PHYSIOLOGY

Signatures of aging and disease in a single organelle

Changes in lysosomal metabolites are associated with both aging organs and lysosomal storage diseases

Jeeyoon Na[1,2] and **Anne Brunet**[1,3]

Lysosomes are central to cellular metabolism, and their function declines substantially in many degenerative diseases and during aging (*1*–*5*). But how content of these organelles changes with age and whether these changes differ across tissues remain unknown. On page 488 of this issue, Puszynska *et al.* (*6*) describe a multitissue atlas of lysosomal metabolites during aging. Several metabolites accumulate with age across multiple tissues in several mammalian species. Notably, those that increase with age also accumulate in lysosomal storage disorders—devastating diseases that predominantly affect children—providing an intriguing connection between these diseases and aging.

Lysosomes are present in most cells across many species, and their functions include degrading and recycling cellular macromolecular waste, as well as sensing nutrients (*3*, *5*, *7*). Mutations in genes encoding lysosomal proteins lead to lysosomal storage disorders that manifest early in life and are often fatal (*2*, *3*, *8*). These conditions are characterized by abnormal accumulation of specific metabolites in the lysosome (*2*, *3*, *8*). Lysosomal function also declines in aging and in several age-associated diseases (*1*, *4*). For example, defective repair of compromised lysosomes or impaired lysosomal acidification contributes to the accumulation of toxic protein aggregates during aging and in Alzheimer's disease (*1*, *4*). Although age-dependent metabolic changes across different tissues have been profiled (*9*), metabolic changes specific to lysosomes were uncharacterized.

...lysosomal metabolites can estimate age with high accuracy...

Puszynska *et al.* used a genetically modified mouse line called "LysoTag" (*3*), which allows rapid isolation of tagged lysosomes from tissues. Lysosomes from young and old LysoTag mice were isolated from many tissues, and their metabolite content was measured with mass spectrometry. Surprisingly, lysosomes from the brain, heart, skeletal muscle, and white adipose tissue of old mice showed accumulation of metabolites belonging to the glycerophosphodiester (GPD) class as well as cystine. These metabolites are also known to increase in lysosomal storage disorders. GPDs accumulate in Batten disease, and cystine accumulates in cystinosis (*3*, *8*, *10*). The authors further developed a "tag-free" method that enables purification of lysosomes without having to genetically modify the animal. Using this approach in mice, rats, and rhesus macaques, Puszynska *et al.* observed increases in the same metabolites—GPDs and cystine—in aged lysosomes in a tissue-specific manner across these different mammalian species. The connection between aging and lysosomal storage disorders was further strengthened through lipidomic characterization of aged lysosomes in mice and rats, which showed an increase in bis(monoacylglycero)phosphate, a lipid that accumulates in several lysosomal storage diseases (*2*).

Can age-dependent metabolic changes in lysosomes be used to estimate tissue aging and the impact of interventions? Aging "clocks" are machine-learning models that can be built to estimate age on the basis of transcriptomic (gene expression) and epigenetic (chemical modifications that regulate gene activity) signatures (*11*, *12*). Puszynska *et al.* generated an organelle-based aging clock built on the lysosomal metabolites that change with age. The results show that lysosomal metabolites can estimate age with high accuracy in the brain, heart, and skeletal muscle of mice, with a precision similar to that of other aging clocks, such as spatial transcriptomic clocks in the brain (*12*).

Several "rejuvenation" interventions, including exercise and caloric restriction, reverse both molecular signatures and some phenotypes of aging (*12*, *13*). To determine whether metabolic signatures of aging lysosomes are affected by caloric restriction in old animals, Puszynska *et al.* analyzed lysosomes from hearts, skeletal muscle, and brains of young and old mice fed ad libitum, as well as old mice with lifelong caloric restriction. Notably, accumulation of GPDs and cystine was attenuated in lysosomes from the heart and skeletal muscle in calorie-restricted mice. Thus, GPDs and cystine in lysosomes may represent new biomarkers, at least in peripheral tissues, for estimating the benefit of interventions.

What mechanisms underlie the accumulation of GPDs and cystine with age? It will be interesting to test whether accumulation of these metabolites in aged lysosomes results from decreased catabolism due to defects in lysosomal enzyme activity or from increased flux of upstream metabolites. It is also unclear whether metabolite accumulation could itself cause age-related lysosome dysfunction, perhaps as part of a feed-forward mechanism. These metabolites could directly disrupt lysosomal function in old tissues, just as accumulated lysosomal GPDs inhibit glycerophospholipid catabolism in Batten disease (*10*). Although Puszynska *et al.* show that caloric restriction attenuates the accumulation of GPDs and cystine in lysosomes across several aged tissues in mice, it is not known whether preventing this accumulation is sufficient for functional rejuvenation. Examining whether other interventions, such as exercise, also attenuate age-related increases in these lysosomal metabolites could confirm that this accumulation is malleable. It will also be interesting to test whether specifically preventing GPD and cystine accumulation in lysosomes could rejuvenate an old tissue's function or even extend organismal lifespan.

The findings of Puszynska *et al.* offer insights into how biochemical tools can be leveraged to uncover new facets of aging. Advances in mass spectrometry technologies, including single-cell and spatial metabolomics, and in methods that use artificial intelligence–based chemical language models to identify new metabolites should move the field forward (*14*, *15*). In the future, lysosomal metabolites could be used as new biomarkers to assess lysosomal health in the context of age-related conditions such as neurodegenerative diseases. □

REFERENCES AND NOTES

1. C.-C. Chou *et al.*, *Nat. Cell Biol.* **27**, 619 (2025).
2. U. N. Medoh *et al.*, *Science* **381**, 1182 (2023).
3. N. N. Laqtom *et al.*, *Nature* **609**, 1005 (2022).
4. D. S. Leeman *et al.*, *Science* **359**, 1277 (2018).
5. Y. Yu *et al.*, *eLife* **13**, e85214 (2024).
6. A. M. Puszynska *et al.*, *Science* **393** eady0832 (2026).
7. R. Zoncu *et al.*, *Science* **334**, 678 (2011).
8. F. M. Platt *et al.*, *Nat. Rev. Dis. Primers* **4**, 27 (2018).
9. S. E. Pilley *et al.*, *Cell Metab.* **38**, 399 (2026).
10. K. Nyame *et al.*, *Mol. Cell* **84**, 1354 (2024).
11. S. Horvath, *Genome Biol.* **14**, 3156 (2013).
12. E. D. Sun *et al.*, *Nature* **638**, 160 (2025).
13. A. Di Francesco *et al.*, *Nature* **634**, 684 (2024).
14. J. Delafiori *et al.*, *Cell* **188**, 6028 (2025).
15. H. Qiang *et al.*, *Nature* **651**, 211 (2026).

10.1126/science.aej5901

[1]Department of Genetics, Stanford University, Stanford, CA, USA. [2]Institute for Stem Cell Biology and Regenerative Medicine Graduate Program, Stanford University, Stanford, CA, USA. [3]Glenn Laboratories for the Biology of Aging, Stanford University, Stanford, CA, USA. Email: abrunet1@stanford.edu

Signatures of aging and disease in a single organelle

Jeeyoon Na and Anne Brunet

Science **393** (6810), . DOI: 10.1126/science.aej5901