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Niacin Status Impacts Chromatin Structure[1–3]

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Abstract

Niacin is required to form NAD and NADP, which are involved in many essential redox reactions in cellular metabolism. In addition, NAD^+ acts as a substrate for a variety of ADP-ribosylation reactions, including poly- and mono-ADP-ribosylation of proteins, formation of cyclic ADP-ribose, and the generation of O-acetyl-ADP-ribose in deacetylation reactions. These nonredox reactions are critical in the regulation of cellular metabolism, and they are sensitive to dietary niacin status. There are 4 known mechanisms by which ADP-ribosylation reactions directly regulate chromatin structure. These include the covalent modification of histones with poly(ADP-ribose), the extraction of histones from chromatin by noncovalent binding to poly(ADP-ribose) on poly(ADP-ribose) polymerase-1, poly ADP-ribosylation of telomeric repeat-binding factor-1 within telomeres, and deacetylation of histones by the sirtuins. These reactions produce a variety of localized effects in chromatin structure, and altered function in response to changes in niacin status may have dramatic effects on genomic stability, cell division and differentiation, and apoptosis. J. Nutr. 139: 2397–2401, 2009.

Introduction

Dietary forms of niacin include nicotinic acid (from plants), nicotinamide (mainly from animal products), and tryptophan (present in most proteins) (**Fig. 1**). Dietary nicotinic acid is converted into NAD in the intestine and liver and subsequently cleaved to release nicotinamide into the bloodstream for uptake by extrahepatic tissues (1). Nicotinamide can then be rapidly reincorporated into NAD by the salvage pathway. Tryptophan will generate some NAD in a complex pathway that is not effectively regulated by niacin status (2).

Niacin deficiency in humans is usually associated with the consumption of corn, which is low in tryptophan and requires alkaline treatment to release protein-bound niacin for absorption (2). The expansion of worldwide corn use led to widespread occurrence of the disease pellagra, which is characterized by sun sensitivity and dementia. These unique endpoints were not well explained by the redox functions of niacin cofactors, but they made more sense as various ADP-ribosylation reactions were discovered and characterized (Fig. 1). We now know that poly (ADP-ribose) metabolism is critical in DNA repair and chromosomal stability, and impaired function in this area likely explains the sun sensitivity of pellagra (3). Cyclic ADP-ribose controls calcium release in neurons and is probably involved in the dementia observed during niacin deficiency (4). Although most developed countries fortify niacin in the food supply, there remains a proportion of the population with suboptimal niacin nutrition (5). However, more common and severe deficiencies are observed in subpopulations such as alcoholics and cancer patients, and these problems are likely underdiagnosed (2).

Mechanisms for control of chromatin structure

Poly(ADP-ribose) polymerase-1 (PARP-1)[4] was the first enzyme discovered to make chains of ADP-ribose units on proteins, using NAD^+ as a substrate. It was found to be activated by DNA strand breaks and to subsequently play a multitude of roles in DNA repair and in the cellular genotoxicity response. These roles include local chromatin relaxation, assembly of other proteins into repair complexes, regulation of signal cascades through proteins such as p53, and control of cell cycle arrest and apoptosis. The complexity of this system was further appreciated with the discovery of 16 other genes with active site homology to PARP-1 (6). In addition to these posttranslational modifications, cyclic ADP-ribose regulates intracellular calcium signaling, and the sirtuins cleave NAD^+ in the removal of acetyl groups from cellular proteins, including histones and p53. Thus, we are just starting to appreciate the breadth and complexity of the cellular response to variations in niacin status and NAD levels.

Altered chromatin structure was one of the first endpoints associated with poly(ADP-ribose) formation (7). We now know that there are at least 4 mechanisms by which NAD^+-dependent reactions can directly control chromatin structure, and the remainder of this article focuses on those aspects of ADP-ribose metabolism. These 4 mechanisms are listed below.

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[4] Abbreviations used: NMNAT, nicotinamide mononucleotide adenylyltransferase; PARP, poly(ADP-ribose) polymerase; SIRT1–7, sirtuins 1-7; TRF, telomeric repeat-binding factor.

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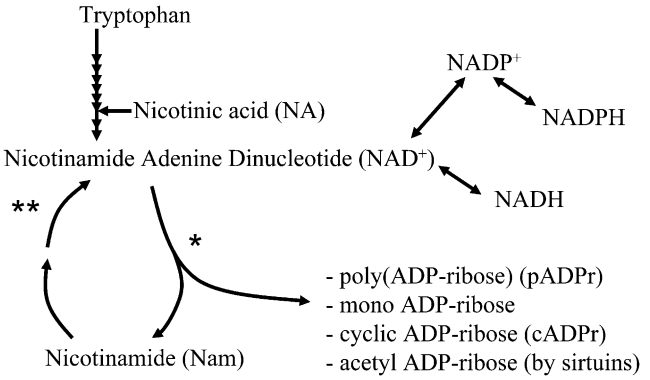

FIGURE 1 Niacin is obtained from the diet in the form of tryptophan, nicotinic acid, and nicotinamide. NAD^+ can participate in redox metabolism or participate in ADP-ribosylation reactions. *NAD^+ is cleaved in all ADP-ribosylation reactions, releasing nicotinamide **the final step in the synthesis of NAD^+ from nicotinamide is catalyzed by 3 different nicotinamide mononucleotide adenylyltransferase (NMNAT) enzymes. [Adapted with permission from Kirkland (1)].

1*) Covalent ADP-ribosylation of histones.* PARP-1 has 2 zinc fingers, which bind to DNA strand breaks, leading to catalytic activation. A large number of nuclear proteins act as PARP-1 substrates, accepting various lengths of polymer chains (7). Poly(ADP-ribose) is strongly anionic, and when covalently attached to a protein, it will tend to force that protein away from DNA, which is also negatively charged. Rouleau et al. have effectively reviewed the early literature in this area (7), and Quénet et al. have reviewed more recent advances (8). Histones H1, H2A, and H2B are the major histone substrates for poly (ADP-ribosyl)ation, but H3, H4, and H5 may also be covalently modified. These modifications occur on carboxylate groups of glutamate side chains or at the carboxy terminus of the protein. When histones are modified in this way, they dissociate from DNA, and chromatin relaxation will occur. There are 2 forms of relaxation, depending on the site of poly(ADP-ribose) synthesis and the length of the chains. When PARP-1 is maximally activated in the presence of high levels of NAD^+, modification of H1 will predominate, and chromatin will relax to the "beads on a string" conformation associated with histone H1 depletion. Interestingly, the histone H1 remains associated with the chromatin, and if the poly(ADP-ribose) is degraded by glycohydrolase activity, the chromatin will return to the condensed state. Conversely, when in vitro systems are designed to generate lower levels of poly(ADP-ribose) (using lower NAD^+ or adding glycohydrolase to create polymer turnover), there is a shift from histone H1 modification to histone H2A and H2B modification. Poly(ADP-ribosyl)ation of core histones leads to subtle changes in chromatin structure that can be observed as a lack of responsiveness to H1-induced condensation as well as increased availability of histone epitopes for antibody binding (9). PARP-1 can also relax higher-order chromatin structure via covalent modification of lamins, high-mobility-group proteins (7), and heterochromatin proteins (8).

These experiments have been conducted in vitro, and there is no direct work on the effect of dietary niacin status on histone poly(ADP-ribosyl)ation or chromatin structure in vivo. It seems likely from the different in vitro models that core histone modification will occur under normal in vivo conditions of NAD^+ status and rapid polymer turnover rate (10), but high dietary niacin and/or high levels of DNA damage may lead to more predominant modification of histone H1.

Recent research has been increasing our appreciation for the involvement of other members of the PARP family. PARP-2, for example, heterodimerizes with PARP-1 and is also activated by DNA strand breaks. The current thinking is that PARP-1 and -2 together play a major role in the regulation of heterochromatin structure (8), which is critical in transcriptional control, as illustrated by the PARP-dependent formation of puffs in transcriptionally active areas of *Drosophila* chromosomes (11).

2*) High-affinity poly(ADP-ribose) binding and histone shuttling.* PARP-1 actually functions at strand breaks as a dimer, and the majority of polymer is synthesized on the neighboring PARP-1 enzyme. This probably serves several functions, including repulsion of PARP-1 from the strand break to allow completion of repair. However, it was also discovered that histones, and many other proteins, have high-affinity poly (ADP-ribose) binding sites. These noncovalent interactions are strong enough to draw histones out of nearby chromatin structure onto the clouds of polymer covalently attached to PARP-1.

This concept of histones transiently shuttling out of chromatin was developed by Felix Althaus and has been reviewed by his group (12) and others (7). High-affinity polymer binding sites exist on histones H1, H2A, H2B, H3, and H4. It is thought that a polymer of 40 ADP-ribose units attached to PARP-1 is capable of dissociating nearby nucleosomes. This localized relaxation is reversible, as the histones are held in place until PARP-1 activity dissipates, and the existing poly(ADP-ribose) is degraded by glycohydrolase activity, allowing the histones to return to the chromatin environment. Presumably, during this time, processes such as DNA repair and regulation of transcription can take place in a relaxed form of chromatin. Other PARP enzymes may play a role in this process, especially PARP-2, which heterodimerizes with PARP-1 and is also activated by DNA strand breaks.

3*) Poly(ADP-ribose) formation in telomeres.* The terminal portions of chromosomes can not be fully replicated during cell division and erode over time, leading to senescence. Telomeres in proliferative cells may be extended by a reverse transcriptase enzyme called telomerase. The tips also represent double strand breaks, which may be sensitive to dangerous recombination events. To control telomere elongation and prevent telomere instability, these sections are folded backward over specialized proteins, including telomeric repeat-binding factor-1 (TRF1) and TRF2. During telomere elongation, this structure needs to be transiently relaxed. This is accomplished by a PARP enzyme referred to as tankyrase 1, which covalently modifies TRF1 with poly(ADP-ribose), relaxing the telomere region. A closely related enzyme, tankyrase 2, appears to have similar activities but has not been confirmed to act at human telomeres (13). Mice lacking functional genes for either tankyrase 1 or 2 survive but die during fetal development when both are deleted, indicating that there are critical functions that these enzymes share (14).

Tankyrase 1 appears to have a very high K_m for NAD^+ (of ~1.5 mmol/L), suggesting that the amount and chain length of poly(ADP-ribose) will be responsive to [NAD^+] throughout the physiological range (15) and should be responsive to low and high dietary intakes of niacin, although in vitro conditions may create artifacts in enzyme kinetics.

4*) Histone deacetylation by sirtuins.* The sirtuins (silent mating type information regulation 2 homolog) have attracted attention recently as the gene products responsible for the

lifespan extension caused by caloric restriction. These sirtuins (SIRT) are actually NAD^+-dependent deacetylases, which cleave NAD^+ to create an ADP-ribose acceptor for the acetyl group. There are 7 members of the mammalian family of sirtuins, designated SIRT1–7. SIRT1 is homologous to Sir2 found in yeast, worms, and flies and has been the main object of research because of its role in lifespan extension and genomic stability (16). Overexpression of this gene increases lifespan, as does treatment with resveratrol, a catalytic activator of the enzyme (16).

Histones have basic tails that bind to DNA, and histone acetyl transferases target lysine residues within these tails, leading to local relaxation and enhanced transcription of nearby genes. SIRT1 counters these effects by deacetylating the tails, leading to compaction of chromatin and transcriptional silencing. It should be recognized that many nonhistone proteins are also regulated by acetylation and deacetylation reactions (17). Although extended lifespan associated with high SIRT1 function may be partially a result of the increased stability of compact chromatin, there are many different cellular processes that are altered by changing cellular acetylation status.

The affinity of SIRT1 for NAD^+ is not clear from the literature. Published K_m values vary from 12 μmol/L (18) to over 500 μmol/L (19), suggesting that in vitro conditions and artificial substrates have a significant effect on enzyme kinetics. At the lower end of this range, SIRT1 function could be protected during niacin deficiency but would be quite sensitive to physiological changes in NAD^+ levels if the higher values are accurate.

Dietary niacin status and chromatin structure

There are essentially no data in the literature directly assessing this relationship. The summaries above show that there are several distinct mechanisms by which NAD-dependent reactions control various aspects of chromatin structure and that the enzymes involved have K_m values for NAD^+ that make them susceptible to decreased function during niacin deficiency and increased function during pharmacological intakes of niacin. Roughly, tissue NAD^+ concentrations may vary from 100–1500 μmol/L in different tissues on different levels of dietary niacin (20,21), and most of the K_m values fall in this range. This is a simplification that ignores subcellular distribution (2). It appears that the redox functions of pyridine nucleotides are relatively protected during niacin deficiency, and various ADP-ribosylation reactions lose function, leading to the unique pathologies of pellagra (2). Human data on niacin deficiency and tissue pyridine nucleotides are quite limited (22). Rat models show that NAD^+ concentrations vary dramatically among tissues and that tissues respond very differently to deficient and pharmacological dietary niacin intakes (2). Cell culture models may not be representative, as NAD^+ can be depleted by over 90% before cell division is impaired (23). Severely niacin-deficient rats display decreases in tissue NAD^+ of 20–50% in most tissues, with sensitive proliferative tissues (bone marrow) depleting by 75–80% (20). It is clear that pathologies exist in the whole animal at milder degrees of NAD^+ depletion than those in cell culture models. This may be because of additional stresses, such as DNA damage, occurring in vivo, or the extra requirements for regulation of cellular function in model systems with multiple cell types and tissues.

In bone marrow cells, decreased NAD^+ causes a dramatic decrease in poly(ADP-ribose) content (20). Conversely, feeding pharmacological intakes of niacin increases bone marrow NAD^+ and poly(ADP-ribose) content (21). In this model of deficient through pharmacological niacin intake, bone marrow NAD^+ varies 30-fold, and damage-induced poly(ADP-ribose) 65-fold. Because most of this polymer is synthesized by PARP-1, it is clear that this PARP family member, in this tissue, is very responsive to dietary niacin status. We have also shown that brain cyclic ADP-ribose is sensitive to dietary niacin intake (4), but no other ADP-ribosylation processes have been characterized with respect to niacin status in vivo.

From this starting point, we can jump forward to look at various metabolic and pathological endpoints that could reasonably result from altered poly(ADP-ribose) metabolism. Along these lines, niacin deficiency in rat bone marrow has been shown to delay DNA excision repair (24), deregulate p53 expression, impair cell cycle arrest and apoptosis (25), and to cause dramatic genomic instability, including formation of micronuclei, chromosomal aberrations, and the development of leukemias (24,26). Human data on niacin status and cancer are limited but are suggestive of increased cancer risk on low-niacin diets (27).

Multiple PARP family members, mono ADP-ribosyltransferases, ADP-ribosyl cyclases, and sirtuins could be playing mechanistic roles in these endpoints. From the perspective of chromatin structure, it is not known whether dietary niacin status changes the poly(ADP-ribosyl)ation or acetylation state of histones or causes any measurable change in the degree of chromatin condensation. Of interest, the 2 major NAD-dependent processes controlling chromatin structure have opposite effects on condensation. Direct poly(ADP-ribosyl)ation of histones and histone shuttling cause chromatin relaxation, whereas SIRT1-catalyzed deacetylation causes chromatin compaction (**Fig. 2**). It is interesting to speculate how these 2 processes would respond to progressive decreases in tissue NAD^+ content. It is likely that ADP-ribosylation reactions will be lost at different points as NAD depletes, depending on their essentiality for cell survival or their signaling roles, which may be intentionally tied into NAD status.

Because PARP-1 and SIRT1 are both functioning in the nucleus, it seems that their competition for decreasing substrate will be a fairly simple matter of substrate affinity, or the K_m for NAD^+. Unfortunately, both enzymes have complex reaction conditions, and in vitro kinetics may be altered by choices such as type of activating DNA structures for PARP-1 or the artificial peptide used as a substrate for SIRT1. PARP-1 is thought to have

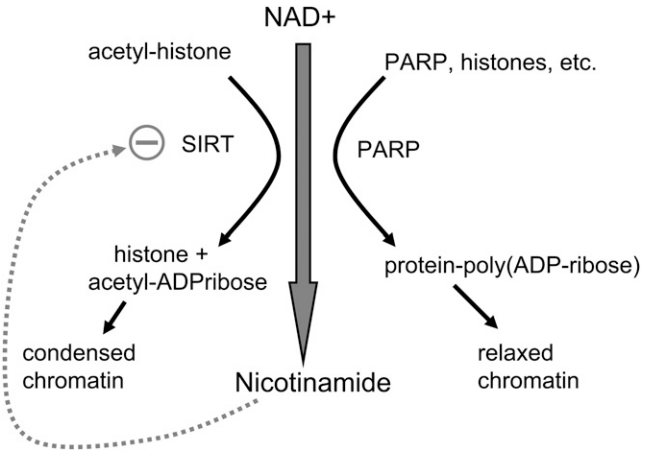

FIGURE 2 The relationships among poly(ADP-ribose) metabolism, sirtuin activity, and chromatin structure. Poly(ADP-ribose) polymerase (PARP), sirtuins (SIRT).

a K_m for NAD^+ of 20–80 μmol/L (2), whereas literature values for SIRT1 vary widely, from <20 μmol/L (18) to >500 μmol/L (19). Thus, in vitro kinetics data do not give a clear picture of how these enzymes will compete for NAD^+.

In addition, there are other mechanisms that will impact on this competition for NAD^+. All ADP-ribosylation reactions release nicotinamide (Fig. 1), and PARP-1 has a high capacity for NAD cleavage. When PARP-1 is actively forming polymer, local concentrations of nicotinamide will increase. Although nicotinamide is a weak inhibitor of PARP-1, it is a relatively effective inhibitor of SIRT1 (28), suggesting that PARP-1 activity around the site of a strand break could suppress SIRT1 to ensure chromatin relaxation.

Another possible interaction exists in the subcellular distribution of NAD^+. The final enzyme in the conversion of nicotinamide to NAD^+, nicotinamide mononucleotide adenylyltransferase (NMNAT), has 3 isoforms, with localization to the nucleus, Golgi apparatus, and mitochondria. The relative expression of these genes will likely control the subcellular distribution of NAD. Mitochondria are thought to make NAD^+ slowly and then sequester it with a high efficiency, maintaining levels much higher than those found in the cytosol (2). NAD^+ should diffuse freely between the nucleus and cytosol through nuclear pores, but nuclear synthesis of NAD^+ may direct it toward nuclear enzymes. Additionally, the nuclear NMNAT has been shown to bind to both PARP-1 (29) and SIRT1 (30). Thus, a high expression of nuclear NMNAT and subsequent regulation of specific protein interactions may direct newly synthesized NAD^+ preferentially to the PARP-1 or SIRT1 active sites.

A useful experiment would be to establish a range of cellular NAD^+ levels, through dietary restriction in vivo or cell culture niacin levels, and then challenge the cells to synthesize poly (ADP-ribose) (DNA damage) or deacetylate histones (e.g., resveratrol treatment). Maintaining intact cellular structure and nuclear function would give a more accurate idea of how these 2 processes function as NAD^+ levels decrease. In conclusion, there is ample evidence to suspect that niacin status will impact on chromatin structure, leading to many of the observed longer-term changes in genomic stability and carcinogenesis. Future experiments should improve our knowledge of the interactions between NAD-dependent processes in chromatin as niacin status is altered.

Other articles in the supplement include references (31–34).

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