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Review

Niacin requirements for genomic stability

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ABSTRACT

Through its involvement in over 400 NAD(P)-dependent reactions, niacin status has the potential to influence every area of metabolism. Niacin deficiency has been linked to genomic instability largely through impaired function of the poly ADP-ribose polymerase (PARP) family of enzymes. In various models, niacin deficiency has been found to cause impaired cell cycle arrest and apoptosis, delayed DNA excision repair, accumulation of single and double strand breaks, chromosomal breakage, telomere erosion and cancer development. Rat models suggest that most aspects of genomic instability are minimized by the recommended levels of niacin found in AIN-93 formulations; however, some beneficial responses do occur in the range from adequate up to pharmacological niacin intakes. Mouse models show a wide range of protection against UV-induced skin cancer well into pharmacological levels of niacin intake. It is currently a challenge to compare animal and human data to estimate the role of niacin status in the risk of genomic instability in human populations. It seems fairly certain that some portion of even affluent populations will benefit from niacin supplementation, and some subpopulations are likely well below an optimal intake of this vitamin. With exposure to stressors, like chemotherapy or excess sunlight, suraphysiological doses of niacin may be beneficial.

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1. Introduction

Through its history, the growing understanding of niacin deficiency pathologies has gone hand in hand with emerging fields of genomic instability and ADP-ribose metabolism. Pellagra, the human disease of niacin deficiency, ravaged certain corn-consuming populations for several hundred years, producing the

Abbreviations: NAD, nicotinamide adenine dinucleotide; PAR, poly(ADP-ribose); PARP, poly(ADP-ribose) polymerase.

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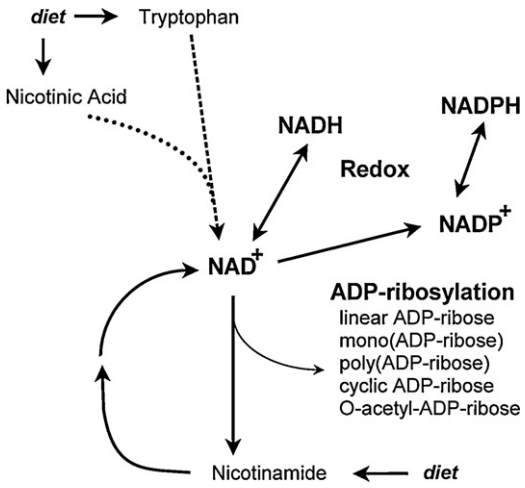

Fig. 1. A summary of dietary niacin precursors, pyridine nucleotide formation, and participation of NAD^+ in ADP-ribosylation reactions.

unique end points of sun-sensitivity and dementia [1]. A real understanding of sun-sensitive dermatitis was only possible after the discovery of poly(ADP-ribose) in 1966 [2]. Since that time, there has been tremendous progress in describing the many roles of poly(ADP-ribose) in DNA damage responses, which will be briefly summarized later in this article. Animal models have examined the impact of niacin status on genomic instability and cancer development in several tissues. However, there is a lack of human data on the association of niacin status and skin cancer risk, or of niacin status and the risk of genomic instability in other tissues that were not an obvious aspect of the pellagra spectrum. Thus, it will be difficult to make detailed recommendations about niacin status and genomic instability in human populations, but we can create a framework and identify some areas which show promise.

1.1. Mechanisms linking niacin status to genomic instability

To characterize the impact of niacin status on genomic instability, one must determine which categories of NAD-dependent reactions are required to maintain genomic stability, and then determine which are at risk of failure as niacin deficiency progresses. Many essential roles of NAD will be preserved by enzyme affinity and subcellular localization, while other functions will fail as deficiency progresses. As shown in Fig. 1, dietary precursors lead to the production of NAD^+, which can be reduced to NADH, or phosphorylated to contribute to the $NADP^+$ and NADPH pools. The large majority of metabolic functions are based on the dinucleotide structures (NAD, NADP), although nicotinic acid and nicotinamide have some interesting metabolic properties, especially at pharmacological levels. The NAD^+/NADH redox couple participates in ~400 reactions, while that of $NADP^+$/NADPH redox couple participates in ~30 others, and there appear to be ~50 reactions in the sirtuin/ADP-ribosylation/cyclization groups, that degrade NAD^+ as a substrate [3,4]. It would not have been surprising to early researchers that niacin deficiency would have severe health consequences given the multitude of redox reactions that depended on it. However, the unique pathologies of pellagra were puzzling given that other redox nutrients like iron and riboflavin participate in the same pathways of energy metabolism, but deficiencies do not lead to sun sensitivity. Riboflavin deficiency does cause skin pathologies and causes oxidant stress and DNA damage in cultured cells, so there might be more overlap in function than is currently appreciated [5].

It is logical to suggest that deficits in redox function during niacin and riboflavin deficiencies could lead to oxidant stress, through a decrease in NADPH, and its ability to maintain GSH levels. In fact, oxidant stress, including oxidant injury to DNA, has been observed during niacin deficiency, in vitro and in vivo [6,7]. However, during niacin deficiency in human [8], animal [9] or cell culture [7] models, it is the NAD+ pool that tends to decrease, while the NADH, $NADP^+$ and NADPH pools are maintained. This suggests that the NADP(H) redox couple is continuing to function and that NAD^+ redox functions are sufficient to maintain the required pools of NADH to drive mitochondrial respiration. It has been observed that the GSH/GSSG couple, which is maintained by NADPH, is not impaired by niacin deficiency [6,7], also supporting the conclusion above. In contrast, riboflavin deficiency does decrease the flow of reducing equivalents from NADPH to GSH [5]. The increase in oxidant stress during niacin deficiency is proposed to result from a disruption in inflammatory signalling [7]. The current thinking is that redox functions and energy metabolism are well maintained during niacin deficiency, either through the selective maintenance of NADH, $NADP^+$ and NADPH, different affinity of enzymes for NAD, or subcellular localization of NAD pools [1].

Conversely, some NAD^+ consuming enzymes are significantly impaired during niacin deficiency. Cultured cells were shown to grow and divide normally with up to a 90% depletion of NAD levels, suggesting adequate redox metabolism, while poly(ADP-ribose) formation was largely abolished by a 50% decrease in NAD [10]. In rat models, poly(ADP-ribose) metabolism has been shown to be sensitive to dietary niacin status in several tissues, although not to the same extent. Liver [11,12] and lung [13] have relatively high basal NAD levels and are less responsive to low and high dietary niacin intakes. Conversely, poly(ADP-ribose) levels in bone marrow cells are extremely sensitive to dietary niacin status, in both the deficient [14] and pharmacological [15] ranges of intake. This modest body of work on niacin status and poly(ADP-ribose) metabolism lacks information on many tissues in whole animal models, and lacks data on human responses. Also, as we will discuss below, the majority of cellular poly(ADP-ribose) is made by PARP-1, so total polymer measurements are mainly reflective of PARP-1 function, and we now know that there are other members of the PARP family of enzymes with specific roles in genomic stability. There is essentially no literature data on the impact of niacin status on mono ADP-ribosyltransferases, sirtuins or PARPs other than PARP-1. Brain levels of cyclic ADP-ribose have been shown to be altered by low and high niacin status [16], but it is not known if cyclic ADP-ribose plays significant roles in genomic stability.

1.2. Roles of poly(ADP-ribose) metabolism in genomic stability

PARP-1 is a 116 kDa nuclear protein which binds to and is activated by DNA strand breaks. PARP-1 makes the majority of PAR in most cells. It is important to note that PAR carries a strong negative charge, and will be repelled from DNA, and may compete for DNA binding sites on proteins. There are 3 general mechanisms by which PAR formation regulates cellular responses.

(1) Chains of PAR are covalently attached to protein acceptors. Various DNA repair proteins are covalent acceptors, including DNA ligases and polymerases [17]. Signalling molecules, like p53 [17], fos and jun [18] may also be modified, controlling signals like cell cycle arrest and apoptosis. Histones are covalently modified [17], which forces them away from DNA, causing local chromatin relaxation. PARP-1 itself is the major acceptor, in a reaction referred to as automodification. This likely has several roles; the cloud of PAR attracts proteins with high affinity binding sites (mechanism 2), is a substrate to release free polymer (mechanism 3), and it eventually forces PARP-1 off the negatively charged strand break, allowing DNA repair to be completed. The cloud of negatively charged PAR may also