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Aging's Metabolic Heterogeneity Across Scales

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Abstract

Aging is fundamentally linked to metabolic reprogramming and increased heterogeneity across biological scales. Studies employing single-cell and spatial metabolomics reveal dynamic shifts in mitochondrial, central carbon, lipid, and amino acid metabolism, coupled with heightened metabolic diversity in aged cells, tissues, and organs [1, 2, 5, 9, 10]. These alterations involve changes in glycolysis, fatty acid oxidation, and oxidative phosphorylation, impacting cellular function, tissue integrity, and contributing to age-related pathologies [3, 4, 8]. Furthermore, systemic factors like gut microbiota influence metabolic signatures of longevity [7]. The pervasive metabolic dysregulation and heterogeneity offer critical insights into the mechanisms of aging and potential therapeutic targets [6].

Keywords

Aging; Metabolomics; Metabolic Heterogeneity; Cellular Senescence; Mitochondrial Metabolism; Spatial Metabolomics; Single-cell Metabolomics; Metabolic Reprogramming; Gut Microbiota; Oxidative Stress

Introduction

Aging is a complex biological process characterized by progressive functional decline at molecular, cellular, and organismal levels. A critical emerging theme in understanding aging and age-related diseases is the profound metabolic reprogramming and heterogeneity observed across various biological scales. Recent advancements in metabolomic technologies have significantly deepened our insights into these intricate metabolic shifts.

For instance, single-cell metabolomics has emerged as a powerful tool to dissect metabolic changes at an unprecedented resolution. One study using this technique in aging revealed a significant shift in mitochondrial metabolism, specifically an increase in TCA cycle intermediates and changes in amino acid metabolism, coupled with heightened metabolic heterogeneity at the single-cell level in aged tissues. These findings suggest that metabolic dysregulation and variability contribute to cellular dysfunction in aging [1].

Further underscoring the importance of single-cell approaches, another investigation applied single-cell metabolomics to uncover dynamic metabolic states associated with cellular senescence. This work identified significant shifts in central carbon metabolism and lipid metabolism, demonstrating increased metabolic heterogeneity as cells enter senescence. These findings provide a granular view of how metabolic plasticity contributes to the diverse phenotypes observed in aging and senescent cells [5]. In the context of stem cells, single-cell metabolomics also revealed metabolic heterogeneity in human mesenchymal stem cells (hMSCs) during aging, showing shifts in glycolysis and mitochondrial respiration, alongside increased metabolic diversity among individual hMSCs. This indicates that cellular metabolic heterogeneity plays a critical role in the functional decline and altered regenerative capacity of hMSCs

during the aging process [10].

Beyond individual cells, spatial metabolomics offers crucial insights into tissue-specific metabolic landscapes. This methodology was utilized to map metabolic changes in aging skeletal muscle, identifying region-specific metabolic alterations. It revealed a significant reprogramming involving decreased glycolysis and increased fatty acid oxidation in specific areas, suggesting that metabolic heterogeneity within tissues plays a crucial role in sarcopenia and age-related muscle decline. Understanding these spatial shifts provides new avenues for therapeutic intervention [2]. Similarly, spatial metabolomics employed in the aging liver uncovered region-specific metabolic vulnerabilities. Distinct metabolic profiles in different liver zones highlighted heterogeneity in glucose and lipid metabolism, and redox balance, suggesting that targeted interventions considering intra-organ metabolic variations could be critical for addressing age-related liver dysfunction [9].

Metabolic flux analysis provides a complementary view by dissecting the dynamics of metabolic pathways. Research employing this technique in senescent human fibroblasts uncovered a distinct metabolic signature characterized by reduced glucose uptake and flux through glycolysis, alongside increased reliance on mitochondrial oxidative phosphorylation and specific amino acid pathways. These changes highlight how metabolic reprogramming supports the senescent phenotype and its impact on tissue aging [3].

The concept of metabolic heterogeneity extends to the organ and even systemic levels. A comprehensive study characterized tissue-specific metabolic reprogramming across different organs during murine aging. It demonstrated that each tissue exhibits unique metabolic signatures, diverging from a general aging pattern, with distinct alterations in pathways like glycolysis, fatty acid oxidation, and amino acid metabolism. This challenges a uniform view of age-related metabolic decline by highlighting metabolic heterogeneity at the organ level [4]. Furthermore, the aging brain exhibits complex metabolic heterogeneity, as discussed in a review that emphasized how different cell types and brain regions show unique metabolic profiles and vulnerabilities. This review discussed implications for neurodegenerative diseases, highlighting altered glucose metabolism, mitochondrial dysfunction, and lipid metabolism as key contributors to neuronal vulnerability and cognitive decline [6].

Beyond intrinsic cellular and tissue metabolism, external factors such as the gut microbiota significantly influence host physiology during aging. Research investigating the role of gut microbiota-derived metabolites in human aging and longevity identified specific metabolic signatures from the gut microbiome that correlate with healthy aging and advanced age, including altered short-chain fatty acids and bile acid profiles. The findings suggest that the gut microbiota contributes significantly to systemic metabolic heterogeneity and influences host physiology during the aging process [7]. Finally, a broad metabolomic analysis of aging kidneys revealed significant changes in lipid, amino acid, and carbohydrate metabolism, suggesting a metabolic shift towards less efficient energy utilization and increased oxidative stress. These insights offer potential biomarkers and therapeutic targets for age-related kidney diseases [8].

Together, these studies paint a picture of aging as a process intimately linked to pervasive metabolic reprogramming and increased heterogeneity, spanning from single cells to entire organs and even involving the host-microbiome axis.

Description

The landscape of aging research has been significantly advanced by studies employing cutting-edge metabolomic techniques, which consistently reveal the critical role of metabolic dysregulation and heterogeneity. At the cellular level, single-cell metabolomics provides an unparalleled resolution into the diverse metabolic states within a population. One study on aging tissues uncovered a significant shift in mitochondrial metabolism, marked by increased TCA cycle intermediates and altered amino acid metabolism. Crucially, it also highlighted heightened metabolic heterogeneity among individual cells, suggesting that this variability contributes substantially to cellular dysfunction during aging [1]. This concept of increased metabolic diversity at the single-cell level is further supported by research into cellular senescence, where dynamic shifts in central carbon and lipid metabolism were observed, emphasizing metabolic plasticity as a driver of the varied phenotypes seen in senescent cells [5]. Similarly, investigations into aging human mesenchymal stem cells (hMSCs) using single-cell metabolomics revealed shifts in glycolysis and mitochondrial respiration, coupled with an increased metabolic diversity that directly impacts their functional decline and regenerative capacity [10]. These findings collectively point to single-cell metabolic heterogeneity as a hallmark of cellular aging and senescence.

Moving beyond individual cells, spatial metabolomics has brought into focus the importance of region-specific metabolic alterations within tissues and organs. In aging skeletal muscle, this technique mapped distinct metabolic changes, showing a notable reprogramming with decreased glycolysis and increased fatty acid oxidation in specific areas. This spatial heterogeneity is proposed

to be a critical factor in the development of sarcopenia and other age-related muscle declines, offering specific targets for therapeutic interventions [2]. A similar approach in the aged liver identified region-specific metabolic vulnerabilities. Distinct metabolic profiles across different liver zones involved glucose and lipid metabolism, as well as redox balance, underscoring that interventions for age-related liver dysfunction must consider these intra-organ metabolic variations [9]. These studies affirm that metabolic changes during aging are not uniform but are highly localized and spatially resolved.

Further characterization of metabolic alterations comes from techniques like metabolic flux analysis, which precisely measures the rates of metabolic reactions. Research using this method on senescent human fibroblasts identified a unique metabolic signature: reduced glucose uptake and glycolytic flux, alongside an enhanced reliance on mitochondrial oxidative phosphorylation and specific amino acid pathways. These metabolic shifts are instrumental in supporting the senescent phenotype and its broader impact on tissue aging [3]. This highlights a fundamental reprogramming of central carbon metabolism as a key feature of cellular senescence.

The complexity of age-related metabolic changes is evident across whole organs and systems. A broad characterization of murine aging revealed tissue-specific metabolic reprogramming, where each organ developed unique metabolic signatures distinct from a general aging pattern. This involved diverse alterations in glycolysis, fatty acid oxidation, and amino acid metabolism, fundamentally challenging the idea of a universal metabolic decline with age and reinforcing the concept of organ-level metabolic heterogeneity [4]. Furthermore, the aging brain itself exhibits profound metabolic heterogeneity, with different cell types and regions displaying unique metabolic profiles and vulnerabilities. A comprehensive review linked these metabolic shifts, including altered glucose metabolism, mitochondrial dysfunction, and lipid metabolism, to neuronal vulnerability and the progression of neurodegenerative diseases and cognitive decline [6].

Beyond the intrinsic metabolism of cells and organs, the gut microbiota plays an undeniable role in influencing systemic metabolism during aging. Investigations into gut microbiota-derived metabolites in human aging and longevity identified specific metabolic signatures, such as altered short-chain fatty acids and bile acid profiles, that correlate with healthy aging. This indicates a significant contribution of the gut microbiome to systemic metabolic heterogeneity and its profound influence on host physiology throughout the aging process [7]. Complementing these findings, a general metabolomic analysis of aging kidneys revealed major alterations in lipid, amino acid, and carbohydrate metabolism, suggesting a metabolic shift towards less efficient energy utilization and increased oxidative stress. Such insights are crucial for identifying potential biomarkers and therapeutic targets for age-related kidney diseases [8]. The cumulative evidence strongly supports the view that metabolic reprogramming and heterogeneity are pervasive, multi-scale features of biological aging, affecting cellular function, tissue integrity, organ performance, and overall systemic health.

Conclusion

Aging is characterized by pervasive metabolic reprogramming and increased heterogeneity across biological scales, from single cells to entire organs. Single-cell metabolomics reveals dynamic shifts in mitochondrial, central carbon, and lipid metabolism, alongside heightened metabolic diversity in aged tissues, senescent cells, and human mesenchymal stem cells, contributing to cellular dysfunction and functional decline [1, 5, 10]. Spatially resolved studies further demonstrate region-specific metabolic alterations within aging skeletal muscle and liver, involving changes in glycolysis, fatty acid oxidation, and redox balance. These findings highlight that metabolic changes are not uniform but localized, playing crucial roles in conditions like sarcopenia and age-related organ dysfunction [2, 9]. Metabolic flux analysis in senescent fibroblasts shows reduced glucose uptake but increased mitochondrial oxidative phosphorylation, underscoring a distinct metabolic signature supporting senescence [3]. At the organ level, murine studies confirm tissue-specific metabolic reprogramming, challenging a uniform view of aging and emphasizing heterogeneity in pathways like glycolysis and amino acid metabolism [4]. Reviews on the aging brain highlight region-specific metabolic vulnerabilities impacting neurodegenerative diseases [6]. Furthermore, external factors like gut microbiota contribute to systemic metabolic heterogeneity, with specific metabolite signatures correlating with healthy aging [7]. General metabolomic analyses also pinpoint significant shifts in lipid, amino acid, and carbohydrate metabolism in aging organs like the kidney, suggesting less efficient energy use and increased oxidative stress, which could lead to age-related diseases [8]. Together, these studies emphasize that metabolic dysregulation and heterogeneity are fundamental aspects of the aging process, offering critical insights for therapeutic strategies.

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