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Commentary

# Role of NAD+ Metabolism in Aging and Longevity

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## DESCRIPTION

Nicotinamide Adenine Dinucleotide ($NAD^+$) is a vital coenzyme involved in numerous cellular processes, including energy metabolism, DNA repair and cellular signaling. $NAD^+$ levels decline with age, contributing to metabolic dysfunction, increased susceptibility to age-related diseases and reduced lifespan. Understanding the role of $NAD^+$ metabolism in aging and longevity provides insights into potential therapeutic strategies aimed at maintaining cellular homeostasis and promoting healthy aging.

### NAD+ and cellular metabolism

NAD+ serves as an important cofactor in redox reactions, facilitating ATP production through glycolysis, the Tricarboxylic Acid (TCA) cycle and oxidative phosphorylation. Additionally, $NAD^+$ is a substrate for several enzyme families that regulate aging and longevity, including sirtuins, poly(ADP-ribose) Polymerases (PARPs) and CD38/CD157 ectoenzymes.

**Sirtuins:** $NAD^+$ dependent deacetylases that regulate mitochondrial function, genomic stability and metabolic health. SIRT1, SIRT3 and SIRT6 have been implicated in extending lifespan by enhancing stress resistance and reducing inflammation.

**PARPs:** DNA repair enzymes that consume $NAD^+$ to maintain genomic integrity. While important for preventing mutations, excessive PARP activity can deplete cellular $NAD^+$ pools.

**CD38/CD157:** Ectoenzymes that degrade $NAD^+$ and regulate immune function. CD38 levels increase with age, accelerating NAD+ depletion and contributing to metabolic decline.

### $NAD^+$ decline and aging

Aging is associated with a progressive decline in $NAD^+$ levels, primarily due to increased $NAD^+$ consumption and decreased biosynthesis. This decline contributes to several hallmarks of aging:

**Mitochondrial dysfunction:** Reduced $NAD^+$ impairs oxidative phosphorylation, leading to decreased ATP production and energy metabolism.

**Genomic instability:** Insufficient $NAD^+$ compromises DNA repair mechanisms, increasing the risk of mutations and cellular senescence.

**Inflammation and immune dysfunction:** Elevated CD38 activity increases $NAD^+$ depletion, promoting chronic inflammation and immune aging.

**Metabolic dysregulation:** $NAD^+$ depletion impairs glucose and lipid metabolism, increasing the risk of age-related metabolic diseases.

### Therapeutic strategies to boost NAD+ levels

Given the critical role of $NAD^+$ in aging, several interventions have been explored to restore $NAD^+$ levels and promote longevity:

**NAD+ precursors:** Supplementation with Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN) has shown promise in increasing $NAD^+$ levels, improving mitochondrial function and extending lifespan in preclinical models.

**Caloric restriction and fasting:** Dietary interventions enhance NAD+ biosynthesis and sirtuin activity, representing the benefits of longevity-promoting strategies.

**CD38 inhibition:** Reducing CD38 activity through pharmacological inhibitors or genetic interventions helps preserve $NAD^+$ levels and mitigate age-related decline.

**Exercise and lifestyle modifications:** Physical activity has been shown to enhance $NAD^+$ metabolism, improve mitochondrial health and extend healthspan.

## CONCLUSION

$NAD^+$ metabolism plays a fundamental role in aging and longevity by regulating mitochondrial function, genomic stability

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and cellular resilience. Targeting $NAD^+$ decline through supplementation, lifestyle interventions and pharmacological approaches offers potential strategies for extending healthspan and delaying age-related diseases. Continued research into $NAD^+$ metabolism will provide deeper insights into its therapeutic potential for promoting healthy aging.