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Metabolism and Aging in Co-Evolution: Bidirectional Regulatory Mechanisms and Intervention Strategies

Xingyu Liu

School of Public Health, University of Washington, Seattle, USA
xl243@uw.edu

Abstract. The connections between metabolism and ageing are becoming pivotal as two-way relations rather than one-way. Although metabolic processes, including mitochondrial activity, nutrient sensing, and autophagy, have been known to affect the rate at which one ages, the ageing process conversely impairs metabolic efficiency and regulatory mechanisms. As discussed in this paper, the relationship between these two forces is dynamic, and some questions that are prone to emerge are: which force is the driver of ageing, and which is the driven force? Metabolic ageing represents a nascent research frontier spanning molecular biology, gerontology, and pharmacology, and the essay will reflect on how metabolic degradation leads to cellular senescence and how age-induced dysregulation compromises metabolic pathways. By using the comparative analysis of the interventions, such as caloric restriction, metformin, and NAD+ supplementation, the paper points to the strategies that would address metabolism to slow down the ageing process. Finally, the essay demonstrates that a cyclical model is the most likely, where metabolism and ageing are co-evolving. This framework offers translational pathways for leveraging the association to promote healthy longevity

Keywords: Metabolism, Ageing, Mitochondria, Nutrient Sensing, Longevity

1. Introduction

Ageing is a biologically complex process that is characterised by the progressive loss of physiological functions, increased susceptibility to disease, and diminished repair and regenerative capacity. Conventionally, ageing was considered a passive outcome of wear-and-tear accumulation in time. Nevertheless, recent studies indicate that metabolic pathways actively participate in the process of ageing. Metabolism involves the biochemical mechanisms that support life, such as the production of energy, the usage of nutrients, and cell repair. These processes contribute not only to survival but are essential in the determination of the rate and quality of ageing. This paper aims to determine whether metabolism influences ageing or ageing influences metabolism. This raises fundamental questions regarding causal relationships and bidirectional feedback mechanisms. On the one side, metabolic disorders that have been shown to increase the rate of ageing include mitochondrial degeneration, oxidative stress, and malfunctioning nutrient sensing. Ageing, on the other hand, destabilizes the metabolic homeostasis by stimulating hormonal changes, epigenetic drift, and chronic inflammation. This reciprocal connection indicates that ageing and metabolism

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have a complex, reciprocal relationship. This essay addresses three core questions: How does metabolism influence the onset and progression of ageing? In what ways does ageing impair metabolic function? Can interventions targeting metabolism effectively delay ageing? This study holds significant value for developing anti-aging interventions targeting metabolic pathways.

2. Metabolism as a driver of ageing

2.1. Mitochondrial dysfunction and ROS accumulation

Mitochondria are vital organelles that produce cellular energy through oxidative phosphorylation, a process that inherently generates reactive oxygen species (ROS) as byproducts. Under normal conditions, cells maintain a balance between ROS production and antioxidant defenses. However, with age, this equilibrium is disrupted, leading to ROS accumulation and oxidative stress. This stress causes impairment of mitochondrial dynamics, including damage to mitochondrial DNA, proteins, and lipids, resulting in decreased ATP production [1,2]. Additionally, mitochondria may release their DNA due to ROS-mediated damage, which not only disrupts mitochondrial fusion and fission dynamics but also activates the NLRP3 inflammasome pathway. Not only do these impairments undermine energy metabolism, but they also stimulate cellular senescence and apoptosis, reinforcing the ageing phenotype. Critically, mitochondrial dysfunction does not just accompany the process of ageing but is a direct causative factor in the ageing process as it intensifies oxidative damage and disrupts cellular homeostasis. Mitochondrial quality control interventions have demonstrated potential in restoring mitochondrial structure and function and decreasing ROS levels, including exercise, caloric restriction, and NAD+ supplementation [3]. Thus, preserving mitochondrial integrity is of paramount concern to metabolic health and an important target in slowing the effects of the aging process.

Mitochondria play a crucial role in cellular energy metabolism by producing ATP through oxidative phosphorylation of nutrients. Nonetheless, reactive oxygen species (ROS) are generated in this process by default. Unless properly counteracted by free radical scavenging mechanisms, ROS can cause harm by damaging cellular products such as DNA, proteins, and lipids. With time, ROS can accumulate and result in oxidative stress, which disrupts the functioning of the mitochondrion and promotes cellular senescence. This damage is further complicated by mutations in the mitochondrial DNA (mtDNA), which occur more often as the mtDNA is adjacent to the electron transport chain with fewer repair pathways [4]. With declining mitochondrial efficiency, cells have lowered energy production and greater susceptibility to stress, which speeds up the ageing process. Enhancement of mitochondrial biogenesis via exposure to interventions like aerobic exercise and caloric restriction has been demonstrated to induce PGC-1alpha, a primary driver of mitochondrial renewal, consequently improving metabolic resilience and the delay of age-related degeneration [5]. Therefore, mitochondrial health is not just an outcome of ageing, but it determines the course of ageing.

2.2. Nutrient sensing pathways: mtor, AMPK, and sirtuins

Nutrient-sensing pathways serve as master regulators of cellular metabolism, growth, and longevity, dynamically responding to nutrient and energy availability The most studied pathways—mTOR, AMPK, and sirtuins—exert distinct yet interconnected effects on cell fate, promoting anabolism and growth under nutrient-rich conditions, but contributing to ageing and disease when chronically suppressed [4]. In contrast, AMPK and sirtuins act as energy sensors, activated during low-nutrient

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states (e.g., fasting or exercise) to promote catabolism, mitochondrial biogenesis, and stress resistance [6,7]. Longevity pathways not only mediate metabolic homeostasis but also affect gene expression, inflammation, and DNA repair, thus representing key targets of ageing-slowing interventions [8]. A deeper insight into the subtle interaction between all of these nutrient-sensing pathways will give us the background on how we can develop therapeutics to regulate ageing at the molecular level.

Metabolic regulation is closely connected with the nutrient-sensing pathways, which control the growth, repair, and survival of the cells. Of these, the mechanistic target of rapamycin (mTOR) has been recognised as the most important mechanism in enhancing anabolic processes, including protein synthesis and cell growth. Although crucial to the development and maintenance of tissue, sustained activation of mTOR in a mature organism has also been shown to decrease autophagy and increase cellular stress, which can lead to ageing and age-related diseases [9]. By contrast, the AMP-activated protein kinase (AMPK) and sirtuins are metabolic guardians that facilitate catabolic pathways, stimulate mitochondrial activities, and increase stress-resistance in the face of nutrient insufficiencies. Caloric restriction and intermittent fasting are pathways that are activated by low nutrient availability and have been demonstrated to increase lifespan in a variety of organisms [8]. Thus, the mTOR/AMPK/sirtuin signalling balance critically influences metabolic health and longevity. The rate of ageing can be affected by regulating these pathways to decrease the metabolic dysfunction burden.

2.3. Autophagy and cellular maintenance

Autophagy is the cellular housekeeping process that degrades and recycles damaged organelles, misfolded proteins, and other waste. This process maintains cellular homeostasis and prevents the accumulation of toxic aggregates that impair cellular function. Ageing is associated with decreasing rates of autophagy, causing a cumulative accumulation of cellular garbage and predisposition to neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [10]. Declining autophagy results from reduced expression of autophagy-related genes and diminished sensitivity to metabolic stress. Pharmacological interventions have demonstrated that boosting autophagy by using drugs such as spermidine and rapamycin stimulates cellular housekeeping and prolongs lifespan in animal models [11]. These findings underscore autophagy’s dual role—both reactive and proactive—in modulating ageing. Ensuring effective autophagic flux is thus a primary intervention tactic in healthy ageing.

3. Ageing as a disruptor of metabolism

3.1. Hormonal and enzymatic changes

As ageing progresses, it severely impacts endocrine hormones, altering both secretion levels and sensitivity of key metabolic hormones. The most significant alteration is the decrease in insulin sensitivity leading to the development of metabolic syndrome, type 2 diabetes, and cardiovascular disease. This decline results from chronic inflammation, reduced physical activity, and altered adipose tissue distribution—all of which impair glucose uptake and utilization [12]. Moreover, they may tend to reduce the levels of thyroid hormones with age, providing an overall slowed basal metabolism rate and thermogenesis capabilities. These hormonal changes disrupt lipid metabolism, protein turnover, and energy balance, which further aggravate the impact of metabolic decline. Age-related decline in enzymatic activity impairs hepatic detoxification and intestinal nutrient absorption.

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In combination, these hormonal and enzymatic adaptations depict how ageing compromises metabolic control, which contributes to the feedback loop of accelerated physiological decline.

3.2. Epigenetic modifications and gene expression

In addition to the hormonal alterations, the ageing process is also linked to epigenetic adjustment of the genes without altering the underlying DNA. These alterations encompass DNA methylation, histone acetylation, and chromatin rearrangement, which have general effects on the transcription of metabolic genes. With time, epigenetic drift accumulates and causes silencing of the protective genes and activation of pro-inflammatory and pro-ageing pathways [13]. The so-called epigenetic clock has become a strong methodology for assessing biological age using methylation profiles and revealing the connection between metabolic health and ageing. As an example, patients who experience faster epigenetic ageing usually have features of metabolic disorders, such as insulin resistance (IR) and dyslipidaemia [14]. These observations indicate that epigenetic alterations do not simply serve as ageing indices but are dynamic elements in the ageing process of metabolism. Targeting epigenetic dysregulation therefore represents a promising therapeutic strategy for restoring metabolic homeostasis and extending longevity.

3.3. Inflammation and metabolic decline

Chronic low-grade inflammation (inflammaging) is a hallmark of ageing and a major contributor to metabolic dysfunction. This condition is also distinguished by the presence of increased levels of pro-inflammatory cytokine proteins, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-Alpha), and C-reactive protein (CRP), which inhibit insulin signalling, disturb metabolism of lipids, and cause mitochondrial dysfunction [15]. The causes of inflammaging are related to many factors, such as cellular senescence, microbial dysbiosis, and the reorganisation of the immune system. These inflammatory mediators not only harm tissues but also distort the activity of nutrient-sensing pathways, worsening metabolic deterioration. Dietary interventions rich in polyphenols, omega-3 fatty acids, and fibre have shown efficacy in reducing systemic inflammation and improving metabolic outcomes in older adults [16]. As a result, it is imperative to mitigate inflammaging to maintain metabolic integrity and postpone age-related disorders.

4. Interventions and the bidirectional model

4.1. Caloric restriction and fasting

Two of the most investigated interventions to promote a healthy metabolism and improve longevity are caloric restriction (CR) and intermittent fasting (IF). These dietary interventions decrease calorie intake without malnutrition, leading to adaptive responses that increase cell repair, resistance to stress, and metabolism. CR and IF induce AMPK and sirtuins, inhibit mTOR, and promote autophagy, thus enhancing mitochondrial activity and decreasing oxidative harm [17]. Clinical studies demonstrate these interventions can reduce blood glucose levels, improve lipid metabolism, and lower inflammatory markers, and thereby improving metabolic resilience. However, CR and IF face challenges in long-term sustainability, especially in the older population with different nutritional requirements. Despite this, their metabolic improvements of CR and IF support why dietary interventions hold promise in postponing the ageing process and improving health span.

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4.2. Pharmacological agents: metformin, rapamycin, NAD+ boosters

Besides diet-based interventions, pharmacological interventions aimed at metabolic processes have been of interest in their anti-ageing potential. As a first-line treatment for type 2 diabetes, metformin activates AMPK while reducing hepatic glucose production, thereby improving insulin sensitivity and minimising oxidative stress. In the Targeting Ageing with Metformin (TAME) trial, the preliminary results indicate that metformin has the potential to decrease the occurrence of age-related diseases and increase health span [12]. Another mTOR inhibitor, rapamycin, was demonstrated to increase the lifespan of mice by boosting autophagy and alleviating cellular stresses; however, due to the issue of immunosuppression, rapamycin is unlikely to be used in humans [18]. The next potential direction is the stimulation of the NAD+ levels, whose age-related depletion interferes with the work of mitochondria and sirtuins. Experimental supplements of nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) have been shown to have the potential to rebuild NAD+ levels and enhance metabolic outcomes in preclinical models [19]. While these pharmacologic approaches show promise in modulating metabolism and delaying ageing, their long-term efficacy and safety require further evaluation.

4.3. Toward a cyclical model of ageing and metabolism

Emerging evidence reveals a bidirectional interplay between metabolism and ageing, where each process influences and exacerbates the other. Metabolic dysfunction accelerates ageing by impairing cellular maintenance and stress responses, while ageing disrupts metabolic regulation via hormonal shifts, epigenetic alterations, and chronic inflammation. This two-way interaction implies that both metabolic and ageing-related factors should be treated during effective interventions. For instance, while mitochondrial function modulation may slow ageing, sustained benefits require concurrent reversal of age-related mitochondrial DNA mutations. Similarly, the induction of autophagy can enhance cell health, but age-related impairments of autophagy will need to be restored to achieve effectiveness. A comprehensive rather than a reductionist approach to longevity science is made possible through the understanding of this cyclical relationship between the three primary ways of increasing longevity: dietary, pharmacological, and lifestyle changes.

5. Conclusion

This essay has highlighted that there is a reciprocal relationship between metabolism and ageing and that each function influences and supports the other. Accelerated ageing occurs due to metabolic instabilities like mitochondrial degradation, poor nutrient sensitivity, and diminished autophagy. On the other hand, ageing alters metabolic regulation by changing the levels of hormones, experiencing epigenetic drift, and having chronic inflammation. These data can fit into a two-way model where metabolism and ageing are in a reciprocal relationship. Reductions in calories, metformin, and supplementation with NAD+ have been promising to slow ageing through their effects on metabolism. Their efficacy is, however, limited by the treatment of age-related impairment in metabolism. Current findings are constrained by reliance on animal models and paucity of longitudinal human data. Future investigations should prioritize personalized metabolic therapies integrating multi-omics data, including genomic and epigenetic profiling. By unravelling the way metabolism and ageing interplay, we can come up with methods of extending health span, reducing age-related diseases, and improving the quality of life. The two-way model suggested here provides an outlook on further research and clinical practice in the science of longevity.

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In the future, the insights presented in this study may be used in the creation of specific therapeutic techniques that correct metabolic imbalances among ageing populations. Longitudinal human studies, combinatorial interventions, using genomic and epigenetic profiling, and using the data to personalize treatments should be priorities of future research. Clinically, these results can inform preventive policies concerning age-related diseases, and in public health, they can inform policies to promote metabolic health by increasing diet, exercise, and early screening. With awareness and utilisation of the cyclicality of metabolism and ageing, it is possible to get much closer to the definition of ageing, no longer seeing it as inevitable decay, but, instead, a process that can be modified and one that holds tremendous power.

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