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Spotlight

Do metabolic fluxes change with age?

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Metabolomes change with age. Yet, fluxomics points to a contradiction: Jankowski *et al*. in *Cell Metabolism* report shifts in metabolite concentrations in aged mice, alongside largely preserved metabolite fluxes, evoking important questions on the nature of age-related metabolic disturbances. We discuss how this might recalibrate our understanding of aging metabolism.

Metabolomics, the comprehensive investigation of metabolites and small molecules in biological specimens, often using liquid chromatography–mass spectrometry (LC-MS) or NMR methods, is a relatively young field that has been widely applied to the study of aging biology. It has mapped broad, reproducible age associations across plasma and tissues [1,2]. Those datasets have often been interpreted as evidence for an age-related 'metabolic slowdown' [3], with long lists of metabolites that rise or fall with age and correlations to disease burden, specifically age-associated diseases [4]. However, steady-state concentrations are shaped by synthesis, consumption, storage, and compartmentalization—they do not reveal metabolic flux. As the field eyes metabolism-centered interventions [5] (e.g., NAD boosting, amino acid, spermidine, and taurine supplementation), discriminating net changes from altered fluxes during aging is essential. Since metabolites serve multiple purposes, from energy fuels to signaling, post-translational protein modification, and cell-to-cell or intertissue communication, understanding metabolite alterations with age holds significant therapeutic promise.

Reporting in *Cell Metabolism*, Jankowski *et al.* took the next step by pairing LC-MS metabolomic profiling with steady-state tracer infusions to quantify circulatory turnover flux (Fcirc) across the mouse lifespan [6]. They confirmed that in naturally aged C57BL/6 J mice, many serum metabolites (roughly a third of the identified 170 metabolites) change in concentration, and those changes occurred in a quasi-linear fashion in a separate lifespan cohort. In contrast, most systemic core fluxes, including glucose, lactate, glycerol, acetate, ketone bodies, and many amino acids, were remarkably preserved in aged organisms. Among the assayed 'core' metabolites, only glutamine showed a significant flux increase (30%), whereas lysine flux was rewired from the saccharopine route toward pipecolate, with increases in pipecolic acid level and flux. These conclusions hold across both sexes and were assessed primarily after an 8-h fast, with young obese ob/ob mice providing a useful and aging-relevant disease comparison. Notably, fluxes changed more with obesity than with aging, suggesting that the nature of metabolome disturbances between obesity and aging may stem from different, although overlapping, processes, at least in mice. This highlights the need to view age-related obesity as a confounding factor for metabolism measurements.

Changes in hormones are consistent with this physiology, as indicated by higher insulin and leptin in aged mice, which support the decrease in glucose, ketone bodies, and triglycerides, while total free fatty acids remain stable [6]. The endocrine context could help explain why reservoir levels shift without significant changes in systemic exchange rates. Still, the central finding is that most major fluxes do not collapse with age.

How can aging alter serum metabolite concentrations while turnover rates stay stable? Whole-body energy demand, for instance, ATP for ion pumping, thermogenesis, and biosynthesis, sets a generally required traffic of metabolites between organs. Back-and-forth exchanges can act as a buffering system. For instance, muscle and other tissues export lactate that the liver reconverts to glucose (the Cori cycle), and adipose tissue hydrolyzes and re-esterifies triglycerides (fatty acid/glycerol cycling). Abundant and dynamic membrane transporters move these substrates quickly across cell barriers. Thus, concentrations can drift with hormonal changes or tissue uptake while total throughput (Fcirc) stays in range. In obesity, this system seems to derail, while it is largely maintained during physiological aging—at least at the assessed age windows [6]. Also, normalization approaches matter when body composition differs between compared groups. For instance, the preferential increase in adipose tissue in heavier animals warrants a per-animal (as done in Ref. [6]) or per-lean-mass approach.

This 'changing concentrations, steady flows' theme is not unprecedented. In aged mice, tissue NAD^+ concentrations decline, yet isotope tracing indicates that NAD^+ biosynthetic flux is broadly maintained [7]. Jankowski *et al*. extend this notion from a single cofactor to the bloodstream's main carbon and nitrogen sources [6]. Mechanistically, the lone outlier, glutamine, warrants further investigation during aging: modestly elevated Fcirc rates could reflect enhanced glutaminolysis or transamination pressure, reallocating nitrogen and anaplerotic carbon, potentially stabilizing the tricarboxylic acid (TCA)cycle.

Beyond core metabolism, some 'peripheral' metabolites show aligned changes in both concentration and flux rates [6]. The lysine rerouting (saccharopine to pipecolate preference) is one example. Others, such

as 4-hydroxyproline, which is a consequence of collagen turnover, also exhibit coherent shifts. Whether these aligned changes are more significant to functional aging processes remains to be seen. The present work also adds to a heated debate: taurine and aging. A 2023 publication proposed taurine deficiency as an important driver of aging [8], fueling interest in its supplementation. Here, taurine concentration and flux were not decreased with age, and the authors note disagreement between isotope-dilution LC-MS and commercial ELISA kits, which is consistent with recent human and animal longitudinal analyses also questioning taurine as a reliable, singular aging biomarker [9].

Importantly, key knowledge gaps remain. First, previous studies have shown that aging mice do not exhibit a significant decline in their basal metabolic rate as measured by VO_2 [10]. Only 2-year-old mice undergoing treadmill exercise displayed a notable decrease in VO_{2max}, indicating an age-related decline under stress [10]. In contrast, humans typically show a decline in basal energy expenditure with age [3], along with reductions in total energy expenditure [3] and VO_{2max} [11]. It remains unclear whether the differences in how aging affects whole-body metabolism in mice and humans are due to fundamental mechanistic reasons or if they result from complex factors, such as behavior and activity changes with age, that influence such measurements. Second, the 'black box' of unknown or poorly annotated metabolites persists, and even for known compounds, underlying mechanisms and consequences are unclear. Third, concentration changes do not reveal sources or metabolic sinks, nor do they truly depict changes in the sites of production, metabolization, consumption, or storage (the comprehensive metabolome data sets provided will be useful in future analyses). Moreover, dietary changes with age and microbiome contributions are difficult-to-assess confounding factors in studying systemic metabolism. Fourth, Fcirc is a whole-body metric and might miss subtle changes in various tissues that change in opposite directions. Comparing serum flux with tissue-internal pathway flux requires organ-resolved measurements, as done for tissue metabolomics [1]. Arterial–venous sampling organ studies and multitracer designs could help fill this gap and should be combined with modeling to quantify competing routes (cycling vs. oxidation vs. storage). Finally, most measurements were performed in 8 h-fasted mice [6]. Changes in metabolic flux during the circadian rhythm, dietary status, and acute stress or physical activity may reshape flux. Importantly, aging is believed to impair metabolic flexibility/elasticity (the quick and transient reaction of metabolic pathways across different molecular layers to stress, such as nutrient deprivation) [12]. Challenging aged mice with external stressors while infusing stable isotopes might reveal hidden inflexibility in metabolic flux regulation. Importantly, the authors released a comprehensive tissue/serum dataset [6] that enables the community to explore flux patterns across multiple organs, a welcome step toward transparency and resource reuse.

The cellular consequences of dissociating metabolite concentration regulation from flux remain unknown. Autophagy, a major lysosomal recycling process, is regulated by metabolic cues (including measured amino acids and lipid species in [6]) and decreases functionally with age, playing a key role in age-related health decline [13]. Glutamine, for instance, is increased in concentration and systemic flux and activates mTORC1, which limits autophagy. This potentially restraining effect of glutamine on age-related autophagy thus warrants closer examination. Autophagy is also essential for maintaining cellular metabolite demands and homeostasis, and it would be interesting to assess how altered autophagic capacity with age contributes to specific metabolites' Fcirc, such as amino acids [14].

What does this mean for humans and trials aiming at correcting metabolic profiles? The data could argue against attempts to change the rates of specific metabolic pathways. If aging maintains core metabolite throughput while reallocating substrates, then informed interventions should target allocation or cell/tissue utilization. Future studies should address whether preserved flux persists outside fasting conditions and whether interactions between age, diet, activity, and genotype exist. Importantly, recent data have highlighted that molecular aging does not occur linearly and that specific life phases are associated with accelerated biological aging in humans [15] (e.g., peri-/postmenopause, transitioning around the approximate retirement age). Human tracer methods have been established for glucose, lactate, glycerol, and some amino acids [16], but have not been extensively applied so far, particularly across different age groups. Moreover, multitracer approaches, circadian-stratified studies in middle-aged and older adults with controlled diet/activity and microbiome profiling would help advance our understanding of metabolic fluxes across the human lifespan.

Concluding remarks

Jankowski *et al*. show that previously untested metabolite fluxes, reflecting major carbon and nitrogen flows, do not change during aging. By demonstrating that such major fluxes are largely preserved at the assessed advanced age, while metabolite pools and pathway choices shift in some cases, Jankowski *et al*. recalibrate the targets for metabolism-centered gerotherapeutics. A 'metabolic rheostat' of Fcirc that derails during specific phases of the lifespan could potentially better explain the emerging view of metabolism during aging than a universal slowdown model (Figure 1). Next

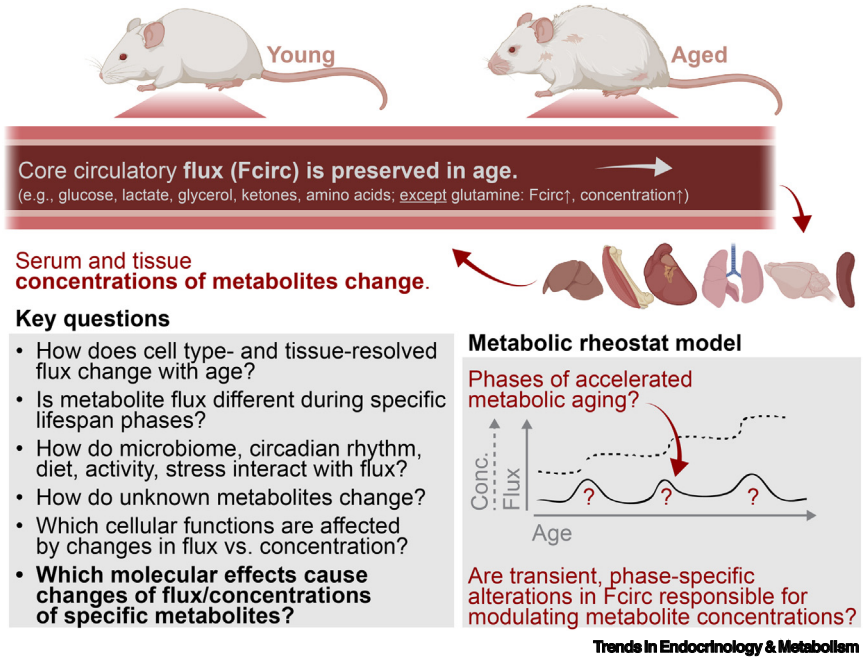

Figure 1. A potential phase-sensitive metabolic rheostat of aging metabolism. Age shifts circulating metabolite concentrations while most core circulatory fluxes of glucose, lactate, glycerol, ketone bodies, and many amino acids remain relatively preserved. Glutamine flux increases, while lysine flux is rerouted toward pipecolate, suggesting pathway-specific remodeling alongside stable whole-body metabolism. Tissue levels change, indicating organ- and cell type-specific allocation and tissue flux may change even when systemic flux appears unchanged. The lower right panel illustrates the hypothesis that flux is not strictly constant throughout the lifespan but may transiently deviate at specific phases of accelerated metabolic aging (disturbed 'metabolic rheostat' model), potentially shifting metabolite pools into new steady states. Key open questions remain about tissue-resolved and cell type-specific flux, confounding modifiers (diet, microbiome, circadian rhythm, activity, and stress), poorly annotated metabolites, and how concentration and/or flux changes affect cellular functions such as autophagy and physiological aging phenotypes. Figure partly created in https://BioRender.com.

steps should include a human and murine (tissue-resolved), circadian, microbiome-aware flux program spanning key life phases and genetic backgrounds. Finally, dissecting the importance of level changes versus flux changes on cellular functionality, such as autophagy regulation, will be an important addition in the future, which will help to understand and ultimately restore the cellular metabolic housekeeping that keeps aged metabolism functional.

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Declaration of interests

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Declaration of Generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT (GPT-5.1, OpenAI) to assist with language and grammar editing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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