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ARTD1 (PARP1) activation and NAD$^+$ in DNA repair and cell death

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ABSTRACT

Nicotinamide adenine dinucleotide, NAD$^+$, is a small metabolite coenzyme that is essential for the progress of crucial cellular pathways including glycolysis, the tricarboxylic acid cycle (TCA) and mitochondrial respiration. These processes consume and produce both oxidative and reduced forms of NAD (NAD$^+$ and NADH). NAD$^+$ is also important for ADP(ribosyl)ation reactions mediated by the ADP-ribosyltransferase enzymes (ARTDs) or deacetylation reactions catalyzed by the sirtuins (SIRTs) which use NAD$^+$ as a substrate. In this review, we highlight the significance of NAD$^+$ catabolism in DNA repair and cell death through its utilization by ARTDs and SIRTs. We summarize the current findings on the involvement of ARTD1 activity in DNA repair and most specifically its involvement in the trigger of cell death mediated by ARTD1 activation and energy depletion. By sharing the same substrate, the activities of ARTDs and SIRTs are tightly linked, are dependent on each other and are thereby involved in the same cellular processes that play an important role in cancer biology, inflammatory diseases and ischaemia/reperfusion.

1. NAD$^+$/NADH coenzyme

1.1. NAD$^+$ production pathways

Nicotinamide adenine dinucleotide is an essential metabolite and coenzyme present in cells in both an oxidized form (NAD$^+$) and reduced form (NADH). It is composed of two nucleotides, an adenine monophosphate (AMP) and a nicotinamide mononucleotide (NMN) (Fig. 1A). NAD is an electron carrier and is involved in redox reactions occurring during cell metabolism. It is synthesized *de novo* from the amino acid tryptophan [1] but can also be produced by salvage pathways from three precursors: nicotinic acid (Na) (vitamin B3 or niacin), nicotinamide (Nam) and nicotinamide riboside (NR). Nam is also directly released from the ADP-ribose transfer reaction that consumes NAD$^+$ (Fig. 1B). This recycling pathway is mostly activated under cellular stress when the exogenous precursors are not directly available.

1.2. NAD$^+$ catabolism pathways

1.2.1. Redox roles of NAD$^+$

NAD$^+$ and NADH have an essential role in glycolysis, in the mitochondrial electron transport chain and in the tricarboxylic acid (TCA) cycle. These three important cellular pathways are interconnected through a process of provider/consumer of both forms of NAD and towards the goal of ATP production (Fig. 2). Therefore, cells maintain a high concentration of both NAD$^+$ and NADH.

Glycolysis produces pyruvate from glucose through several different steps including the reduction of NAD$^+$ to NADH in the cytosol. NADH can be transferred into the mitochondria through NADH shuttles [2,3] and affects oxidative phosphorylation. The mitochondrial TCA cycle is also a consumer of NAD$^+$ and the main provider of reduced NAD to the respiratory chain. NADH is the electron donor and its oxidation to NAD$^+$ is mediated by complex I of the respiratory chain. The electron is then transferred through the different respiratory chain complexes until ATP synthase, or complex V, generates ATP through oxidative phosphorylation [4].

Abbreviations: AMP, adenine monophosphate; ARTD, ADP-ribosyltransferase diphtheria toxin-like; HK1, hexokinase 1; NAD, nicotinamide andenine dinucleotide; Nam, nicotinamide; NR, nicotinamide riboside; Na, nicotinic acid; MNNG, N-methyl-N′-nitro-N-nitrosoguanidine; PBM, poly(ADP-ribose)AR binding motif; pADPr, poly(ADP-ribose); PARG, poly(ADP-ribosyl) glycohydroalse; SIRT, silent information regulator 1; TCA, tricarboxylic acid; VDAC, voltage dependent anion channel.

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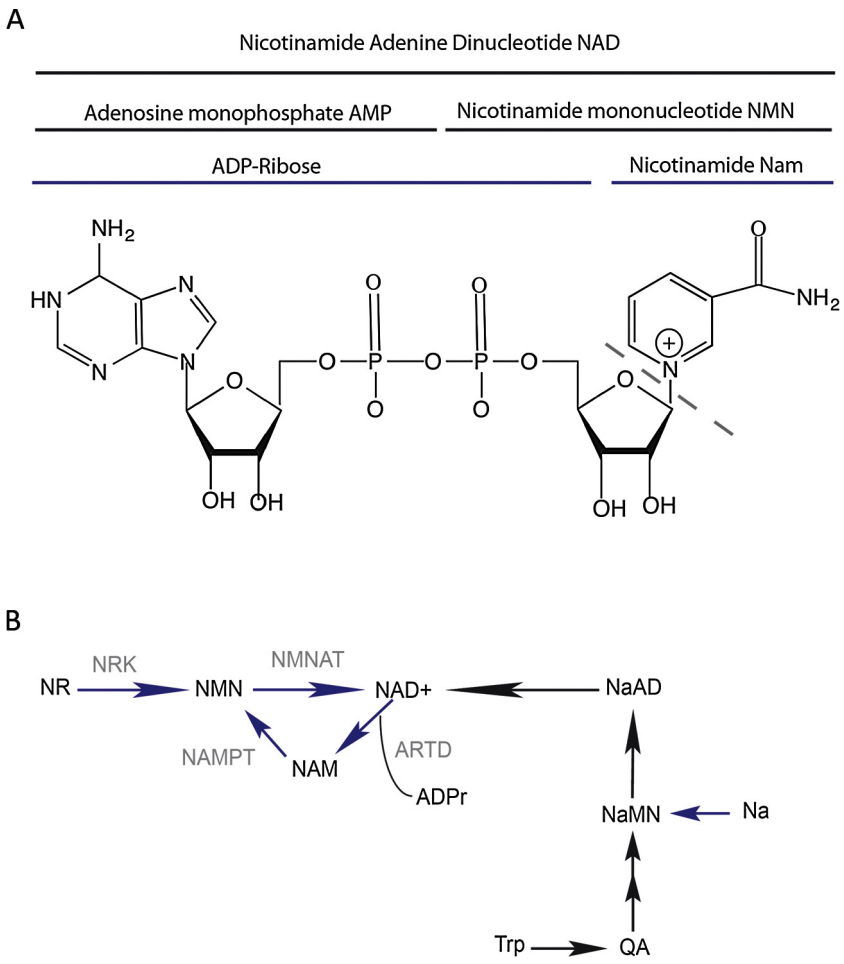

Fig. 1. (A) Structure of NAD. Nicotinamide adenine dinucleotide (NAD^+) is composed of two nucleotides, an adenine monophosphate (AMP) and a nicotinamide mononucleotide (NMN) linked together by two phosphate groups. During the ADP-ribosylation reaction the ADP-ribose unit is transferred to target proteins by ARTD enzymes and a unit of nicotinamide (Nam) is released. (B) Pathways of NAD^+ synthesis. NAD^+ is synthesized by a *de novo* pathway from the amino acid tryptophan (black arrows) and by a salvage pathway (Blue arrows).

1.2.2. Non-redox roles of NAD^+

Beside its role in energy production, the NAD^+ coenzyme is a substrate of the ADP-ribosyltransferase enzymes (ARTD or PARP) [5] and of the sirtuins, NAD-dependent deacetylases [6].

1.2.2.1. Poly(ADP-ribosylation). Poly(ADP-ribosyl)ation is a posttranslational modification of proteins catalyzed by the poly(ADP-ribose) polymerases (PARPs), newly named ADP-ribosyltransferases diphtheria toxin-like proteins (ARTDs) [5]. The ARTD family is composed of 17 enzymes involved in multiple cellular pathways such as DNA repair response, chromatin remodelling, transcription, telomere homeostasis or cell death [7–9]. Some ARTDs are able to catalyze the poly(ADP-ribosyl)ation reaction while others are responsible for mono(ADP-ribosyl)ation [5]. In both cases, ARTDs transfer the ADR-ribose moiety of NAD^+ to the carboxyl group of lysine, aspartic and glutamic acid residues of the acceptor proteins [10,11] and release the nicotinamide unit (Fig. 1B). ARTD activity is the main NAD^+ catabolic process in the cell and forces the cell to continuously synthesize NAD^+ from the *de novo* pathway or recycling pathway in the case of cellular stress, mostly during the DNA repair process. The founding member of the ARTD family, ARTD1 (PARP1), as well as ARTD2 (PARP2) and ARTD3 (PARP3), are involved in DNA repair and are referred to as DNA dependent-ARTDs. ARTD3 has been shown to play a major role in the repair of DNA double-strand breaks [12,13], while ARTD1 and ARTD2 activation is triggered by DNA single-strand breaks occurring during Base Excision Repair [14].

1.2.2.2. Deacetylation. Sirtuins belong to a seven-member family of NAD^+ dependent deacetylases. The budding yeast gene *Sir2* (*Silencing information regulator* 2) was the first sirtuin gene discovered [15]. The mammalian sirtuin family is composed of 7 isoforms (SIRT1-7) and each have functions with distinct subcellular localization [16]. They have been shown to play pivotal roles in genome stability, mitochondrial and oxidative metabolism [17] and lifespan regulation. The sirtuins catalyze the removal of an acetyl group present on proteins by using NAD^+ and releasing nicotinamide and acetyl-ADP-ribose units [18,19]. As an NAD^+ consumer, sirtuin activity is greatly dependent on the availability of the coenzyme and several studies have shown that the other NAD^+ consuming enzymes such as ARTDs or cADP-ribose synthase might influence sirtuin activity by reducing NAD^+ availability [20].

2. Role of NAD^+ catabolism in DNA repair and cell death

ARTD1 involvement in DNA repair has been the first and the most extensively described role of the enzyme in past decades. However, this role of ARTD1 in DNA repair is primarily following moderate levels of DNA damage. Conversely, in response to excessive DNA damage, pADPr can become a death signal for the cell enduring the genotoxic insult.