



Integrative cross-tissue analysis unveils complement-immunoglobulin augmentation and dysbiosis-related fatty acid metabolic remodeling during mammalian aging

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Introduction

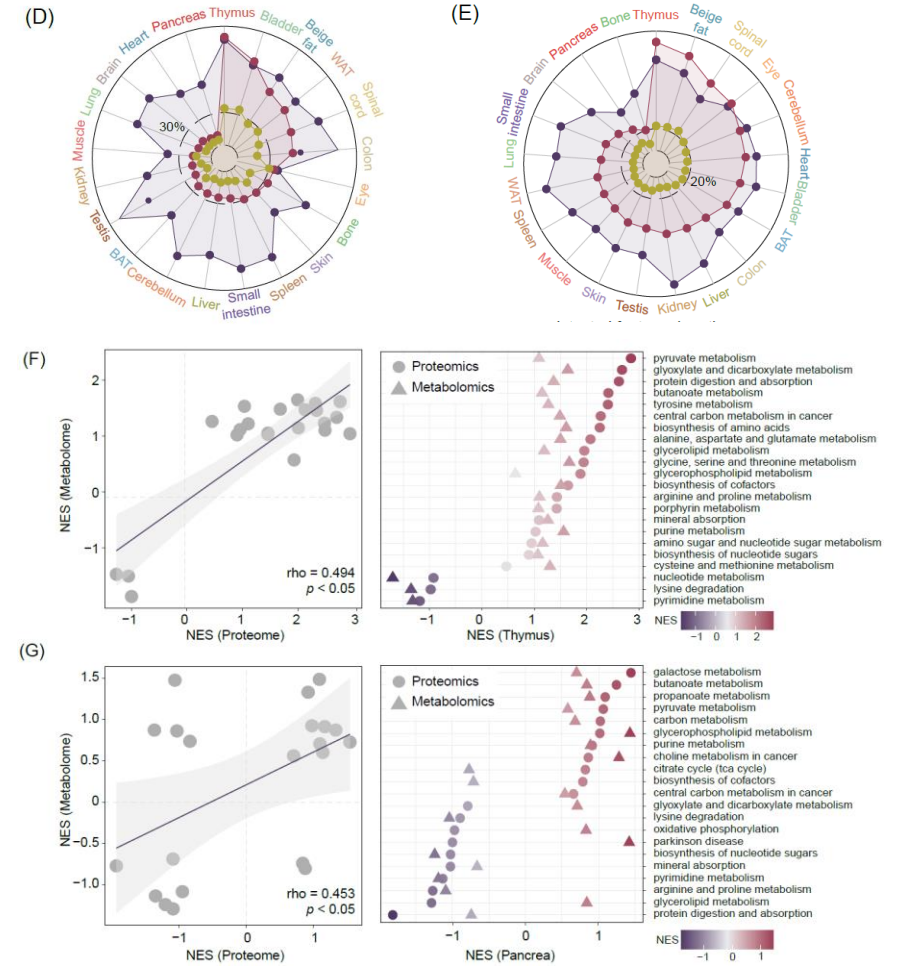
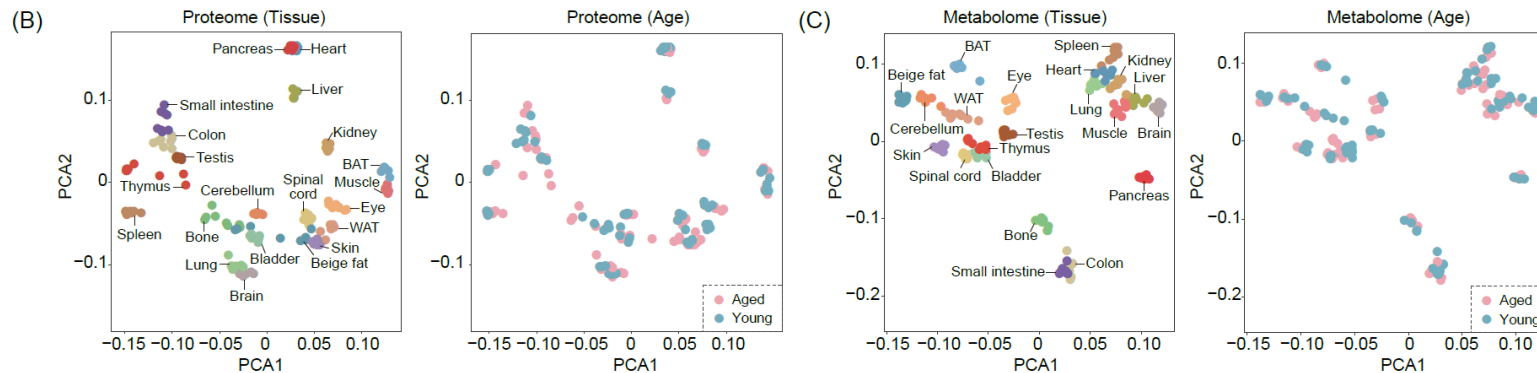
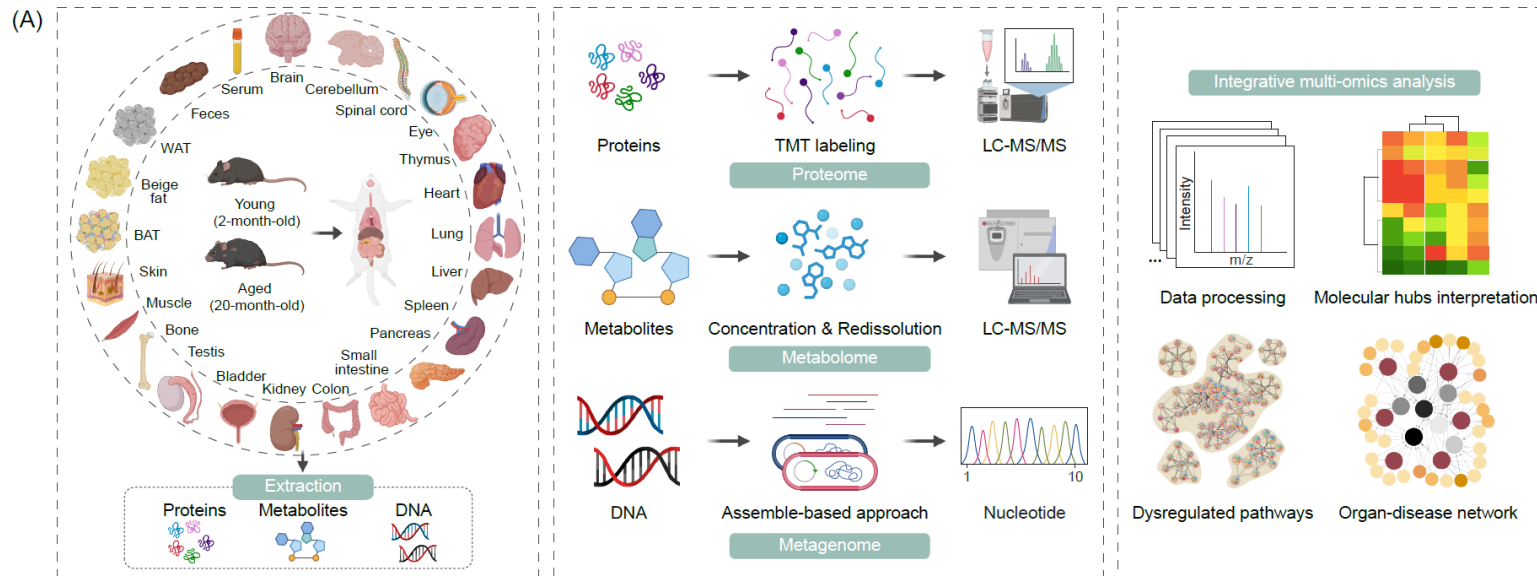
○ Multi-organ dysfunction in aging stems from metabolic dysregulation and chronic inflammation through inter-organ networks. Unraveling these interactions requires cross-tissue analyses to identify therapeutic targets.

○ While omics technologies have mapped aging-related molecular changes, plasma-tissue proteome correlations remain elusive. Defining their interplay and proteome-metabolome hubs is crucial for understanding aging mechanisms.

○ The gut microbiota regulates core aging processes including chronic inflammation and metabolic reprogramming. Our multi-omics approach reveals complement-immunoglobulin activation and microbiota-derived lipid dysregulation as pivotal aging drivers.

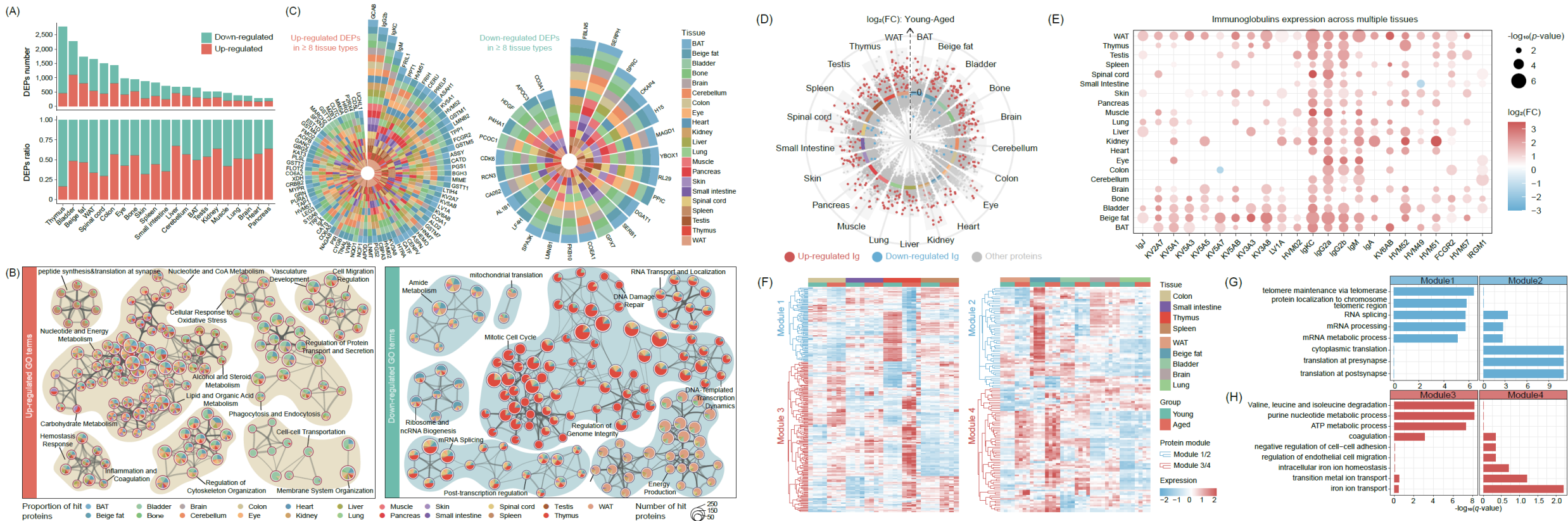


Multi-Tissue Aging Proteome-Metabolome Atlas



We systematically analyzed the proteome and metabolome of 21 solid organs from 2-month-old and 20-month-old male mice, establishing a comprehensive protein-metabolic atlas of multi-tissue aging. The results revealed marked differences in organ-specific aging susceptibility, with the thymus and pancreas showing the most pronounced changes.

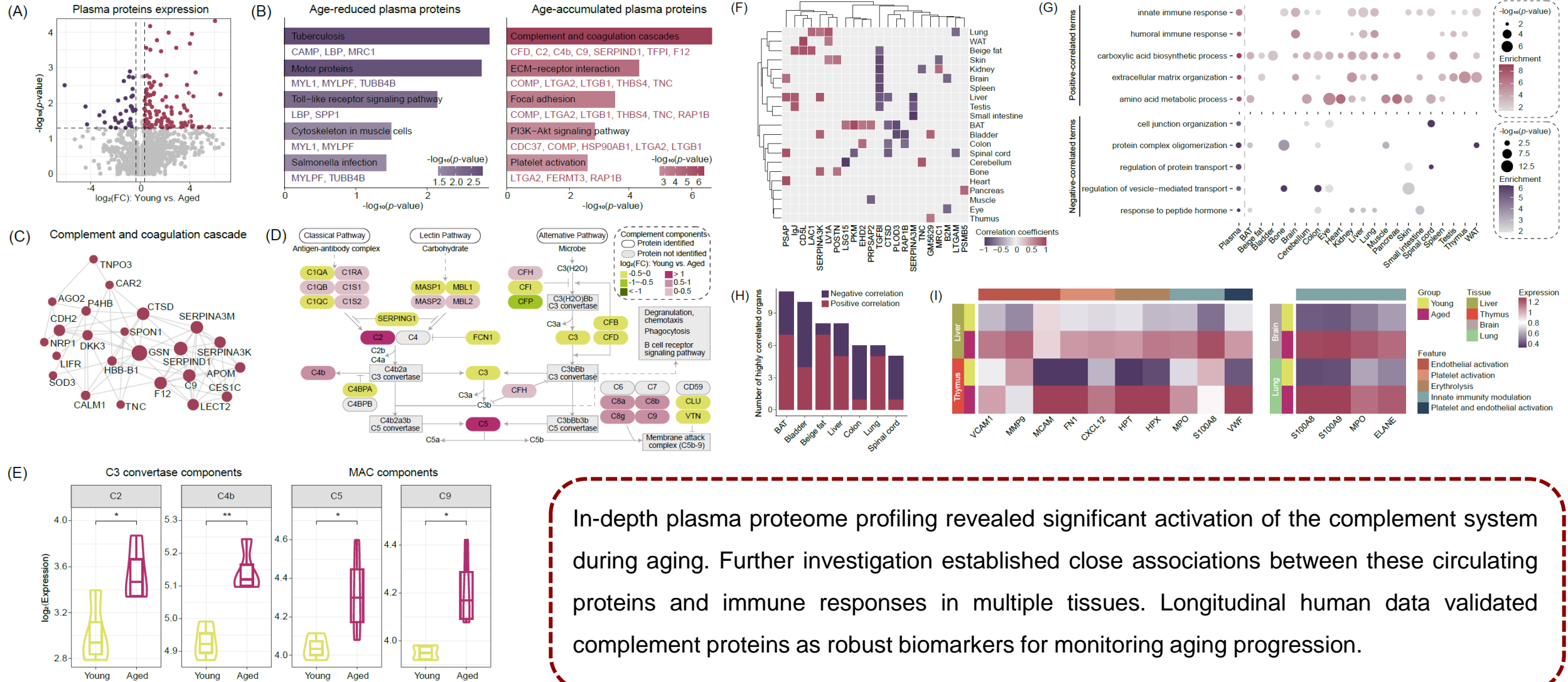
Tissue-Shared Aging Protein Signatures



Using differential protein analysis and functional enrichment approaches, we systematically characterized aging patterns across tissues. The study found widespread upregulation of immunoglobulins in multiple aged tissues, indicating chronic inflammation as a hallmark of aging. Protein co-expression network analysis for the first time demonstrated inter-organ coordinated aging and identified two distinct organ clusters sharing similar aging patterns.

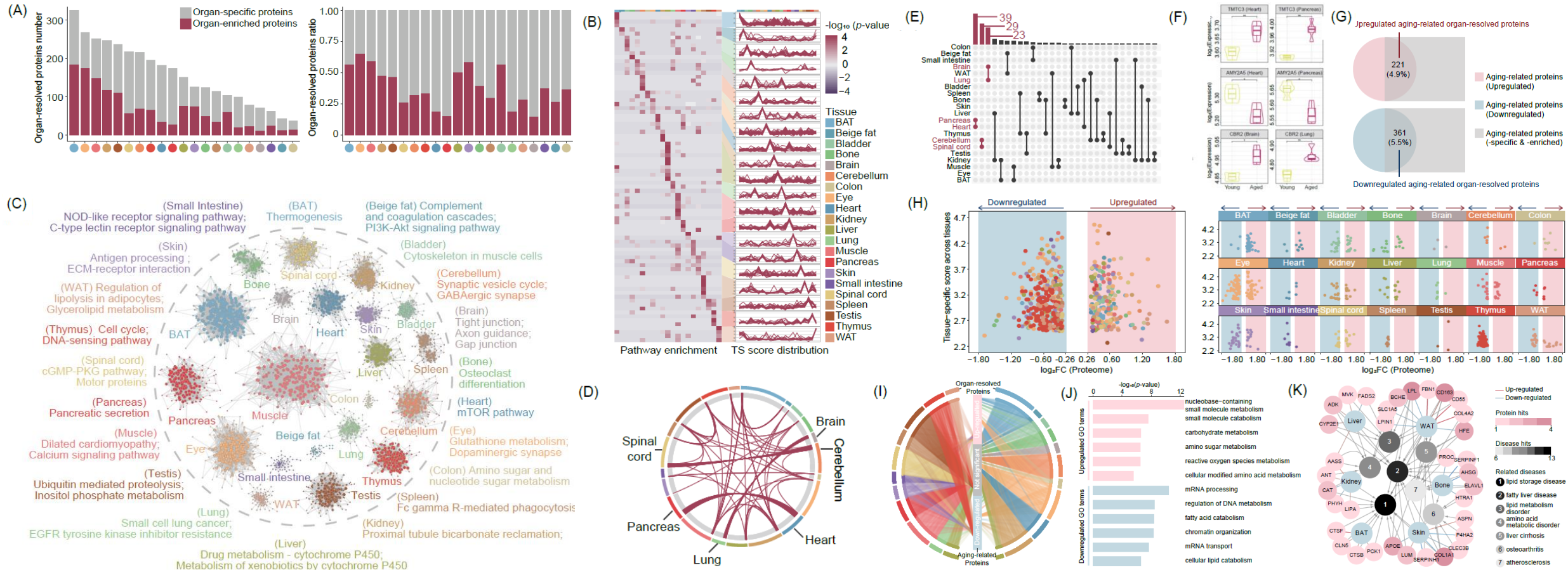


Plasma-Tissue Inflammatory Communication



In-depth plasma proteome profiling revealed significant activation of the complement system during aging. Further investigation established close associations between these circulating proteins and immune responses in multiple tissues. Longitudinal human data validated complement proteins as robust biomarkers for monitoring aging progression.

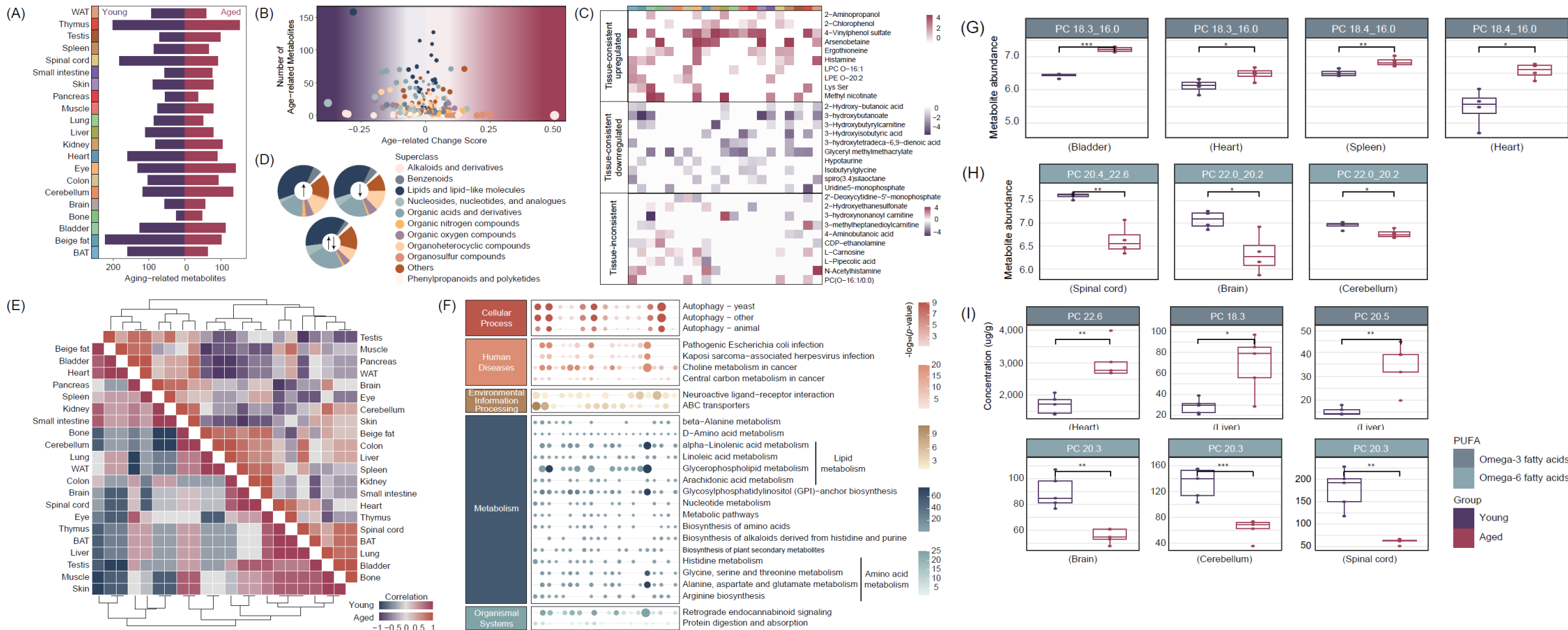
Organ-Specific Aging and Lipid Metabolism Dysregulation



We developed a novel tissue-specific scoring system to precisely identify organ-specific proteins. Notably, we discovered shared aging signature molecules between organ pairs such as heart-pancreas and brain-lung, providing critical insights into organ-specific aging mechanisms. Our analysis revealed a global downregulation of lipid metabolism pathways (e.g., fatty acid β -oxidation) during aging, with liver and adipose tissue-specific proteins showing significant associations with metabolic disorders including fatty liver disease and liver cirrhosis.



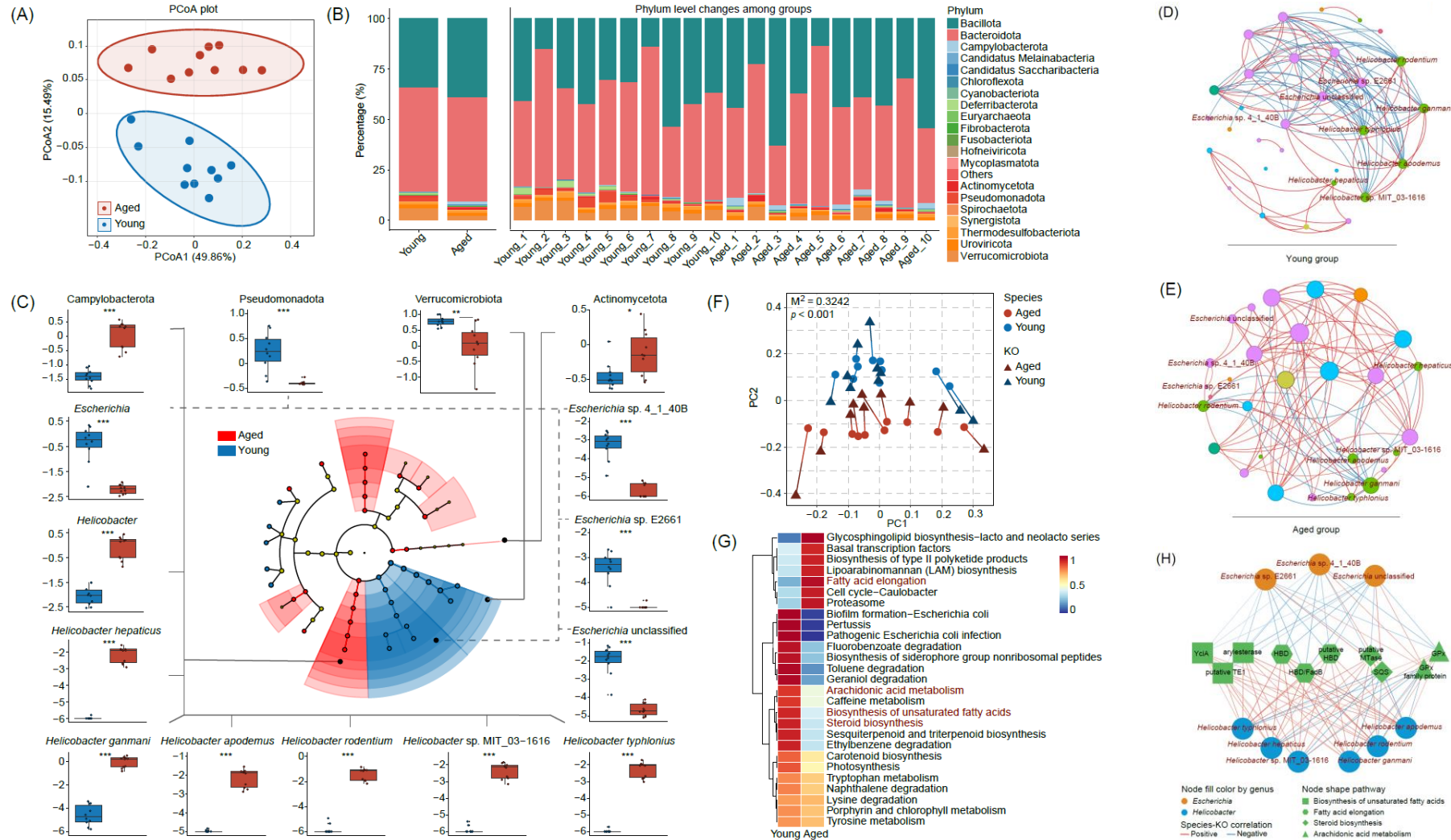
Cross-Tissue Metabolic Reprogramming



Comprehensive metabolomic profiling uncovered tissue-specific metabolic signatures. Lipid metabolism pathways exhibited the most significant age-related alterations, particularly characteristic redistribution of ω -3 and ω -6 fatty acids across tissues that may functionally impact multiple organs.



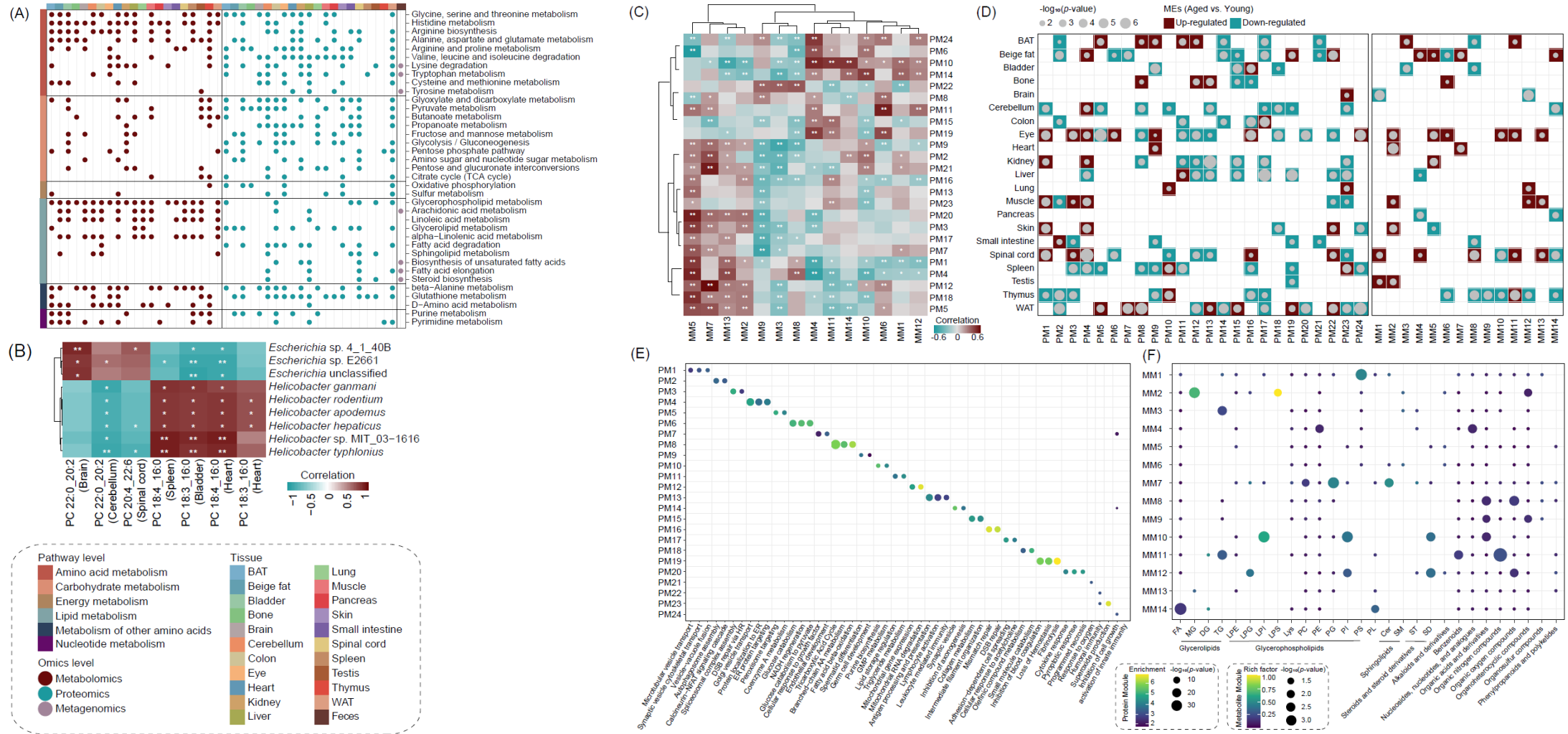
Gut Microbiota-Host Metabolic Axis Dysregulation



Metagenomic analysis demonstrated substantial compositional changes in aged mouse gut microbiota, particularly *Escherichia* and *Helicobacter* species. Functional analyses linked these changes to host lipid metabolism dysregulation, suggesting microbiota dysbiosis as a potential driver of metabolic aging.



Integrated Multi-Omics Hub Network



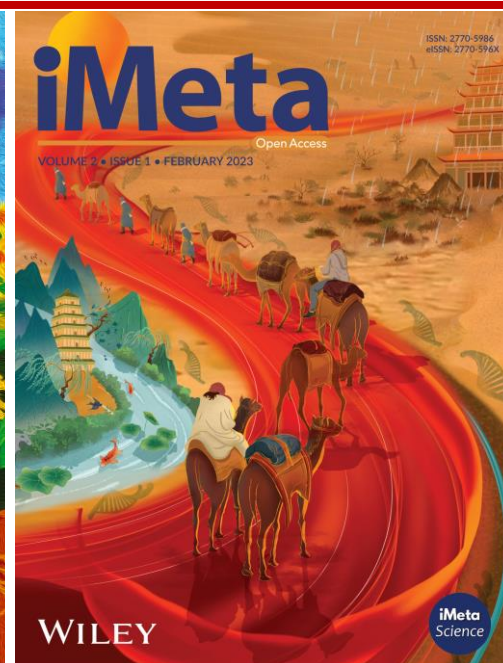
By integrating proteomic, metabolomic and microbiota data, we constructed a cross-tissue aging molecular network. Chronic inflammation activation and microbiota-driven lipid metabolism dysregulation emerged as key nodes in multi-organ coordinated aging, offering novel perspectives for developing aging intervention strategies.



Summary




- ❑ Integrated multi-omics analysis systematically revealed both conserved molecular signatures across tissues and organ-specific regulatory patterns during aging in mice.
- ❑ Aberrant immunoglobulin accumulation in parenchymal tissues synergized with overactivated circulating complement system to collectively drive the progression of chronic systemic inflammation.
- ❑ Aging-related tissue protein dysfunction and fatty acid metabolic pathway disruption constitute critical molecular underpinnings of lipid metabolism disorder-associated diseases.
- ❑ Our study elucidated significant associations between specific gut microbiota dysbiosis (Escherichia/Helicobacter) and host polyunsaturated fatty acid metabolic dysregulation.


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