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Review

NAD metabolism: Implications in aging and longevity

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ABSTRACT

Nicotinamide adenine dinucleotide (NAD) is an important co-factor involved in numerous physiological processes, including metabolism, post-translational protein modification, and DNA repair. In living organisms, a careful balance between NAD production and degradation serves to regulate NAD levels. Recently, a number of studies have demonstrated that NAD levels decrease with age, and the deterioration of NAD metabolism promotes several aging-associated diseases, including metabolic and neurodegenerative diseases and various cancers. Conversely, the upregulation of NAD metabolism, including dietary supplementation with NAD precursors, has been shown to prevent the decline of NAD and exhibits beneficial effects against aging and aging-associated diseases. In addition, many studies have demonstrated that genetic and/or nutritional activation of NAD metabolism can extend the lifespan of diverse organisms. Collectively, it is clear that NAD metabolism plays important roles in aging and longevity. In this review, we summarize the basic functions of the enzymes involved in NAD synthesis and degradation, as well as the outcomes of their dysregulation in various aging processes. In addition, a particular focus is given on the role of NAD metabolism in the longevity of various organisms, with a discussion of the remaining obstacles in this research field.

1. Introduction

Nicotinamide adenine dinucleotide (NAD) is an essential co-cofactor that serves to mediate various biological processes, including metabolism, DNA repair, and gene expression (Canto et al., 2015; Magni et al., 2004). NAD was originally discovered in 1906 as a co-enzyme involved in yeast fermentation (Harden and Young, 1906), and has been considered a classical metabolite. However, recent studies have highlighted the various roles of NAD metabolism in aging and longevity. It is indicated that NAD levels decrease with age due to an alteration in the balance between NAD synthesis and consumption. Decreased NAD levels are associated with several aging-related disease, including metabolic diseases, cancer, and neurodegenerative diseases. Accordingly, the dietary administration of NAD precursors has been shown to replenish NAD levels in aged tissues and exhibit beneficial effects against aging and aging-related diseases (Fang et al., 2017; Katsyuba and Auwerx, 2017; Rajman et al., 2018; Yoshino et al., 2017). Most importantly, boosting NAD metabolism has been shown to extend the lifespan of various organisms, such as yeast, worms, flies, and rodents.

As a co-enzyme, NAD is involved in numerous enzymatic reactions. In particular, NAD plays a central role in the regulation of energy metabolism pathways, including glycolysis, fatty acid oxidation (β-oxidation), the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (Canto et al., 2015). The redox interplay between the oxidized (i.e., NAD^+) and reduced forms of NAD (i.e. NADH) mediates the enzymatic reactions of NAD-dependent enzymes in these pathways (Anderson et al., 2017; Magni et al., 2004). On the other hand, NAD is consumed in the processes of protein deacetylation and ADP-ribosylation by sirtuin and poly (ADP-ribose) polymerase (PARP), respectively (Canto et al., 2015; Magni et al., 2004). The NAD glycohydrolases, CD38 and CD157 (BST1), also consume NAD through the conversion of NAD into ADP-ribose (ADPR) or cyclic-ADPR (Quarona et al., 2013). Therefore, based on these findings, it is believed that NAD metabolism regulates various aging processes through these critical pathways (Fig. 1). In mammals, NAD is synthesized through three pathways: 1) from tryptophan (Trp) in the *de novo* pathway, 2) from nicotinic acid (NA) in the Preiss-Handler pathway, and 3) from nicotinamide (NAM) in the salvage pathway. In addition to these pathways, nicotinamide riboside (NR) is also used to generate NAD (Bieganowski and Brenner, 2004).

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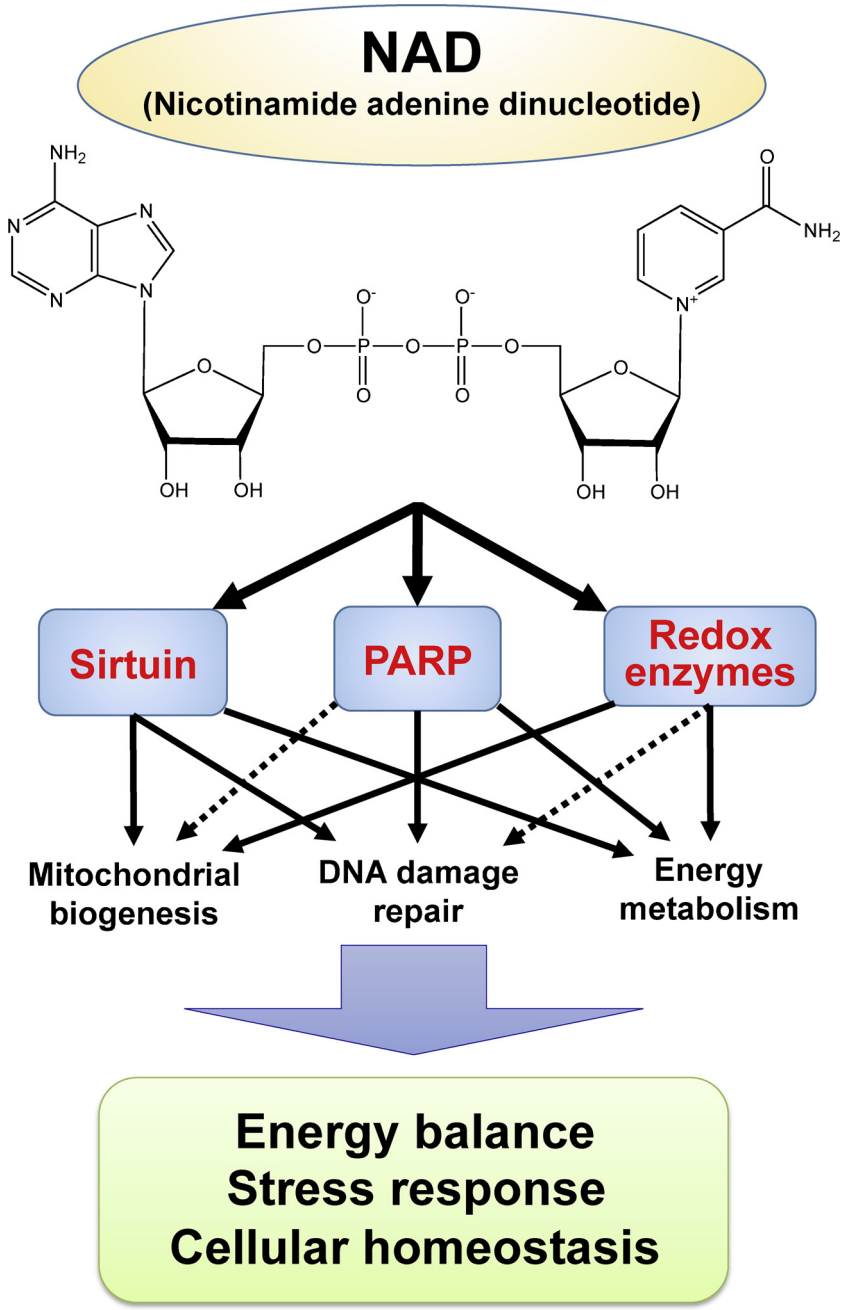

Fig. 1. Biological functions of NAD.
NAD regulates the energy balance, stress response, and cellular homeostasis through sirtuins, PARPs and various redox enzymes.

Accumulating evidence has demonstrated that NAD is a key molecule involved in governing the aging process in many organisms. Recent studies have suggested that the intermediates of NAD metabolism, as well as NAD-related metabolites, also possess some unique biological functions in aging and longevity regulation. In addition, new technologies such as metabolomics and genetically modified mice have advanced the understanding of the NAD metabolism pathways. In this review, we comprehensively summarize the state-of-the-science regarding NAD-synthesizing and – consuming enzymes and their roles in aging. In addition, we present a particular focus on the role of NAD metabolism in the regulation of longevity, with a discussion of the remaining obstacles in this research area for the practical application to humans in the near future.

2. NAD synthesis pathways and corresponding enzymes

2.1. Salvage pathway

In mammals, the salvage pathway is considered the most important pathway for producing and maintaining intracellular NAD levels (Revollo et al., 2004). In this pathway, the synthesis of NAD starts from NAM, which is a by-product of NAD-consuming enzymes such as sirtuin, PARP, and NAD glycohydrolase (Fig. 2). NAM is also imported as a dietary nutrient from various foods. NAM is then converted to NAD through a two-step reaction. The initial step in this process is catalyzed by nicotinamide phosphoribosyltransferase (Nampt), which generates nicotinamide mononucleotide (NMN) from NAM and 5-phosphoribosyl-1-pyrophosphate (PRPP) (Revollo et al., 2004). Subsequently, nicotinamide mononucleotide adenylyltransferase (Nmnat) produces NAD by