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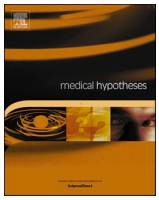

Research Article

The aging spiral hypothesis: mitochondrial decline, CO_2 regulation, and the metabolic collapse of aging

Masato Hiki

*Koshokai Hiki Clinic***

A B S T R A C T

Aging has conventionally been explained by factors such as oxidative damage, telomere shortening, and epigenetic changes. However, these models fall short in explaining how cellular-level changes lead to systemic aging, particularly the selective vulnerability of high-energy-demanding tissues and the cascading failure of metabolic regulation. In this paper, we propose the "Aging Spiral Hypothesis," which posits that aging is initiated by a quantitative and functional decline in mitochondria, leading to ATP deficiency. This triggers adaptive metabolic suppression, resulting in reduced CO_2 production. The consequent attenuation of the Bohr effect impairs oxygen delivery, thereby further exacerbating mitochondrial dysfunction in a self-reinforcing metabolic spiral. This hypothesis redefines CO_2 not merely as a metabolic byproduct, but as a metabolic switch regulating oxygen supply, thereby framing aging as a cascade of systemic metabolic collapse. This hypothesis may offer new directions for therapeutic interventions targeting mitochondrial metabolism and CO_2-mediated oxygen regulation.

Introduction

Aging is widely regarded as a complex biological process involving oxidative molecular damage, telomere attrition, and epigenetic alterations [1,2]. One of the most accepted theories emphasizes the accumulation of molecular damage caused by reactive oxygen species (ROS) generated through mitochondrial respiration [3]. However, individuals with significant mitochondrial DNA damage do not always exhibit signs of premature aging. Moreover, damaged mitochondria are often eliminated via mitophagy, suggesting that ROS accumulation does not inevitably lead to aging [4,5].

These conventional models may account for aging-related changes at the level of individual cells, but they fail to clarify how such local phenomena lead to systemic and organism-wide aging.

This gap reflects the absence of a unifying "meta-theory" that can explain aging as a coherent, system-level process.

Hypothesis

Recent studies increasingly propose that a decline in mitochondrial function leads to reduced ATP production, prompting cells to adaptively suppress metabolically expensive activities as a form of energy conservation. However, this hypothesis goes a step further by proposing a novel aging mechanism: that metabolic suppression leads to decreased carbon dioxide (CO_2) production in the TCA cycle, which in turn impairs oxygen delivery itself, ultimately resulting in further mitochondrial dysfunction—a self-reinforcing negative spiral we term the "Aging Spiral Hypothesis."

The aging spiral begins with mitochondrial loss and unfolds through a feedback loop: energy deficiency → adaptive downregulation → decreased cellular activity → reduced CO_2 production → impaired oxygen supply → further mitochondrial decline.

At the heart of this hypothesis lies the role of CO_2. While CO_2 is generally regarded as a mere metabolic waste product, we propose that it functions as a metabolic switch that regulates oxygen delivery. This perspective reframes aging not as a process driven solely by oxidative damage, but as a cascading failure of metabolic regulation, offering a new vantage point to existing theories of aging.

In addition, as the spiral progresses and mitochondrial deterioration advances, intracellular energy levels fall below the threshold required to sustain cell division, causing cells to irreversibly transition into an aging state (Fig. 1).

Development of the Hypothesis

1. CO_2 production in the TCA cycle and the Bohr effect

CO_2 is not merely a waste product but functions as a signaling molecule that regulates oxygen delivery. In the TCA cycle, CO_2 is released during the conversion of isocitrate to α-ketoglutarate and from α-ketoglutarate to succinyl-CoA [6]. The generated CO_2 enters red blood cells, where carbonic anhydrase catalyzes its hydration to bicarbonate and hydrogen ions. The increase in hydrogen ions promotes oxygen unloading from hemoglobin, a process known as the Bohr effect [7,8].

Thus, reduced activity of the TCA cycle leads to diminished CO_2 production, weakened Bohr effect, and impaired oxygen unloading. Although a minor fraction of oxygen transport occurs via dissolved oxygen in plasma, its quantitative contribution is negligible, and CO_2-

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driven modulation of hemoglobin affinity through the Bohr effect represents the major mechanism of oxygen delivery. As a result, oxygen availability to tissues is compromised, mitochondrial oxidative phosphorylation is inhibited, and a vicious cycle is established in which mitochondrial dysfunction deepens further through impaired oxygen supply (Fig. 2).

2. Amplification of mitochondrial decline by hypoxia

When oxygen delivery is impaired, cells initiate hypoxic responses. HIF-1 becomes stabilized under hypoxia and shifts cellular metabolism toward reduced energy expenditure. Specifically, HIF-1 induces pyruvate dehydrogenase kinase (PDK), which inhibits pyruvate dehydrogenase (PDH), thereby limiting the entry of pyruvate into the TCA cycle. It also suppresses mitochondrial biogenesis via PGC-1α and promotes mitophagy through the BNIP3/NIX pathway [9,10]. While adaptive in the short term, these responses accelerate the quantitative and qualitative decline of mitochondria, worsening ATP deficiency. Thus, a second feedback loop—hypoxia → HIF-1 activation → mitochondrial suppression—merges with the first CO_2–Bohr loop, reinforcing the aging spiral.

3. Reversibility and transition to cellular senescence

A decline in mitochondrial function leads to ATP deficiency, and the cell begins metabolic self-suppression (adaptive downregulation). As a result, if intracellular energy falls below the threshold required for cell division, cell division stops, and the spiral accelerates.

Cells that fall out of this spiral transition into an irreversible aging state.

This perspective shows that the Aging Spiral Hypothesis does not contradict but complements the established hallmarks of aging.

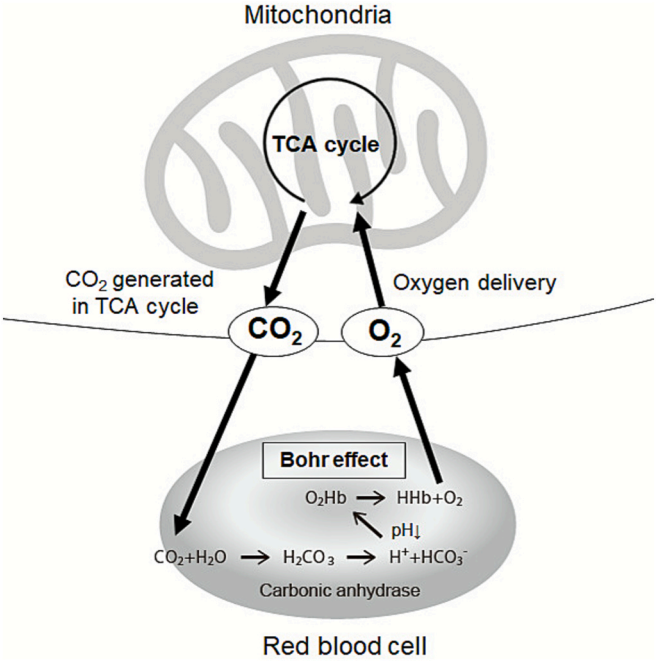

Fig. 2. Metabolic regulation of oxygen delivery via CO_2. CO_2 generated by the TCA cycle promotes oxygen unloading from red blood cells via the Bohr effect, mediated by carbonic anhydrase–induced acidification. A decline in mitochondrial CO_2 production—such as during aging—may weaken this signal, impairing oxygen delivery to tissues and creating a metabolic bottleneck that contributes to age-related functional decline.

Testing the hypothesis

The Aging Spiral Hypothesis proposes that age-related mitochondrial decline reduces intracellular CO_2 production, weakening the Bohr effect

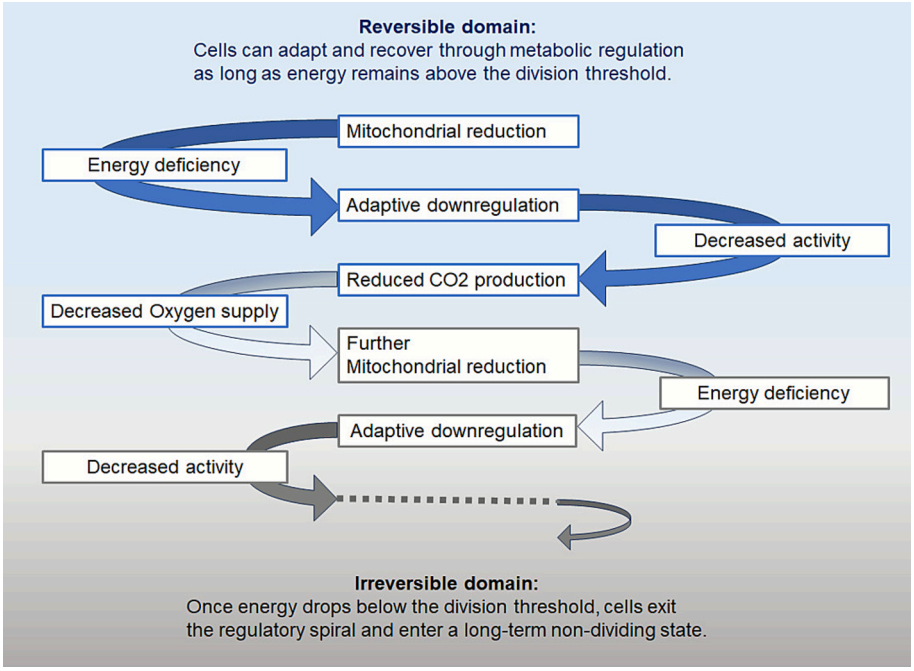

Fig. 1. Structure of the aging spiral hypothesis. The proposed Aging Spiral begins with mitochondrial decline, leading to ATP deficiency and adaptive downregulation of metabolically costly functions. This results in decreased cellular activity and reduced CO_2 production, which impairs oxygen delivery via the Bohr effect. The subsequent hypoxia exacerbates mitochondrial dysfunction, reinforcing the spiral. As long as intracellular energy remains above the threshold required for cell division, this process is reversible through metabolic regulation. However, once energy drops below this threshold, cells exit the spiral and enter a long-term, non-dividing state—marking the transition to an irreversible aging domain.

and impairing local oxygen delivery. This leads to further mitochondrial dysfunction and establishes a self-reinforcing downward spiral. To evaluate this hypothesis, we outline complementary approaches below.

1. Experimental Validation

a. **In vivo experiments:** To evaluate the physiological relevance of therapeutic interventions targeting the aging spiral, both localized and systemic CO_2 exposure models will be employed. In both models, the effects of CO_2 will be assessed using shared outcome measures: aging markers ($p16^{INK4a}$, SA-β-gal), mitochondrial indicators (ATP levels, TOM20 expression), and oxidative stress (8-OHdG).

Aged mice will be treated with CO_2-generating gel packs, which produce carbon dioxide through chemical reactions and allow for its transdermal absorption. This represents a non-invasive form of carboxytherapy. Localized CO_2 application enables direct evaluation of its effects on tissue-specific oxygenation and mitochondrial function.

In parallel, mice will undergo low-concentration CO_2 inhalation (2–5 %), which induces mild respiratory acidosis and enables in vivo assessment of the Bohr effect without systemic toxicity. This systemic approach complements the localized model and offers a broader view of CO_2-mediated physiological modulation.

By comparing these two delivery routes using the same biomarkers, this study aims to clarify how different modes of CO_2 exposure influence mitochondrial health and aging processes.

Clinical studies have already suggested that transdermal application of CO_2 may be effective against human skin aging. For example, Bagherani et al. (2023) reported in a randomized controlled trial that repeated application of CO_2-generating gel packs led to significant changes in the expression of aging-related genes [11]. Such findings support the validity of CO_2-based interventions and provide a rationale for the preclinical evaluation conducted in this study.

b. **In vitro experiments:** Fibroblasts or keratinocytes will be cultured under varying CO_2 concentrations to evaluate its effects on mitochondrial function, oxygen consumption, and the expression of aging-related genes such as p21 and p53. These experiments aim to determine whether CO_2 alone, in the absence of systemic oxygen delivery mechanisms such as the Bohr effect, can modulate cellular aging processes.

c. **Functional evaluation of Bohr effect:** To induce localized acidification in vivo, a CO_2-generating gel pack will be applied to the dorsal skin of mice. This treatment promotes the formation of carbonic acid in subcutaneous tissue, leading to a reduction in local pH.

Under these conditions, changes in oxygen release will be continuously monitored in real time using near-infrared spectroscopy (NIRS), while local pH dynamics will be assessed using fluorescence-based pH probes and pH microelectrodes.

The aim is to determine whether measurable changes in oxygen release from hemoglobin occur via the Bohr effect by quantitatively evaluating the correlation between pH and oxygen unloading.

2. Indirect validation via surrogate markers

To indirectly evaluate age-related changes in mitochondrial CO_2 production and its metabolic consequences, ^{13}C tracer-based metabolic flux analysis will be conducted using primary fibroblasts and freshly isolated skeletal muscle slices from both young and aged mice. Uniformly labeled ^{13}C-glucose will be administered, and downstream isotopically labeled metabolites will be tracked via mass spectrometry. This allows quantitative assessment of TCA cycle fluxes—particularly CO_2-releasing steps—and provides a systems-level indicator of mitochondrial metabolic decline associated with aging.

3. Gene-modified models

To assess the causal role of mitochondrial quantity and oxygen sensing in the aging spiral, gene-modified models will be utilized.

PGC-1α knockout mice, with impaired mitochondrial biogenesis, serve to evaluate the effects of reduced mitochondrial capacity on CO_2 production and oxygen delivery.

HIF-1α overexpression models, mimicking chronic hypoxia, allow assessment of how hypoxia-induced metabolic shifts accelerate aging. These models help validate whether mitochondrial loss and oxygen regulation disruption act synergistically to drive the self-reinforcing spiral.

Implications

The “Aging Spiral Hypothesis” provides an integrative framework that links intracellular metabolic collapse to organ-level dysfunction and aging-related diseases (Fig. 3). At the core of this hypothesis is the idea that mitochondrial dysfunction leads to a reduction in CO_2 production, which weakens oxygen delivery via the Bohr effect and further exacerbates energy deficiency. This sequence of changes forms a self-reinforcing cycle that promotes functional decline across various tissues. Below, we present representative implications in key pathological domains.

Neurons and neurodegenerative diseases

Neurons are high-energy-demand cells that rely almost entirely on oxidative phosphorylation for ATP production. As such, mitochondrial decline makes neurons particularly prone to energy deficiency and susceptible to the effects of adaptive downregulation. This may help explain the selective vulnerability observed in disorders such as Alzheimer’s and Parkinson’s disease [12].

Muscle cells and sarcopenia

Muscle contraction requires large amounts of ATP, and mitochondrial dysfunction directly leads to reduced muscle strength. Furthermore, impaired oxygen delivery amplifies this effect, potentially contributing to the progression of age-related muscle atrophy seen in sarcopenia.

Fibroblasts, keratinocytes, and skin aging

Fibroblasts synthesize collagen in an oxygen-dependent manner, and hypoxia inhibits collagen synthesis, making the skin more susceptible to loss of firmness and elasticity. Moreover, keratinocytes depend on mitochondrial metabolism, and their dysfunction adversely affects barrier formation and differentiation, ultimately accelerating skin aging [13].

Cancer cells

In cancer cells, mitochondrial respiration is suppressed even in the presence of oxygen, resulting in a metabolic shift toward glycolysis—known as the “Warburg effect.” The sustained maintenance of this metabolic profile is thought to require not only hypoxia and HIF-1 activation in the tumor microenvironment but also a persistent decline in mitochondrial function as one of its key contributing factors. This suggests that the spiral of disrupted oxygen and energy metabolism may play a role in metabolic adaptation and malignant progression in cancer [14,15].

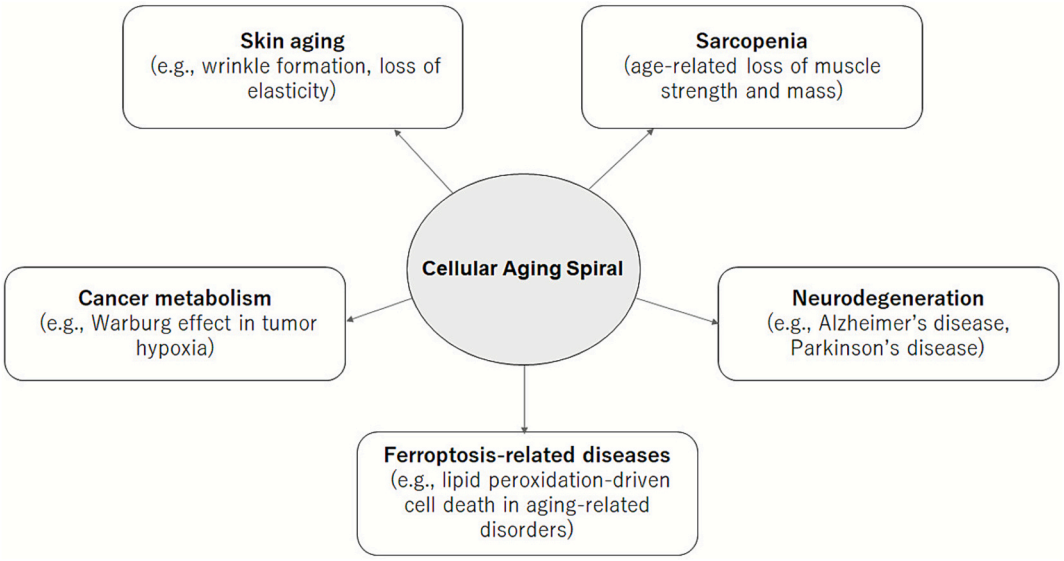

Fig. 3. The aging spiral and its link to age-related diseases. The cellular aging spiral—driven by mitochondrial decline, ATP deficiency, and impaired CO_2-mediated oxygen delivery—may contribute to a range of age-related conditions. These include neurodegeneration (e.g., Alzheimer's and Parkinson's disease), sarcopenia, impaired collagen synthesis and skin aging, cancer progression via metabolic reprogramming (e.g., the Warburg effect), and ferroptosis-related disorders.

Ferroptosis-related diseases

Mitochondria are also deeply involved in ferroptosis, a form of cell death driven by iron-dependent lipid peroxidation. Recent studies have shown that hypoxia and energy deficiency increase susceptibility to ferroptosis, suggesting that chronic deficits in oxygen and energy, triggered by the metabolic spiral, may be linked to tissue aging, neurodegeneration, and organ dysfunction [16,17].

These examples demonstrate that the Aging Spiral Hypothesis is not merely theoretical, but has the potential to function as a meta-theory that enables the unified understanding of diverse aging-related conditions—such as neurodegenerative diseases, sarcopenia, skin aging, cancer, and ferroptosis-related disorders—based on a shared metabolic mechanism.

In this context, effective anti-aging interventions may aim to interrupt or reverse the aging spiral. Such strategies could include activation of mitochondrial function, enhancement of systemic metabolism, increased CO_2 production, and improved oxygen supply. Interventions such as exercise therapy, carboxytherapy using CO_2-generating skin packs, and oxygen-based therapies (e.g., hyperbaric oxygen therapy or CPAP therapy in sleep apnea) may serve as promising approaches to counteract aging-related decline.

Conclusion

The Aging Spiral Hypothesis proposes that aging is driven by a self-reinforcing spiral initiated by a quantitative and functional decline in mitochondria. Therefore, aging should be redefined not as the accumulation of molecular damage, but as a dynamic failure of metabolic regulation.

This hypothesis suggests that targeting CO_2-mediated oxygen delivery regulation (the CO_2–oxygen switch) may offer a novel direction for anti-aging strategies. Furthermore, it aligns with existing pathogenic understandings of diverse aging-related diseases—including neurodegeneration, sarcopenia, skin aging, cancer, and ferroptosis—and may provide a foundation for integrated therapeutic approaches.

Ethics statement

This article does not involve any studies with human participants or animals performed by the author. Therefore, ethical approval was not required.

The manuscript is a theoretical work and presents a novel hypothesis based on a reinterpretation of existing scientific literature. No experiments, clinical data, or patient information were used in this research.

CRediT authorship contribution statement

Masato Hiki: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization.

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Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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