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Editorial

Intermittent fasting, tissue by tissue: from shared metabolic adaptation to divergent aging

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1 One intervention, many biological responses

Intermittent fasting (IF) is frequently conceptualized as a unitary intervention acting through a common metabolic mechanism: periodic nutrient deprivation triggers a shift from glucose utilization toward fatty acid oxidation and ketogenesis, thereby promoting metabolic health. Such a framework, while conceptually attractive, oversimplifies the biological complexity of the fasting response. Organisms do not respond to nutrient scarcity as homogeneous systems. Rather, fasting is interpreted by a mosaic of tissues that differ fundamentally in developmental origin, cellular composition, energetic requirements, circadian organization, and stress-response architecture [1]. Consequently, a common nutritional stimulus is superimposed upon distinct physiological constraints. The liver must maintain systemic energy homeostasis through coordinated substrate redistribution; skeletal muscle must balance fuel utilization with preservation of contractile function; the brain must sustain information processing despite fluctuations in nutrient availability; and the heart must continuously generate mechanical work with minimal tolerance for energetic instability. The critical biological question is therefore not whether fasting induces metabolic adaptation, but how a conserved systemic signal is decoded into tissue-specific molecular and functional programs. Understanding this divergence is essential because the physiological consequences of fasting are likely to emerge not from a single canonical pathway, but from the collective integration of organ-specific adaptive responses.

The key issue, therefore, is not whether IF induces metabolic reprogramming, but how a conserved systemic signal generated by intermittent nutrient deprivation is decoded into tissue-specific molecular responses and whether these responses collectively enhance organismal robustness during aging. Increasingly, multi-omics studies indicate that IF promotes a shared adaptive state characterized by metabolic flexibility, improved stress responsiveness, and maintenance of cellular homeostasis. Yet the mechanisms through which this state is established differ markedly across organs, reflecting their distinct physiological roles and regulatory architectures. Consequently, IF is unlikely to function as a singular longevity pathway. Rather, it appears to operate as a distributed biological stimulus that engages multiple tissue-specific programs whose integrated effects may support resilience against age-related functional decline. Understanding how these diverse responses are coordinated spatially and temporally has become a central challenge for the biology of fasting and healthy aging.

2 Shared metabolic switching, divergent tissue programs

The most widely recognized systemic response to IF is the transition from continuous glucose utilization toward increased fatty acid mobilization and ketone body production. This systemic metabolic switch creates a common physiological framework across organs while allowing individual tissues to engage distinct adaptive mechanisms (Fig. 1).

A recent integrated transcriptomic and proteomic analysis of liver, skeletal muscle, and cerebral cortex provides a compelling illustration of this principle [2]. Following four months of daily 16-hour IF in young male mice, the liver exhibited the most extensive molecular remodeling, characterized by upregulation of pathways involved in fatty acid oxidation, ketogenesis, glycan degradation, and other processes that coordinate whole-body energy redistribution. In skeletal muscle, IF altered pyruvate and lipid metabolism, activated AMPK-associated pathways, and reduced signatures linked to oxidative phosphorylation and thermogenesis. In contrast, the cerebral cortex displayed enrichment of autophagy, PPAR signaling, and broader stress-adaptation

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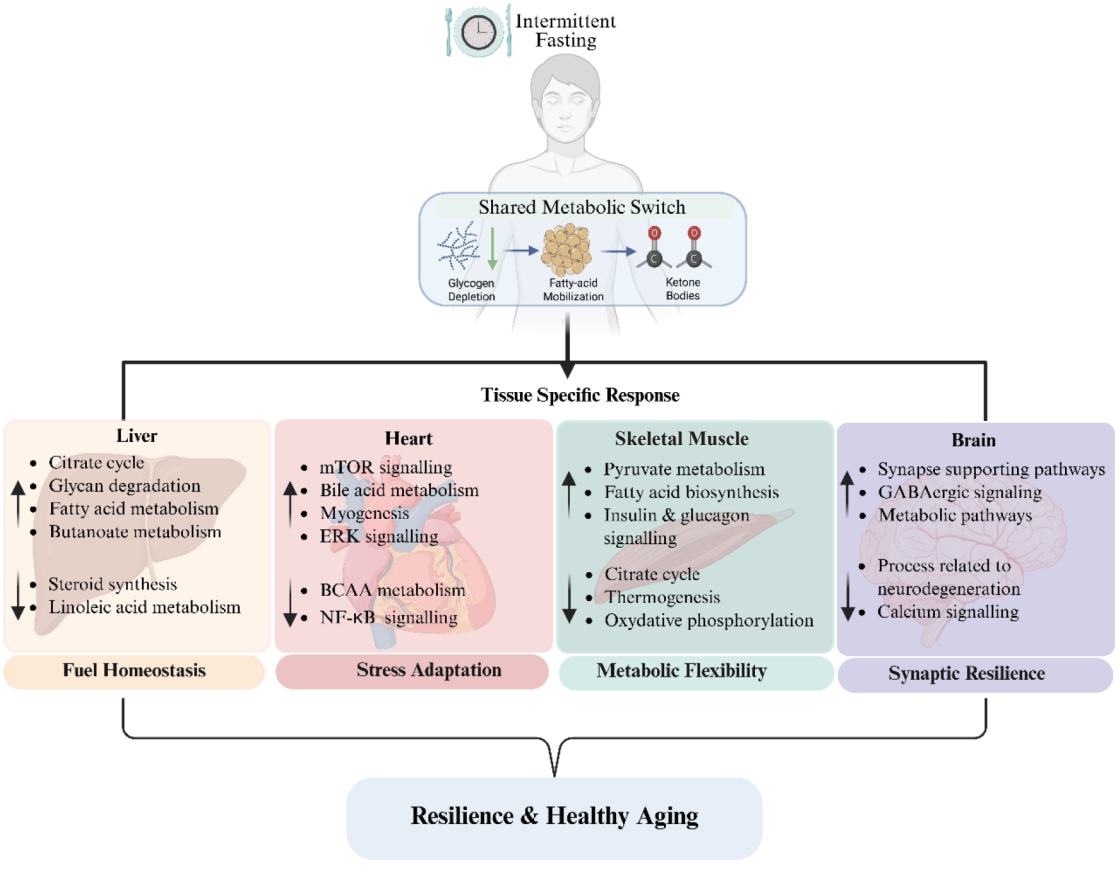


Figure 1 Tissue-specific metabolic adaptations to intermittent fasting. Intermittent fasting initiates a shared metabolic switch characterized by glycogen depletion, fatty-acid mobilization and increased ketone-body availability. This systemic signal is translated into distinct tissue-specific responses. In the liver, fasting promotes ketogenesis and fatty-acid oxidation to support fuel homeostasis. In the heart, AMPK- and cAMP-associated signaling contributes to adaptation to physiological stress. In skeletal muscle, changes in pyruvate and fatty-acid metabolism support metabolic flexibility. In the brain, fasting-associated metabolic and cellular adaptations may promote synaptic resilience. These organ-specific responses may collectively contribute to potential healthspan resilience, although their effects are influenced by biological context, including age, sex and circadian timing. The figure emphasizes that intermittent fasting does not impose a uniform molecular program across the body; rather, a shared metabolic signal is interpreted differently by each tissue.

pathways, accompanied by changes involving TGF-β and p53-associated regulatory networks.

These findings challenge the notion that fasting elicits a stereotyped molecular response throughout the body. The same intervention can promote one biological process in a given tissue while suppressing a related process elsewhere. Even putative systemic mediators of fasting responses appear highly context dependent. The study identified only modest overlap among differentially expressed proteins across tissues, and transcriptomic changes only partially corresponded with proteomic alterations. Such discordance should not be considered a technical limitation. Rather, it reflects an important biological reality whereby post-transcriptional regulation, protein turnover, cellular composition, and tissue-specific signaling determine whether gene-expression changes ultimately translate into functional outcomes.

The heart offers another striking example of tissue-specific adaptation. Multi-omics analyses of mice subjected to 12-hour fasting, 16-hour fasting, or every-other-day fasting revealed extensive remodeling of carbohydrate, lipid, and amino acid metabolism together with alterations in cyclic GMP signaling, cAMP/PKA pathways, cell adhesion, inflammatory processes, and contractile machinery [3]. Importantly, the nature and magnitude of these changes depended on fasting duration. Moreover, fasting enhanced cardiac performance under pharmacological stress, suggesting that cardiac benefits may arise not merely from reduced metabolic burden but from an enhanced capacity to respond to physiological challenge. Such findings support the emerging concept that resilience, rather than baseline function alone, may be a critical biological outcome of IF.

At the level of genomic regulation, fasting may engage an additional dimension of tissue specificity. Recent work demonstrated widespread remodeling of transposable element expression in the liver, a more modest response in skeletal muscle, and minimal changes in the cortex [4]. IF-responsive transposable elements were integrated within co-expression networks governing hepatic metabolism, protein translation, mitochondrial function, muscle contraction, and chromatin organization. These observations raise the intriguing possibility that the repeatome is not simply a passive marker of metabolic stress but may actively contribute to adaptive gene regulation. Whether such elements serve causal regulatory functions remains unclear, and evidence for direct effects on chromatin structure, transcriptional control, or protein expression is still lacking. Nevertheless, these findings reinforce a broader principle: tissue identity shapes how IF-induced signals are interpreted and translated into adaptive responses.

3 From metabolic flexibility to resilience and healthy aging

The relevance of these observations to aging extends beyond metabolism itself. Many hallmarks of aging, including mitochondrial dysfunction, impaired proteostasis, chronic inflammation, reduced vascular integrity, and diminished stress resistance, do not occur in isolation. Rather, they represent interconnected failures in the ability of tissues to adapt to environmental and physiological stress. IF may counteract these processes by repeatedly exposing cells to a mild metabolic challenge that strengthens adaptive capacity. Importantly, the form that resilience takes appears highly tissue-specific.

In the brain, preservation of synaptic function may be more important than changes in bulk energy metabolism. Evidence from models of vascular cognitive impairment strongly supports this view. In a mouse model of chronic cerebral hypoperfusion, 16-hour daily fasting initiated before vascular injury improved learning and memory, reduced white matter damage, attenuated neuronal loss, and shifted cortical DNA methylation patterns toward a less pathological state [5]. Subsequent work in the same disease context extended these observations from epigenetic remodeling to synaptic preservation [6]. IF maintained cognitive performance and synaptic density despite persistent cerebral hypoperfusion, while proteomic analyses revealed enhanced expression of synapse-supportive pathways, strengthened GABAergic signaling, and reduced neuroinflammatory mediators.

Notably, protection was not necessarily associated with large increases in the abundance of major synaptic proteins. This distinction is important because it suggests that resilience may emerge from improved synaptic organization, turnover, signaling efficiency, or resistance to inflammatory injury rather than from simply producing more structural proteins. Such findings emphasize a recurring theme in aging biology: preservation of function often depends more on maintaining dynamic homeostasis than on increasing the quantity of individual molecular components.

Viewed collectively, these studies suggest that different tissues interpret the IF signal in fundamentally different ways. The liver prioritizes energy redistribution, the brain promotes synaptic stability, and the heart enhances stress-adaptive performance. What unites these responses is not a shared molecular pathway but a shared functional objective: the preservation of physiological competence under conditions of stress. This resilience-centered framework may ultimately prove more informative for healthy aging research than continued efforts to identify a single master fasting mechanism.

4 What remains unresolved

Despite growing enthusiasm surrounding IF, substantial challenges remain before fasting can be confidently positioned as an intervention for human aging.

First, the majority of mechanistic evidence derives from young male C57BL/6 mice subjected to relatively standardized fasting paradigms. Aging tissues differ profoundly from young tissues in circadian organization, mitochondrial reserve, immune regulation, proteostatic capacity, and epigenetic architecture. Consequently, IF responses observed in young animals may not accurately predict responses in older organisms. Indeed, the transposable-element study explicitly highlights the possibility that age-related repeatome dysregulation could fundamentally alter fasting responsiveness [4].

Second, most studies focus on molecular signatures and intermediate phenotypes rather than definitive measures of healthspan or lifespan. Improvements in metabolite profiles, cardiac stress responses, or cognitive performance are encouraging but do not necessarily demonstrate delayed biological aging. Establishing such a connection will require long-term studies linking molecular adaptation to sustained preservation of physiological function.

Third, bulk tissue profiling obscures cellular heterogeneity. The molecular signature detected in a whole organ represents the combined behavior of highly diverse cell populations. Single-cell and spatial multi-omics approaches are therefore essential for identifying precisely which neuronal, glial, immune, vascular, myocyte, or stromal populations benefit from fasting and which might be adversely affected.

Finally, the biological effects of fasting cannot be separated from context. Fasting duration, feeding-window timing, age, sex, genotype, dietary composition, physical activity, sleep, and circadian alignment are all likely to influence outcomes. A 16-hour fast imposed under controlled laboratory conditions in nocturnal mice cannot be directly equated with time-restricted eating in humans living in complex behavioral environments. Moreover, pair-fed controls and rigorous assessment of body composition remain critical for distinguishing fasting-specific effects from those attributable simply to reduced caloric intake or weight loss.

Mechanistic uncertainty also persists. Candidate mediators including ketone bodies, AMPK signaling, PPAR activation, epigenetic remodeling, synaptic stabilization pathways, and transposable elements remain largely associative. Determining whether these mechanisms are necessary or sufficient for IF-induced benefits will require targeted perturbation studies in specific tissues and cell populations.

5 Outlook: toward tissue-aware gerotherapeutics

The next phase of IF research should move beyond asking whether fasting is beneficial and instead ask for whom, in which tissue, at what age, and under what circumstances. Three priorities emerge.

First, future studies should integrate longitudinal functional phenotyping with single-cell, spatial, epigenomic, transcriptomic, proteomic, and metabolomic analyses across the lifespan in both sexes. Second, molecular signatures should be directly linked to organ-level outcomes, including cognition and synaptic physiology in the brain, metabolic and contractile reserve in muscle and heart, and systemic fuel handling by the liver. Third, causal interrogation of candidate pathways must replace reliance on correlation-based inference.

Translation to humans will require similarly sophisticated approaches. Adaptive clinical trials should compare fasting regimens while accounting for circadian alignment, body composition, metabolic status, cognitive function, physical

performance, and tissue-specific biomarkers. The ultimate goal is unlikely to be a universal fasting prescription. Instead, it should be the development of a precision framework in which fasting interventions are matched to biological context, monitored using objective biomarkers, and tailored to maximize benefit while minimizing risk.

IF is best viewed as a distributed biological signal rather than a singular metabolic intervention. It does not impose a uniform program upon the body; instead, it reveals how individual tissues negotiate periods of nutrient scarcity according to their unique physiological priorities. The emerging evidence therefore offers both encouragement and caution. Shared metabolic adaptation may create the conditions necessary for resilience, but the biological meaning of that adaptation is written differently across organs. Understanding that divergence may prove essential for transforming intermittent fasting from a promising lifestyle strategy into a rational, tissue-aware approach to promoting healthy aging.

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