Biochimica et Biophysica Acta 1804 (2010) 1591–1603

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbapap

Review

Sirtuin chemical mechanisms

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ARTICLE INFO

Article history:
Received 17 October 2009
Received in revised form 20 January 2010
Accepted 26 January 2010
Available online 2 February 2010

Keywords:
Sirtuin
AADPR
Protein deacetylation
Enzyme mechanism
NAD

ABSTRACT

Sirtuins are ancient proteins widely distributed in all lifeforms of earth. These proteins are universally able to bind NAD^+, and activate it to effect ADP-ribosylation of cellular nucleophiles. The most commonly observed sirtuin reaction is the ADP-ribosylation of acetyllysine, which leads to NAD^+-dependent deacetylation. Other types of ADP-ribosylation have also been observed, including protein ADP-ribosylation, NAD^+ solvolysis and ADP-ribosyltransfer to 5,6-dimethylbenzimidazole, a reaction involved in eubacterial cobalamin biosynthesis. This review broadly surveys the chemistries and chemical mechanisms of these enzymes.

Sirtuins are a broadly conserved family of enzymes found in all phyla of life including archaea, eubacteria, yeast, plasmodia, metazoans, mammals and even viruses [1–3]. These are ancient proteins that have a common catalytic architecture, which allows these proteins to recognize universally a metabolically central and abundant compound, NAD^+. The most common reaction catalyzed by sirtuin enzymes is that of NAD^+ dependent protein deacetylation, which consumes a mole equivalent of NAD^+ per acetyl group removed [1]. The reaction effects an acetyl group transfer to ADPR to form a novel compound called 2′-*O*-acetyl-ADPR (2′-AADPR, Scheme 1 [1]). Select sirtuins also catalyze other reactions, such as protein ADP-ribosyltransfer, NAD^+ hydrolysis and many if not all seem to catalyze acetyllysine-dependent nicotinamide base-exchange into NAD^+. Sirtuins have been implicated in organism adaptations to nutrient intake, and are regulators of aging in a variety of organisms, ranging from yeast, flies, worms and probably in mammals as well [4,5].

The detailed active site recognition of NAD^+ has been delineated by X-ray crystal structures of sirtuins co-complexed with this substrate [6,7]. NAD^+ complexed to a sirtuin active site is a chemically reactive form of NAD^+ [6], capable of undergoing chemistry with nucleophiles such that ADP-ribosyltransfer occurs with inversion of stereochemistry [8–12] (Scheme 2). Characterized general nucleophiles for NAD^+ include acetyllysine substrates or thioacetyllysine inhibitors [11–13]. Close proximities of NAD^+ and the acetyllysine group (or thioacetyl group) enforced by the active site structure leads to ADP-ribosylation of acetyllysine to form an imidate (or thioimidate, Scheme 2, top). The imidate is proposed to account for deacetylation as well as base-exchange catalyzed by these enzymes [9,12,14,15]. On several sirtuin enzymes other nucleophiles have also been found to react directly with NAD^+ such as methanol [10] (Scheme 2, middle), and water [10], characteristic of an NAD^+ glycohydrolase activity. NAD^+ (and possibly NaMN) can also react with inversion with the nucleophile 5, 6-benzimidazole catalyzed by CobB, a Sir2 found in eubacteria (Scheme 2, bottom) [8,16]. It has been suggested that some sirtuins catalyze a reaction where NAD^+ reacts directly with protein nucleophilic amino acid side chains [16,17]. Indeed, there are multiple examples in which sirtuins have been reported to catalyze ADP-ribosyltransfer to proteins [18–22].

The common mechanistic thread in all of these chemistries is that sirtuins activate NAD^+ as a chemical partner to react with nucleophiles to effect different reaction outcomes. We continue to learn more about how sirtuin chemistry varies from species to species and from isoform to isoform. Nature has honed the chemistry platform provided by sirtuin enzymes to accomplish specificity, regulatory control, and linkage to metabolism, which in turn disposes these enzymes to regulate a variety of fundamental cellular processes. In this review, we examine the mechanisms of sirtuin chemistries with an emphasis on the relationships to known chemistries, the differences of chemistries discovered for different sirtuins, and we discuss the functional and chemical components of sirtuin reactions.

1. Sirtuin deacetylation reaction

The most biologically relevant of the reactions that sirtuin enzymes catalyze is protein deacetylation [1,3]. The reaction has been demonstrated for sirtuins isolated from a variety of phylogenetically distributed species, from archaea to human enzymes [2,7,9,23]. The reaction stoichiometry in Scheme 1 is catalyzed by sirtuins derived from yeast, archaeal, eubacterial and mammalian

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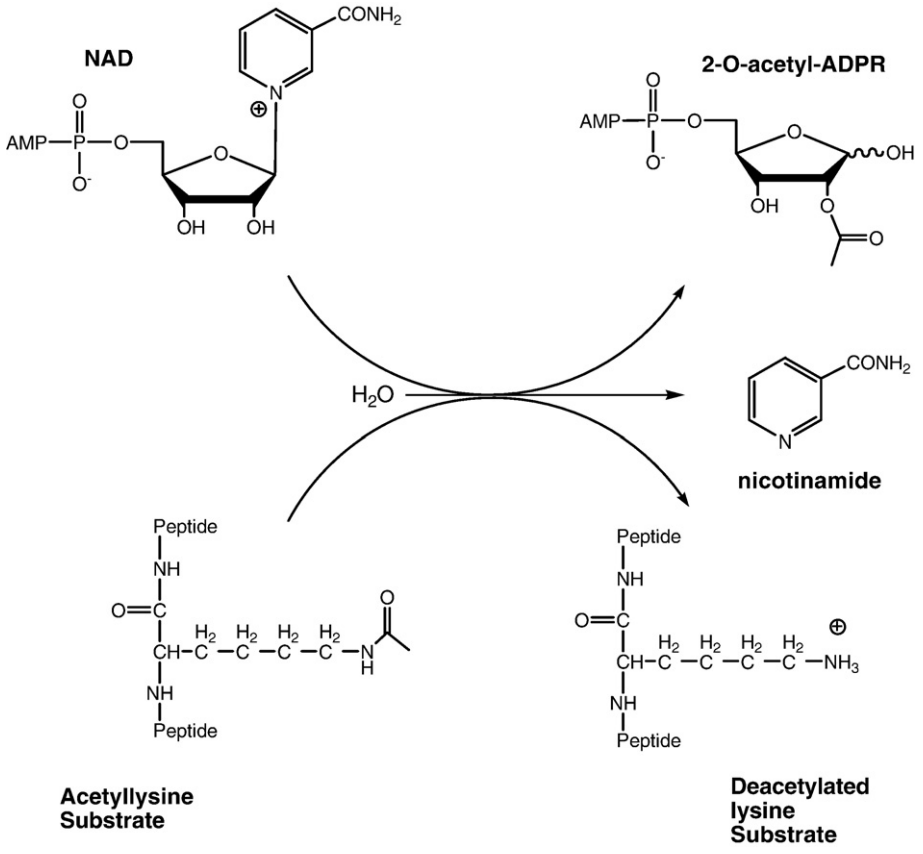
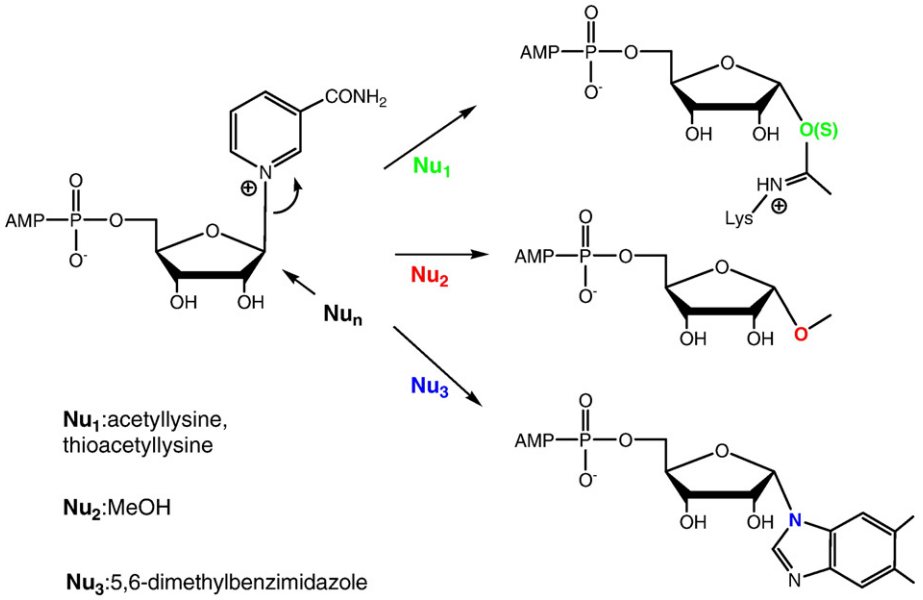
1570-9639/$ – see front matter
doi:10.1016/j.bbapap.2010.01.021



Scheme 1. Overall stoichiometry determined for the NAD^+-dependent deacetylation reaction.

sirtuins [9,24,25]. Among other things, the reaction is unusual in that it generates 2′-AADPR [1,9,24]. The full characterization of 2′-AADPR established that sirtuins catalyze the synthesis of an ester from an amide, a thermodynamically challenging reaction paid for by NAD^+ degradation [1]. This reaction outcome, the biological distribution of the reaction and the structural and sequence similarities of sirtuins provide evidence that sirtuins utilize a common mechanistic strategy to achieve deacetylation. The function of 2′-AADPR in cells, which spontaneously and non-enzymatically equilibrates with the 3′-AADPR isomer [9,24], is currently poorly understood, but is the topic of an extended review in this journal issue.

The sirtuin deacetylation reaction, in addition to restoring the free amino group of lysine and producing AADPR, also generates nicotinamide as a product in all cases [9,26,27] indicating that the deacetylation



Scheme 2. Direct reaction of NAD^+ with nucleophiles determined for distinct sirtuin enzymes. The top reaction depicts imidate and thioimidate formation. The second reaction depicts a direct solvolysis reaction characterized for a *Plasmodium falciparum* sirtuin enzyme. The bottom reaction represents an ADP-ribosyltransfer reaction determined for the CobB enzyme, a sirtuin from eubacteria.