Review

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Interplay between aging and metabolic diseases: from molecular mechanisms to therapeutic horizons

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Abstract: Aging and metabolic diseases are intricately linked through bidirectional molecular mechanisms that foster a harmful cycle of physiological decline. This cycle is driven by several key factors, including altered nutrient sensing, mitochondrial dysfunction, cellular senescence, chronic inflammation, epigenetic modifications, circadian rhythm disruptions, and imbalances in the gut microbiota. Emerging interventions targeting this aging-metabolism axis hold significant promise for extending healthspan. These approaches include the use of pharmacological mimetics, senolytics, multi-omics strategies, and microbiome modulation, all of which aim to restore metabolic homeostasis and mitigate age-related pathologies. However, several challenges remain in translating these strategies into clinical practice. These include the need for tissue-specific targeting, ensuring the long-term safety of interventions, and addressing socioeconomic disparities in healthcare access. Future research efforts are focusing on integrating multi-omic technologies, organoid and human cellular models, and developing equitable precision medicine frameworks. These initiatives aim to extend healthspan and reduce the global impact of aging-related metabolic diseases.

Keywords: aging; metabolic diseases; bidirectional mechanisms; therapeutics; healthspan

Introduction

Aging is an unavoidable biological process characterized by a gradual decline in physiological integrity, resulting in impaired cellular repair mechanisms, metabolic dysregulation, and increased susceptibility to chronic diseases [1]. Central to this decline is the disruption of metabolic homeostasis, a hallmark shared with conditions such as diabetes, obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular diseases (CVDs), neurodegenerative diseases, and intestinal dysbiosis, which remain rising global prevalence, contribute to morbidity, mortality, and healthcare expenditures, particularly within aging populations where metabolic decline intersects with age-related frailty and multi-organ dysfunction [2, 3]. For example, over 25 % of adults aged 65 and older are affected by diabetes, while MASLD – now impacting nearly 40 % of adults worldwide – progresses to liver fibrosis and cancer more rapidly in the elderly [4, 5]. The bidirectional interplay between aging and metabolic dysfunction exacerbates disease severity: metabolic stressors like hyperglycemia and lipotoxicity accelerate cellular senescence and mitochondrial damage [6], while senescent cells amplify systemic inflammation and insulin resistance, creating a self-perpetuating cycle that resists conventional therapies [7].

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Over the past decade, research has increasingly acknowledged that aging and metabolic diseases are not isolated phenomena but are intricately connected processes governed by overlapping molecular pathways. These pathways include altered nutrient sensing, mitochondrial dysfunction, chronic low-grade inflammation, and cellular senescence – mechanisms that collectively contribute to systemic tissue damage and functional decline [8]. Epigenetic modifications, such as DNA hypermethylation and histone deacetylation, alter the expression of metabolic genes with advancing age, while metabolic disturbances further disrupt epigenetic stability, creating a self-perpetuating cycle [9]. Additionally, disruptions in circadian rhythms and nutrient-sensing pathways, such as AMPK and mTOR, exacerbate both aging and metabolic dysfunction. Emerging evidence also underscores the role of the gut microbiota as a crucial modulator of the interactions between aging and metabolism [10]. Age-related dysbiosis, characterized by reduced microbial diversity and an increase in pathogenic taxa, alters the production of metabolites such as short-chain fatty acids (SCFAs) and phenylacetylglutamine (PAGln) [11, 12]. While SCFAs like butyrate support metabolic health by enhancing gut barrier function and insulin sensitivity, elevated PAGln – a gut derived metabolite – activates adrenergic receptors to disrupt mitochondrial dynamics and promote senescence in multiple organs [11]. The findings highlight the microbiome's dual role as both a potential exacerbator and alleviator of age-related metabolic disorders. These interconnected pathways create a vicious cycle in which aging and metabolic diseases mutually reinforce each other, which underscores the necessity for multi-targeted therapeutic approaches to interrupt this harmful cycle.

Targeting the aging-metabolism axis presents promising therapeutic opportunities. For instance, caloric restriction mimetics (such as metformin, rapamycin) are believed to promote health and longevity via targeting pathways like insulin/IGF-1, AMPK, mTOR and sirtuin [13]. Senolytic agents (such as dasatinib quercetin, D&Q), which selectively eliminate senescent cells, have been shown to enhance glucose tolerance and reduce hepatic lipid accumulation in aged preclinical models [14, 15]. Moreover, the gut microbiome plays a significant role in modulating host metabolism and aging through metabolites such as PAGln and SCFAs, adding another layer of complexity [16]. Importantly, the rapid advancement of multi-omics technologies has enabled a deeper understanding of aging and related diseases [17]. Understanding the bidirectional interaction between aging and metabolism will necessitate the integration of multi-omics approaches with longitudinal clinical data, thereby linking mechanistic insights to translational breakthroughs.

Despite recent advances, critical challenges remain. Biomarkers that can reliably differentiate chronological age from biological age, such as proteomic clocks or senescence-associated markers, require validation across diverse populations. Similarly, therapeutic strategies such as senolytics and NAD^+ boosters demonstrate promise in preclinical models but face challenges related to tissue specificity and long-term safety in humans. Furthermore, the influence of socioeconomic and environmental factors on the aging-metabolism axis remains insufficiently explored, particularly in low-resource settings where metabolic diseases are escalating most rapidly. A comprehensive understanding of these metabolic shifts is crucial for deciphering the complex biological landscape of aging.

This review aims to systematically summarize the key metabolic alterations that occur during aging, explore their underlying molecular mechanisms, and elucidate how these changes contribute to functional decline in tissues and organs, as well as the development of age-related diseases. Furthermore, we will critically evaluate current and emerging metabolic interventions that hold promise for delaying aging and promoting healthspan, while also addressing the challenges and limitations of these strategies.

Tissue-specific metabolic alterations in aging

Aging triggers distinct metabolic alterations in different tissues, which collectively contribute to systemic functional decline and heightened disease risk. These tissue-specific metabolic shifts are central to the aging process, driving age-related functional deterioration, frailty, and increased susceptibility to various diseases (Figure 1).

Brain

Aging is linked to significant metabolic changes in the brain, which contribute to cognitive decline and heightened susceptibility to neurodegenerative diseases [18]. Notable alterations include a progressive decline in glucose utilization, particularly in memory-related brain regions, resulting in energy deficits [19]. The disruption of astrocyte-neuron metabolic coupling further limits lactate supply to neurons, exacerbating the energy insufficiency. While glucose remains the brain's primary fuel, ketones offer an alternative that can be metabolized by neurons independent of insulin, potentially bypassing insulin resistance. However, the aged brain shows a reduced capacity to efficiently utilize ketone

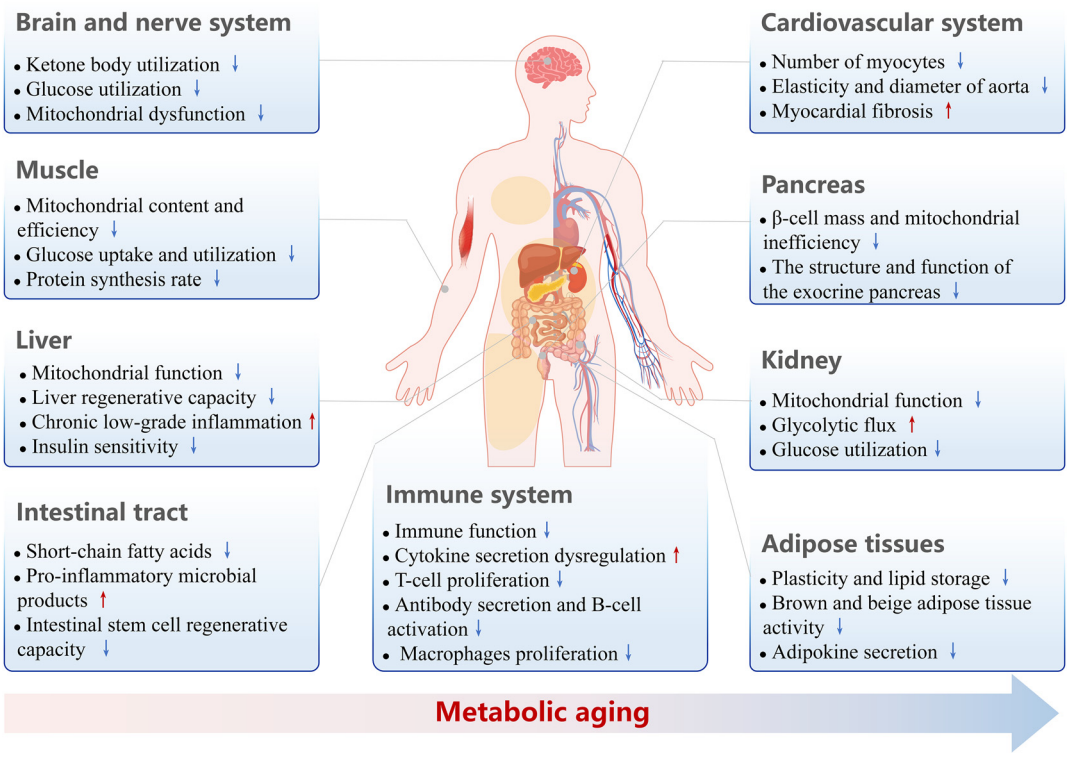

Figure 1: Metabolic aging and the targeted tissues.

bodies, limiting its metabolic flexibility [20]. Additionally, Mitochondrial dysfunction, characterized by decreased oxidative phosphorylation and elevated oxidative stress, impairs ATP production and exacerbates neuronal damage [21]. Moreover, changes in neurotransmitter synthesis and turnover, along with altered lipid metabolism and increased accumulation of toxic metabolic byproducts, further contribute to cognitive decline [22]. Collectively, these metabolic shifts foster an environment of energy deficiency, increased oxidative damage, and disrupted neuronal communication, accelerating brain aging and facilitating the onset of age-related neurological disorders such as Alzheimer's and Parkinson's disease.

Pancreas

Pancreatic aging is marked by progressive metabolic dysfunction that impairs both endocrine and exocrine functions [23]. In the endocrine pancreas, aging leads to compromised glucose sensing and diminished insulin secretion due to β-cell senescence and dysfunction, reduced β-cell mass, and mitochondrial inefficiency [24]. These changes contribute to glucose intolerance and elevate the risk of type 2 diabetes in the elderly. Aged β-cells also experience increased oxidative stress, endoplasmic reticulum (ER) stress, and a decline in autophagy capacity, which further impair cellular function and survival [25]. Simultaneously, the exocrine pancreas undergoes structural and functional decline, including reduced enzyme production, fibrosis, and chronic low-grade inflammation, all of which impair digestive capacity [26]. Additionally, alterations in islet microenvironment, such as disrupted islet vascularization and heightened infiltration of pro-inflammatory immune cells, exacerbate β-cell metabolic stress and insulin resistance [27]. Together, these metabolic disturbances in pancreatic aging contribute to systemic metabolic dysregulation, diminished insulin responsiveness, and an increased susceptibility to metabolic diseases.

Liver

Liver aging is characterized by distinct metabolic alterations that impair hepatic function and contribute to systemic metabolic dysregulation. A key feature of liver aging is the decline in mitochondrial function, leading to reduced oxidative phosphorylation, decreased ATP production, and increased generation of reactive oxygen species (ROS). These changes collectively promote oxidative stress and

hepatocellular damage [28]. Additionally, hepatic lipid metabolism becomes dysregulated, often resulting in lipid accumulation, steatosis, and an increased susceptibility to MASLD [29]. Aging also impairs hepatic glucose metabolism, leading to reduced insulin sensitivity, increased gluconeogenesis, and disrupted glycogen storage, all of which contribute to systemic glucose intolerance [30]. Moreover, liver aging is associated with alterations in bile acid synthesis and cholesterol homeostasis, further affecting metabolic balance [31]. As the liver ages, it exhibits chronic low-grade inflammation and increased cellular senescence, both of which exacerbate hepatic metabolic dysfunction and accelerate fibrosis progression. Together, these metabolic changes compromise liver regeneration, heighten vulnerability to liver diseases, and contribute to age-related metabolic disorders such as insulin resistance and dyslipidemia.

Muscle

Muscle aging, often referred to as sarcopenia, is characterized by profound metabolic alterations that lead to the progressive loss of muscle mass, strength, and function. The decline in mitochondrial content and efficiency results in reduced oxidative phosphorylation, lower ATP production, and increased accumulation of ROS, contributing to muscle fatigue and atrophy [32, 33]. Aged muscles also exhibit impaired glucose uptake and utilization, primarily due to reduced insulin sensitivity and decreased expression of glucose transporters, which promotes systemic insulin resistance [34]. Lipid metabolism is also dysregulated during muscle aging, with increased intramuscular fat deposition (myosteatosis) and impaired fatty acid oxidation, further exacerbating metabolic stress and reducing muscle quality [35]. Additionally, protein synthesis rates decline while protein degradation pathways, such as the ubiquitin-proteasome system and autophagy-lysosome pathway, become dysregulated, tipping the balance toward muscle protein loss [36]. Chronic low-grade inflammation and altered muscle stem cell (satellite cell) function further contribute to the impaired regenerative capacity of aged muscle [37]. Collectively, these metabolic disturbances drive the progression of sarcopenia and are closely linked to increased frailty, metabolic diseases, and functional decline in the elderly.

Kidney

Kidney aging is characterized by progressive metabolic dysfunction that impairs renal structure and function. During kidney aging, glucose metabolism is altered, with increased renal insulin resistance, impaired glucose utilization, and enhanced glycolytic flux, contributing to cellular stress and fibrosis [38]. Lipid metabolism becomes dysregulated, leading to abnormal lipid accumulation in renal tissues, which promotes lipotoxicity, inflammation, and tubular injury [39]. Additionally, aged kidneys exhibit disrupted amino acid metabolism and a reduced capacity for ammoniagenesis, potentially impairing acid-base homeostasis [40]. Autophagy and mitophagy processes are markedly diminished during kidney aging, leading to the accumulation of damaged proteins and organelles [41]. Chronic low-grade inflammation, cellular senescence, and extracellular matrix deposition further exacerbate metabolic dysfunction and promote age-related kidney diseases such as chronic kidney disease (CKD) [42, 43]. Together, these core metabolic changes drive renal aging, reduce kidney resilience, and contribute to the increased susceptibility to metabolic and cardiovascular complications in the elderly.

Cardiovascular system

Cardiovascular aging is marked by fundamental metabolic remodeling that fosters the development and worsening of heart failure, atherosclerosis, and hypertension. With aging, the heart undergoes a metabolic shift from fatty acid oxidation to greater reliance on glucose and ketone bodies for energy, reflecting reduced metabolic flexibility and adaptive capacity [44]. However, insulin resistance frequently develops with age, impairing glucose uptake and utilization, which exacerbates energy deficits and promotes cardiac dysfunction [45]. Lipid metabolism becomes dysregulated in vascular tissues, contributing to lipid accumulation, foam cell formation, and atherosclerotic plaque development [46]. Aging is also associated with chronic low-grade inflammation, endothelial dysfunction, impaired nitric oxide (NO) signaling, and increased vascular stiffness, all of which are metabolically driven contributors to CVDs progression [47]. Together, these metabolic shifts reduce cardiovascular efficiency, compromise vascular integrity, and significantly increase the risk of age-related cardiovascular diseases.

Adipose tissues

Aging in adipose tissue is marked by significant metabolic alterations that contribute to systemic metabolic dysfunction and increased risk of metabolic diseases. One major change is the decline in adipose tissue plasticity and its

capacity for lipid storage, leading to ectopic fat accumulation in non-adipose organs such as liver and muscle. This lipotoxicity exacerbates insulin resistance and chronic inflammation [48]. Meanwhile, the activities of brown and beige adipose tissue decline with age, reducing thermogenesis and energy expenditure, thereby contributing to weight gain and metabolic imbalance [49]. Impaired adipokines secretion, including reduced adiponectin and increased leptin resistance, further exacerbates metabolic disturbances [50]. Collectively, these core metabolic changes in adipose tissue during aging play a central role in the development of insulin resistance, type 2 diabetes, and other age-related metabolic disorders.

Intestinal tract

Aging of the intestinal tract is accompanied by significant metabolic alterations that impair nutrient absorption, barrier function, and gut homeostasis. Alterations in carbohydrate, lipid, and amino acid metabolism within the gut epithelium affect nutrient processing and local immune responses [51]. Aging also disrupts the metabolic crosstalk between the gut microbiota and host, resulting in dysbiosis, reduced production of beneficial metabolites such as SCFAs, and increased pro-inflammatory microbial products [52]. These changes exacerbate inflammaging and contribute to impaired intestinal permeability. Furthermore, age-related reductions in autophagy and regenerative capacity of intestinal stem cells impair mucosal renewal, further compromising metabolic and barrier functions [53]. Collectively, these metabolic disturbances in the intestinal tract during aging contribute to systemic inflammation, nutrient malabsorption, and increased susceptibility to gastrointestinal and metabolic diseases.

Immune system

Aging of the immune system is accompanied by metabolic changes, including increased glycolysis, mitochondrial dysfunction, and increased ROS [54]. Aging has multifaceted effects on various immune cells such as macrophages, T-cells, and B-cells, leading to a decline in immune function. Aged T-cells undergo metabolic reprogramming, shifting from oxidative phosphorylation to glycolysis, leading to a decrease in ATP production efficiency and impairing immune functions such as cell proliferation and cytokine production [55]. In some aged B-cells, mitochondrial mass and mitochondrial ROS increase, which affects mitochondrial energy production, influences antibody secretion and B-cell activation [56]. Aging also causes oxidative stress, mitochondrial abnormalities, and excessive activation of the NLRP3 inflammasome in macrophages, reducing their proliferation and DNA repair capabilities, resulting in increased tissue damage and delayed resolution of inflammation [57]. In addition, senescence-associated secretory phenotype (SASP) produced by senescent cells affects macrophages and exacerbates age-related pathologies [58]. In summary, these metabolic change characteristics of immunosenescence impair immune function and are closely related to the high incidence and mortality of age-related diseases such as cardiovascular diseases, neurodegenerative diseases, autoimmune diseases, metabolic diseases, and cancer in elderly patients.

Molecular mechanisms underlying the aging-metabolism axis

Aging is accompanied by characteristic metabolic alterations that contribute to the gradual decline of cellular and tissue function. These interconnected metabolic changes drive the aging process, impair regeneration capacity, and increase susceptibility to age-related diseases, highlighting metabolism as a central target for interventions aiming to promote healthy aging and longevity (Figure 2).

Altered nutrient sensing and signaling

Nutrient sensing and signaling pathways are fundamental regulators of cellular metabolism, growth, and longevity.

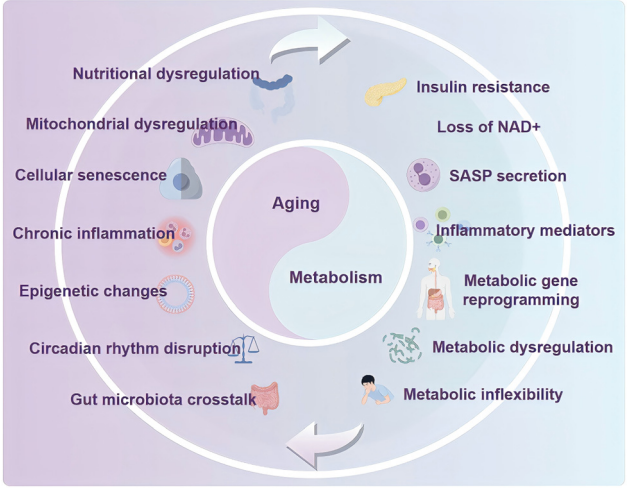

Figure 2: The interplay mechanisms between aging and metabolic diseases.

During aging, these pathways undergo significant alterations that disrupt metabolic homeostasis and contribute to age-associated functional decline. Key nutrient sensing systems include the insulin/IGF-1 signaling pathway, mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins, all of which integrate environmental and intracellular nutrient cues to regulate anabolic and catabolic processes [59]. With aging, insulin/IGF-1 signaling often becomes impaired, leading to insulin resistance and altered glucose metabolism. Concurrently, chronic activation of mTOR signaling promotes cellular growth and proliferation but suppresses autophagy, reducing the cell's ability to clear damaged proteins and organelles, thus accelerating cellular senescence. AMPK activity, which typically responds to energy stress by activating catabolic pathways and promoting mitochondrial biogenesis, declines with age, further impairing energy balance. Similarly, the function of sirtuins, particularly SIRT1, decreases with aging, diminishing their role in DNA repair, mitochondrial function, and metabolic regulation.

The cumulative dysregulation of these nutrient-sensing and signaling pathways contributes to metabolic inflexibility, increased oxidative stress, chronic inflammation, and decreased cellular resilience. Modulation of these pathways through dietary interventions, pharmacological agents, or lifestyle changes holds promise for promoting healthy aging and extending lifespan.

Mitochondrial dysregulation

Aging is intricately linked to mitochondrial dysfunction, a central driver of metabolic diseases such as type 2 diabetes, obesity, and metabolic syndrome. With advancing age, mitochondria exhibit declining efficiency due to accumulated DNA mutations, reduced oxidative phosphorylation capacity, and impaired mitophagy – the process responsible for clearing damaged mitochondria [60]. These age-related mitochondrial deficits lead to diminished ATP production, elevated ROS, and chronic low-grade inflammation, all of which exacerbate systemic metabolic dysregulation. For instance, impaired mitochondrial fatty acid oxidation in skeletal muscle and liver contributes to ectopic lipid deposition, insulin resistance, and hepatic steatosis [61]. Conversely, metabolic stressors like hyperglycemia and lipotoxicity further compromise mitochondrial integrity by disrupting electron transport chain activity and promoting oxidative damage, creating a vicious cycle that accelerates both aging and metabolic pathology.

Emerging research highlights bidirectional crosstalk between mitochondrial dysfunction and metabolic diseases. In type 2 diabetes, mitochondrial fragmentation and reduced NAD^+ levels impair insulin signaling, while obesity-induced inflammation suppresses peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) – a key regulator of cellular energy metabolism often referred to as the "master regulator" of mitochondrial biogenesis [62]. Therapeutic strategies targeting mitochondrial health – such as NAD^+ boosters (e.g., NMN, NR), AMPK activators (e.g., metformin), and compounds enhancing mitophagy – show promise in restoring metabolic homeostasis and mitigating age-related decline [63]. Addressing mitochondrial dysregulation offers a pivotal avenue to disrupt the aging-metabolism axis, potentially extending healthspan and alleviating the global burden of metabolic diseases in aging populations.

Cellular senescence

Cellular senescence, a state of irreversible growth arrest triggered by stressors like DNA damage or telomere shortening, is both a driver and consequence of metabolic decline. With age, senescent cells accumulate across mammalian tissues, likely due to increased induction and impaired immune clearance. A defining feature is cell-cycle arrest mediated by CDK inhibitors, notably $p21^{CIP1}$ ($p21^{high}$) and $p16^{INK4a}$ ($p16^{high}$) [64]. Senescent cells adopt a senescence-associated secretory phenotype (SASP), releasing pro-inflammatory cytokines, proteases, and growth factors that disrupt tissue microenvironments [65]; for example, SASP factors such as IL-6 and TGF-β impair insulin signaling in adipose tissue and liver, exacerbating lipid accumulation and gluconeogenesis [25].

Importantly, cellular senescence is not confined to chronological aging. It can be robustly and relatively rapidly induced under stress conditions such as obesity; over a lifespan, senescent cells tend to accumulate, and their burden becomes especially marked in later aging. Studies show that $p16^{high}$ and $p21^{high}$ senescent cells accumulate in multiple tissues, where they disrupt pancreatic β-cell function and adipose-tissue homeostasis, contributing to insulin resistance, impaired glucose metabolism, and altered lipid storage dynamics [66, 67]. Recent work further reveals that metabolic stressors like excess free fatty acids or advanced glycation end-products (AGEs) directly induce senescence in pancreatic β-cells and hepatocytes, impairing insulin secretion and promoting hepatic steatosis [68]. Senescent cells accumulate in aged metabolic organs, such as adipose tissue, where their SASP amplifies local inflammation and insulin resistance [69]. This bidirectional relationship underscores senescence as a critical node linking aging and metabolic

disease pathogenesis, indicating therapeutic strategies targeting senescent cells offer promising potential for mitigating metabolic disruptions.

Chronic inflammation

Chronic inflammation is increasingly recognized as a shared mechanism underlying the aging process and the development of metabolic diseases. This persistent, low-grade inflammation, often referred to as "inflammaging", is characterized by an upregulation of pro-inflammatory mediators and is a significant risk factor for age-related diseases [70]. The concept of inflammaging suggests that the chronic inflammation observed in aging is not merely a consequence of age-related diseases, but also a contributing factor to their development. One of the key pathways involved in this process is the NF-κB signaling pathway, which is known to regulate the expression of various pro-inflammatory cytokines [71]. The activation of NF-κB is associated with increased transcriptional activity in tissues aging, contributing to the pathogenesis of diseases such as Alzheimer's, diabetes, and osteoporosis. Furthermore, oxidative stress and mitochondrial dysfunction are critical factors that exacerbate chronic inflammation by activating inflammasomes, such as the NLRP3 inflammasome, which further promotes inflammatory responses and is linked to several age-related diseases [72]. Moreover, the concept of senoinflammation, a major mediator underlying age-related metabolic dysregulation, has been proposed to describe the unresolved and uncontrolled inflammation that exacerbates aging and age-related diseases [73]. This encompasses the age-related upregulation of various inflammatory pathways, including NF-κB signaling, cytokines, and inflammasomes, and highlights the importance of targeting these pathways for therapeutic interventions. Understanding the molecular underpinnings of this inflammation provides insights into potential interventions that may mitigate the aging process and reduce the burden of age-related metabolic diseases.

Epigenetic changes

Aging-associated epigenetic changes, such as DNA hypermethylation and histone modification loss, reprogram metabolic gene expression. For example, age-related downregulation of SIRT1, a NAD^+-dependent deacetylase, disrupts mitochondrial biogenesis and fatty acid oxidation, contributing to lipid dysregulation [74]. Simultaneously, metabolic disturbances alter epigenetic landscapes: hyperinsulinemia increases histone acetylation at pro-inflammatory gene promoters, perpetuating inflammation [75]. Mitochondrial dysfunction further bridges aging and metabolism. Declining mitophagy in aged cells leads to the accumulation of damaged mitochondria, which produce excess ROS [76]. ROS not only damage macromolecules but also activate stress kinases, impairing insulin receptor signaling. Intriguingly, interventions like caloric restriction or AMPK activators mitigate both aging and metabolic defects by enhancing mitochondrial efficiency and epigenetic stability, highlighting their interconnected regulatory axes [77]. Briefly, aging and metabolic dysfunction are tightly interconnected through epigenetic alterations and mitochondrial impairment, forming a bidirectional regulatory axis that can be modulated by interventions like caloric restriction and AMPK activation.

Circadian rhythm disruption

Aging disrupts circadian rhythms, which govern daily oscillations in metabolic processes, exacerbating the risk of obesity, type 2 diabetes, and cardiovascular diseases [78]. Core clock genes, such as BMAL1 and CLOCK, regulate nutrient-sensing pathways and mitochondrial function, but their expression declines with age, leading to desynchronized lipid and glucose metabolism [79]. Conversely, metabolic disturbances – such as hyperlipidemia and insulin resistance – worsen circadian misalignment by altering histone acetylation patterns and reducing BMAL1 expression, creating a bidirectional feedback loop [80]. Moreover, age-related circadian disruption also perturbs gut microbiota rhythms, reducing beneficial metabolites like butyrate and elevating pro-inflammatory molecules (e.g., lipopolysaccharides), which impair intestinal barrier function and systemic insulin sensitivity [81]. In MASLD, disrupted hepatic circadian clocks promote lipid accumulation by dysregulating PPARα-mediated fatty acid oxidation. Therapeutic strategies, such as time-restricted feeding and melatonin supplementation, restore circadian-metabolic synchrony, improving glucose tolerance and mitochondrial function in preclinical models [82, 83]. Targeting clock-enhancing compounds or NAD^+ boosters may offer novel interventions to decouple aging from metabolic decline. Addressing circadian dysfunction thus represents a critical frontier in mitigating age-related metabolic diseases.

Gut microbiota crosstalk

The aging process is intricately linked with changes in the gut microbiota, which, in turn, can influence the

development of metabolic diseases. As individuals age, the composition of their gut microbiota undergoes significant alterations, which can lead to a state known as dysbiosis [84]. This dysbiosis is characterized by a loss of beneficial microbial diversity and an increase in pathogenic bacteria, contributing to systemic inflammation and metabolic dysfunction. One of the critical roles of the gut microbiota is in maintaining energy homeostasis and metabolic health. Age-related changes in the gut microbiota can disrupt these processes, leading to metabolic disorders such as obesity, diabetes, and cardiovascular diseases [85].

The gut microbiota influences host metabolism through the production of metabolites such as SCFAs, which help regulate glucose and lipid metabolism [86]. Furthermore, the gut microbiota interacts with the host's immune system, and age-related changes in this interaction can exacerbate chronic inflammation, a significant risk factor for the development of metabolic diseases in the elderly. The gut microbiota's influence on the immune system is mediated through various pathways, including the modulation of gut barrier integrity and the production of microbial metabolites that can affect immune cell function [87]. Research has shown that interventions targeting the gut microbiota, such as dietary modifications, prebiotics, and probiotics, can potentially mitigate age-related metabolic diseases [88]. These interventions aim to restore a healthy balance of gut microbiota, thereby reducing inflammation and improving metabolic outcomes. Understanding the complex crosstalk between the gut microbiota and host metabolism during aging is crucial for developing strategies to promote healthy aging and prevent metabolic diseases.

Metabolic interventions for healthy longevity

Metabolic interventions may gradually become potentially powerful strategies to promote healthy longevity by targeting the fundamental metabolic processes that drive aging. These interventions act by modulating key nutrient sensing pathways, optimizing energy utilization, maintaining metabolic homeostasis, and enhancing cellular repair mechanisms, all of which ultimately enhance metabolic flexibility, improve the ability of cells and tissues to adapt to environmental changes, and slow the pace of aging process. By correcting age-related metabolic dysfunctions across multiple organs, metabolic interventions have the potential to not only delay the onset of age-associated diseases but also improve healthspan and functional capacity. Integrating diverse metabolic strategies holds great promise for achieving healthy aging and extending life quality in the elderly population (Figure 3).

Dietary restriction paradigms

Dietary restriction (DR) paradigms, including calorie restriction (CR), intermittent fasting, and time-restricted feeding, have been recognized as effective metabolic interventions to promote healthy longevity. These strategies typically modulate key nutrient sensing pathways such as insulin/IGF-1, mTOR, AMPK, and sirtuins, potentially shifting cellular metabolism from anabolic to catabolic states, which enhances stress resistance, autophagy, and mitochondrial function. DR improves metabolic flexibility, optimizes glucose and lipid metabolism, and reduces chronic low-grade inflammation, collectively delaying the onset of age-related metabolic diseases. Studies in various species consistently demonstrate that DR can extend lifespan and improve healthspan, primarily by optimizing energy utilization, reducing oxidative damage and enhancing cellular repair mechanisms. Importantly, emerging DR-mimetic compounds, such as rapamycin metformin and sirtuin activators, aim to replicate the metabolic benefits of DR without the need for sustained caloric reduction. These metabolic interventions further underscore the value of targeting nutrient sensing and energy metabolism as potential strategies to achieve healthy aging and longevity.

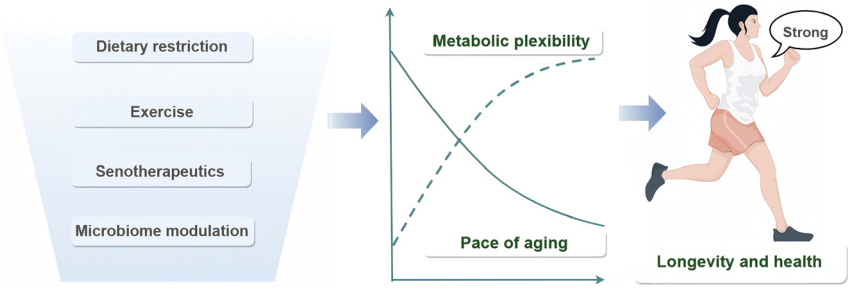

Figure 3: Metabolic interventions for healthy aging and longevity.

Exercise

Exercise represents a well-established and effective metabolic intervention that may promote healthy longevity by enhancing systemic energy metabolism, improving organ function, and delaying age-related decline. Regular physical activity activates key nutrient-sensing pathways, including AMPK, mTOR, and sirtuins, which in turn stimulate mitochondrial biogenesis, autophagy, and improved metabolic flexibility. Exercise enhances glucose uptake, improves insulin sensitivity, and stimulates fatty acid oxidation, effectively counteracting metabolic inflexibility and reducing the risk of age-associated diseases such as type 2 diabetes, cardiovascular disease, and sarcopenia. Additionally, exercise has been shown to reduce chronic low-grade inflammation, mitigate oxidative stress, and support the maintenance of muscle mass and functional capacity. Both aerobic and resistance training have been shown to positively influence the metabolic profiles of tissues aging, including muscle, adipose tissue, liver, and the brain. For individuals unable to engage in regular physical activity, exercise-mimetics, such as compounds that activate AMPK or mimic the effects of exercise, offer promising alternatives to replicate the benefits of exercise on metabolic health [89]. These metabolic benefits collectively contribute to extended healthspan and improved quality of life, positioning exercise as a cornerstone intervention for promoting healthy aging.

Senotherapeutics

Senotherapeutics, including senolytics and senomorphics, represent emerging metabolic interventions aimed at promoting healthy longevity by targeting cellular senescence and modulating the SASP. The accumulation of senescent cells with age may disrupt tissue metabolism through the release of pro-inflammatory cytokines, proteases, and growth factors that contribute to chronic low-grade inflammation, metabolic dysregulation, and tissue dysfunction. Senolytics selectively eliminate senescent cells, potentially reducing the metabolic burden and restoring tissue function, while senomorphics suppress the harmful components of the SASP without clearing the cells, improving the local metabolic environment. These interventions have been shown to attenuate insulin resistance, improve mitochondrial function, and reduce systemic inflammation, all of which are central to metabolic health and longevity. Preclinical studies highlight the therapeutic potential of senolytic drugs such as D&Q, and NAD^+ boosters like NMN, in addressing hepatic steatosis and mitochondrial dysfunction [90, 91]. By modulating the metabolic consequences of cellular senescence, senotherapeutics appear to offer a promising strategy to potentially delay aging processes and prevent age-related metabolic diseases, paving the way for novel therapeutic approaches to extend healthspan.

Multi-omic integration

Multi-omic integration – combining genomics, transcriptomics, proteomics, metabolomics, and epigenomics – provides unprecedented insights into the complex metabolic networks that govern aging and longevity. While not a direct intervention like caloric restriction or exercise, it facilitates the identification of key biomarkers, metabolic signatures, and molecular pathways associated with aging and age-related diseases [92, 93]. By integrating data across multiple omics layers, multi-omic approaches provide a comprehensive understanding of the biological processes underlying aging and metabolic dysfunction [94, 95]. Importantly, multi-omic profiling enables the discovery of individualized “metabolic aging signatures”, supporting precision strategies such as personalized dietary regimens, pharmacological combinations, and exercise prescriptions tailored to a person’s molecular profile. Integrating these data accelerates biomarker discovery, enhances patient stratification, predicts therapeutic response, and helps refine dosing and timing to maximize healthspan while delaying the onset of age-associated diseases.

Single-cell and spatial omics further extend these insights by mapping cell states and microenvironmental contexts *in situ*. In MASLD, for example, spatial transcriptomic and proteomic maps show how aging disrupts liver zonation – spatially distinct metabolic programs across the hepatic lobule – predisposing to steatosis and impaired regeneration [96]. More broadly, spatial omics delineate metabolic stress and senescence gradients across tissues implicated in obesity, diabetes, fatty liver disease, and cardiovascular pathology, underscoring their growing utility in metabolic disease research [97–99]. By localizing dysregulated circuits to specific niches (e.g., periportal vs. pericentral hepatocytes, endothelial or immune cell subsets), these methods reveal targets for zonation-preserving or niche-directed therapies and yield early, tissue-level biomarkers of efficacy.

Together, multi-omic, single-cell, and spatial technologies bridge molecular mechanisms of aging with tissue-level metabolic dysfunction. Their integration provides a practical roadmap for designing, monitoring, and personalizing anti-aging interventions – whether dietary, exercise-based, or pharmacological – to restore metabolic flexibility and extend healthspan.

Microbiome modulation

The gut microbiome plays a pivotal role in regulating host metabolism, immune function, and systemic homeostasis. With aging, its composition and metabolic activity undergo significant shifts, often leading to dysbiosis – a state of microbial imbalance associated with various age-related diseases. Microbiome modulation has emerged as a promising metabolic intervention to promote healthy longevity. Studies demonstrate that centenarians harbor distinct microbial signatures characterized by enhanced biodiversity, enrichment of anti-inflammatory taxa like Christensenellaceae and Akkermansia, and robust production of SCFAs such as butyrate PMID: 37117796 [100, 101]. These microbial features correlate with reduced systemic inflammation and improved metabolic parameters, offering a blueprint for therapeutic interventions. Fecal microbiota transplantation (FMT) has shown promise in transferring these beneficial microbial consortia to aged or metabolically compromised recipients [102]. Clinical trials report FMT-mediated restoration of gut ecosystem stability, suppression of pro-inflammatory cytokines, and improved insulin sensitivity in metabolic syndrome patients, mimicking the anti-inflammatory profile observed in centenarian microbiomes [103]. These interventions may improve insulin sensitivity, modulate lipid metabolism, reduce systemic inflammation, and support the maintenance of energy balance. By reshaping the gut microbiota and its metabolic outputs, microbiome modulation offers a promising avenue to influence host metabolism, delay aging processes, and extend healthspan.

Future directions and challenges

Metabolism is central to the aging process, with key features including mitochondrial dysfunction, impaired nutrient sensing, reduced metabolic flexibility, and chronic low-grade inflammation. These interconnected metabolic disturbances drive energy deficits, oxidative stress, cellular senescence, and systemic decline, accelerating the onset of age-related diseases. Crucially, targeting these metabolic hallmarks through interventions such as dietary modulation, exercise, senotherapeutics, and microbiome regulation holds great promise for promoting healthy aging and preventing age-associated disorders. Metabolic interventions seem to offer an effective, system-wide strategy to restore cellular homeostasis, enhance resilience, and extend healthspan.

Despite significant advances, several critical questions remain unresolved in the field of metabolic aging. First, the precise causal relationship between metabolic alterations and aging is not fully defined – whether metabolic dysfunction is a primary driver of aging or a consequence of the aging process itself is still under debate. Second, the spatiotemporal dynamics of metabolic changes across different tissues and aging stages are poorly understood, limiting our ability to design targeted interventions. Current research lacks a comprehensive understanding of how metabolic alterations unfold in different tissues over time. Third, the molecular basis of inter-individual heterogeneity, including genetic, epigenetic, and environmental factors, in metabolic aging is largely unknown, complicating the development of universal strategies. There is a need to identify personalized intervention points based on molecular signatures. Additionally, the optimal intervention window, dosing, and duration for metabolic therapies to maximize benefits while minimizing risks remain undefined. Long-term safety and potential off-target effects of chronic metabolic interventions also require thorough investigation. Finally, there is an urgent need to develop more precise, dynamic biomarkers to effectively assess metabolic health and monitor intervention outcomes in aging populations. In summary, bridging precision diagnostics, physiologically relevant models, equitable clinical translation and optimized lifestyle interventions will be critical to disrupting the aging-metabolism axis. Addressing these challenges demands interdisciplinary collaboration, ethical innovation frameworks, and policies prioritizing healthspan extension in aging populations.

Future research in metabolic aging may focus on integrating multi-omic technologies, including metabolomics, proteomics, and single-cell sequencing, to enable system-wide and tissue-specific analyses of metabolic dynamics. Advancing *in vivo* metabolic imaging and real-time monitoring techniques will be essential to capture metabolic changes with greater spatial and temporal precision. Mechanistic studies utilizing organoids and human cellular models will offer more physiologically relevant insights into human metabolic aging. Additionally, there is a critical need to design large-scale, rigorous, and long-term clinical trials to validate the efficacy and safety of metabolic interventions in diverse human populations. Moving forward, the development of precision nutrition and personalized aging interventions will be key to tailoring strategies based on individual metabolic profiles.

Collectively, a deeper understanding of the metabolic mechanisms of aging and the development of safe, effective interventions hold tremendous potential for addressing the

global challenge of population aging and achieving the goal of healthy longevity.

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