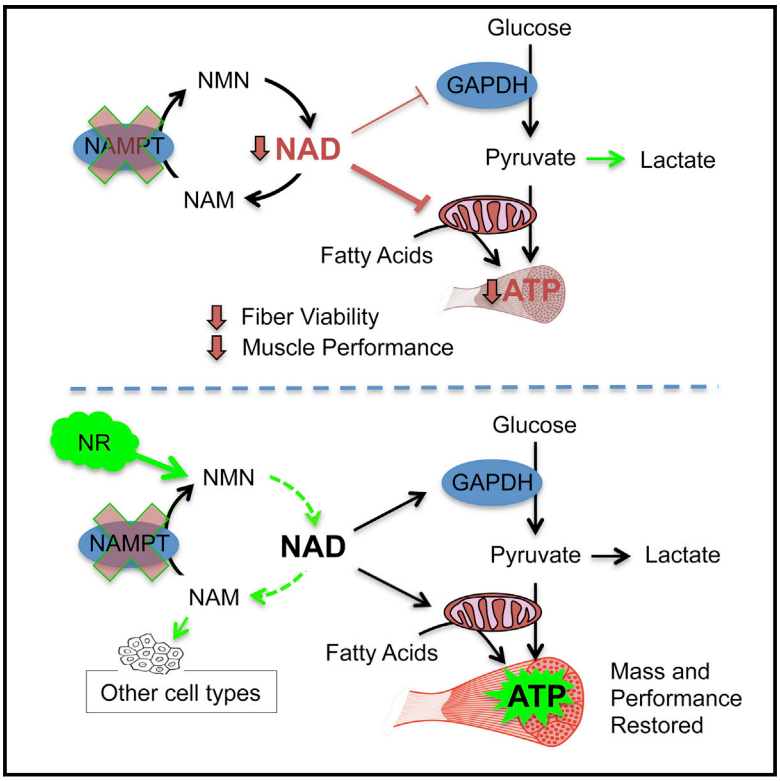
Article

Cell Metabolism

Loss of NAD Homeostasis Leads to Progressive and Reversible Degeneration of Skeletal Muscle

Graphical Abstract



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In Brief

NAD levels decline in multiple tissues with age or in disease. Frederick et al. show that impaired intramuscular NAD synthesis compromises skeletal muscle mass and strength over time but can be quickly restored with an oral NAD precursor. Upregulation of the NAD salvage pathway preserves exercise performance in aged mice.

Highlights

- Mice with ~85% NAD depletion in skeletal muscle are grossly normal as young adults
- Reduced NAD content impairs mitochondrial function and fiber integrity over time
- Progressive muscle dysfunction can be reversed by the NAD precursor NR
- Preventing muscle NAD loss during aging partially preserves exercise performance

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Loss of NAD Homeostasis Leads to Progressive and Reversible Degeneration of Skeletal Muscle

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SUMMARY

NAD is an obligate co-factor for the catabolism of metabolic fuels in all cell types. However, the availability of NAD in several tissues can become limited during genotoxic stress and the course of natural aging. The point at which NAD restriction imposes functional limitations on tissue physiology remains unknown. We examined this question in murine skeletal muscle by specifically depleting Nampt, an essential enzyme in the NAD salvage pathway. Knockout mice exhibited a dramatic 85% decline in intramuscular NAD content, accompanied by fiber degeneration and progressive loss of both muscle strength and treadmill endurance. Administration of the NAD precursor nicotinamide riboside rapidly ameliorated functional deficits and restored muscle mass despite having only a modest effect on the intramuscular NAD pool. Additionally, lifelong overexpression of Nampt preserved muscle NAD levels and exercise capacity in aged mice, supporting a critical role for tissue-autonomous NAD homeostasis in maintaining muscle mass and function.

INTRODUCTION

The flow of carbon and energy through glycolysis and oxidative phosphorylation is dependent on the electron-shuttling nature of nicotinamide adenine dinucleotide (NAD^+ or NAD), necessitating a tightly controlled balance between synthesis and degradation of this dinucleotide within the cell. NAD also serves as a co-substrate for enzymes that create signaling metabolites or post-translationally modify protein substrates. The resulting NAD-dependent signaling networks modify chromatin and transcription factor dynamics, as well as the kinetics of numerous enzymes, to coordinate physiological responses to circadian rhythms and feeding status (Asher and Sassone-Corsi, 2015). Accordingly, localized restrictions in NAD bioavailability could potentially have profound effects on cellular function by dampening these signals or impairing the production of ATP. Such restrictions have been reported during states of genotoxic stress that accompany a growing list of diseases, including cancer and neurodegeneration, as well as the course of natural aging (Cantó et al., 2015).

Since NAD contains a nicotinamide (NAM) moiety that cannot be synthesized by most tissues de novo, the vast majority of mammalian cells must instead rely on a salvage pathway to locally regenerate degraded NAD. An essential enzyme in this pathway, nicotinamide phosphoribosyltransferase (Nampt), as well as its product, nicotinamide mononucleotide (NMN), are found in both intracellular and extracellular compartments, suggesting a systemic element to the salvage and distribution of NAD (Revollo et al., 2007a). With this in mind, recent strategies to globally augment the NAD salvage pathway in rodents have employed dietary supplementation of NAM-containing compounds, including NMN and nicotinamide riboside (NR). The latter compound can be phosphorylated by dedicated kinases to generate intracellular NMN through a Nampt-independent route (Bieganowski and Brenner, 2004). The multitude of physiological benefits stimulated by these vitamins, including enhanced oxidative metabolism, synaptic plasticity, and insulin sensitivity, has been attributed to increased NAD levels in tissues such as the liver, brain, and skeletal muscle (Cantó et al., 2012; Gong et al., 2013; Yoshino et al., 2011). However, the specific