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Highlight

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A comprehensive multi-organ proteomic atlas of human aging across 50 years

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Multi-organ map of aging by proteomics

Aging leads to a progressive decline in tissue function and structure across all organ systems, underlying the risk of various chronic diseases (Guo et al., 2022). Although studies in animals have shown that different organs have distinct aging rates, the molecular trajectories of aging across different human organs remain largely unexplored (Oh et al., 2023). In a recent landmark study, Ding and colleagues constructed the most comprehensive proteomic atlas of human aging, profiling over 12,771 proteins in 516 samples across 13 tissues from donors aged 14–68 (Ding et al., 2025). This extensive dataset of diverse organs, such as heart, lung, liver, spleen, muscle, intestine, skin, and blood vessels, provides an unprecedented "proteome blueprint" of the dynamic aging process of our organs over five decades (Fig. 1). Using state-of-the-art mass spectrometry, Ding et al. quantified thousands of proteins per tissue and paired this with transcriptomics data from the same sample. An interesting finding was a widespread dissociation between mRNA and protein expression during the aging process. This transcriptome-proteome decoupling phenomenon has also been identified by many studies in individual human organ (Khatir et al., 2023; Llewellyn et al., 2024; Wei et al., 2015). The decoupling identified in various human organ suggests that aged tissue starts to lose control over translating original genetic information into functional proteins. Notably, many proteins critical for fundamental tissue maintenance showed this decoupling in aged tissues (e.g., proteins regulating B-cell activation in the spleen), underscoring that the proteomic level of aging should be directly examined, rather than only at the transcriptomics level. This finding aligns with the decline in proteostasis observed during aging, including decreased levels of protein synthesis machinery (ribosomal proteins and tRNA synthetases).

This study revealed that the breakdown of proteostasis and the resulting impaired protein quality control, decoupling of mRNA-protein, as well as accumulation of protein aggregates, are all recognized hallmarks of aging (Hipp et al., 2019). Notably, they observed the accumulation of misfolded, aggregated proteins, including amyloid proteins, along with upregulated immune proteins like immunoglobulins IGLC, IGH, and complement factors in aged tissues. This points to the "amyloidosis-inflammaging" axis, where aberrant protein aggregates trigger chronic inflammation (Abbatecola et al., 2024; Bart et al., 2025). For example, serum amyloid P-component, a canonical amyloid factor, was found to be elevated in multiple aged tissues and may particularly contribute to vascular aging, as validated in human aortic endothelial cells. These findings suggest protein aggregates like amyloids are not merely byproducts of aging but also serve as universal contributors to various organ dysfunctions.

Proteomic aging clocks across organs reveal vascular aging as a "senohub"

One major advancement from this work is the development of new proteomic aging clocks. Building on the previous plasma proteomic aging clocks (Argentieri et al., 2024; Kuo et al., 2024; Oh et al., 2023), and employing elastic-net regression models on proteomic data from 13 human organs, they identified panels of proteins that could predict the chronological age of each organ with high accuracy (correlation coefficients of 0.74–0.95 between predicted and actual age). These proteomic clocks add to the developing biological aging clock types since Horvath's

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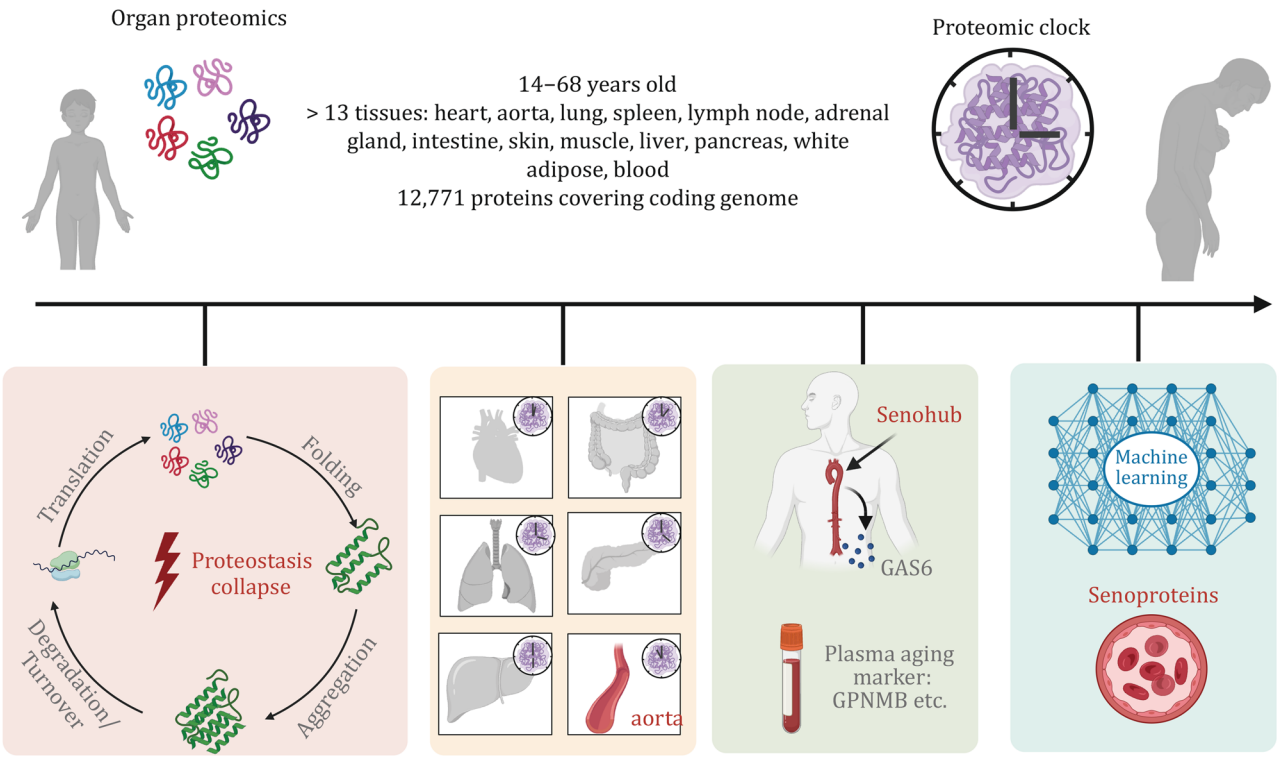

Figure 1. Comprehensive human multi-organ proteomic atlas by Ding et al., 2025 revealing multifaceted aging processes, including the collapse of proteostasis, early-onset aging in the aorta functioning as a central "senohub" influencing other organs, and circulating "senoproteins" as potential drivers and therapeutic targets.

first epigenetic clock (Horvath, 2013). Intriguingly, most organ clocks showed an acceleration of aging around age 50, where aging-related proteomics changes surged.

Strikingly, the aortic vessels stood out as aging earlier and more dramatically than other organs, with significant changes detectable as early as the 30s and compounded at the 50s. This finding positions the vasculature as a potential "senohub"—an organ highly sensitive to aging stress that in turn drives systemic aging processes via circulating proteins. Circulating factors in vessels that can influence aging are supported by heterochronic parabiosis studies, where joining the blood circulation of a young and old animal rejuvenated the older one's tissues (Conboy et al., 2005). Consistently, network analysis of inter-tissue communication found that the crosstalk between organs via secreted ligand-receptor pairs intensifies with age, especially between vascular and immune tissues. In particular, inflammatory chemokines (CXCL12/14) showed increased inter-organ interactions in older individuals, whereas regenerative signaling (such as Ephrin-Eph receptor pathway) diminished with aging. By identifying the aorta as an early-aging organ, the proteomic atlas highlights the need to protect the vasculature in mid-life as a strategy to attenuate overall aging.

Circulating "senoproteins" as drivers and therapeutic targets

By cross-comparing changes in organ tissues with blood plasma proteins, the authors pinpointed a set of proteins that were upregulated during aging in both tissues and blood. These proteins, named "senoproteins" in this study, could serve as both new blood biomarkers of organ aging and contributors that promote aging. For instance, GAS6 was upregulated in aged aortas and plasma from older adults. Moreover, exposing cultured human endothelial cells and smooth muscle cells to GAS6 caused the cells to exhibit classic hallmarks of senescence and functional decline. In vivo injection of GAS6 protein accelerates aging phenotypes in mice: accumulated fat in the liver, loss of youthful heterochromatin marks in immune cells, and structural disorganization and inflammation in spleens.

By cross-referencing plasma and tissue proteomes from 13 organs, the authors further uncovered 211 age-associated proteins whose levels shift in blood and at least 1 tissue in the same direction, with the aorta, adrenal gland, and spleen contributing the most changes. Upregulated markers such as GPNMB, COMP, CHI3L1, NOTCH3, ITLN1, EFEMP1, HTRA1, and LTBP2 accumulate markedly in aged plasma, as validated by ELISA and histology, whereas proteins like HARS1, CCT5/7, and PSMB1 show consistent decline. Machine-learning models built on these plasma signatures accurately recapitulate organ-specific proteomic clocks, enabling non-invasive blood markers of tissue ageing. Functionally, seven of the rising factors (GPNMB, COMP, HTRA1, SLPI, IGFBP7, NEGR1, NOTCH3) act as senoproteins similar to GAS6, accelerating vascular damage, inflammation and systemic frailty, directly contributing to organ aging.

Conclusions and future directions

This comprehensive proteomic atlas of human aging is a tour de force that significantly deepens our understanding of how aging progresses across the body at the protein level. It demonstrates that aging is a multi-faceted process—shared hallmarks like proteostasis collapse and inflammation emerge nearly everywhere. Emerging scalable and high-throughput RNA-linked CRISPR screening technologies hold great promise for elucidating the mechanistic role of RNA metabolic processes in proteostasis collapse and identifying causal regulators as potential therapeutic targets (Nugent et al., 2025). The finding that blood vessels age faster than other tissues and can broadcast aging signals to other organs positions them as a hub. Equally important, the study identified pan-tissue proteomic clocks, which play an invaluable role in quantifying biological aging at the tissue level. This study builds upon a series of previous work from the same team, consistently identifying inflammaging axis, such as HERV-K reactivation triggering NF-κB senescence and ectopic IgG amplification aging (Liu et al., 2023; Ma et al., 2024). Moreover, they have discovered countermeasures for aging—betaine to block TBK1/SASP and FOXO3-engineered senescence-resistant cells (Geng et al., 2025; Lei et al., 2025). This proteomic approach further revealed dozens of novel aging signals, particularly highlighting the potential of neutralizing vascular senoproteins, restoring proteostasis, and thus decelerating whole-body aging in human.

Conflicts of interest

The authors declare that they have no competing interests.

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Data availability

Schematic figure was created with BioRender.com.

Ethical approval

Not applicable.

Consent to participate

The authors declare their agreement to participate.

Consent for publication

The authors declare their agreement to publish.

Code availability

Not applicable.

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