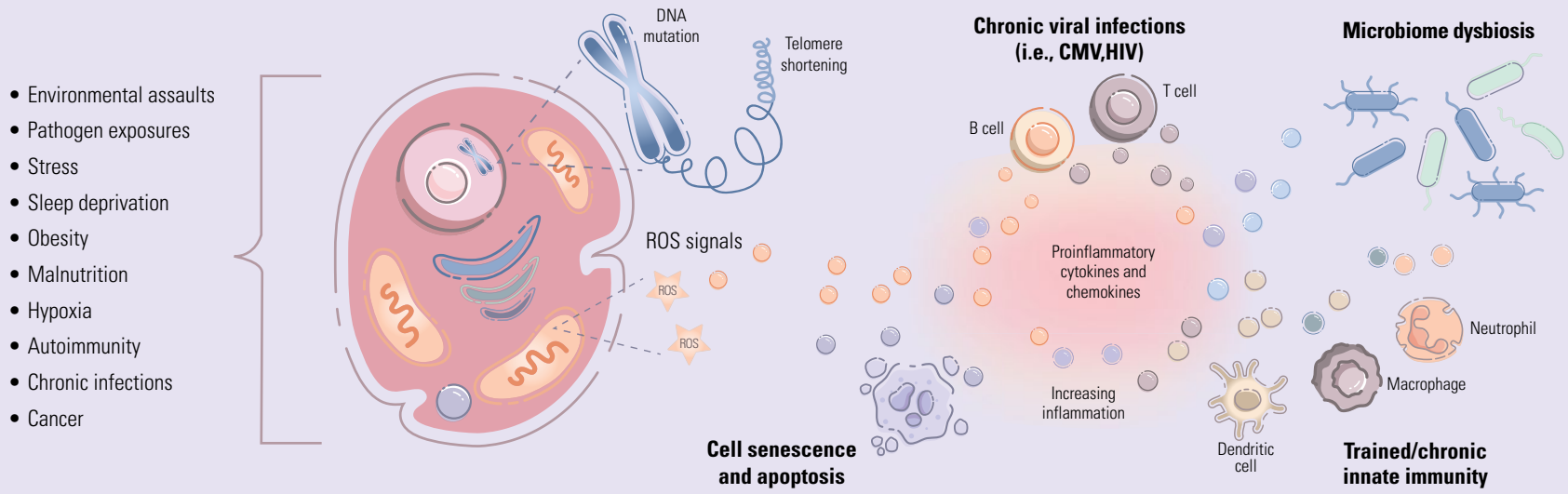
This gives older individuals more innate than adaptive immune cells. However, even innate immune cells have age-induced defects that cause cell senescence, apoptosis, and reduced phagocytosis and chemotaxis (6,7).

Why does the immune system age?

Age-related changes aren't exclusive to immune cells. Throughout the body, cells in every tissue cope with everyday environmental assaults such as lack of sleep, pathogens, toxicological agents, poor nutrition, or pre-existing conditions (7). Over time, these stressors cause DNA mutations and mitochondrial dysfunction. Dysfunctional mitochondria release high levels of reactive oxygen species (ROS) into the cytosol, where they oxidize lipids, proteins, and DNA, and they signal innate immune responses such as toll-like receptors that trigger inflammation in the tissue. Mitochondrial stress also accelerates telomere shortening, further contributing to cell senescence (8,9).

Increasing cell stress limits the immune system's ability to effectively clear senescent cells, leading to the accumulation of senescent signals such as proinflammatory cytokines and chemokines. Elevated inflammation forms a positive feedback loop that stresses surrounding cells, leading to further cell senescence and chronic inflammation (4). This gradual increase in low-grade inflammation is known as inflammaging, which is characterized by a senescence-associated secretory phenotype (SASP), wherein senescent cells, including immune and tissue cells, release high levels of inflammatory cytokines, ROS, immune modulators, growth factors, and proteases (8).

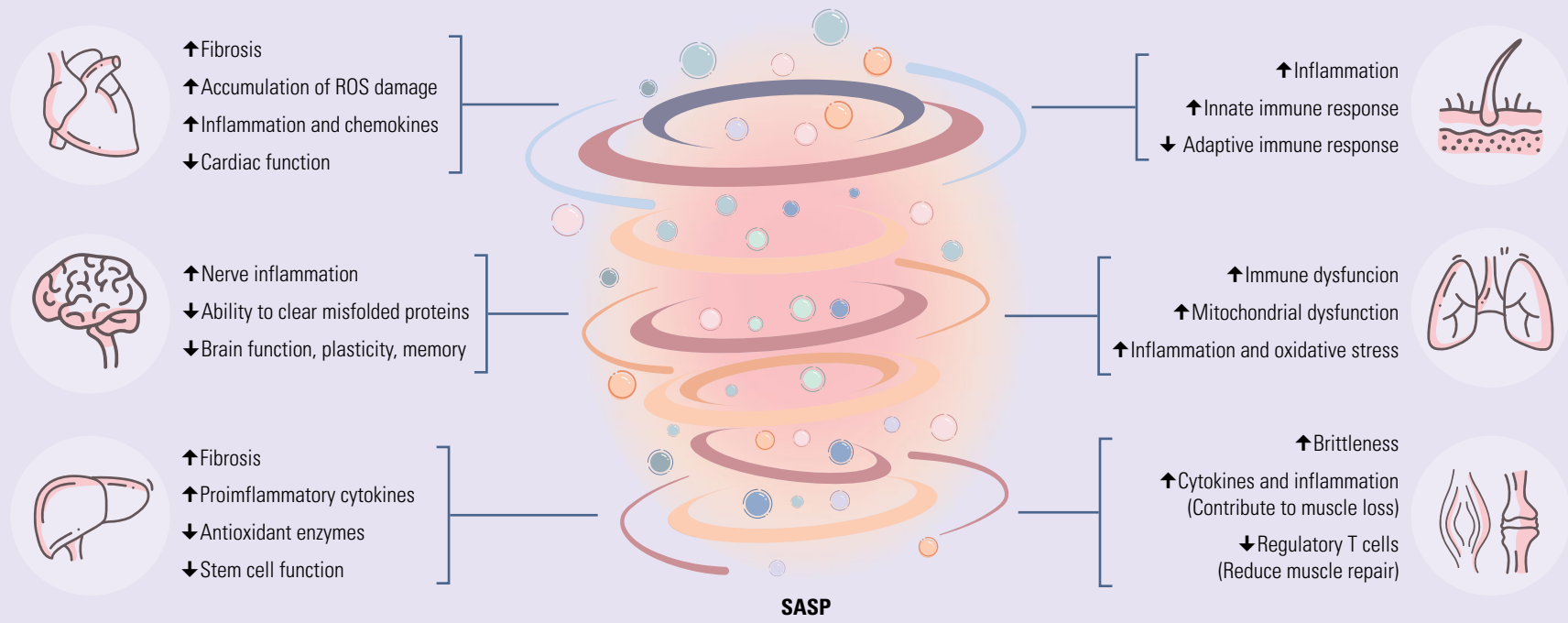
Other molecular events may also contribute to elevated inflammation. An imbalance between commensal and invasive microbes in the gut may trigger proinflammatory mediators (8). Similarly, the switch to more innate immune cell production means more reliance on the innate immune system. As such, the innate immune system remains chronically activated, which prepares the body for a broad range of assaults but also contributes to low-grade chronic inflammation (8). Lastly, chronic viral infections, where the pathogen is always present, change an already limited number of naïve lymphocytes into memory T cells. This decreases their ability to respond effectively to new pathogens and exaggerates cytokine storms by stimulating ROS, chemokine, and cytokine release, further contributing to inflammation and SASP (7).



How does immune system aging affect the body?

The SASP spreads through autocrine and paracrine signaling, perpetuating the senescent phenotype in surrounding cells and leading to gradual tissue decline with age (8). This process occurs across the body's organs in both tissue and immune cells, and because the immune system plays a central role in responding to cell damage and mitigating inflammation, it takes center stage in the process of systemic aging. This premise is supported by a study where researchers depleted a DNA damage repair protein in hematopoietic cells to induce cell senescence specifically in lymphoid cells but observed senescence markers across non-lymphoid organs in mice as well (10).

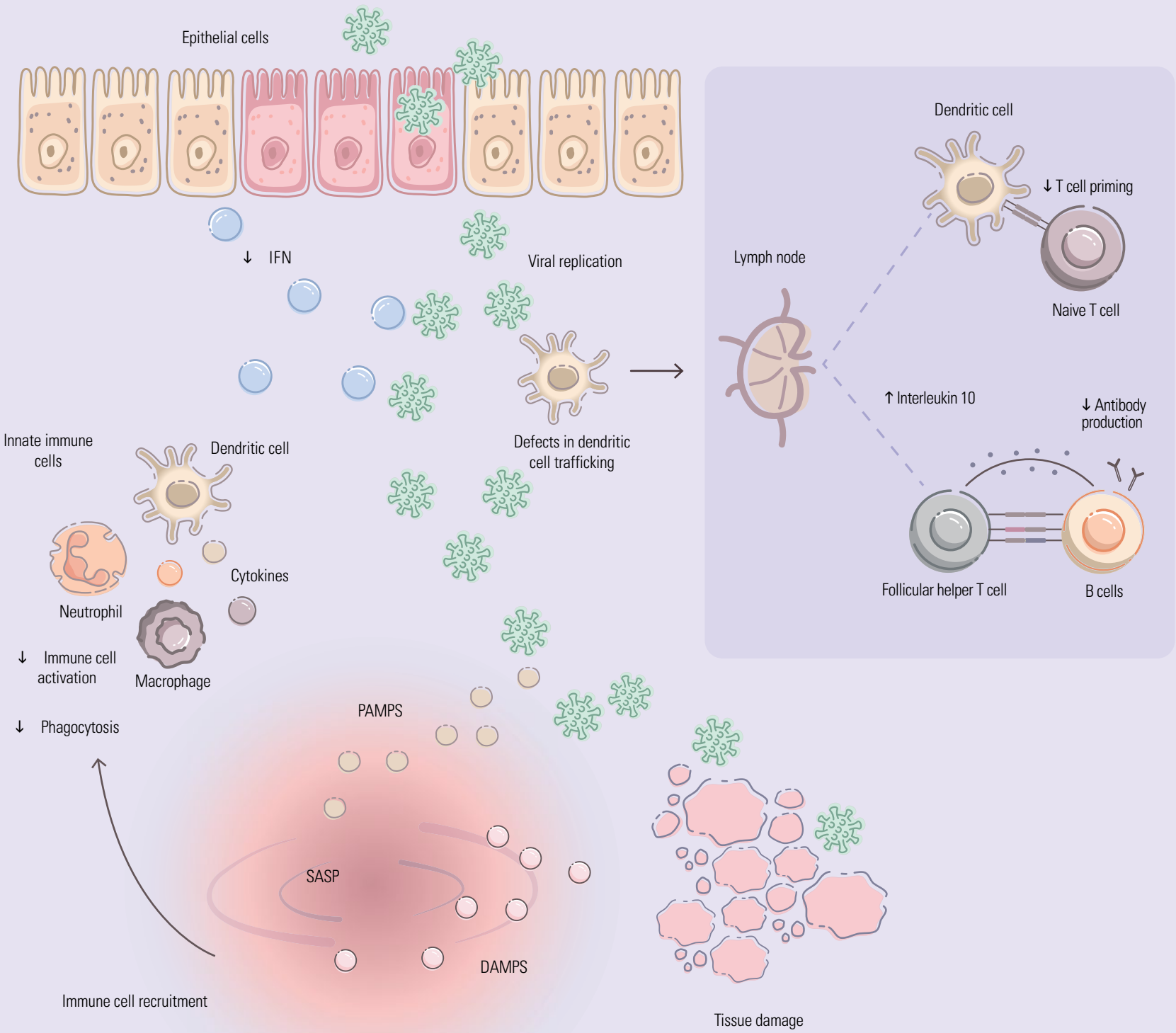
One non-immune related organ affected by aging immune cells is the brain. During aging, microglia, the innate immune cells of the brain and central nervous system, begin upregulating inflammatory related pathways. Microglia also gradually lose the ability to effectively clear misfolded proteins, leading to neuroinflammation. Altogether, these changes contribute to neurodegeneration, cognitive decline, and shrinkage in brain tissue (4,7). Similarly, in the heart, macrophages a play critical role in eliminating senescent and dying cells, which contribute to homeostasis in the myocardium, but aging macrophages exhibit a pro-inflammatory phenotype (4). Aging muscle cells also express elevated levels of cytokines, which contribute to inflammation, muscle loss, and reduced numbers of regulatory T cells, which typically assist in muscle repair (7). Lastly, the compromised immune system at large produces higher levels of self-reactive autoantibodies and may overlook key cellular damage that could cause cancer, aligning with the higher incidence of cancer in older individuals (11,12).



How does immune system aging influence infectious disease response?

The aging immune system not only compromises tissue homeostasis, which may lead to disease onset, but also weakens the body's response to infectious pathogens. During aging, the primary and secondary signaling pathways of the retinoic acid-inducible gene change, leading to a delay in type I interferon (IFN) viral sensing responses. Older dendritic cells also produce lower levels of type I IFN (13). This couples with a sluggish or aberrant innate immune cell response to cause slow or ineffective viral clearance (14). This buys the virus time to propagate, which produces pathogen-associated molecular patterns (PAMPS) and causes cell death that signals damage-associated molecular pathways (DAMPS). PAMPS and DAMPS prompt innate immune cell recruitment and the production of more proinflammatory cytokines, adding to an already inflamed microenvironment (13).

For the adaptive immune system to step in and launch a targeted response, it needs reliable antigen presentation. However, over time, antigen presenting cells, such as dendritic cells, downregulate key cell surface markers needed to interact with T cells (13). Aged antigen presenting cells also exhibit migration defects that inhibit their ability to travel to the lymph node for T cell priming (14). The T cell repertoire also decreases with time, resulting in more memory T cells from past infections than naïve T cells, which leaves fewer cells available to prime against new pathogens. This is exacerbated in patients with chronic viral infections (13). Fewer B cells and greater B cell senescence couple with rising levels of interleukin 10, an anti-inflammatory cytokine produced by follicular helper T cells, to limit antibody production (14). Altogether, this results in older individuals having a higher susceptibility to infectious diseases and poorer vaccination responses.



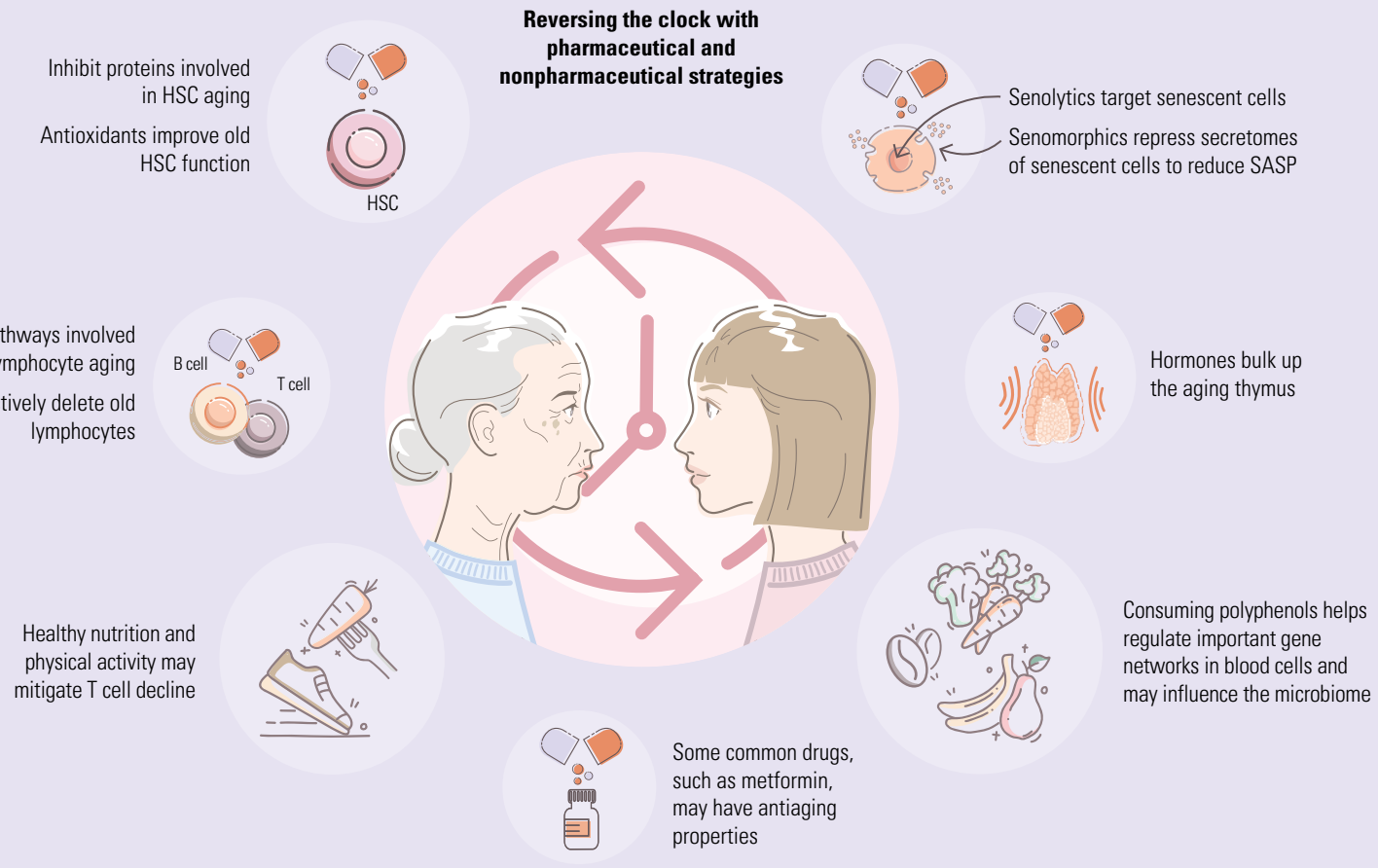
Is there a way to reverse immune system aging?

Researchers have improved vaccination responses in the elderly by providing higher dose or adjuvanted flu vaccines that help create stronger immune responses, but is it possible to reverse the hands of time entirely?

Pharmaceutical and nonpharmaceutical approaches may help slow or even reverse immune system aging. One approach involves inhibiting proteins implicated in HSC aging, while another approach uses antioxidants to improve old HSC function. Other strategies involve targeting specific pathways in aged lymphocytes or selectively deleting mature memory T and B cells, which stimulates lymphopoiesis and creates space for new cells (6,8).

Senolytic and senomorphic compounds that reduce senescent cell burden and SASP inflammation may also help improve immune response. Even old drugs may have new functions in the context of aging. For example, metformin, a common drug used to treat diabetes, may act as a senomophic that modulates immune system aging by enhancing nutrient sensing, autophagy, intercellular communication, and mitochondrial function. It also protects against macromolecular damage, delaying stem cell aging, and regulating transcription (8).

However, these approaches still exist in an inflamed tissue microenvironment. Other approaches aim to rejuvenate tissues. Using hormones, it may be possible to increase thymus mass, which would increase T cell output (6). Nonpharmaceutical approaches also target aging at a systemic level. Physical activity and healthy nutrition decrease T cell decline and may mitigate physiological, metabolic, and molecular changes associated with age-related diseases (6,8). Consuming polyphenols, plant compounds with antioxidant properties, such as those found in fruits, vegetables, and cocoa help modulate important gene networks in blood cells that regulate interactions with the vascular endothelium. These gene networks control oxidative stress, cell-cell adhesion, apoptotic and senescence processes, and cellular transport. Consuming polyphenols also influences the gut microbiota, which can contribute to SASP (8). Researchers are also investigating other natural products with anti-inflammatory properties that may mitigate immune system aging (6).



Nothing but a number

Despite the potential of pharmaceutical and nonpharmaceutical approaches to potentially delay or even reverse immune system aging, some big questions remain unanswered. Given the gradual decline of the immune system, when is the best time to begin administering interventions? Additionally, how long should interventions last? What is the ideal threshold of immune system rejuvenation, and can it be maintained homeostatically without further intervention (6)? Aging immune systems are not exclusive to older individuals. Similar to older populations, people with chronic stress, malnutrition, or obesity also produce fewer antibodies and have poor vaccination responses. People with these conditions, autoimmune diseases, or chronic infections such as cytomegalovirus, human immunodeficiency virus, or malaria also display an altered immune landscape consistent with increased age despite being well under the age of sixty. These data highlight the importance of cellular stress caused by genetics, pre-existing conditions, environmental stressors, and epigenetics on accelerating immune system aging. Altogether, this suggests that chronological age might indeed be just a number, and that age might be better measured as a host of molecular and cellular changes. Researchers are now hunting for molecular signatures of cell senescence and inflammation that indicate a person's true biological age (7).

REFERENCES

1. Weyand, C.M. & Goronzy, J.J. Aging of the immune system. Mechanisms and therapeutic targets. *Ann Am Thorac Soc* **13**, S422-S428 (2016)
2. Márquez, E.J. *et al.* Sexual-dimorphism in human immune system aging. *Nature Communications* **11**, 751 (2020).
3. Montecino-Rodrigues, E., Berent-Maoz, B., & Dorshkind, K. Causes, consequences, and reversal of immune system aging. *The Journal of Clinical Investigation* **123**, 958-963 (2013).
4. Li, X. *et al.* Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduction and Targeted Therapy* **8**, 293 (2023).
5. Labrie, J.E. *et al.* Bone marrow microenvironmental changes underlie reduced RAG-mediated recombination and B cell generation in aged mice. *J Exp Med* **200**, 411-423 (2004).
6. Rodrigues, L.P. *et al.* Hallmarks of aging and immunosenescence: Connecting the dots. *Cytokine and Growth Factor Reviews* **59**, 9-21 (2021).
7. Xu, E., Wong, G., Hwang, Y.Y., & Larbi, A. The untwining of immunosenescence and aging. *Seminars in Immunopathology* **42**, 559-572 (2020).
8. Saavedra, D. *et al.* Aging and chronic inflammation: highlights from a multidisciplinary workshop. *Immunity & Aging* **20**, 25 (2023).
9. Cisneros, B. *et al.* Immune system modulation in aging: Molecular mechanisms and therapeutic targets. *Frontiers in Immunology* **13**, 1059173 (2022)
10. Cui, Y. *et al.* An aged immune system drives senescence and ageing of solid organs. *Nature* **594**, 100-105 (2021).
11. de Mol, J., Kuiper, J., Tsiantoulas, D., & Foks, A.C. The dynamics of B cell aging in health and disease. *Frontiers in Immunology* **12**, 733566 (2021).
12. Weyand, C.M. & Goronzy J.J. Transatlantic Airway Conference: Aging of the immune system. *Annals of the American Thoracic Society* **13**, S422-S428 (2016).
13. Bartleson, J.M. *et al.* SARS-CoV-2, COVID-19 and the aging immune system. *Nature Aging* **1**, 769-782 (2021).
14. Lee, K-A. *et al.* Immune senescence, immunosenescence and aging. *Frontiers in Aging* **3**, 900028 (2022).