

Editorial

Aging as a Networked Process: Systems, Signals, and Interventions Across the Lifespan

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ABSTRACT: As global populations age, chronic disease burden rises across multiple organ systems. This special issue treats aging as a multi-system process shaped by biology, environment, and behavior. Across 30 original studies and reviews, the collection centers on shared mechanisms of decline, including mitochondrial dysfunction, circadian disruption, hypoxia, inter-organ signaling, and cellular senescence. The articles track how these processes change across tissues and across time. Multiple contributions link systemic changes to tissue-level dysfunction. Vascular, immune, and metabolic shifts appear repeatedly as upstream drivers. The issue also emphasizes local context. Tissue microenvironments shape how the same systemic stressor produces different outcomes, which helps explain heterogeneity in aging trajectories. Several papers move toward translation. They propose biomarkers and diagnostic strategies aimed at earlier detection, risk stratification, and longitudinal monitoring. The strongest translational value comes when authors connect a proposed tool to a defined endpoint and a defined use case, rather than broad “precision” framing. Overall, the issue argues for tighter alignment between mechanism and measurable outcomes. The collection also highlights critical areas where further validation and integration are needed to support clinical translation.

Keywords: aging biology, cellular senescence, mitochondrial dysfunction, inter-organ communication, biomarkers, precision medicine

Framing Aging as a Systems Process

Advances in modern medicine have significantly reduced mortality rates, contributing to longer life expectancy. However, this increased longevity has also led to a rise in age-associated conditions, including neurodegenerative, cardiometabolic, oncologic, and musculoskeletal diseases. These conditions rarely occur in isolation; instead, they emerge from interacting biological mechanisms and cumulative lifetime exposures that act across multiple organ systems over decades.

This special issue adopts a system-level perspective on aging. The featured articles encompass mechanistic investigations into mitochondrial dysfunction, organokine

signaling, circadian disruption, hypoxia, and cellular senescence. They also present translational studies on biomarkers, regenerative strategies, and data platforms focused on brain and systemic aging. Rather than viewing aging as a single, linear trajectory, this collection maps the complex interplay of pathways and identifies opportunities for measurement, modulation, and intervention.

Aging as a Network of Systems, Signals, and Exposures

Several articles challenge linear models of aging. Liang et al. [1] reassess mitochondrial health and argue that

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mitochondrial DNA mutations often track broader metabolic decline rather than serving as a single initiating cause. Fang et al. [2] propose a “ROS-inflammation-immune balance” framework and apply entropy-based concepts to describe how destabilization across linked systems accumulates with age. They connect these ideas to measurable features in animal and human studies, including oxidative stress markers and immune imbalance, and discuss how adipose inflammation can influence brain function through circulating cytokines. Together, these papers shift emphasis from single lesions to interacting metabolic and immune networks.

Ni et al. [3] extend this perspective to inter-organ communication. They review organokines released by adipose tissue, liver, muscle, and bone and describe how these signals shape obesity-related type 2 diabetes through coordinated metabolic and inflammatory pathways. Nisar et al. [4] review how hypoxia signaling influences aging biology and discuss contexts where adaptive responses to low oxygen are associated with healthier aging trajectories.

Long-term exposures also reshape these networks. Xu et al. [5] review BMAL1 and SIRT1 as regulators of circadian alignment and summarize links between circadian disruption, cancer biology, and immune dysfunction. Basel et al. [6] report multigenerational animal data suggesting parental alcohol exposure programs offspring liver cancer susceptibility, supported by epigenetic and mitochondrial functional assays.

Endocrine aging provides another system's entry point. El-Hage et al. [7] describe sex differences in lipid metabolism in Alzheimer's disease and argue for deeper lipidomic profiling across populations. Liu et al. [8] frame ovarian aging as a systemic transition with downstream effects beyond reproduction, with implications for long-term health planning and fertility preservation.

Integrative comment: Across these studies, endocrine, inflammatory, and mitochondrial signals repeatedly emerge as shared pathways linking organ systems to age-related dysfunction.

Cellular Stress, Senescence, and Tissue Resilience

Several studies connect cellular stress responses to tissue-level decline and repair. Lin et al. [9] report increased DNA damage and cGAS-STING activation in alveolar type II cells in aged smokers, linking inflammatory signaling to impaired lung repair and fibrosis. In vascular aging, Cui and Zhan [10] review evidence that TRPV1 activation by capsaicin associates with improved endothelial function and attenuation of aging phenotypes in experimental models.

The issue also emphasizes the role of tissue microenvironments. Qiu et al. [11] review evidence that

senescent support cells impair skeletal muscle regeneration, which supports strategies that target niche restoration rather than focusing only on parenchymal cells.

Multiple contributions advance detection and intervention. Singam et al. [12] describe a label-free approach to track microglial lipid droplets during oxidative stress-related senescence. Tang et al. [13] use AI-assisted screening to identify TNIK inhibition as a senomorphic strategy and report INS018_055 as a compound that reduces inflammatory secretions across senescence models. Hou et al. [14] review nanozyme-based approaches designed to remodel oxidative and immune environments in tumors and to address immunotherapy resistance.

In this issue, Sharma et al. [15] present a compelling approach to skeletal aging by leveraging quercetin-capped selenium nanoparticles (Qu-SeNPs) for localized bone regeneration. Their study highlights how nanostructured bioactives can activate osteogenic pathways such as WNT, BMP, and miR-206/Connexin43, offering a mechanistically grounded strategy for enhancing bone healing in age-related defects.

Regenerative work follows similar principles. An et al. [16] report that mesenchymal stem cells activated by cyanogenic compounds improve cartilage repair when delivered in a hyaluronic acid hydrogel. Aparicio et al. [17] report *Drosophila* findings that link rosemary and ginger extracts to improved aging phenotypes and stress-response pathways.

Integrative comment: Across these studies, stress responses and niche composition appear modifiable through pharmacologic, nutritional, and biomaterial-based strategies.

Brain Aging and the Vascular–Immune–Systemic Interface

A consistent message across brain-focused articles is that neurodegeneration reflects systemic inputs. Expanding on the role of systemic interactions, Su et al. [18] review the gut–brain–microbiota axis in dementia-related complications. They synthesize evidence that gut dysbiosis contributes to neuroinflammation, cognitive decline, and emotional dysregulation, underscoring microbial interventions as a potentially tractable pathway for modifying neurodegenerative trajectories.

In their original research, Ran and Gao [19] investigate the impact of chronic unpredictable mild stress (CUMS) on aging-related phenotypes in mice. Their findings demonstrate that long-term stress not only accelerates cognitive and metabolic decline but also alters inflammatory and endocrine parameters, reinforcing stress as a key multisystem modulator of aging.

Vascular and immune mechanisms recur across studies. Sun et al. [20] review cerebral small vessel disease and place cognitive decline and stroke risk in the context of microvascular dysfunction. Selvaraji et al. [21] review epigenetic regulation in vascular cognitive impairment and highlight methylation targets with potential reversibility. Gong et al. [22] report associations between natural killer cell subsets, including CD16–CD56 bright cells, and ALS progression, suggesting immune profiling as a candidate biomarker approach.

Metabolic signaling also intersects with cognition. Vered et al. [23] report associations between circulating endocannabinoids and cognitive performance, with stronger links in ApoEε4 carriers and older women. Li et al. [24] review shared pathways between Alzheimer's disease and osteoporosis, emphasizing overlapping hormonal, inflammatory, and genetic influences.

Integrative comment: These findings reinforce brain aging as a process deeply embedded in immune, vascular, and metabolic systems.

Diagnostics, Biomarkers, and Data Platforms

Several papers focus on measurement tools intended to support more actionable risk profiling. Hobert et al. [25] review stable-isotope fractionation as a diagnostic approach for tracking metabolic processes. Wyroba et al. [26] critique overreliance on anti-Müllerian hormone for IVF prediction and argue for multi-parameter hormonal assessment.

The issue also addresses practical challenges in older cohorts. Liu et al. [27] review advances in hydrocephalus management across diagnosis and treatment. Foo et al. [28] show that dementia reduces optical coherence tomography image quality, which supports protocol adaptation for cognitively impaired patients. Kon Kfir et al. [29] link sarcopenia with accelerated cognitive decline in hospitalized older adults, reinforcing the need to assess physical and cognitive vulnerability together.

Oh et al. [30] introduce the BRIDGE platform in South Korea, which integrates clinical, imaging, and biomarker data to support longitudinal research in brain disease. These infrastructure efforts improve cross-study comparability and help define system-level patterns across populations.

Integrative comment: These tools and platforms reflect a shift from isolated metrics toward integrated profiling approaches that can inform longitudinal risk assessment.

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