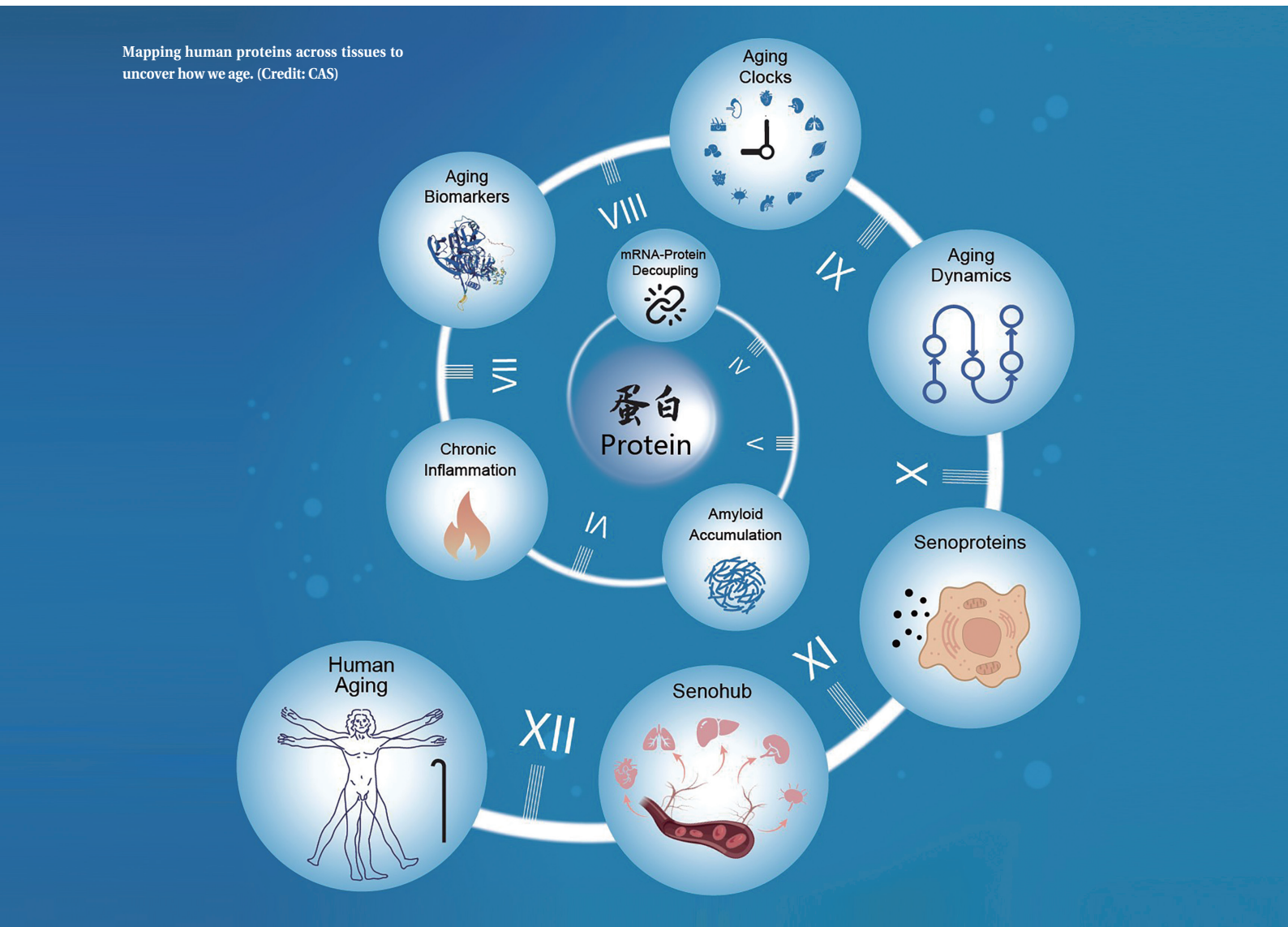
Unraveling Aging: Proteostasis Loss and the Vascular Senescence Nexus

By YAN Fusheng

Your arteries aren't just plumbing—they're also molecular timekeepers. A recent *Cell* study positions the aorta, the main artery of the body, as a crucial "senohub", in which "seno" is a shorthand prefix derived from senescence. Far from passive victims of time, these vital conduits actively dispatch "senoproteins", like unwanted couriers, spreading aging signals throughout the entire physiological landscape.



Mapping human proteins across tissues to uncover how we age. (Credit: CAS)

Time leaves its marks on our bodies as wrinkles, fading strength, and the gradual decline that we call aging. Yet a central mystery remains: do different organs follow a unified rhythm of aging? Is there a unifying mechanism that coordinates this system-wide deterioration? For decades, scientists have sought answers to these questions, but their insights have remained partial, like scattered fragments of a much larger puzzle.

Now, a joint team spearheaded by scientists from two institutes under the Chinese Academy of Sciences—the Institute of Zoology and the China National Center for Bioinformation and Beijing Institute of Genomics, together with their collaborators from the West China Hospital of Sichuan University, has unveiled an unprecedented "proteomic blueprint" of human aging—a veritable molecular chronicle charting how proteins, the very cornerstone of life, transform across five decades in different tissues and bodily systems. Their results were published in *Cell* on July 25, 2025.

Across a 50-year Lifespan

The study, a colossal undertaking, involved a comprehensive proteomic and histological analysis of 516 samples meticulously collected from 13 different human tissues, spanning seven crucial bodily systems (cardiovascular, digestive, immune, endocrine, respiratory, integumentary, and musculoskeletal), plus blood, from individuals aged 14 to 68. Utilizing state-of-the-art mass spectrometry and sophisticated machine learning algorithms, the team charted the dynamic landscape of over 12,771 distinct proteins, providing the most detailed molecular atlas of human aging to date.

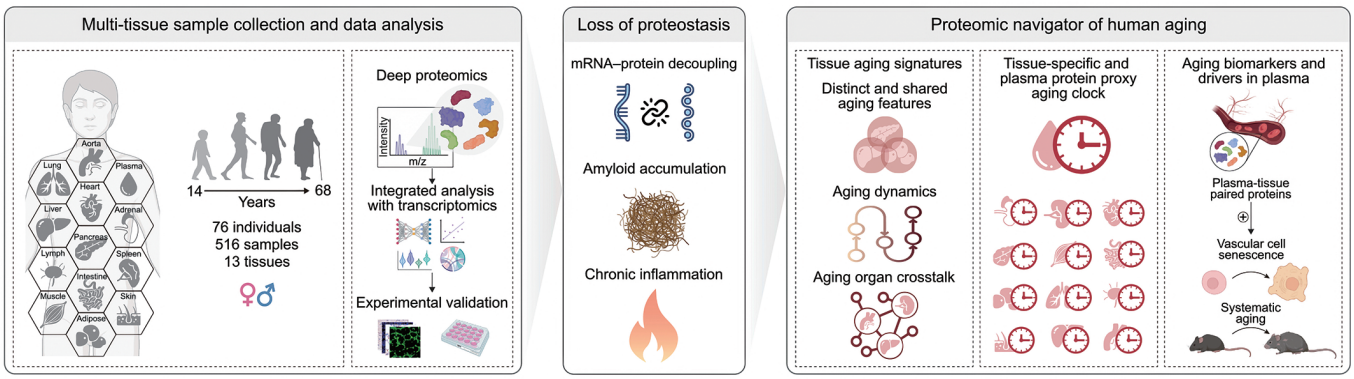
The Crumble of Protein Homeostasis

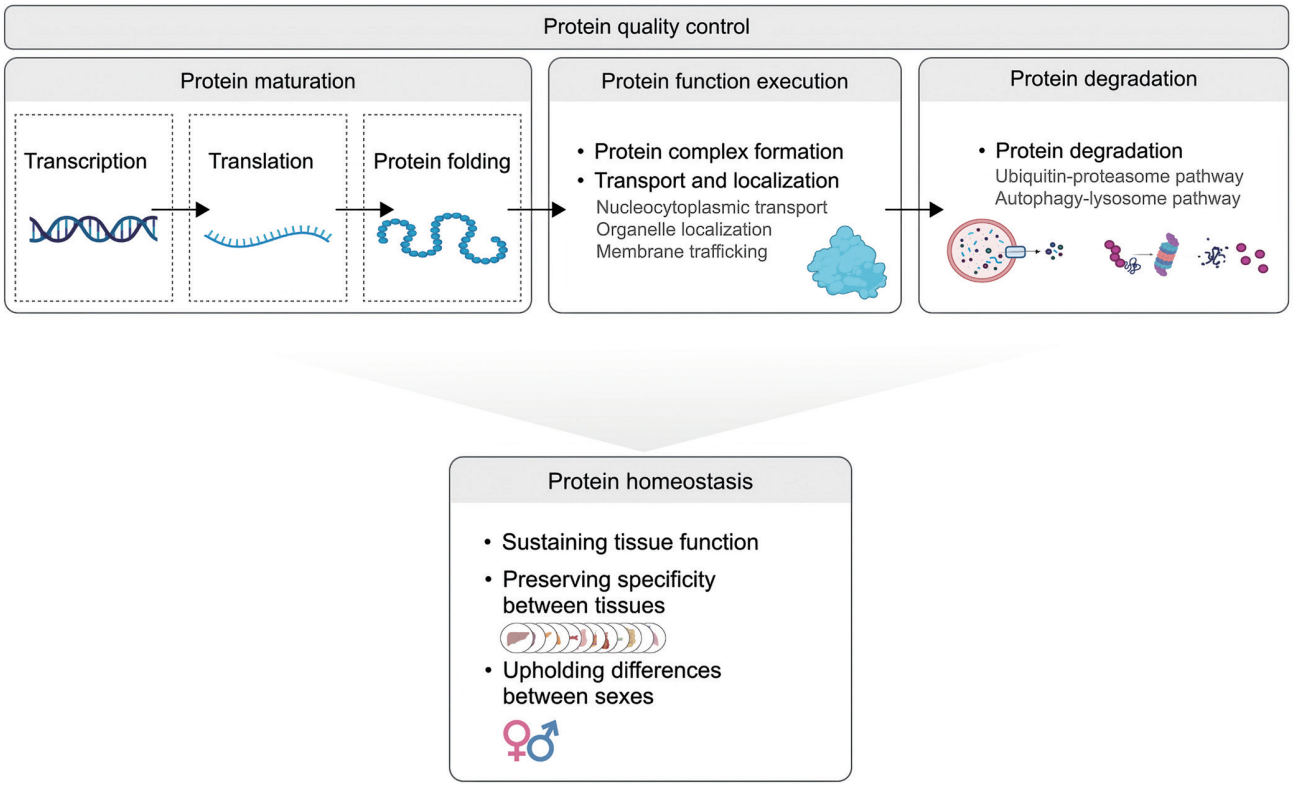
At the heart of their findings lies the pervasive phenomenon of "proteostasis loss"—a systemic breakdown in the delicate balance, or the so-called protein homeostasis that governs protein synthesis, folding, modification, transport, and degradation. Imagine the cell as a meticulously managed factory, with proteins as its products and machinery. In healthy, youthful cells, every step—from drafting the blueprints (mRNA) to assembling the final product (protein)—is tightly controlled. This research, however, reveals that with age, this precision falters. A widespread "transcriptome-proteome decoupling" emerges, meaning the genetic instructions (mRNA) are no longer accurately translated into the abundance of functional proteins.

"We observed transcriptome-proteome decoupling, indicating reduced central dogma-based information flow with age," wrote the authors. The decoupling is like the factory's design department and production floor are no longer communicating effectively. This "broken information flow" manifests across aging organs, leading to a cascade of problems.

Delving deeper, the researchers observed a universal decline

Study scheme. Proteomic, transcriptomic, and histological profiling of 516 samples from 13 tissues across 76 donors (age span >50 years) enabled building a multi-tissue aging atlas with tissue-specific aging clocks. (Graphic: Ding et al., 2025)





Scheme of protein homeostasis maintenance. Protein quality control occurs at transcription, translation, folding, modification, transport, localization, and function as complexes. Proteostasis ensures normal tissue function and specificity, and contributes to sex-based differences. (Adapted from Ding et al., 2025)

in the protein quality control system. Essential components—such as ribosomal proteins (involved in protein synthesis), molecular chaperones (aiding in protein folding), and proteasome subunits (responsible for protein degradation)—were found to be universally downregulated across most aged tissues. Simultaneously, a sinister accumulation of "pathological proteins" takes hold. Amyloid proteins, alongside immunoglobulins and complement components, build up in aging tissues, forming a pro-inflammatory network—the molecular bedrock of what the researchers termed as "inflammaging." Among these, Serum Amyloid P-component (SAP) emerged as a particularly ubiquitous culprit, universally upregulated across most aged tissues. In laboratory experiments, SAP was shown to directly impair young vascular endothelial cells, inducing hallmarks of aging and promoting inflammation, highlighting its active role in driving early aging.

Organs Are Aging at Different Paces

One of the study's most profound revelations came from the development of tissue-specific proteomic "aging clocks" for each of the 13 human tissues and organs. These clocks, based on age-associated protein changes, allowed scientists to quantitatively assess the unique aging trajectories of different organs, revealing a remarkable heterogeneity in how various parts of our body succumb to time's relentless tide. While many tissues generally experienced a significant increase in their aging rate around the age of 50—featuring with a veritable "molecular cascading storm" of differentially expressed proteins (DEPs)—the research pinpointed specific organs as early accelerators of this process.

Not Just Plumbing, But a Crucial "Senohub"

Remarkably, the study pinpointed the aorta—the body's main artery—as a "pioneer tissue" in aging. Its protein profile shifts early and continuously, starting around age 30, indicating that vascular changes may trigger body-wide aging. The adrenal gland also showed early changes, suggesting endocrine disruption may contribute to declining vitality.

However, the aorta's role goes beyond merely being an early indicator. The study proposes a powerful "vascular senohub" hypothesis (seno, short for senescence): the aging aorta doesn't just suffer the ravages of time; it actively broadcasts pro-aging signals throughout the body. As the primary senohub, blood vessels act as both highly sensitive detectors of aging-related factors from peripheral tissues and major producers of "senoproteins"—secretory senescence-promoting proteins—that amplify systemic aging signals.

The team identified Growth Arrest Specific 6 (GAS6) as a particularly potent senoprotein. This protein was found to be significantly elevated in both aged aortic tissue and the circulating plasma. In a series of compelling experiments, treating human aortic endothelial cells and vascular smooth muscle cells with recombinant GAS6 protein induced hallmark features of vascular senescence, including increased cellular aging markers, impaired function, and heightened inflammation. The implications for public health are profound. This suggests that a protein circulating in our blood, derived from our own aging arteries, could be actively accelerating the aging of other organs.

To confirm this systemic effect, researchers administered recombinant mouse GAS6 to middle-aged mice. The results were striking: GAS6-treated mice exhibited impaired physical performance, including reduced grip strength and compromised balancing ability. Histological analysis revealed accelerated aging across multiple organs, not just the vasculature, but also in the liver, spleen, lymph nodes, and adrenal glands—marked by increased cell cycle arrest, DNA damage, inflammation, and lipid accumulation.

This multi-dimensional evidence firmly supports the "aging diffusion" theory, where local aged tissues—like the aorta—drive a cascading wave of senescence in distant organs through specific secretory factors, shifting the paradigm of aging research from isolated cellular mechanisms to interconnected inter-organ communication networks. Other senoproteins, such as GPNMB, COMP, HTRA1, and IGFBP7, were also shown to induce vascular cell senescence, with GPNMB injections in mice replicating systemic accelerated aging phenotypes. Collectively, these findings reveal that senoproteins released by aging tissues propagate senescence signals, driving vascular and systemic degeneration.

Translational Potential

The translational potential of this research is immense. By identifying 211 "plasma-tissue paired DEPs"—proteins that change concordantly in both plasma and tissues—the study has laid the groundwork for developing non-invasive, blood-based biomarkers to predict organ aging. The team even developed a "plasma protein proxy tissue aging clock" that achieved comparable accuracy to clocks derived directly from tissue protein matrices, paving the way for simpler, less invasive aging assessments.

These discoveries also open new avenues for protein-targeted geroprotective interventions. Imagine senolytic vaccines designed to clear senescent cells by targeting specific aging-associated cell surface proteins, or neutralizing antibodies that block circulating senoproteins from spreading their harmful signals.

In summary, this work has provided scientists with a new lens through which to view aging—not as a simple, uniform decline, but as a dynamic, heterogeneous process driven by complex protein networks and inter-organ communication. By "cracking the protein code" of human aging, these researchers have illuminated key drivers and potential therapeutic targets, offering hope for developing interventions that could extend not just lifespan, but crucially, healthspan for older adults globally.

Reference

Ding, Y., Zuo, Y., Zhang, B., Fan, Y., Xu, G., Cheng, Z., . . . Liu, G. H. (2025). Comprehensive human proteome profiles across a 50-year lifespan reveal aging trajectories and signatures. *Cell*. doi:10.1016/j.cell.2025.06.047