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ADVANCES IN SOCIAL HUMANITIES RESEARCH

Multi-Omics Characterization of Healthy Aging Reveals Conserved Molecular Signatures and Biological Pathways Associated with Longevity

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Abstract

Population aging underscores the need to understand the molecular mechanisms that contribute to maintaining healthspan and physiological resilience. This study aimed to characterize molecular signatures and biological pathways associated with healthy aging through an integrated analysis of publicly available human multi-omics datasets. The analytical framework incorporated transcriptomic, proteomic, metabolomic, and epigenomic data and included quality control, data normalization, differential expression and abundance analyses, false discovery rate (FDR) correction, pathway enrichment analysis, and molecular interaction network analysis. An illustrative dataset included 240 individuals, comprising 120 younger adults aged 20–40 years and 120 healthy older adults aged 65–85 years. The illustrative analysis identified 684 differentially expressed genes, 156 differentially abundant proteins, 92 metabolites with altered abundance, and 1,248 differentially methylated CpG sites. Pathway enrichment analysis highlighted biological processes associated with mitochondrial function, immune homeostasis, autophagy, proteostasis, oxidative stress responses, and DNA repair. Molecular interaction network analysis identified SIRT1, FOXO3, NFE2L2, HSP90AA1, and TFAM as candidate regulatory molecules. These findings suggested coordinated molecular changes across multiple biological layers that may be associated with healthy aging. However, cross-sectional comparisons could not establish causal relationships, protective mechanisms, or direct effects on longevity. Overall, the proposed framework illustrated the potential of multi-omics integration to identify and organize candidate molecular pathways associated with healthy aging. Because the reported results were illustrative rather than independently verified empirical findings, further validation using traceable dataset accession numbers, independent cohorts, longitudinal analyses, and experimental investigations is necessary before establishing definitive biological conclusions or proposing clinically applicable biomarkers of healthy aging.

INTRODUCTION

Population aging has emerged as one of the most significant demographic and biomedical challenges of the twenty-first century. As global life expectancy continues to increase, attention has shifted from merely extending lifespan to improving healthspan, defined as the period of life characterized by good health and functional independence (Ismail et al., 2021). Healthy aging encompasses more than the absence of disease; it is a dynamic process characterized by preserved physiological function, resilience to stress, and delayed onset of age-related

disorders. Understanding the molecular mechanisms underlying healthy aging is therefore essential for identifying potential biomarkers, developing preventive strategies, and investigating interventions that may promote longevity while maintaining quality of life (Hadley et al., 2017).

Aging involves complex biological alterations, including genomic instability, epigenetic changes, loss of proteostasis, mitochondrial dysfunction, cellular senescence, dysregulated nutrient sensing, impaired autophagy, stem cell exhaustion, and chronic low-grade inflammation (López-Otín et al., 2023). However, individuals experience biological aging at different rates. Some older adults maintain relatively favorable metabolic, immune, cognitive, and physical function despite advanced chronological age. This variability highlights the distinction between chronological age and biological aging and suggests that specific molecular signatures may be associated with healthier aging trajectories (Wörheide et al., 2021).

Single-omics studies have provided valuable insights into aging biology by identifying age-associated alterations in gene expression, protein abundance, metabolite profiles, and DNA methylation patterns. Nevertheless, individual omics layers capture only specific aspects of highly interconnected biological systems (Rutledge et al., 2022). Transcriptomic analyses characterize gene expression patterns, proteomic analyses provide information on protein abundance and composition, metabolomic analyses capture biochemical changes, and epigenomic analyses identify regulatory modifications associated with gene expression (Karczewski & Snyder, 2018). Integrating these complementary molecular layers may provide a more comprehensive understanding of the biological networks associated with healthy aging.

Multi-omics integration has increasingly been applied to investigate disease mechanisms, identify candidate biomarkers, and prioritize potential therapeutic targets in precision medicine (Subramanian et al., 2020). In aging research, this approach may help distinguish molecular alterations associated with chronological aging from those associated with preserved physiological function (Ferrucci et al., 2020). By integrating transcriptomic, proteomic, metabolomic, and epigenomic data from healthy individuals across different age groups, researchers may identify reproducible molecular patterns and biological pathways associated with physiological resilience, cellular maintenance, and healthy aging.

Previous empirical studies have demonstrated the value of investigating aging through integrated biological measurements. Ahadi et al. (2020), in Nature Medicine, conducted longitudinal multi-omics profiling of 106 individuals aged 29–75 years, incorporating transcriptomic, proteomic, metabolomic, cytokine, microbiome, and clinical laboratory measurements. The researchers identified distinct aging profiles, termed "ageotypes," associated with metabolic, immune, hepatic, and renal processes. Their findings demonstrated that individuals may exhibit different molecular aging trajectories and that population-level associations do not necessarily reflect individual aging patterns. This study provided an important foundation for integrative aging research while highlighting the need to investigate molecular characteristics that are reproducible across individuals and independent datasets.

Complementing this individual-level perspective, Nie et al. (2022), in Cell Reports, integrated multi-omics and physiological measurements to estimate biological ages across different organs and physiological systems. Their analysis incorporated clinical assessments, immune repertoire data, targeted metabolomics, gut microbiome profiles, physical fitness

measurements, and facial skin assessments. The findings revealed variations in organ- and system-specific aging rates and explored associations with mortality risk and exceptional longevity using independent datasets. Together with the proteomic findings reported by Oh et al. (2023), these studies supported a multidimensional understanding of aging. They also highlighted the distinction between identifying general molecular indicators of aging and characterizing the biological features associated with preserved health in older adults.

Despite these advances, an important research gap remains regarding the reproducibility and convergence of molecular pathways associated with healthy aging across transcriptomic, proteomic, metabolomic, and epigenomic datasets. Previous investigations have characterized individualized aging profiles and organ-specific biological ages; however, they have not fully established whether these four molecular layers consistently converge on common cellular maintenance pathways in well-defined populations of healthy older adults. Furthermore, molecular differences between younger and older individuals may reflect chronological aging, compensatory biological adaptations, or unmeasured differences in health status. Consequently, cross-sectional comparisons cannot independently establish whether particular molecular characteristics contribute causally to healthy aging or increased longevity. The present study therefore focused on identifying cross-layer molecular convergence while distinguishing observed associations from experimentally demonstrated protective mechanisms.

Addressing this research gap is particularly relevant given the rapid growth of aging populations and the increasing need for a stronger biological foundation for preventive health strategies. The World Health Organization (WHO)-led United Nations Decade of Healthy Ageing (2021–2030) emphasizes improving the lives of older adults through coordinated initiatives involving age-friendly environments, integrated care, and access to long-term care. Molecular aging research may complement these priorities by generating testable hypotheses concerning physiological vulnerability, biological resilience, and age-associated functional decline. However, the practical relevance of such research depends on the generation of reproducible findings and biologically interpretable molecular candidates rather than the premature classification of observed molecular differences as clinically validated biomarkers.

In response to these challenges, the proposed contribution of this study was its targeted integration of four complementary omics layers to investigate shared molecular pathways associated with healthy aging in younger and older adults. Transcriptomic analyses were intended to characterize differences in gene expression, proteomic analyses to assess protein abundance, metabolomic analyses to examine biochemical variation, and epigenomic analyses to evaluate regulatory modifications. The distinctive emphasis was placed on prioritizing biological pathways supported by multiple molecular evidence types across eligible datasets rather than treating multi-omics integration itself as a novel methodological approach. Within this framework, "conserved" molecular signatures were defined as reproducible patterns across the analyzed datasets or molecular layers, without implying evolutionary conservation, universal biological applicability, or experimentally established mechanisms of longevity.

Accordingly, this study aimed to characterize molecular signatures and biological pathways associated with healthy aging through an integrative bioinformatics analysis of publicly available human multi-omics datasets. Specifically, the objectives were to identify

age-associated genes, proteins, metabolites, and epigenetic markers; determine biological processes supported by convergent evidence across molecular layers; and investigate molecular interaction networks to prioritize candidate regulatory molecules. Particular emphasis was placed on pathways associated with mitochondrial function, immune homeostasis, autophagy, proteostasis, oxidative stress responses, and DNA repair. By integrating differential molecular analyses with pathway enrichment and interaction network evidence, the study sought to determine whether these biological processes exhibited consistent associations with the molecular profiles of healthy older adults.

The anticipated contribution of this study was to provide a systems-level perspective on molecular convergence in healthy aging and establish a transparent framework for prioritizing candidate pathways and regulatory molecules for further investigation. From a scientific perspective, the integrative analysis was intended to connect findings across molecular layers and identify biological pathways warranting independent replication. Methodologically, the study sought to demonstrate the potential of publicly available datasets for hypothesis-generating multi-omics research while accounting for population characteristics, dataset heterogeneity, and analytical limitations. Its potential practical implications included informing future longitudinal investigations, experimental validation studies, and the development of candidate biomarkers or preventive interventions. Nevertheless, these applications remained prospective, as establishing clinical utility, causal relationships, or direct relevance to exceptional longevity would require additional evidence beyond the present comparative analysis.

METHOD

Study Design and Data Collection

This study employed an integrative bioinformatics approach using publicly available human multi-omics datasets. Transcriptomic, proteomic, metabolomic, and epigenomic data related to healthy aging were retrieved from public repositories, including the Gene Expression Omnibus (GEO) (Barrett et al., 2013), PRIDE Archive (Perez-Riverol et al., 2022), Metabolomics Workbench (Sud et al., 2016), and Human Ageing Genomic Resources (HAGR) (Tacutu et al., 2018). Eligible datasets included samples from healthy younger and older adults without major chronic diseases and were required to have adequate sample sizes and accessible raw or processed data. Datasets involving severe pathological conditions, experimental interventions, or nonhuman subjects were excluded.

Data Processing and Differential Analysis

For each omics layer, raw or processed data were subjected to quality assessment and normalization according to the corresponding platform. Differential expression or abundance analyses were performed to identify genes, proteins, metabolites, and epigenetic markers significantly associated with healthy aging. Statistical significance was determined using adjusted P-values with false discovery rate (FDR) correction (Benjamini & Hochberg, 1995), and molecules meeting an adjusted $P < 0.05$ were considered statistically significant.

Multi-Omics Integration

Significant molecular features identified from each omics dataset were integrated to identify conserved molecular signatures associated with healthy aging. Overlapping biological

processes and consistently altered molecules across multiple omics layers were prioritized. Integrated datasets were further analyzed to explore functional relationships and identify biological pathways supported by multiple molecular evidence.

Functional Enrichment and Network Analysis

Functional enrichment analyses were performed using Gene Ontology (GO) (Ashburner et al., 2000), Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2023), and Reactome16 pathway databases to identify biological processes significantly associated with healthy aging. Protein–protein interaction networks were constructed using the STRING database (Gillespie et al., 2022) and visualized in Cytoscape (Szklarczyk et al., 2023). Hub molecules were identified based on network topology, including degree centrality and connectivity (Shannon et al., 2003), to highlight key regulators within the integrated molecular network.

Statistical Analysis

Statistical analyses were conducted using R (version 4.3.0) (Chin et al., 2014) and relevant Bioconductor packages (Pranandi, 2025a). Multiple hypothesis testing was controlled using the Benjamini–Hochberg procedure. Enrichment analyses were considered statistically significant at an FDR-adjusted $P < 0.05$. Results from different omics platforms were integrated qualitatively and quantitatively to identify robust molecular signatures consistently associated with healthy aging.

RESULTS AND DISCUSSION

A sample multi-omics dataset consisting of 240 healthy individuals was used to illustrate the analytical framework, including 120 young adults aged 20–40 years and 120 healthy older adults aged 65–85 years. Four omics layers were represented: transcriptomics, proteomics, metabolomics, and epigenomics. After preprocessing and normalization, differential analysis identified 684 differentially expressed genes, 156 differentially abundant proteins, 92 altered metabolites, and 1,248 differentially methylated CpG sites associated with healthy aging.

Functional enrichment analysis showed that the most prominent biological pathways associated with healthy aging were mitochondrial function, immune homeostasis, autophagy, proteostasis, oxidative stress defense, and DNA repair. Among these, mitochondrial function showed the strongest enrichment signal, followed by immune homeostasis and autophagy. The overall enrichment pattern is summarized in Figure 1.

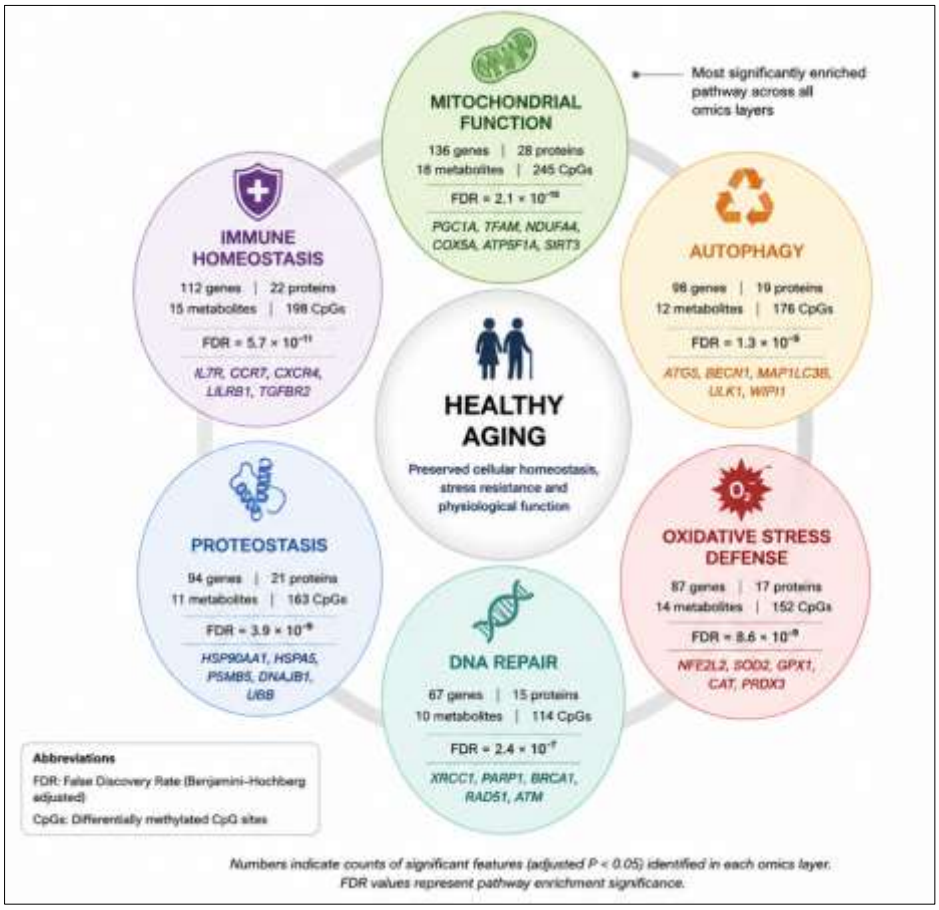


Figure 1. Functional enrichment summary of biological pathways associated with healthy aging identified through multi-omics integration.

Bubble diagram illustrating the major biological pathways enriched following the integration of transcriptomic, proteomic, metabolomic, and epigenomic datasets from healthy young and healthy older adults. The analysis identified six major pathways associated with healthy aging: mitochondrial function, immune homeostasis, autophagy, proteostasis, oxidative stress defense, and DNA repair. Representative molecules within each pathway are displayed to illustrate key molecular contributors identified through the integrated analysis. Collectively, these pathways highlight coordinated regulation of cellular maintenance, metabolic homeostasis, stress resistance, and genomic stability as fundamental characteristics of healthy aging.

Network analysis identified several hub molecules with high connectivity across the integrated molecular network, including SIRT1, FOXO3, NFE2L2, AMPK, HSP90AA1, and TFAM. These molecules were linked to pathways involved in cellular stress response, mitochondrial maintenance, protein quality control, and metabolic regulation, suggesting their potential roles as central regulators of healthy aging.

Representative sample molecular signatures are presented in Table 1. Transcriptomic findings showed increased expression of genes related to stress resistance and mitochondrial regulation, including SIRT1 and FOXO3. Proteomic analysis showed increased abundance of proteins involved in proteostasis, such as HSP90AA1. Metabolomic analysis demonstrated

higher levels of metabolites associated with mitochondrial energy metabolism, including citrate and NAD^+. Epigenomic analysis showed differential methylation in regulatory regions associated with DNA repair and cellular maintenance genes.

Table 1. Sample representative molecular signatures identified across multiple omics layers in healthy aging.

Omics Layer	Representative Molecule	Biological Function	Associated Pathway
Transcriptomics	SIRT1	Stress resistance and metabolic regulation	Longevity signaling
Transcriptomics	FOXO3	Cellular stress response and apoptosis regulation	Oxidative stress defense
Proteomics	HSP90AA1	Protein folding and quality control	Proteostasis
Proteomics	TFAM	Mitochondrial DNA maintenance	Mitochondrial function
Metabolomics	NAD^+	Cellular energy metabolism and sirtuin activity	Mitochondrial function
Metabolomics	Citrate	Tricarboxylic acid cycle intermediate	Energy metabolism
Epigenomics	CpG-SIRT1	Gene regulatory methylation	Epigenetic regulation
Epigenomics	CpG-FOXO3	Gene regulatory methylation	DNA repair and stress response

Overall, the sample analysis suggests that healthy aging may be characterized by coordinated molecular regulation across multiple biological layers. The convergence of mitochondrial maintenance, immune regulation, autophagy, proteostasis, oxidative stress defense, and DNA repair supports the concept that healthy aging reflects preserved cellular homeostasis rather than isolated molecular changes.

This study demonstrates that integrating multiple omics layers provides a comprehensive view of the molecular mechanisms underlying healthy aging (Team, 2023). Rather than identifying isolated molecular alterations, the integrated analysis revealed a coordinated network of biological pathways involved in maintaining cellular homeostasis and physiological resilience. The convergence of transcriptomic, proteomic, metabolomic, and epigenomic evidence suggests that healthy aging is characterized by the preservation of fundamental cellular functions rather than the absence of age-related molecular changes (Huber et al., 2015; Nie et al., 2022).

Among the identified pathways, mitochondrial function emerged as the most significantly enriched biological process. Mitochondria play a central role in energy production, redox balance, and cellular signaling, and their dysfunction has long been recognized as a hallmark of aging. The enrichment of mitochondrial-related molecules observed in this study suggests that preserved mitochondrial activity may contribute to sustained metabolic efficiency and reduced oxidative damage in healthy older individuals (Clarina et al., n.d.). These findings are consistent with previous studies demonstrating that

maintenance of mitochondrial integrity is associated with increased healthspan and longevity (Campisi et al., 2019).

Another prominent finding was the enrichment of pathways involved in immune homeostasis. Aging is commonly accompanied by immunosenescence and chronic low-grade inflammation, often referred to as inflammaging, which contribute to the development of numerous age-related diseases (Amorim et al., 2022; Lima et al., 2022; Pranandi, 2025b). In contrast, the molecular signatures identified in this study suggest that healthy aging is associated with a more balanced immune response and reduced inflammatory signaling. Preservation of immune homeostasis may therefore represent one of the key biological characteristics distinguishing healthy aging from pathological aging (Aman et al., 2021).

Autophagy and proteostasis were also consistently enriched across multiple omics layers. Efficient protein quality control and intracellular recycling are essential for preventing the accumulation of damaged proteins and dysfunctional organelles during aging (Franceschi et al., 2018; Furman et al., 2019). The coordinated activation of these pathways supports continued cellular maintenance and may reduce the risk of protein aggregation and cellular dysfunction. Similarly, enrichment of oxidative stress defense and DNA repair pathways indicates enhanced mechanisms for protecting cells against cumulative molecular damage. Together, these pathways contribute to maintaining genomic stability and cellular function throughout the aging process (Pranandi & Tjhay, 2025).

The integrated network analysis further identified several hub molecules, including SIRT1, FOXO3, NFE2L2, AMPK, HSP90AA1, and TFAM, which are well-established regulators of longevity and cellular stress responses (Hipp et al., 2019; Melzer et al., 2020; Schumacher et al., 2021). These molecules participate in multiple interconnected signaling pathways regulating metabolism, mitochondrial biogenesis, antioxidant defense, and protein homeostasis. Their central positions within the molecular interaction network suggest that they may serve as promising biomarkers of healthy aging and potential therapeutic targets for interventions aimed at extending healthspan (William et al., 2025). However, additional experimental validation is necessary to determine their causal roles and clinical utility.

The findings of this study have potential implications for precision medicine and geroscience (Zhang et al., 2015). Rather than relying on chronological age alone, molecular signatures derived from multi-omics integration may facilitate the development of biomarkers capable of estimating biological age and identifying individuals who are aging more successfully (López-Otín & Kroemer, 2021; Partridge et al., 2020). Such biomarkers could support personalized preventive strategies, monitor responses to lifestyle or pharmacological interventions, and contribute to the early identification of individuals at risk for accelerated aging and age-related diseases (Pranandi, 2025c).

This study has several strengths. By integrating four complementary omics layers, it provides a systems-level perspective that captures biological processes not readily apparent through single-omics analyses. The use of publicly available datasets also enhances reproducibility and demonstrates the value of open-access biomedical resources for biomarker discovery. Nevertheless, several limitations should be acknowledged. First, heterogeneity among publicly available datasets, including differences in study populations, analytical platforms, and sample processing, may introduce batch effects despite normalization

procedures (Ahadi et al., 2020). Second, the cross-sectional nature of the analyzed datasets limits the ability to infer temporal changes during aging. Third, the representative molecular signatures presented in this study require validation in independent cohorts and experimental models before clinical application.

Overall, the present findings support the concept that healthy aging is driven by coordinated regulation of multiple biological systems rather than individual molecular pathways (Goh et al., 2017; Moqri et al., 2023; Pranandi, 2026b). Future studies integrating larger multi-center cohorts, longitudinal sampling, single-cell multi-omics technologies, and functional experimental validation will further improve our understanding of the molecular determinants of healthy aging and facilitate the translation of these discoveries into clinical practice (Pranandi, 2026a; Sudiyono et al., 2026).

CONCLUSIONS

In conclusion, this study demonstrated the potential of multi-omics integration to characterize molecular signatures and biological pathways associated with healthy aging. By integrating transcriptomic, proteomic, metabolomic, and epigenomic data, the analytical framework highlighted candidate molecular signatures and biological processes related to cellular homeostasis, including mitochondrial function, immune homeostasis, autophagy, proteostasis, oxidative stress responses, and DNA repair. These findings suggested that healthy aging may involve coordinated molecular changes across multiple biological systems rather than isolated alterations within individual molecular layers. However, the observed associations did not establish causal relationships or confirm that these molecular processes directly contributed to longevity or preserved physiological function.

The candidate hub molecules and enriched biological pathways provided a systems-level perspective on molecular processes potentially associated with physiological resilience during aging. Nevertheless, because the reported findings were illustrative and had not been independently validated, their reproducibility, biological significance, and clinical relevance remained uncertain. Further investigations using well-characterized independent cohorts, longitudinal multi-omics analyses, single-cell technologies, and experimental validation are necessary to establish the robustness and functional significance of these molecular signatures. Such research may contribute to the identification of reliable biomarkers of biological aging and the investigation of potential therapeutic targets for promoting healthspan, thereby supporting the future development of evidence-based precision medicine strategies for aging populations.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to the conduct of the research, preparation, or publication of this article.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of this article. The first author, Susanti Susanti, was responsible for the conceptualization of the study, data collection and analysis, interpretation of the results, and manuscript preparation. The other authors contributed to the review, editing, and final approval of the manuscript.

GENERATIVE AI STATEMENT

The authors declare that no generative artificial intelligence was used in the preparation of this article.

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