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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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Contents

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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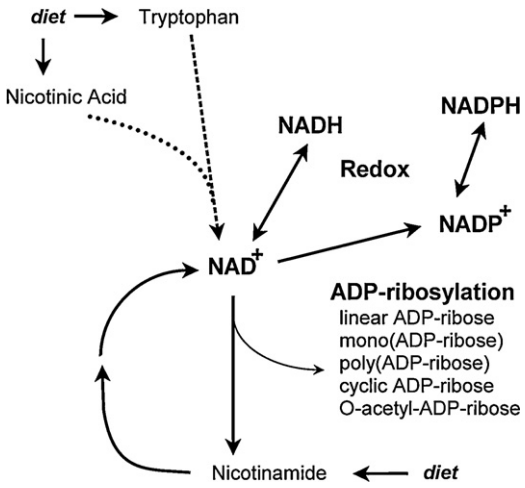

Fig. 1. A summary of dietary niacin precursors, pyridine nucleotide formation, and participation of NAD^+ in ADP-ribosylation reactions.

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

repel other DNA ends from the site of damage, preventing non-homologous recombination events.

(2) Clouds of PAR control protein localization and function through non-covalent high affinity binding sites. A large family of proteins have been identified to have very high affinity binding to PAR chains, including DNA repair and signalling proteins like p23, p21, DNA-PK, NF-kB, XRCC1, and p53 [19]. Histones are also drawn away from DNA by high affinity binding. Thus, the cloud of PAR on PARP-1 at the site of damage organizes chromatin relaxation, assembly of a complex of repair proteins and mediates damage response signals like cell cycle arrest and apoptosis.

(3) Fragments of PAR are released through poly(ADP-ribose) glycohydrolase activity, and these act as soluble signalling molecules. These fragments can leave the nucleus and bind to various proteins to signal the level of damage taking place in the nucleus. One example of this is the activation of caspase-independent apoptosis. Apoptosis-inducing factor (AIF) is a protein that is normally found in the mitochondria [20], but upon binding to free PAR, AIF translocates to the nucleus and initiates caspase-independent apoptosis. It appears likely that other extra-nuclear proteins will be found that are regulated by PAR binding.

1.3. Roles of alternate PARPs in genomic stability

Low residual levels of PAR in PARP-1 knockout mice led to the discovery of 17 other human genes with homology to the active site of PARP-1 [21]. Some of these have been shown to synthesize PAR; some of the remainder are likely to be mono ADP-ribosyltransferases. Several alternate PARPs appear to play important roles in genomic stability. Like PARP-1, PARP-2 is activated by DNA damage, and deletion of PARP-1 and -2 is developmentally lethal [22]. PARP-1 and -2 have been shown to function as heterodimers at DNA strand breaks [22]. A recent "interactome" study of binding partners for PARP-1 and -2 found a family of common interactors involved in DNA repair and apoptosis [23].

PARP-3 is stimulated by double strand breaks, and appears to work with PARP-1 in double strand break repair [24,25]. PARP-3 appears to collaborate with tankyrase-1 in the maintenance of telomere integrity. Additionally, PARP-3 stabilizes the mitotic spindle. Thus, niacin deficiency could cause numerous forms of genomic instability through impaired PARP-3 activity, but its response to varying niacin status has not been determined.

Tankyrase-1 and -2 (PARP-5a/b) covalently add PAR to TRF1 proteins, relaxing telomere structure and allowing telomerase to access and lengthen telomeres. Mice can survive deletion of each of the tankyrases, but not both [26]. In addition to regulating telomerase activity and telomere length, tankyrases work with PARP-3 in the maintenance of telomere integrity [25]. Tankyrase-1 has been found to be active in the process of mitotic spindle pole assembly, during which automodification of tankyrase-1 gathers additional proteins through high affinity binding to the cloud of PAR [27]. Again, niacin deficiency could induce various forms of genomic instability through decreased tankyrase activities, and this remains uncharacterized.

1.4. Roles of other ADP-ribosylation reactions in genomic stability

Mono ADP-ribosyltransferases modify the activity of various proteins, including G-proteins, chaperones, elongation factor-2, and others [28]. ADP-ribosylcyclases use NAD^+ to form cyclic ADP-ribose, which causes the release of calcium from intracellular stores [29]. Both of these classes of reactions could regulate cell function during genotoxic stress, and could be sites of dysfunction during niacin deficiency. The sirtuins are a family of NAD-dependent protein deacetylases that catalyze a reaction in which the leaving acetyl group is ADP-ribosylated using NAD^+ as a substrate [30]. The sirtuins have been strongly implicated in genomic stability and aging; age extension due to caloric restriction is dependent on the activation of sirt1/sir2, which leads to more condensed chromatin, and the regulation of nuclear proteins like p53. Resveratrol may function as a sirtuin activator and has been shown in several animal models to extend lifespan [31]. The impact of low or high niacin status has not been studied in whole animal models examining these classes of reactions.

2. Animal models of niacin status and genomic stability

2.1. Liver and lung

Early work on PAR metabolism was hampered by poor sensitivity and focussed on larger tissues, but this generated some interesting perspectives when more responsive tissues were subsequently characterized. In rats, liver NAD^+ levels decreased in response to niacin deficiency, but from control levels of around 900 μM down to 600 μM [11], which is still far above the K_m of most NAD^+-utilizing enzymes. While PARP-1 appears to be quite sensitive to niacin status, it has a K_m for NAD^+ in the range of 20–80 μM [32], so it was not surprising that nitrosamine-induced PAR formation was not hindered and that liver cancer was not enhanced by niacin deficiency [11]. Although rat lung NAD^+ levels are less than half of that in the liver [33], and although the PAR response to hyperoxia was blunted by niacin deficiency, there was no change in the measures of tissue injury due to niacin deficiency [13], suggesting that the decrease in PAR formation was not great enough to sensitize the lung to oxidant injury. Studies with more acute lung injury, using bleomycin, have shown that niacin supplementation, above requirement, can be protective [34].

An important aspect of the deficiency experiments on lung and liver PAR metabolism is that these rats were severely deficient models of clinical pellagra, with growth depression, dermatitis and diarrhea [11,13], and yet the lung and liver sensitivity to DNA damage appeared to be unaffected. This is likely to be true in human health as well; modest levels of niacin deficiency may sensitize certain tissues to genomic instability while severe deficiency leaves other unaffected.

2.2. Bone marrow

We became interested in bone marrow responses to niacin status for several reasons. As the most proliferative tissue in the body, it was likely to become more depleted during niacin deficiency. Proliferation also makes cells more sensitive to DNA damage, and bone marrow suppression is the most common pathology limiting chemotherapy in cancer patients. While bone marrow is not one of the classic components of clinical pellagra, anemia is observed in pellagrins [1]. In our rat model, we found that bone marrow had relatively low control levels of NAD^+, and experienced the greatest decrease during niacin deficiency (~80% depression) of any tissue we characterized [14]. Based on the fact that cancer patients are frequently niacin deficient [35,36], while facing maximally tolerated doses of genotoxic drugs, we investigated the bone marrow effects in a model combining niacin deficiency and chronic nitrosourea exposure. Niacin deficiency sensitized rats to the acute bone marrow suppressive effects of nitrosourea toxicity [37]. When niacin deficient and control rats were placed on control diets following the end of nitrosourea treatment and monitored for cancer development, the previously deficient rats developed a greater frequency of leukemias [38]. These were similar in nature to the

secondary, or treatment-related leukemias which occur in human cancer survivors who were exposed to large doses of chemotherapy, especially alkylating agents and topoisomerase 2 inhibitors.

Short term mechanistic studies revealed a dramatic spectrum of genomic instability in niacin deficient bone marrow cells. Consistent with the idea that catalytically-inactive PARP-1 can remain bound to strand breaks and block repair, niacin deficiency delayed the excision repair of ethyl adducts in rat bone morrow [39]. Delayed excision repair coincided with an accumulation of double strand breaks. Even in the absence of exposure to genotoxic stress, niacin deficient bone marrow cells had dramatic increases in micronuclei, sister chromatid exchanges and chromosome breaks [39,40]. Niacin deficiency also changed p53 expression and impaired cell cycle arrest and apoptosis [41]. The combined effect of cells failing to clear alkylation injury and double strand breaks, while failing to arrest the cell cycle, and resisting apoptosis, creates a perfect storm for the generation of leukemic precursors in the bone marrow. Again, most of these deficiency experiments were in a severe model similar to clinical pellagra. In one experiment, micronuclei were examined across a range of severity of niacin deficiency. In the mild model, with a 20% depression in NAD^+, there was no increase in micronuclei. The intermediate model displayed a 50% depression in NAD^+, and a doubling of micronuclei, while the severe model had an 80% depression in NAD^+, and a 5-fold elevation in micronuclei [39]. The intermediate model did not display clinical signs of pellagra, and suggests that there is potential for genomic instability with subclinical deficiencies of niacin.

Pharmacological doses of niacin were also examined in this model. Dietary niacin intakes about 100-fold higher than requirement significantly increased bone marrow NAD^+ and PAR levels above those on adequate niacin intake [15]. Interestingly, high niacin status did not change any of the short term markers of genomic instability [40], but it did further enhance the apoptotic response of bone marrow cells to nitrosourea treatment [41]. When these rats where followed long term, the high niacin diet did appear to further decrease the development of leukemias [38], suggesting that active apoptosis in damaged bone marrow cells is important in avoiding alkylation-induced leukemias.

2.3. Skin

The skin is the site of pathologies that are usually used to identify clinical pellagra, although the skin can be relatively normal if the patient avoids sun exposure [1]. The role of sun exposure implicates DNA damage and repair responses in the etiology of pellagra, and we now have a better understanding of these, through research on ADP-ribosylation reactions and DNA repair. However, we will see below that niacin has a variety of metabolic effects in the skin, especially at higher doses. Despite the strong connection between niacin status and skin health, there are relatively few studies in the literature using animal or human models. Rainbow trout have been found to be sensitive to ultraviolet-B induced skin lesions when niacin deficient [42]. One difficulty with niacin research models is that mice convert tryptophan to NAD more efficiently than rats or humans, and thus do not get severely deficient. Despite this, mild niacin deficiency in mice caused an increased incidence of ultraviolet-B induced skin cancers [43]. This single animal model suggests that subclinical niacin deficiency could lead to increased skin cancer risk in human populations. The lack of human data will be discussed in Section 3.

In addition to this small literature base on deficiency, there are some interesting animal experiments on high niacin and skin health. There is a history of interest in the effects of high doses of nicotinic acid on skin health, due to the dramatic flush response caused by vasodilation, secondary to prostaglandin formation. This will be discussed further in Section 3. Some interesting animal experiments have examined high niacin intake and skin health. Gensler et al. fed mice either the required level of niacin (0.03 g/kg diet) or diets with supplements of 1, 5 or 10 g/kg diet, representing up to 333-fold above requirement [44]. The mice were exposed to UVB radiation (5×30 min/wk for 22 wk) and later assessed for skin cancer incidence. High doses of niacin progressively decreased skin cancer incidence from 68% of controls to 28% of the highest supplement group. Skin NAD content also increased progressively with niacin dosing level, so it is unclear whether the cancer prevention was due to NAD levels, pharmacological actions of nicotinic acid, or some other related intermediate. An important factor in skin cancer progression is photo-immune suppression. In a separate experiment, the authors showed that the same high niacin diets progressively improved the immune surveillance of transplanted tumors, showing that niacin supplementation may be acting through prevention of photo-immune suppression. In this model the benefits of supplementation could be due to direct effects of nicotinic acid, or the impact of increased NAD pools on poly, mono or cyclic ADP-ribose formation. In addition to the known roles of poly(ADP-ribose) in genomic stability, cyclic ADP-ribose is a known signalling molecule in the immune system [45], so this could explain the prevention of photo-immune suppression.

Some other animal experiments have shown a benefit to skin health with the supplementation of nicotinamide, instead of nicotinic acid. Nicotinamide, via intraperitoneal injection, has been shown to decrease some forms of skin damage from the chemical warfare agent, sulphur mustard [46]. In the area of skin research, there is actually more work done in human than animal models, as discussed in Section 3.

3. Niacin and genomic stability in humans

3.1. Niacin status in human populations

Many developing countries with a dependence on corn still experience outbreaks of pellagra [47], and these populations will definitely be suffering from genomic instability, in the skin, and probably some other tissues, and would obviously benefit from niacin supplementation. Clinical deficiencies of niacin have varied historically and geographically depending on the implementation of food fortification programs, which exist now in most developed countries. In the United States, it has been estimated that the average niacin intake has increased from 16 to 32 mg/d between 1940 and 2000 [48]. However, NHANES data reminds us that while young men have high average intakes of niacin in foods, women consume lower amounts, and intake decreases progressively in the elderly of both sexes [49]. The same data shows that supplement use dramatically increases average niacin intake, but it hides a large individual disparity. Even if the average intake appears to be adequate, it is important to know whether subgroups within these populations may still have suboptimal niacin status. To accomplish this, you need to have an effective measure of functional niacin status. The traditional measure of niacin status is a ratio of urinary excretion products, which is largely reflective of recent intake. A clinical trial conducted by Fu et al. placed human subjects in a clinical ward on niacin deficient diets and made various urine and blood measurements. They found that erythrocyte NAD decreased by up to 70% during 6 weeks of consuming 6 or 10 mg of niacin/d [8]. During this time the NADP pool was relatively stable, and the ratio of NAD/NADP was a sensitive measure of niacin status, where a value of <1.0 could be considered deficient. Despite the availability if these assessment tools, there are only a few modern studies of niacin status in human populations. A population of women in Malmo, Sweden, displayed a bimodal distribution of niacin status with about 15% in the suboptimal range [50], suggesting that fortification does not eliminate low niacin status in developed countries.

The level of niacin deficiency is significantly higher in certain subpopulations. Low niacin status was found in 27% of long term care patients in a hospital setting in Canada [51]. Low niacin status and clinical pellagra are common in alcoholics [52,53]. Niacin deficiency may occur in HIV/AIDS [53], and during the progression of anorexia nervosa [54]. Cancer patients have a strong susceptibility to niacin deficiency [35,36], and require larger amounts of niacin to correct deficiency [35]. Carcinoid tumors cause depletion of tryptophan, which is an additional stress on niacin status [55].

Thus, it is clear that poor niacin status still does occur in developed countries that practice niacin fortification. Some of the susceptible subgroups are exposed to medications that cause DNA damage and niacin supplementation would be expected to improve genomic stability. Learning to identify the genetic, dietary or disease basis for these deficient subpopulations will allow effective supplementation programs to be designed.

3.2. Niacin and cancer epidemiology

If niacin deficiency causes genomic instability in human populations, there should be associations between niacin intake and cancer risk. These surveys are susceptible to confounding and bias, and should be interpreted carefully. In addition, there are not a large number of studies on niacin and cancer risk in the literature. Some studies are conducted in countries with a broad range of niacin status including clinical deficiencies, while others look at more subtle variations in countries with fortified foods.

In countries that consume a corn or maize-based diet and do not have niacin fortification, there tends to be an association of high corn consumption with upper digestive tract cancers. The strongest predictor of esophageal cancer in a native population in South Africa was the frequency of maize consumption [56]. Similar patterns were observed in the Henan province in China [57] and in northern Italy [58]. The occurrence of esophageal cancer in populations with severe niacin deficiencies makes sense given that the earliest signs of pellagra include inflammation of the oral cavity and esophageal mucosa, which could predispose to carcinogenesis [1]. While corn is the dietary staple that tends to cause niacin deficiency, there are other factors that could be at play. Other dietary components that could co-vary with corn contain known esophageal carcinogens, and corn is frequently contaminated with mycotoxins which can act as initiating and promoting agents [59]. These studies did not estimate niacin intake or test participants for niacin status. A large intervention in the Linxian province of China did not find any benefit to esophageal cancer risk with randomized supplementation of niacin, although the study may have been too short to have altered the early stages of cancer development.

Marshall et al. studied a population in western New York and found that oral cancer risk was associated with smoking and alcohol exposures, poor oral hygiene [60], and the status of several nutrients, including low niacin. Fenech surveyed a population in Australia and found that leukocyte micronuclei were higher in people with low status in several micronutrients, including niacin [61]. Pilots with a lower intake of niacin from foods were found to have an increased frequency of leukocyte chromosomal translocations, suggesting that niacin status is important in responding to cosmic radiation [62]. However, supplemental niacin was not protective, suggesting that the finding was secondary to a high intake of grain products and a low intake of red meats.

The impact of pharmacological doses of niacin could be studied in populations of dyslipidemic patients on nicotinic acid therapy, which is usually in the range of 1–3 g/d, or about 50–200-fold above the RDA. These populations will be heavily imbalanced towards existing cardiovascular disease risk, but it seems like a useful source of data. Unfortunately, there is almost nothing in the literature about cancer risk or long-term all cause mortality in these populations. In one long term study, nine years after the end of a 6 year niacin intervention, the group that had been on the niacin treatment showed improvement in all-cause mortality [63]. Another weakness in the literature is in the area of niacin status and skin cancer risk. A 2002 review of diet and skin cancer risk lists no data on niacin status and skin cancer risk in human populations, and no data appears in the literature subsequently [64]. It seems obvious from the dramatic sun-sensitivity of pellagra, and from animal experiments, that niacin deficiency will predispose to human skin cancer risk, but this has not really been addressed or characterized with respect to the niacin dose response.

3.3. Niacin and skin health

There is a history of interest in niacin supplements and skin health, due to the symptoms of pellagra, and the skin flush response to higher doses of nicotinic acid, originally observed in 1937 when nicotinic acid was first used clinically as a cure for pellagra [65]. The skin flush response does not appear to be related to normal niacin function, as physiological blood levels of nicotinic acid do not activate the receptors, which appear to be present to respond to high levels of blood ketones.

While there is a surprising lack of epidemiological data on niacin and skin cancer, there are interesting interventions looking at shorter term endpoints in skin health. Topical nicotinamide gels and oral doses of nicotinamide (which do not cause skin flush) have been used to treat acne vulgaris and acne rosacea [66,67]. These effects would seem to be due to the support of NAD-dependent reactions. Nicotinic acid is also used in skin treatment. To improve topical absorption, nicotinic acid can be esterified with short chain fatty acids. Topical application of myristyl nicotinate has been shown to increase skin NAD, improve skin barrier function, increase the thickness of epidermal and stratum corneum layers, and increase the expression of protein markers for skin differentiation [68,69]. The mechanisms involved are not certain. Increased NAD may be acting to support cellular energy metabolism or fuel ADP-ribosylation reactions. However, skin cells also have a significant expression of “niacin receptors”. GPR109A/B are high and low affinity binders of niacin, although the physiological ligands are likely ketone bodies. GRP109A is linked to an inhibitory G-protein, which causes decreased cAMP levels, leading eventually to the desired improvements in blood lipids and the skin flush response. In normal human skin, receptor protein is expressed from basal through granular layers of the epidermis, becoming more localized to the plasma membrane with differentiation. In cultured cells, primary keratinocytes have functioning, membrane localized receptors, while squamous carcinoma cells show a diffuse distribution of almost non-functional receptors [69]. Thus, it appears that pharmacological doses of nicotinic acid may be useful in encouraging differentiation of skin cells, through mechanisms unrelated to NAD or ADP-ribose metabolism.

Thus, skin cancer risk may be diminished through niacin supplementation by improving cellular energy metabolism, supporting ADP-ribosylation reactions and DNA repair processes, preventing UV-induced immune suppression, increasing skin thickness and barrier function, and encouraging terminal differentiation of dividing cells. These effects would appear to occur at varying levels of niacin supplementation, and skin health seems to be the realm of greatest interest for pharmacological levels of niacin supplementation (in addition to treatment of hyperlidemias).

3.4. Niacin and secondary leukemia in cancer patients

Cancer patients are frequently malnourished, and one of the most common deficiencies is niacin. Although the patient numbers

were small, Inculet found that essentially all cancer patients were niacin deficient at first diagnosis, and almost half were still deficient after being parentally supplemented with the RDA level of niacin [35]. During chemotherapy, the disruption of GI function and appetite, as well as the cytotoxic effects of the drugs, can worsen malnutrition, including niacin status [36,70]. Cancer patients are typically facing maximally tolerated doses of genotoxic drugs while malnourished, and damage to normal tissues is likely to be exacerbated. Animal models have shown that niacin deficiency increases nitrosourea-induced acute bone marrow suppression [37] and the long term development of leukemias [38]. Leukemia incidence in rats is decreased by correction of niacin deficiency, and further improved by pharmacological niacin supplementation [38], suggesting that cancer patients might benefit from high dose niacin supplementation. This should not be pursued until the impact of niacin supplementation on treatment efficacy has been characterized. There is some suggestion that high niacin status will actually increase treatment efficacy, by activating PARP-1 dependent apoptosis pathways in cancer cells [20], but this requires further experimentation.

3.5. Niacin and cardiovascular disease

There is an extensive literature on the use of high dose nicotinic acid in the treatment of dyslipidemia, and the prevention of cardiovascular disease progression. The mechanisms involved are thought to be mainly due to increasing blood HDL levels, decreasing blood LDL levels, and improved metabolic state in ischemia reperfusion [65]. From the focus of this article, it would be interesting to speculate that improved genomic stability might also occur with high dose niacin and play a role in CVD treatment efficacy.

4. Summary

Populations of many developing countries would benefit from niacin supplements. In industrialized nations, niacin fortification has improved status significantly, and there is no strong evidence that niacin supplementation is required to improve genomic stability of the healthy and well fed portions of the population. However, there are subgroups that display poor niacin status and/or face extra genomic stress, and they would likely benefit from niacin supplementation, including those with a high sun exposure and cancer patients. Further work is required to identify sensitive groups and test the efficacy of supplementation.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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