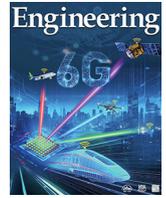




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Pro-Aging Metabolic Reprogramming: A Unified Theory of Aging

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ABSTRACT

Despite recent advances in understanding the biology of aging, the field remains fragmented due to the lack of a central organizing hypothesis. Although there are ongoing debates on whether the aging process is programmed or stochastic, it is now evident that neither perspective alone can fully explain the complexity of aging. Here, we propose the pro-aging metabolic reprogramming (PAMRP) theory, which integrates and unifies the genetic-program and stochastic hypotheses. This theory posits that aging is driven by degenerative metabolic reprogramming (MRP) over time, requiring the emergence of pro-aging substrates and triggers (PASSs and PATs) to predispose cells to cellular and genetic reprogramming (CRP and GRP).

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1. Aging and hallmarks of aging

Aging is commonly defined as the progressive deterioration of an organism over time, wherein the risk of morbidity and mortality increase exponentially with age in the post-reproductive years. This process encompasses a range of metabolic activities involving functional, structural, and biochemical alterations that disrupt the body's natural homeostasis and orderliness, ultimately leading to a state of high entropy [1,2]. The concept of the “hallmarks of aging” was introduced to provide a framework for understanding the underlying mechanisms contributing to the aging process and its associated health decline. Initially proposed in a seminal paper by López-Otín et al. [3] in 2013, which identified nine hallmarks of aging, this framework was revised by the same authors in 2023 to incorporate three additional hallmarks, bringing the total to 12 [4]. The 12 hallmarks include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis

[4] (Fig. 1). These hallmarks are interconnected biological processes that can influence each other, forming a complex network driving the aging process.

While not classified as a disease in itself, aging is the primary key risk factor for the development of numerous debilitating, life-threatening, and age-related pathologies, especially non-communicable chronic conditions such as cardiovascular disease, diabetes, cancer, and neurodegenerative disorders, which significantly impact the quality of life and independence of older people [5]. However, from a clinical perspective, considering aging as a disease or a collection of detrimental conditions inspires and even legitimizes medical efforts and various other interventions aimed at prevention, delay, treatment, and even reversal of the aging process.

2. Pro-aging metabolic reprogramming (PAMRP): A unified theory of aging

Why and how we age are two intertwined questions that have fascinated scientists for many decades. Despite recent progress in understanding the biology of aging, the field remains largely fragmented due to the lack of a central organizing hypothesis that could provide a framework for investigating how fundamental upstream biological processes regulate the timing of age onset

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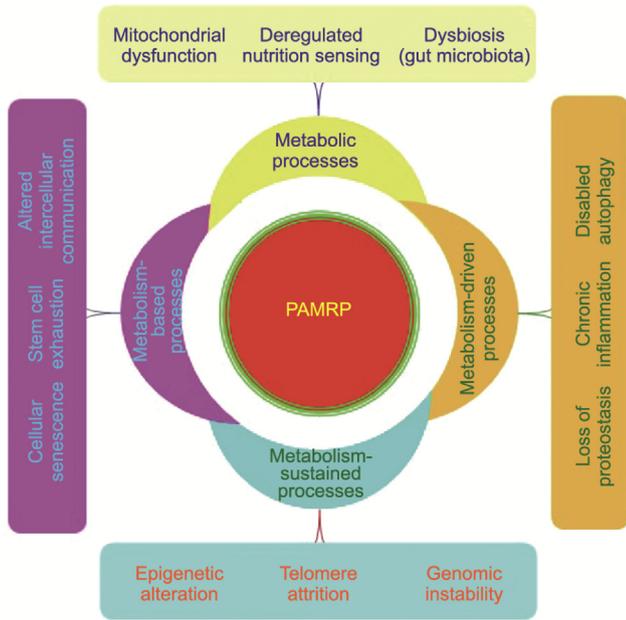


Fig. 1. Relationships between pro-aging metabolic reprogramming (PAMRP) or metabolism and the 12 hallmarks of aging [4].

and progression. While numerous theories on aging have been proposed and efforts have been made to create unifying theories that incorporate various aging-related phenotypes and mechanisms [6–18], none of them constitutes a fully comprehensive doctrine for understanding the aging process in its entirety.

There are ongoing debates on whether the aging process is programmed or stochastic. The programmed theory views aging as a continuation of the orderly genetic program that guides early growth and development, while the stochastic hypothesis considers aging to be a result of the accumulation of random errors. However, neither theory can independently explain the complexity of aging.

2.1. Explanation of the PAMRP theory

The PAMRP theory proposed here posits that aging is determined by degenerative changes in cellular metabolism that occur over time. Specifically, aging has both a programmed and stochastic nature, with its onset requiring both the preexistence of pro-aging substrate (PAS) buildup through degenerative metabolic alterations and the emergence of pro-aging triggers (PAT) induced by stochastic events. The convergence of PAS and PAT initiates metabolic reprogramming (MRP), predisposing the body to cellular reprogramming (CRP) and genetic reprogramming (GRP) and ultimately leading to a self-perpetuating progression of the aging process governed by the genetic program.

The human body's metabolism is genetically preprogrammed but can be epigenetically reprogrammed for good or bad outcomes depending on the specific context. As organisms age, there are significant alterations in metabolic pathways within cells, including shifts in energy production, nutrient utilization, and waste-management processes. Initially, this MRP serves as an adaptive mechanism to cope with varying stress conditions. However, these adaptations come at the cost of accumulating molecular damage, including oxidative stress-induced DNA mutations, protein aggregation, and mitochondrial dysfunction, which are hallmarks of and substrates for aging. Over time, this MRP becomes maladaptive, contributing to a self-perpetuating cycle that maintains the altered metabolic state and exacerbates degenerative

changes in gene expression and regulatory mechanisms. Ultimately, once a threshold level is reached, MRP triggers the genetic aging program, impacting cellular function, tissue homeostasis, and overall organismal health (Fig. 2).

MRP can occur under various conditions whenever an organism is facing cellular stress and metabolic challenges of both intrinsic and extrinsic origins. The most pronounced MRPs typically occur during four stages:

(1) **The transition from rapid growth to reproductive maturity.** This corresponds to the developmental phase for generation, during which cells undergo profound changes in metabolism to support rapid growth, differentiation into specialized cell types, and tissue formation. MRP plays a crucial role in supplying the energy and building blocks necessary for these processes; therefore, we refer to the MRP in this stage as *generative MRP*.

(2) **The transition from adulthood at reproductive age to post-reproductive age.** This stage corresponds to the period of regeneration for tissue maintenance and repair. Accordingly, generative MRP switches to *regenerative MRP*.

(3) **The transition from post-reproduction into the aging process.** This stage corresponds to a period of rapid degeneration, during which regenerative MRP switches to *degenerative MRP*. The PAMRP theory applies to this stage.

(4) **During oncogenesis.** This stage is characterized by abnormal regeneration wherein normal cells transform into cancer cells—a process that involves malignant transformation marked by uncontrolled cell growth induced by adverse metabolic reprogramming (AdvMRP).

Upon reproductive maturity, the primary objective of MRP is to recalibrate the metabolic processes within the body to adapt to the overall transition from rapid growth to reproduction and somatic maintenance and repair. This involves adjustments in energy metabolism, nutrient utilization, hormonal regulation, and metabolic flexibility to support maintenance rather than growth, as reflected from the following metabolic transitions:

(1) **The transition from anabolism to catabolism.** In this transition, MRP involves a continuation of the genetic developmental program aimed at establishing and maintaining a new state of metabolic equilibrium and homeostasis. This includes a reduced emphasis on anabolism and an enhanced focus on catabolism, favoring survival, somatic fitness, and resilience (i.e., the ability to endure or quickly recover from diverse challenges and insults), while also supporting reproductive capacity. Without this MRP to moderate anabolism, organisms would be highly susceptible to

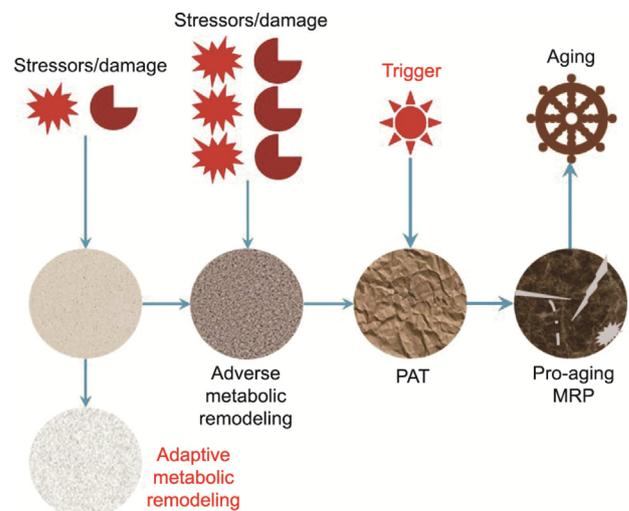


Fig. 2. Schematic illustration of the PAMRP theory of aging.

tumorigenesis, as what was once normal anabolism becomes excessive and detrimental post-development. Conversely, an excessive decline in anabolic processes, marked by a decrease in the synthesis of biomolecules such as proteins and DNA, is a common feature of aging.

(2) **The transition from entropy decrease to low-entropy maintenance.** The second objective of MRP, following the completion of organismal structure development as dictated by the preset developmental program, is to minimize and slow the process of entropy increase or maintain a low-entropy state within the organism by preserving energy homeostasis. Entropy, a thermodynamic parameter associated with energy, measures the amount of energy that is unavailable for performing work or supporting biochemical activities within the body. Mechanistically, entropy also serves as a gauge of the level of disorder or loss of complexity, indicating the deterioration of biophysical and physiological structures and functionalities. This deterioration may manifest as the misfolding or deformation of macromolecules such as proteins, DNA, and RNA, or the disruption of tissues and organs [1–11]. The lower the entropy, the higher the level of orderliness, complexity, and integrity exhibited by an organism's structures and functions at various levels, ranging from individual molecules to the entire body [1,5]. The relationship between MRP and entropy reflects the thermodynamic principles that govern biological systems. During the early development of an organism, there is a reduction in entropy within specific cells and tissues as anabolic processes generate order and complexity. Subsequently, the organism undergoes MRP with the goal of maintaining a dynamic equilibrium between anabolism and catabolism to combat entropy increase. With aging, entropy often increases due to the cumulative effects of environmental insults, cellular damage, and the breakdown of cellular components. This increase can lead to a decrease in the efficiency of biological processes, contributing to aging-related degeneration.

(3) **The transition from vigorous metabolism to low basal metabolic rate (BMR).** BMR plays a significant role in aging, as it directly affects energy expenditure, body composition, and overall metabolic health. With aging, the energy production rate driven by the maximum oxidative phosphorylation rate, or oxidative capacity, declines. Down-tuning the maximal oxidative phosphorylation rate serves as a protective metabolic mechanism for minimizing the production and accumulation of reactive oxygen species (ROS) and other metabolic byproducts that can cause oxidative stress, damaging cells and tissues over time. A lower BMR offers other health benefits such as energy conservation for maintenance and repair and hormesis induction enhancing the body's ability to cope with stress.

(4) **The bioenergetic shift from oxidative phosphorylation to glycolysis.** Bioenergetics undergoes U-shaped changes during the life course. High anaerobic glycolytic activity supports rapid growth and development in early life stages (embryonic and fetal stages, neonatal stage, and childhood and adolescence). In adulthood, the body reaches a more stable metabolic state, with increased reliance on oxidative phosphorylation for energy production and reduced or maintained glycolysis. Late life, or aging, is associated with a decline in mitochondrial function, leading to a shift from oxidative phosphorylation to glycolysis, with progressively decreasing energy production. Senescent cells, which accumulate with age, often show altered metabolic profiles, including increased glycolysis. Such MRP is likely driven by a progressive decline in cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C) after the reproductive peak and a reciprocal increase in pyruvate kinase (PK) [12]. PEPCK-C promotes physical activity to increase adenosine triphosphate (ATP) turnover, the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), fuel oxidation, and food intake [12]. Many effects of PEPCK-C on aging—including lifespan extension—require the activation of AMPK

signaling and/or the inhibition of target of rapamycin (TOR) signaling.

At the cellular level, upon the completion of developmental growth, cells undergo CRP for cell-fate decision, facing four possible pathways:

(1) **Transitioning to the post-mitotic state.** Cells become terminally differentiated somatic cells while maintaining their regenerative capacity, which is essential for maintenance, repair, and cell survival.

(2) **Entering cell cycle arrest.** This leads to cellular senescence, where cells cease to divide but remain metabolically active.

(3) **Initiating programmed cell death.** This includes processes such as apoptosis, which helps eliminate damaged or unnecessary cells.

(4) **Continuing the growth program.** This may lead to adverse regeneration, increasing the risk of carcinogenesis.

MRP provides the necessary energy, biosynthetic precursors, and regulatory metabolites required for CRP, thereby controlling cell fate. These metabolic signaling pathways can converge on transcription factors and gene regulatory elements to coordinate metabolic adaptations in response to physiological changes or stressors. This integration ensures that cellular processes are tightly regulated and aligned with the organism's overall metabolic state and needs.

2.1.1. Adaptive metabolic reprogramming (AdaMRP) vs AdvMRP

AdaMRP is a beneficial and reversible adjustment of cellular metabolism that allows cells and organisms to survive and function under stressful conditions. In contrast, AdvMRP refers to maladaptive and often irreversible changes in cellular metabolism that contribute to disease progression and aging. AdvMRP often occurs due to chronic overnutrition, cancer, chronic inflammation, neurodegenerative diseases, and other aging-related processes.

2.1.2. Regenerative metabolic reprogramming (rMRP) vs degenerative metabolic reprogramming (dMRP)

rMRP supports tissue repair, regeneration, and maintenance of function, while dMRP contributes to functional decline, tissue damage, and disease progression. rMRP and dMRP represent two sides of metabolic adaptation. rMRP aims to repair and restore tissue function by leveraging efficient energy production, a balanced redox state, and enhanced autophagy, thereby promoting self-renewal, self-healing, and self-organization. In contrast, dMRP often results from chronic stress, aging, or disease, leading to impaired energy production, increased oxidative stress, disrupted nutrient sensing, and reduced cellular maintenance.

2.1.3. Adverse rMRP

When MRP becomes maladaptive or deregulated, it transforms into adverse rMRP, leading to adverse outcomes such as excessive production and accumulation of ROS, chronic inflammation, fibrosis, impaired stem cell function and survival, and cancerogenesis.

Cancer is a typical example of adverse rMRP that exhibits the characteristics of both regenerative and degenerative processes. While cancer cells utilize MRP to support their uncontrolled growth and proliferation, resembling regenerative processes, this reprogramming ultimately contributes to the degeneration of normal tissue function and structure in the organism. Cancer cells can create both PASs and PATs, affecting both proximal and distal normal tissues and cells, as detailed in the following subsection.

It is intriguing to note that cancer cells and senescent cells stem from different trajectories of CRP occurring during post-reproductive maturity. While cancer cells exemplify adverse rMRP, senescent cells are representative of dMRP. Although these two distinct types of cells have unique characteristics, particularly in

their metabolism, both can contribute to the aging process through different mechanisms, as outlined below.

(1) Cancer cells frequently undergo MRP to support rapid growth and proliferation, often exhibiting abnormally enhanced anabolism for biosynthesis. This is characterized by the Warburg effect, in which cancer cells rely heavily on glycolysis even in the presence of oxygen. In contrast, senescent cells typically shift toward a more catabolic metabolism, experiencing a reduced capacity for oxidative phosphorylation and relying less on mitochondrial respiration for ATP production.

(2) While cancer cells favor glycolysis, they still utilize oxidative phosphorylation to some extent, especially in more oxygen-rich environments. Although senescent cells may show reduced glycolytic activity compared with cancer cells, they still exhibit some level of glycolysis. This shift is often referred to as the senescence-associated secretory phenotype (SASP), where metabolic changes contribute to the cells' secretory profile. Senescent cells accumulate oxidative stress due to mitochondrial dysfunction, which can further impair their metabolic processes. This stress is partly responsible for the damage they inflict on surrounding tissues.

(3) Cancer cells often produce various metabolites, such as lactate and oncometabolites (e.g., 2-hydroxyglutarate), which can influence the tumor microenvironment and contribute to cancer progression. Senescent cells often have impaired autophagy, leading to the accumulation of damaged organelles and proteins. This dysfunction can contribute to their metabolic abnormalities.

2.2. PAS and pro-aging triggers

The PAMRP theory of aging posits the merging of preexisting PAS and emerging PATs as a prerequisite for the onset and progression of the aging process. Herein, PAS refers to the fundamental biological molecules and structures that undergo metabolic changes contributing to the aging process, such as altered expression, damaged function, and/or disrupted structure of macromolecules (e.g., DNA, RNA, proteins, and lipids) and organelles (e.g., mitochondria). On the other hand, PAT encompasses various factors and mechanisms that initiate and drive the aging process, such as oxidative stress, inflammation, and telomere attrition. These triggers can be intrinsic, originating from within the organism, or extrinsic, stemming from environmental influences. Intrinsic triggers involve internal biological processes, including genetic, cellular, and molecular mechanisms that naturally change over time. Extrinsic triggers include external influences such as lifestyle factors (e.g., diet, exercise), exposure to toxins, and environmental stressors (e.g., pollution and ultraviolet (UV) radiation).

PAS and PAT can interact and transform each other, with metabolism at the core of these interactions. Continuous exposure to intrinsic and extrinsic stressors can result in metabolic disturbances that accumulate within cells over time. If these disturbances are not adequately addressed or corrected, they contribute to the formation of the aging substrate. The emergence of aging triggers in the presence of the aging substrate causes metabolic imbalance, initiating PAMRP (Fig. 2). In essence, the interplay between the aging substrate and the aging triggers revolves around metabolic processes.

2.3. Distinction between the PAMRP theory and other existing theories

It is generally believed that the genetic program prioritizes the critical aspects of survival, fitness, and growth only up to the age of reproductive maturation. Thereafter, it may leave the trajectory of survival and fitness to follow its own course. This is the mainstream view regarding the determinants of longevity in the context of genetic programs and selection forces—a belief that has led to

the generation of several theories explaining longevity, such as the antagonistic pleiotropy theory [13] and the disposable soma theory [14], among others. Nonetheless, it is important to acknowledge that many aspects of longevity challenge these theories, as outlined below:

(1) **The evolutionary perspective.** From an evolutionary perspective, the fundamental goals of organisms are survival and reproduction, both of which are equally crucial. Survival serves as the foundation for successful reproduction, ensuring the continuation of parental lives to the next generation and the expansion of the population.

(2) **Longevity genes.** The existence of longevity genes that play a critical role in the lives of centenarians and supercentenarians contradicts the notion that the forces of genetic program and selection abandon individuals after their reproductive success.

(3) **Antagonistic pleiotropy.** While antagonistic pleiotropy appears to be nearly ubiquitous, most actual antagonistically pleiotropic alleles remain undiscovered in natural populations. In addition, laboratory studies describing alleles that extend lifespan often do not report early fitness effects.

(4) **Fecundity and longevity.** Although negative correlations between fecundity and longevity are observed between different species, such a relationship does not exist within a single species. For example, humans who are in good physical fitness and robust health typically exhibit better fecundity and a longer lifespan. Moreover, a positive correlation between the duration of sexual maturity and the length of lifespan or post-maturity lifespan with maintained fecundity is commonly recognized and supported by evidence, which contradicts the disposable soma theory. Furthermore, the average lifespan in western countries is approximately 6.5 times longer than the time needed to reach reproductive maturation, a fact that cannot be easily explained by tradeoff theories.

(5) **Reproductive period and lifespan.** Women experience a shorter reproductive period, with menopause typically occurring around age 51. However, they often enjoy a longer overall lifespan or post-reproductive lifespan compared with men, who can continue to conceive children naturally well into their 70 and 80s.

(6) **Reproduction and longevity.** Women who bear two to three children tend to live longer than those who bear none or many children, highlighting the idea that reproduction and survival are intertwined, and there is no need to prioritize resources toward reproduction over survival.

The PAMRP theory suggests that longevity is determined by the same purposeful genetic program or genetic blueprint that initially governs early development and growth and subsequently transitions into a phase focused on life maintenance and survival in humans. Reprogramming of this genetic program occurs at the time of reproductive maturation, allowing the organism to adapt to post-reproductive life. In essence, the genetic program for early development and post-reproductive lifespan is a continuous flowchart with modifications taking place at the turning points of an individual's life course. In mammals, the genetic program is established to maintain fitness and survival, while also supporting reproduction, aligning with the respective maximum lifespans of different species.

According to the PAMRP theory, natural selection continually and consistently addresses both of an organism's fundamental and primitive goals: survival and reproduction. There is no scenario in which natural selection acts against survival or favors a decline in somatic fitness. In other words, evolution places equal weight on somatic maintenance and reproductive capacity. This equality stems from the fact that it is not guaranteed that an individual will have offspring who will carry on the family line at the time of their reproductive maturity; an individual may have children long after reaching reproductive maturity, even in their

advanced age. Thus, it is clear that maintaining somatic fitness or prioritizing survival is critical for ensuring reproductive success.

In these regards, the PAMRP theory of aging is essentially aligned with the one proposed by Hayflick [5]. Both theories are grounded in the perspectives of evolutionary biology, molecular biology, and the principles of thermodynamics. What sets our theory apart from others is its strong emphasis on MRP leading to GRP, particularly as it manifests in MRP, which establishes a new state of metabolic equilibrium for better survival while maintaining reproductive capacity. This MRP guides the shift of metabolic activities from prioritizing growth and development, aimed at achieving sexual maturation for reproduction, to favoring survival and maintenance in order to sustain fecundity. In essence, this GRP induced by MRP redirects metabolism from morphogenesis to morphostasis.

3. Evidence for the PAMRP theory of aging

Metabolism encompasses the life-sustaining chemical reactions within organisms. Its primary functions include converting energy from food into usable forms for cellular processes; synthesizing building blocks for proteins, lipids, nucleic acids, and certain carbohydrates from food; repairing and processing damaged macromolecules such as DNA and proteins; and eliminating metabolic wastes and xenobiotics. These enzyme-catalyzed reactions enable and maintain survival, fitness, growth, and reproduction of organisms.

3.1. Metabolism and the aging process

A notable aspect of metabolism is the conservation of basic metabolic pathways across diverse species [15]. For example, the carboxylic acids involved in the citric acid cycle are found universally, in organisms ranging from unicellular bacteria such as *Escherichia coli* to large multicellular organisms such as elephants [16]. These pathways' evolutionary conservation suggests their early appearance and retention due to their efficiency. This conservation resembles the aging process, which occurs in every multicellular animal after reaching a fixed size at reproductive maturity, and in all members of a species after the age of reproductive maturation, transcending virtually all species barriers. The link between metabolism and aging may also be conserved in humans, given the association between longevity and single-nucleotide polymorphisms in the insulin/insulin-like growth factor signaling (IIS) pathway and sirtuins.

3.2. Entropy: The principles of thermodynamics and life

Entropy is a measure of the amount of energy that is unavailable to do work, as well as the chaos, disorderliness, randomness, or uncertainty in any system. According to the universal law of thermodynamics, irreversible or spontaneous processes can occur only in the direction of increasing entropy. This principle applies to both inanimate and living systems. In living systems, a state of disorder signifies the deterioration of physical structures, such as the misfolding or deformation of macromolecules (e.g., proteins, DNA, and RNA) or the disruption of tissues and organs [1,2]. The term "loss of the capability to work" in relation to entropy generation refers to the decline or loss of the physiological functions of molecules, cells, tissues, or organs. In living systems, entropy relates to energy metabolism, and maintaining a low-entropy state—or a high-potential-energy (free-energy) state—is crucial for keeping cells, organs, and organisms in young and healthy states [1,2,5]. Consequently, increasing entropy leads to the pro-

gressive degeneration of the body, as observed in the aging process.

3.3. Mitochondria and energy metabolism

Mitochondria play a central role in energy metabolism by metabolizing nutrients such as glucose, fatty acids, and amino acids to produce ATP, which powers cellular processes and maintains metabolic homeostasis. In addition, mitochondria are vital for cellular homeostasis due to their roles in energy production, managing ROS, calcium regulation, apoptosis, nutrient utilization, and redox balance. Disruptions in mitochondrial function can have far-reaching effects on cellular stability and contribute to various diseases and age-related conditions. Mitochondria are particularly vulnerable to damage and dysfunction as organisms age and are a main source of ROS, which can further contribute to cellular damage and aging. Mitochondrial dysfunction is a hallmark of aging, and many drivers of mitochondrial dysfunction also result in cellular senescence [17].

3.4. Calorie restriction and overall metabolism

Caloric restriction (CR) is a dietary regimen that involves reducing calorie intake without causing malnutrition. CR is the most robust and successful intervention known to extend lifespan and improve health in species, from yeast to non-human primates and humans [18]. The concept of CR is supported by extensive research conducted in organisms such as yeast, flies, worms, mice, rats, monkeys, and even humans. Studies have shown that CR can extend lifespan and delay the onset of age-related diseases [19]. Specifically, a 30% reduction in calories leads to significant reductions in adult-onset diabetes, cardiovascular diseases, and cancer, as well as decreases in markers of aging in monkeys [20] and in humans [21].

Mounting experimental and clinical evidence demonstrates that CR works by regulating key controllers of cellular metabolism. It increases AMPK (a sensor of energy status that maintains cellular energy homeostasis) and phosphoenolpyruvate carboxykinase (a kinase-regulatory enzyme in gluconeogenesis) activity [22] and enhances oxidative metabolism in animals while promoting mitochondrial biogenesis in humans [23]. Concurrently, CR inhibits mammalian target of rapamycin (mTOR) (a central sensor for nutrient availability), PK activity, and glycolysis [22].

CR induces metabolic adaptations aimed at promoting energy conservation and homeostasis and enhancing metabolic efficiency. These adaptations include reduced energy expenditure, improved mitochondrial function, reduced ROS production and oxidative stress, enhanced stress resistance, and alterations in nutrient utilization pathways. Moreover, CR increases autophagy (the cellular cleanup process) and reduces cellular senescence (the aging of cells).

3.5. Caloric restriction mimetics (CRMs) and metabolism

Calorie restriction mimetics (CRMs) are compounds or interventions that mimic the anti-aging effects of long-term CR without requiring a change in eating habits. These mimetics aim to activate pathways and metabolic processes associated with CR, offering potential benefits similar to those observed with traditional CR. A wide range of CRMs or CRM candidates have been identified, including the following: ① intestinal inhibitors of fat and carbohydrate metabolism; ② inhibitors of intracellular glycolysis; ③ Stimulators of the AMPK pathway; ④ sirtuin activators; ⑤ inhibitors of the mTOR pathway; ⑥ polyamines; ⑦ phosphoenolpyruvate carboxykinase (sufficient to delay many key aging-associated metabolic and physiological changes and to increase lifespan) [2,22].

AMPK, nicotinamide adenine dinucleotide (NAD⁺)-sirtuins, mTOR, and insulin-like growth factor 1 (IGF-1) are the major conserved metabolic controllers of aging across various animal species. CR and CMRs primarily activate the AMPK and NAD⁺-sirtuins pathways while suppressing the mTOR and IGF-1 pathways.

Drugs that preserve mitochondrial function belong to a sub-group of CRMs. Chronic low-grade inflammation, known as inflammaging, is associated with aging and age-related diseases. Some CRMs, including metformin, aspirin, berberine, curcumin, and resveratrol, possess anti-inflammatory properties that can reduce inflammation and oxidative stress, thereby promoting healthier aging.

3.6. Aging-promoting or longevity-limiting genes and metabolism

Both longevity-promoting genes/proteins and signaling pathways (e.g., FOXOs, NRF2, APOE, SIRT1/3/6, PPAR- α , PGC1- α , AMPK, TFEB, SREBP, NF- κ B, etc.) and longevity-limiting ones (mTOR, insulin, IGF-1, growth factor, etc.) primarily act on metabolism. The former group promotes metabolic homeostasis, while the latter group causes metabolic imbalance [2].

3.7. Gene expression hallmarks of aging and metabolism

Several studies applying comprehensive RNA-sequencing or other techniques to aging transcriptome analyses have consistently reported differentially expressed genes broadly related to metabolism. These include mitochondrial dysfunction characterized by the downregulation of genes encoding mitochondrial protein, loss of proteostasis with downregulation of the protein synthesis machinery, and elevated inflammation [24,25].

3.8. Hallmarks of aging and metabolism

As depicted in Fig. 1, metabolism—or, more precisely, PAMRP—is the central theme around which the 12 hallmarks of aging are organized [4]. PAMRP serves as the common denominator of these hallmarks, some of which are direct consequences of, driven by, sustained by, or related to undesirable metabolic alterations [17,26].

3.9. Metabolomic age and biological age

Metabolomic age refers to a concept in biological aging research that assesses an individual's biological age based on their metabolic profile rather than their chronological age. Metabolomics—the study of small molecules (metabolites) present in biological samples such as blood, urine, or tissues—is the primary approach for determining metabolomic age. These metabolites are end products of cellular processes, and their levels can reflect the functional state of the biological system.

Metabolomic age is often determined using predictive models that analyze a comprehensive set of metabolites to estimate biological age by identifying metabolic biomarkers. These biomarkers include specific metabolites or patterns of metabolites that correlate with aging processes.

Accumulating evidence indicates that metabolomics will play a critical role in understanding aging and lifespan [26–28]. For example, Yu et al. [29] demonstrated that human serum metabolic profiles are age-dependent and reflect certain aging processes, underscoring the connection between metabolism and aging.

4. Potential implications of the PAMRP theory for anti-aging interventions

According to our PAMRP theory, the aging process is preventable, delayable, and theoretically reversible as well, as PAMRP can be preventable, delayable, and reversible. PAMRP is rooted in the accumulation of metabolic disorders over time, leading to the creation of PASs at the body, organ, tissue, cellular, and molecular levels, from epigenetic alterations to genetic program remodeling. This process can be prevented, delayed, and reversed.

As discussed above, CR, as a component of a healthy lifestyle, is the most robust and successful intervention known to extend lifespan and improve health. CR exemplifies an intervention that regulates key controllers of cellular metabolism, aiming to prevent, delay, and reverse PAMRP without the need for medication. Alternatively, CRMs—compounds or interventions that mimic the anti-aging effects of long-term CR without requiring a change in eating habits—can be used to address PAMRP. Some well-known CRMs are listed below [2]: ① intestinal inhibitors of fat and carbohydrate metabolism, such as acarbose, metformin, and other anti-diabetic medicines including sodium-glucose co-transporter 2 inhibitors; ② inhibitors of intracellular glycolysis, such as 2-deoxy-D-glucose, allantoin, and inhibitors of hexokinase (HK), phosphofructokinase (PFK), PK, lactate dehydrogenase (LDH), and pyruvate dehydrogenase kinase (PDK); ③ stimulators of the AMPK energy-sensing pathway, such as metformin, berberine, and quercetin; ④ sirtuin activators such as resveratrol, and NAD⁺ and its precursor drugs such as nicotinamide mononucleotide (NMN) and nicotinamide riboside; ⑤ inhibitors of the mTOR pathway, such as rapamycin analogs; ⑥ polyamines, such as spermidine and spamine; ⑦ phosphoenolpyruvate carboxykinase activators.

The compounds mentioned above are known to regulate cellular metabolism and maintain metabolic homeostasis by inhibiting pro-aging factors and activating anti-aging factors. It is noteworthy that the majority of these compounds—if not all—act on multiple metabolism-modulating molecules and signaling pathways. This multitargeting effect underlies their anti-aging and longevity efficacy, reflecting the principle of polypharmacology: the “one agent, multiple targets” paradigm [30]. For example, metformin—an oral antidiabetic agent from the biguanide class and an insulin sensitizer—exhibits a pleiotropic mode of action: It activates AMPK to enhance cellular energy metabolism, inhibits the mTOR pathway to improve nutrient sensing, inhibits complex I of the mitochondrial electron transport chain to reduce oxidative stress, suppresses inflammation, alleviates adipocyte senescence, induces autophagy, and influences shifts in the gut microbiota, among other effects.

In theory, all 12 hallmarks of aging [4] could be targets for anti-aging interventions. As depicted in Fig. 1, these hallmarks either directly involve metabolic processes or are driven, sustained, and based on metabolism. The validated efficacy of CRMs in alleviating PAMRP arises from their ability, conferred by their polypharmacological properties, to modulate multiple hallmarks of aging [2,30].

It is also important to note that no elixir or omnipotent intervention currently exists that can entirely reverse PAMRP. Nonetheless, a healthy lifestyle is fundamental for preventing, delaying, and even reversing the aging process, with CR being an effective dietary regimen to combat PAMRP [30].

5. Summary

The PAMRP theory posits that aging is driven by degenerative changes in cellular metabolism over time. Aging requires the accumulation of PASs, which build up through degenerative metabolic changes resulting from environmental-stress-induced epigenomic

alterations, genetic predisposition, and/or genomic damage. The emergence of PATs, created by random intrinsic and extrinsic events, is also necessary. The convergence of PASs and PATs initiates MRP, predisposing cells to CRP and GRP. This sequence ultimately leads to a self-perpetuating progression of the aging process, governed by the genetic program. The PAMRP theory unifies and integrates the genetic program and stochastic hypotheses.

While our hypothesis provides novel insights into the mechanisms underlying the initiation and progression of aging from a metabolic perspective, more solid and conclusive evidence is required from future research. Thus, an important future study should focus on further validating the PAMRP theory. In addition, future research directions in aging biology and anti-aging management should address the following key issues:

(1) Although many metabolism-maintaining compounds, including CRMs, have been investigated for their anti-aging effects in animal models, their efficacy in humans remains to be verified. Large-scale clinical trials are needed to establish their effectiveness in human populations.

(2) It is essential to elucidate the contents and determine the quantitative levels of PASs and PATs. Accurate measurement of these factors will enable the development of more precise approaches for targeting PRMRP in anti-aging interventions.

(3) It is critical to explore strategies for managing two key metabolic switches at pivotal phases of the life course: first, safeguarding the transition from generative MRP to regenerative MRP during the shift from reproductive to post-reproductive age to prevent premature aging; and second, delaying the transition from regenerative MRP to degenerative MRP as individuals enter the aging process in order to postpone the “normal” aging process.

(4) Given that aging is multifactorial and involves both PASs and PATs, targeting only one factor or signaling pathway is insufficient to prevent, delay, or reverse aging. Investigating polypharmacological strategies for anti-aging therapy—focusing on the determinants of PAMRP—is strongly encouraged. Exploring “polyinterventional” approaches that combine medications with lifestyle modifications (e.g., diet and daily exercise) is also valuable.

Compliance with ethics guidelines

Zhiguo Wang and Baofeng Yang declare that they have no conflict of interest or financial conflicts to disclose.

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