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Review

Regulation of NAD biosynthetic enzymes modulates NAD-sensing processes to shape mammalian cell physiology under varying biological cues ☆

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ABSTRACT

In addition to its role as a redox coenzyme, NAD is a substrate of various enzymes that split the molecule to either catalyze covalent modifications of target proteins or convert NAD into biologically active metabolites. The coenzyme bioavailability may be significantly affected by these reactions, with ensuing major impact on energy metabolism, cell survival, and aging. Moreover, through the activity of the NAD-dependent deacetylase sirtuins, NAD behaves as a beacon molecule that reports the cell metabolic state, and accordingly modulates transcriptional responses and metabolic adaptations. In this view, NAD biosynthesis emerges as a highly regulated process: it enables cells to preserve NAD homeostasis in response to significant NAD-consuming events and it can be modulated by various stimuli to induce, via NAD level changes, suitable NAD-mediated metabolic responses. Here we review the current knowledge on the regulation of mammalian NAD biosynthesis, with focus on the relevant rate-limiting enzymes. This article is part of a Special Issue entitled: Cofactor-dependent proteins: Evolution, chemical diversity and bio-applications.

1. Introduction

NAD(H) and NADP(H) are ubiquitous and essential redox coenzymes taking part to most cellular reactions in both catabolism and anabolism: NAD(H) mainly participates in ATP production, whereas NADP(H) is utilized in anabolism and for modulating the cellular redox status [1]. NADP is formed from existing NAD by the ATP-dependent NAD kinase catalyzed reaction, and the intracellular ratio NAD/NADP is largely in favor of NAD. As electron carriers, the coenzyme molecules shuttle between their oxidized and reduced form, while total coenzyme concentration is not altered. On the contrary, several enzymes are known that split the molecule at its N-glycosidic bond, thus rendering its continuous resynthesis indispensable (Fig. 1). These enzymes include i) mono- and poly-ADP ribose (ADPR) transferases (collectively referred as ARTs) which cleave NAD and transfer ADPR, either as a single moiety or as a polymer, to acceptor proteins, resulting in their covalent modification and modulation of their function. ADP ribosylation is involved in a wide range of cellular processes, including DNA damage response, telomere maintenance, transcriptional regulation, control of immune response and cell death [2,3]; ii) the multifunctional NAD glycohydrolase (CD38) that generates the NAD derivatives nicotinic acid adenine dinucleotide phosphate (NAADP), ADPR and cyclic-ADPR, all of them with a well recognized role in calcium signaling [4,5]; iii) sirtuins, most of which catalyze NAD-dependent deacylation of transcription factors, histones and metabolic enzymes, thereby mediating cell adaptation to various kinds of stress, like fasting, exercise, and calorie restriction (CR). In this way, they have been shown to affect energetic metabolism, proliferation, DNA repair, apoptosis, senescence, endocrine signaling, and lifespan [6,7].

Abbreviations: ADPR, ADP ribose; ARTs, ADP ribose transferases; ARTD1, poly-(ADP ribose) polymerase 1; NAADP, nicotinic acid adenine dinucleotide phosphate; CR, calorie restriction; PAR, poly-(ADP ribose); PGC-1, peroxisome proliferator-activated receptor-γ coactivator; Nam, nicotinamide; HFD, high-fat diet; NamPRT, nicotinamide phosphoribosyltransferase; PRPP, phospho-ribosyl pyrophosphate; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; NMNAT, NMN adenylyltransferase; NRK, nicotinamide riboside kinase; PnP, prine nucleoside phosphorylase; NAR, nicotinate riboside; NAMN, nicotinate mononucleotide; NA, nicotinic acid; NAPRT, nicotinate phosphoribosyltransferase; NAAD, nicotinic acid adenine dinucleotide; NADS, NAD synthetase; KP, kynurenine pathway; ACMS, 2-amino-3-carboxymuconate semialdehyde; ACMSD, ACMS decarboxylase; QA, quinolinic acid; QAPRT, quinolinate phosphoribosyltransferase; PA, picolinic acid; CLL, chronic lymphocytic leukemia; HIF, hypoxia-inducible factor; FOXO, O family members of the forkhead transcription factors; AMPK, AMP-activated protein kinase; MIBP, Muscle Integrin Binding Protein; IDO, indoleamine 2,3-dioxygenase; IK, interleukin; AP, activator protein; NF, nuclear factor; IFN, interferon; TNF, tumor necrosis factor

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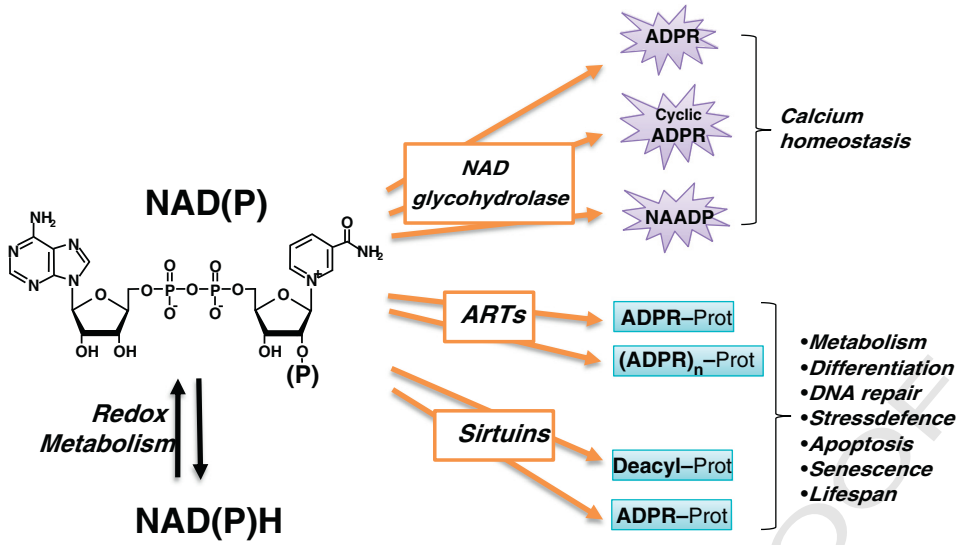

Fig. 1. The dual role of NAD(P) in redox metabolism and signaling.

Among ARTs, ARTD1 (also known as PARP1 [8]), represents the major NAD catabolic enzyme, which consumes cellular NAD at sustained rate under basal conditions [9] and, even more significantly, following oxidative and genotoxic damage [10], thereby forcing cells to continuously synthesize NAD to maintain cell viability. A substantial role in the consumption of intracellular NAD has also been ascribed to CD38 activity [11], that consumes several NAD molecules while synthesizing single molecules of cyclic-ADPR, thus reinforcing the notion that intensive and continuous NAD regeneration is needed. On the other hand, in the last decade mounting evidence indicates that intracellular NAD levels are significantly affected by nutritional and environmental stimuli, and that changes in the NAD content are readily reflected into sirtuin activity modulation. This, in turn, leads to the up- or down-regulation of sirtuin-controlled genes that are central to energetic metabolism and stress response. In this view, it has been shown that maintenance of a proper intracellular NAD concentration is critical for protecting against diet- and age-induced disorders [12,13]. Accordingly, manipulation of NAD biosynthesis appears very promising for therapeutic benefits and, indeed, accumulating data point to enhancement of NAD synthesis as having protective effects in metabolic and neurodegenerative diseases [14].

In this review, we will first emphasize the importance for the cell to maintain a physiological NAD homeostasis, by presenting some of the evidence on how deeply the intracellular NAD availability can influence mammalian physiology. We will then focus on the NAD biosynthetic enzymes that are known to control the maintenance of intracellular NAD levels, with particular attention to the current knowledge on their regulation at transcriptional, post-transcriptional and enzymatic level.

2. The importance of controlling intracellular NAD levels

NAD homeostasis is the result of the balance between a number of NAD cleaving reactions and NAD biosynthetic routes. In this section we focus first on the influence of NAD splitting enzymes on the intracellular NAD availability, and then on the role of NAD as a messenger modulating cellular transcriptional responses and metabolic adaptations.

2.1. ARTD1 activity

The ART family includes a number of enzymes that hydrolyze the N-glycosidic bond of NAD, releasing Nam and transferring the ADPR moiety to target protein acceptors. Some members of the family are able to elongate the protein-bound ADPR to create a polymer, termed poly-(ADP ribose) (PAR). The most studied among the several known ARTs is ARTD1, which is activated in response to specific signaling pathways, and by DNA breaks, leading to the covalent poly-ADP ribosylation of target proteins, thus regulating several processes such as replication, transcription, DNA repair, and metabolism [2]. ARTD1 is a significant contributor to NAD consumption under basal conditions [9], and it can profoundly affect intracellular NAD content under conditions leading to its hyperactivation. As an example, the hyperactivation of the enzyme in a neuronal culture model of acute acquired epilepsy leads to severe NAD loss, energy failure, translocation of the apoptosis-inducing factor from mitochondria to nucleus and neuronal death [15]. Likewise, the permanent activation of ARTD1 in Nijmegen Breakage Syndrome cells unable to repair DNA double strand breaks causes a dramatic decrease in NAD levels leading ultimately to a loss of the antioxidative capacity [16]. Whether NAD depletion and/or PAR accumulation following ARTD1 hyperactivation are the causal event of cell energy failure and death is still a matter of debate [17]. Nevertheless, in several in vitro [18,19] and in vivo [20,21] models of ARTD1 hyperactivation, NAD repletion has been shown to prevent the cell death. In many studies, the NAD protective effect has been shown to depend on sirtuins [15,22], leading to the suggestion that the decline of sirtuin activity due to NAD depletion might play a key role in the ARTD1-mediated cell death. Indeed, experimental evidence has been provided that SIRT1-catalyzed deacetylation is lowered in situations of ARTD1 hyperactivation [22].

2.2. NAD glycohydrolase activity

CD38, originally identified as a lymphocyte antigen, is both a cell surface receptor able to transduce signaling for cell activation and proliferation, and a transmembrane enzyme responsible for the synthesis of the intracellular second messengers cyclic-ADPR and ADPR (using NAD as the splitted substrate) and NAADP (from NADP, in a peculiar pyridine base-exchange reaction), all relevant Ca^{2+} mobilizers [23]. A recent study showed that the enzyme can be found on the membrane in two opposing orientations, with the catalytic domain facing either the outside or the inside of the cell, which might explain the intracellular formation of its second messenger products [24]. Notably, NAD hydrolysis seems to be the enzyme's major catalytic activity, as the reaction appears to yield approximately one molecule of cyclic-ADPR every 100 molecules of NAD hydrolyzed [25]. Conflicting reports on the enzyme localization are available in the literature: it is still debated whether

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