

Move beyond free radical theory of aging

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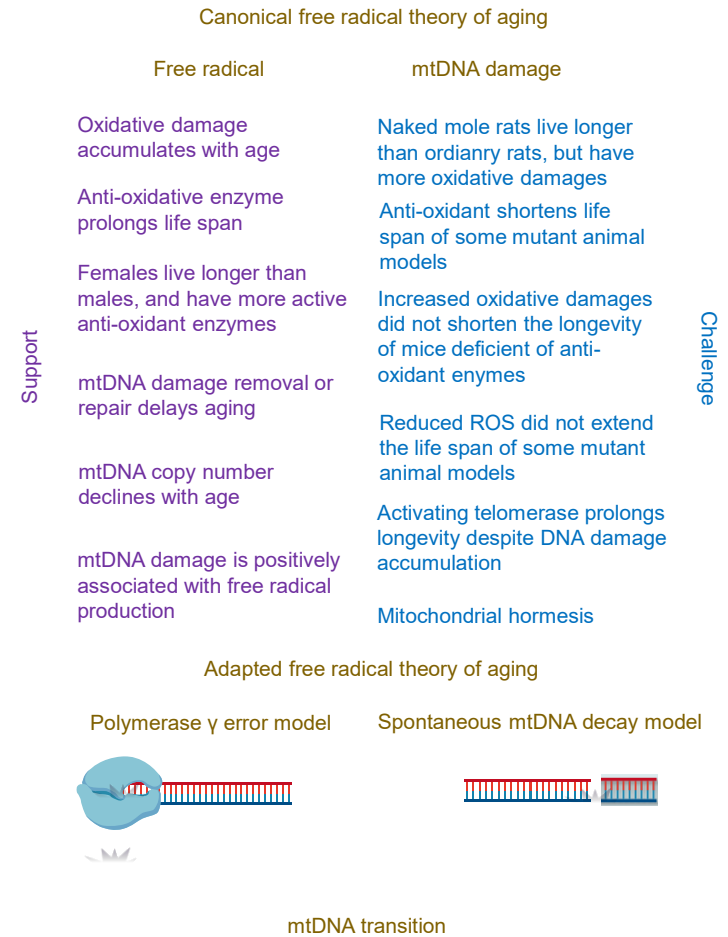


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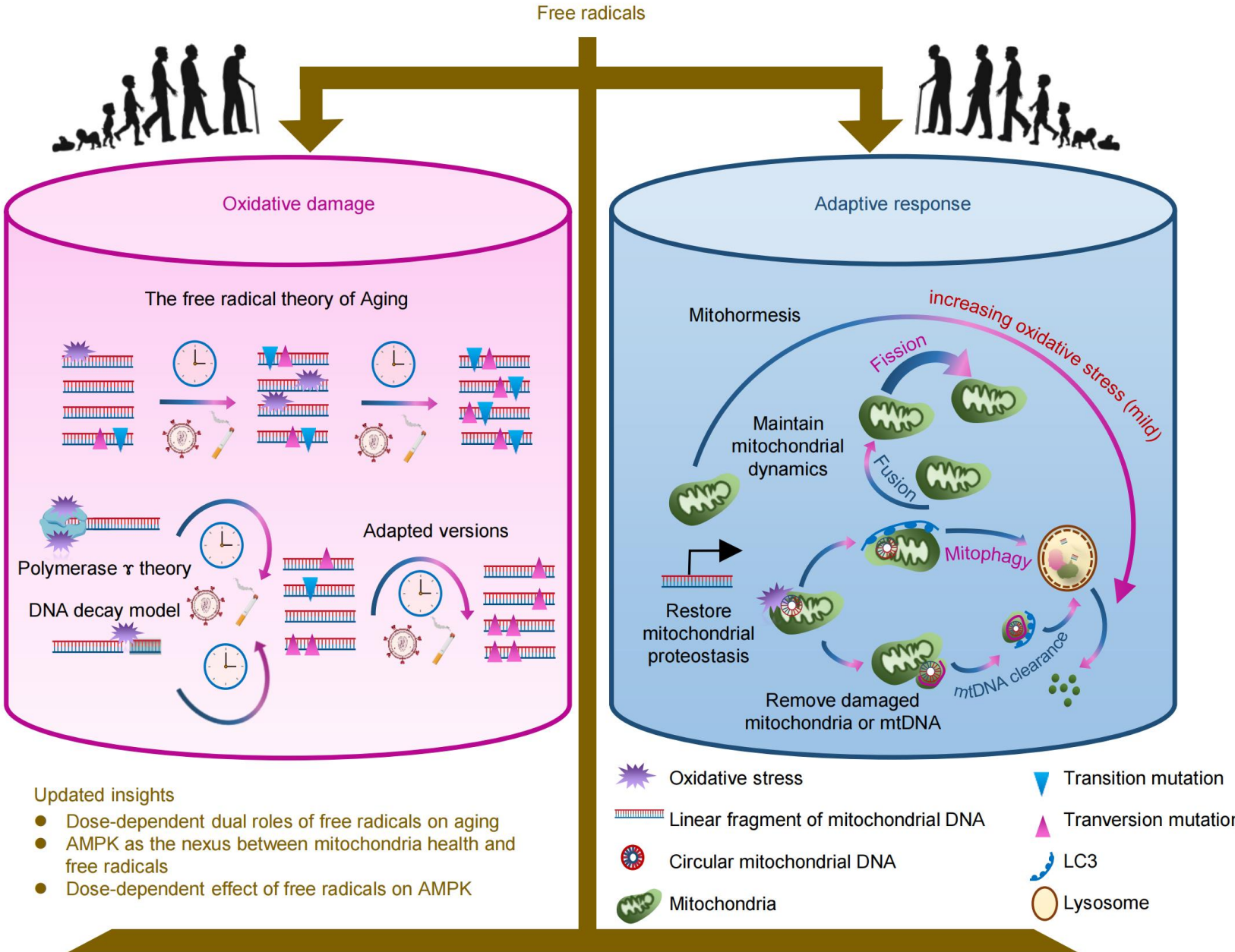


Introduction

- ❑ **Aging Definition:** A gradual pathophysiological process characterized by the loss of functional integrity and increased vulnerability to diseases.
- ❑ **Mitochondrial DNA (mtDNA):** A key regulatory factor in the aging process.
- ❑ **The Canonical Theory:** Historically, aging was attributed to oxidative damage of mtDNA caused by free radicals.
- ❑ **The Need for Revision:** Emerging evidence and "paradoxical" reports (e.g., long-lived species with high oxidative stress) necessitate a more nuanced understanding.



Challenges & New Models



- ❑ **The Pol-gamma Model:** Evidence shows that mtDNA mutations (replication errors) rather than purely oxidative damage are key drivers of mitochondrial dysfunction.
- ❑ **Mitohormesis:** A biological response where low-level oxidative stress triggers adaptive pathways, actually improving cellular fitness and longevity.
- ❑ **Paradoxical Findings:** Long-lived species (like the naked mole-rat) exhibit high levels of oxidative damage without reduced lifespans.



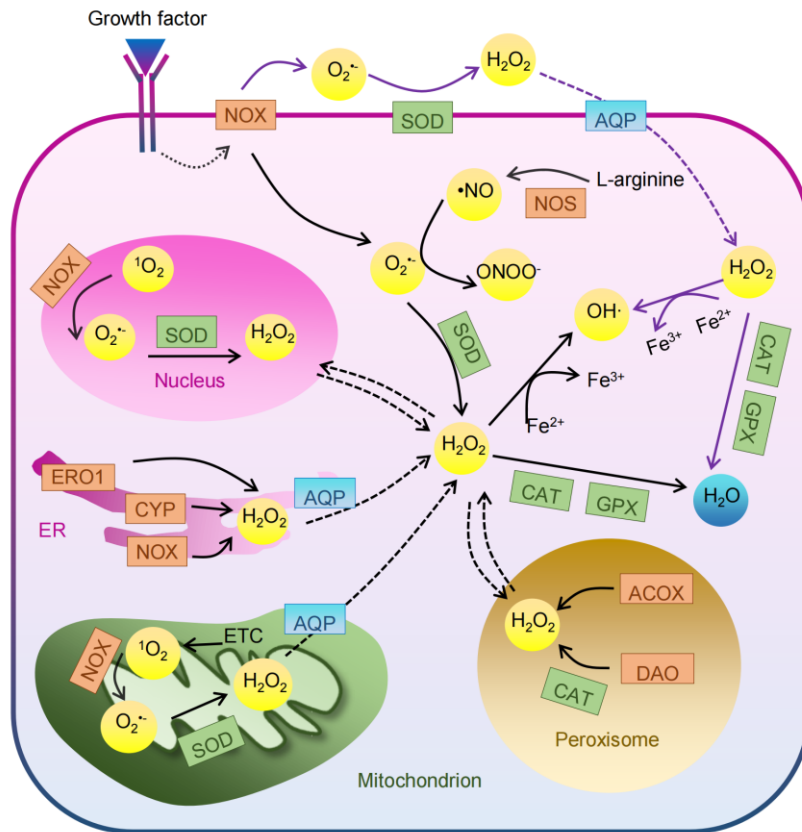
Highlights

- ① **Dual Roles:** Emphasized the dosage-dependent roles of free radicals in aging (signaling vs. damage).
- ② **AMPK as Nexus:** Identified AMPK as the critical link between mitochondrial health and free radical levels.
- ③ **Therapeutic Framework:** Distinguished dosages of free radicals for treating degenerative vs. proliferative diseases.
- ④ **Innovative Tool:** Proposed Cold Atmospheric Plasma (CAP) as a precise tool for redox regulation and anti-aging.



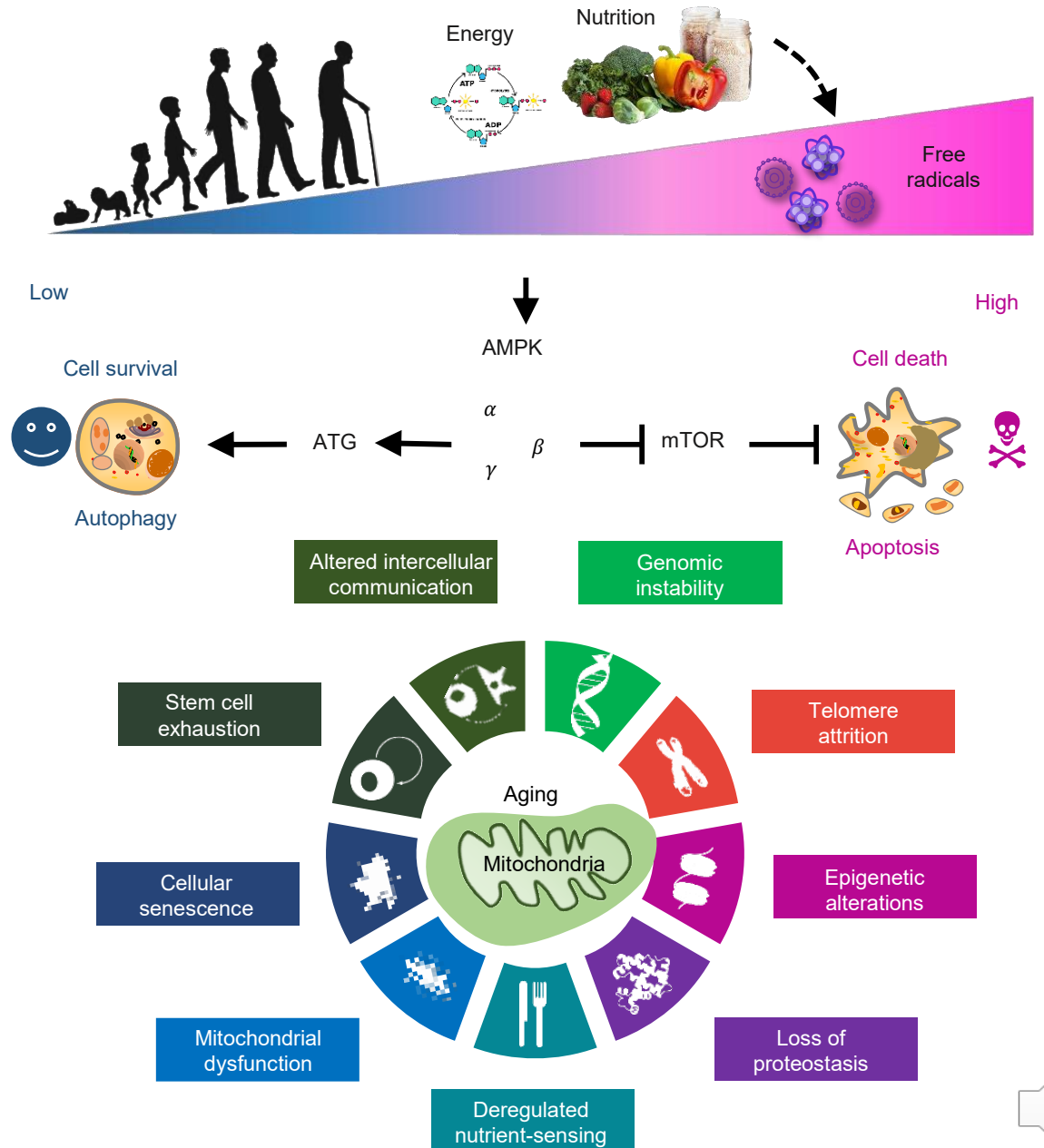
The Core Mechanism: AMPK

- ❑ **Sensory Function:** AMPK senses both energy (AMP/ATP ratio) and redox status within the cell.
- ❑ **The Anti-Aging Pathway:** Low-level ROS activates AMPK -> triggers mitophagy and autophagy -> clears damaged mitochondria -> extends lifespan.
- ❑ **The Pro-Aging Pathway:** Excessive ROS overwhelms the antioxidant system -> causes irreversible damage -> leads to cellular apoptosis and organ aging.

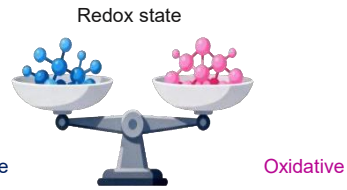
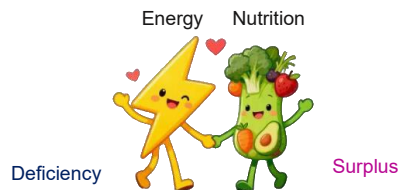


Therapeutic Framework

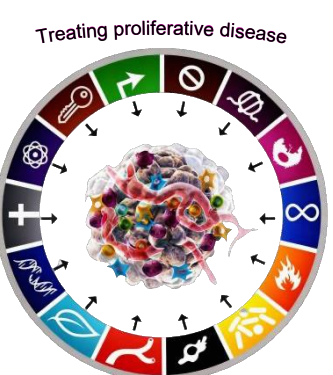
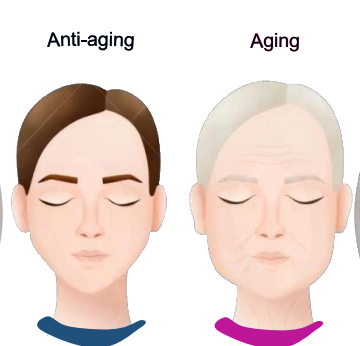
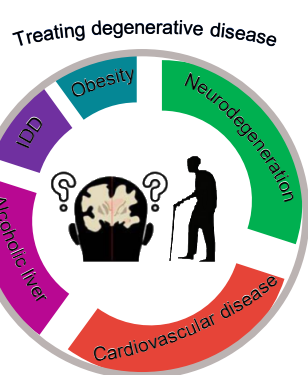
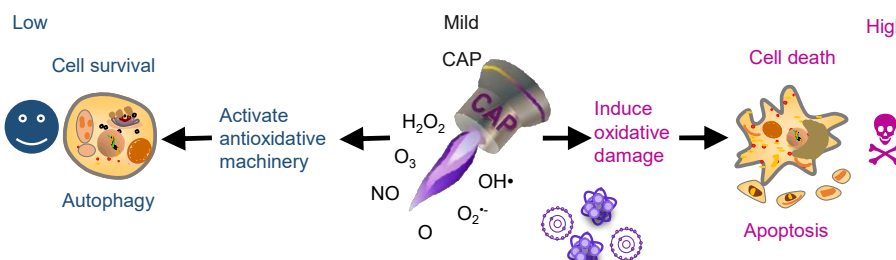
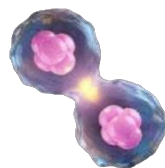
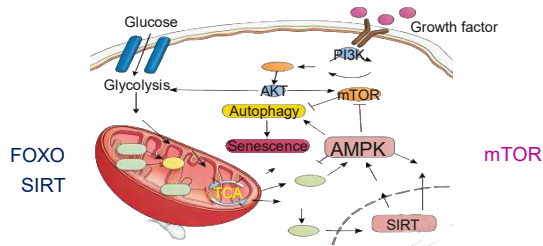
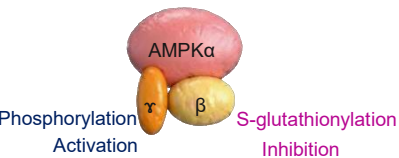
- ❑ **For Degenerative Diseases:** (e.g., Alzheimer's, Osteoporosis) The goal is to enhance cellular resilience and prevent premature cell death by maintaining redox homeostasis.
- ❑ **For Proliferative Diseases:** (e.g., Cancer) The goal is to utilize high-dose reactive species to selectively trigger apoptosis in malignant cells.
- ❑ **Personalized Strategy:** Success depends on "Strategic Redox Balancing" rather than simply eliminating all free radicals.



Cold Atmospheric Plasma (CAP) Application



- ❑ **Definition:** CAP is the "fourth state of matter," generating a cocktail of reactive oxygen and nitrogen species (RONS).
- ❑ **Mechanism:** CAP delivers precise "doses" of oxidative stress to targeted tissues.
- ❑ **Oncology & Beyond:** Proven efficacy in selectively killing melanoma, breast, and pancreatic cancer cells.
- ❑ **Regenerative Medicine:** Shows potential in promoting neural differentiation and skin wound healing via redox signaling.



Low Free radicals High



Summary

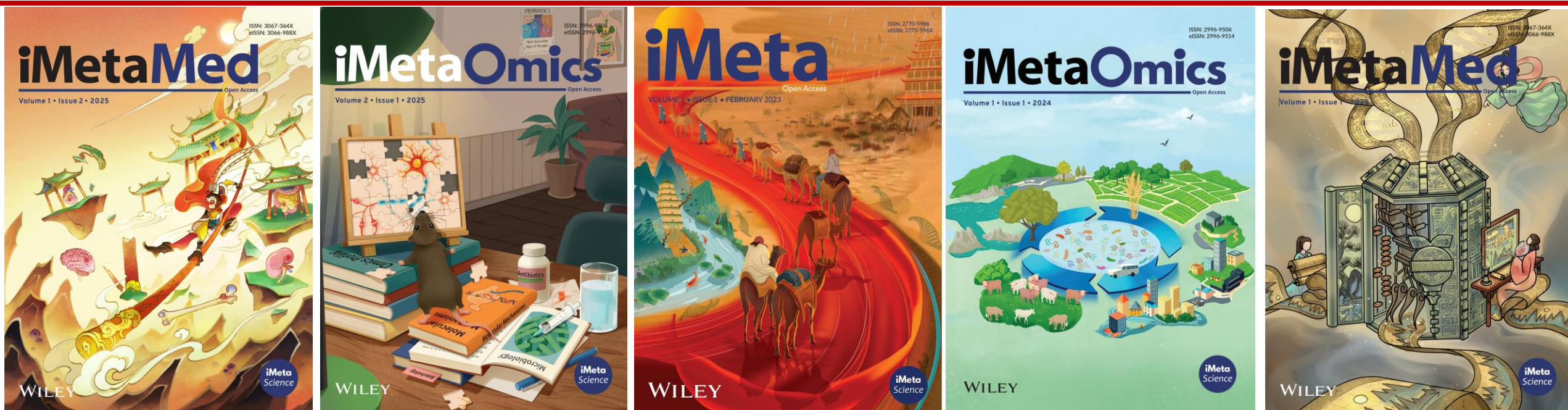
- ❑ **Theoretical Shift:** We must move beyond the "ROS is purely harmful" mindset to a more nuanced "Redox Homeostasis" perspective.
- ❑ **Mitochondrial Focus:** Maintaining mitochondrial integrity through the AMPK pathway remains the most promising anti-aging strategy.
- ❑ **Next Steps:** Future clinical work should focus on utilizing tools like CAP for personalized, dosage-controlled redox interventions.

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