Nonlinear Dynamic Changes During Human Aging Revealed in Multi-omics Profiles

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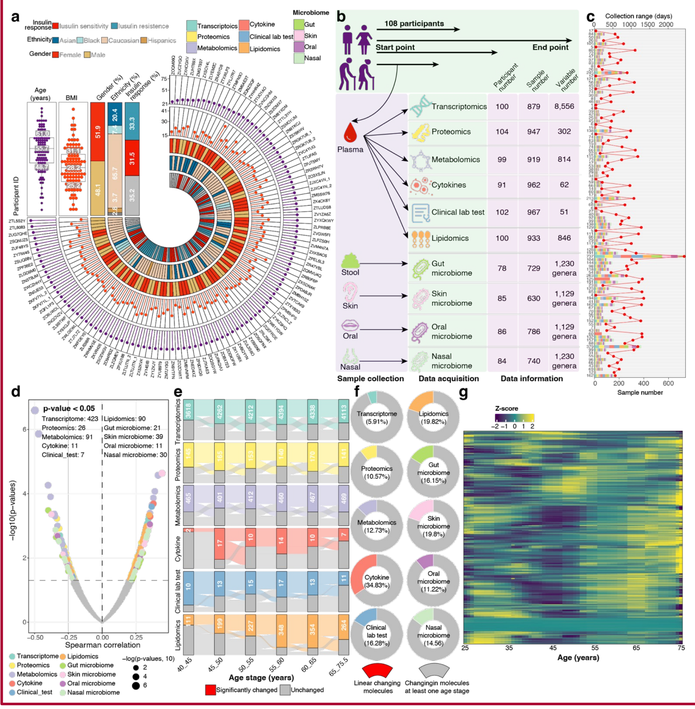
Abstract

Aging is a complex process associated with nearly all diseases. Understanding the molecular changes underlying aging and identifying therapeutic targets for aging-related diseases is crucial for increasing health span. While many studies have explored linear changes during aging, the prevalence of aging-related diseases and mortality risk accelerates after specific time points, indicating the importance of studying nonlinear molecular changes. We conducted deep multi-omics profiling of a longitudinal human cohort aged 25 to 75 years. The analysis revealed consistent nonlinear patterns in molecular markers of aging, with significant dysregulation occurring at two major periods occurring at approximately 40 and 60 years of chronological age. Functional pathways associated with these nonlinear changing molecules were also identified, such as immune regulation and carbohydrate metabolism, occurring during the 60 years transition, indicating that functions and risks of aging-related diseases change nonlinearly across the human lifespan. Overall, this research provides significant biological insights through the global monitoring of nonlinear molecular changes during human aging.

Most of the molecules/microbes change nonlinearly during human aging

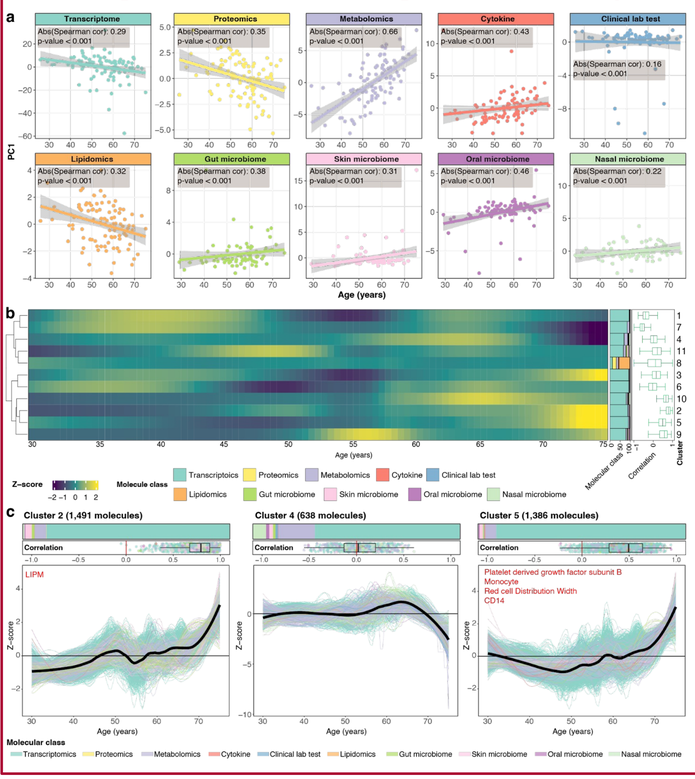


We tracked 108 participants for up to 6.8 years with longitudinal biological sample collection and multi-omics profiling. In total, 5,405 biological samples were collected, and 135,239 biological features were acquired.

Only a small portion of all the molecules and microbes (6.63%) linearly changed during human aging. Next, we examined nonlinear effects by categorizing all participants into distinct age stages according to their ages and investigated the dysregulated molecules within each age stage compared to the baseline.

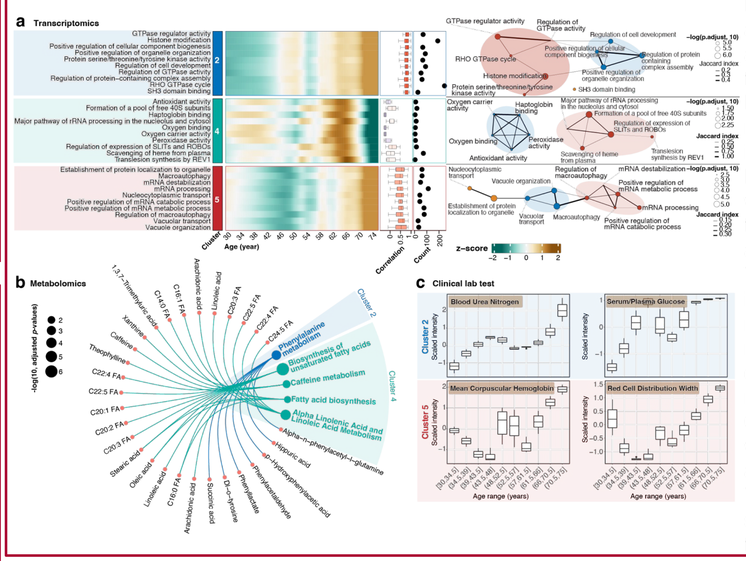
Interestingly, 81.03% of molecules exhibited changes in at least one age stage compared to the baseline. Remarkably, the percentage of linear changing molecules was relatively small compared to the overall dysregulated molecules during aging. Taken together, these findings strongly suggest that a substantial number of molecules and microbes undergo nonlinear changes throughout human aging.

Clustering reveals nonlinear changes in multi-omics profiling during human aging



Our analysis revealed a substantial correlation between a significant proportion of the omics data and the ages of the participants. These findings validate the potential utility of these omics datasets as robust indicators of the aging process. We then grouped all the molecules with similar trajectories using an unsupervised Fuzzy c-means clustering approach. Finally, we identified 11 clusters of molecular trajectories changing during aging. We found that most molecular patterns exhibit nonlinear changes, indicating that aging is not a linear process. Among the 11 identified clusters, three distinct clusters (2, 4, and 5) displayed compelling, straightforward, and easily understandable patterns that spanned the entire lifespan. Cluster 4 exhibits a relatively stable pattern until approximately 60 years old, after which it shows a rapid decrease. Conversely, clusters 2 and 5 display fluctuations before 60 years old, followed by a sharp increase and an upper inflection point at approximately 55-60 years old.

Nonlinear alterations in function and disease risk during the aging process

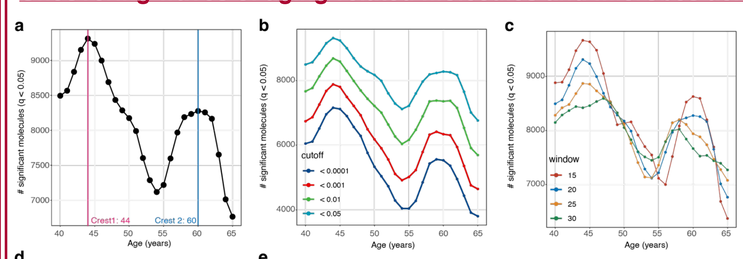


In cluster 2, we identified a transcriptomic module associated with GTPase activity and histone modification. In cluster 4, one transcriptomics module associated with oxidative stress was identified. In cluster 5, the first transcriptomics modules are associated with mRNA stability and autophagy. In cluster 2, the phenylalanine metabolism was identified. The blood urea nitrogen provides important information about kidney function and is detected in cluster 2. This indicates that kidney function nonlinearly decreases. Furthermore, the serum/plasma glucose, a marker of type 2 diabetes, falls within cluster 2. Collectively, these findings suggest a nonlinear escalation in the risk of cardiovascular, kidney diseases, and T2D during aging, particularly after the approximate age of 60 years.

The biosynthesis pathway of unsaturated fatty acids is identified as decreased in cluster 4. Studies have shown that unsaturated fatty acids are useful in reducing CVD risk. The pathway of alpha-linolenic acid and linolenic acid metabolism can reduce aging-associated diseases, such as CVD. We also detected the caffeine metabolism in cluster 4, which suggests that the ability to metabolize caffeine decreases across aging.

Cluster 5 comprises the mean corpuscular hemoglobin and red cell distribution width. These tests assess the average hemoglobin content per red blood cell and the variability in the size and volume of red blood cells, respectively. These findings align with the aforementioned transcriptomic data, which suggests a nonlinear reduction in the oxygen-carrying capacity associated with the aging process.

Uncovering waves of aging-related molecules and microbes across the human lifespan

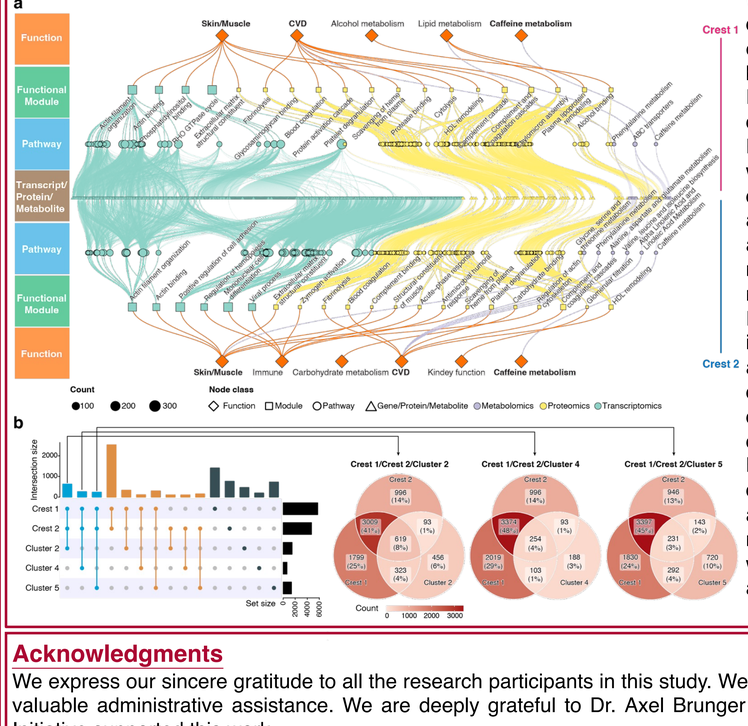


While the trajectory clustering approach described above effectively identifies nonlinear changing molecules and microbes that exhibit clear and compelling patterns throughout human aging, it may not be as effective in capturing significant changes that occur at specific chronological aging periods. To gain a comprehensive understanding of changes in multi-omics profiling during human aging, we utilized a modified version of the DE-SWAN algorithm. This algorithm allowed us to identify dysregulated molecules and microbes throughout the human lifespan. By employing this approach, we could detect changes at specific stages of lifespan and uncover the sequential effects of aging using multi-omics data. Our analysis revealed thousands of molecules exhibiting changing patterns throughout aging, forming distinct waves. Notably, we observed two prominent crests occurring around the ages of 45 and 65, respectively.

The identified crests represent notable milestones in the aging process and suggest specific age ranges where substantial molecular alterations occur. Next, we investigated the age-related waves for each type of omics data. Interestingly, most types of omics data exhibited two distinct crests that were highly robust. Identifying consistent crests across different omics data underscores the robustness and reliability of these molecular milestones in the aging process.

We next investigated the functions of dysregulated molecules within two distinct crests. To focus on the unique biological functions associated with each crest and eliminate commonly occurring molecules, we removed background molecules that were present in most stages.

Interestingly, the analysis identifies many dysregulated functional modules in crests 1 and 2, indicating a nonlinear risk for aging-related diseases. Particularly, in both crest 1 and crest 2, several modules associated with CVD were identified, which is consistent with the above results. In addition, the dysregulation of skin and muscle stability was found to be increased at crest 1 and crest 2. In crest 1, we identified specific modules associated with lipid and alcohol metabolism. It is well-established in previous studies that lipid metabolism declines with human aging. Our analysis revealed several modules related to lipid metabolism, including plasma lipoprotein remodeling. In summary, our analysis identifies the dysregulated functional modules identified in both crest 1 and crest 2 that underlie the risk for various diseases and alterations of biological functions. Notably, we observed an overlap of dysregulated functional modules between clusters 2, 4, and 6 because they overlap on the molecular level. This indicates that certain molecular components are shared between these clusters and the identified crests. However, it is important to note that numerous molecules are specific to each of the two approaches employed in our study. This suggests that these two approaches complement each other in identifying nonlinear changes in molecules and functions during human aging. By utilizing both approaches, we were able to capture a more comprehensive understanding of the molecular alterations associated with aging and their potential implications for diseases.



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