Minireview

Niacin status and treatment-related leukemogenesis

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Abstract

Chemotherapy often causes damage to hematopoietic tissues, leading to acute bone marrow suppression and the long term development of leukemias. Niacin deficiency, which is common in cancer patients, causes dramatic genomic instability in bone marrow cells in an *in vivo* rat model. From a mechanistic perspective, niacin deficiency delays excision repair and causes double strand break accumulation, which in turn favors chromosome breaks and translocations. Niacin deficiency also impairs cell cycle arrest and apoptosis in response to DNA damage, which combine to encourage the survival of cells with leukemogenic potential. Conversely, pharmacological supplementation of rats with niacin increases bone marrow poly (ADP-ribose) formation and apoptosis. Improvement of niacin status in rats significantly decreased nitrosourea-induced leukemia incidence. The data from our rat model suggest that niacin supplementation of cancer patients may decrease the severity of short- and long-term side effects of chemotherapy, and could improve tumor cell killing through activation of poly(ADP-ribose)-dependent apoptosis pathways. [Mol Cancer Ther 2009;8(4):725–32]

Nutritional Status and Response to Chemotherapy

The successful use of chemotherapy is usually a fine balance between effective killing of tumor cells and acceptable levels of damage to normal tissues. For many types of drugs, acute bone marrow suppression may limit the dosage of chemotherapy, and DNA damage in hematopoietic cells leads to the long term development of secondary leukemias. As the success in treating childhood cancers has improved, long term cohorts have been established to monitor the late effects of cancer and chemotherapy (1–3). These studies

have found roughly a 10-fold excess in risk of mortality subsequent to 5-year survival. The main cause of mortality at this stage continues to be recurrence of the original disease, reinforcing the need for treatment efficacy, but there is a significant proportion of secondary malignancies. Following 15 years of survival, there is still a fivefold excess in mortality, and secondary malignancies become the single greatest cause of death. Secondary malignancies tend to be acute myeloid leukemias, with specific presentations and genetic aberrations associated with topoisomerase inhibitors, alkylating agents, and anthracyclines (4). Radiotherapy for cancer and benign diseases also causes increased leukemia risk (5).

Nutritional status in a healthy child may erode rapidly with the onset of cancer followed by chemotherapy treatment, which tends to cause nausea and gastrointestinal dysfunction (6). Malnutrition is very common and underdiagnosed at the point of diagnosis of childhood cancers (7). Nutritional status is multifactorial and likely to have impacts on both treatment efficacy and the occurrence of side effects. This area has lacked the research commitment required to characterize the effects of different nutrients, forms of cancer, and treatment regimens. The research tends to focus on broad scale nutritional support and is divided between models with and without cachexia. However, some studies have found an increase in complications and a decrease in treatment response when chemotherapy patients receive parenteral nutrition (8). It is clear that some nutrients may be deleterious during chemotherapy. For example, excess iron may promote infection (9, 10), and excess folate can encourage cell division and tumor growth (11). Even supplements that protect normal tissues from drug toxicity may be damaging if they also protect tumor cells.

Although the research is still sparse, it is clear that a large proportion of cancer patients are deficient in niacin (vitamin B_3) (12, 13). Chemotherapy may further stress niacin status, as clinical pellagra is sometimes observed during treatment (14). The severity of niacin deficiency during chemotherapy is likely underestimated as these patients will have limited exposure to sunlight, and depression and diarrhea may be attributed to the disease process and chemotherapy treatments.

The human disease of niacin deficiency, pellagra, is characterized by diarrhea, dementia, and sun-sensitive dermatitis, the last of which is suggestive of problems with DNA repair (15–17). Niacin has been viewed traditionally as a central player in catabolic and synthetic pathways through a multitude of redox reactions based on NAD and NADP cofactors. A new appreciation of niacin function in DNA stability has come with the knowledge that NAD^+ participates in a wide variety of ADP-ribosylation reactions. Whereas redox

Tryptophan

Nicotinic acid (NA)

NA adenine dinucleotide

Nicotinamide Adenine Dinucleotide (NAD$^+$)

NADP$^+$

NADPH

NADH

Nicotinamide (Nam)

- poly(ADP-ribose) (pADPr)
- mono ADP-ribose
- cyclic ADP-ribose (cADPr)
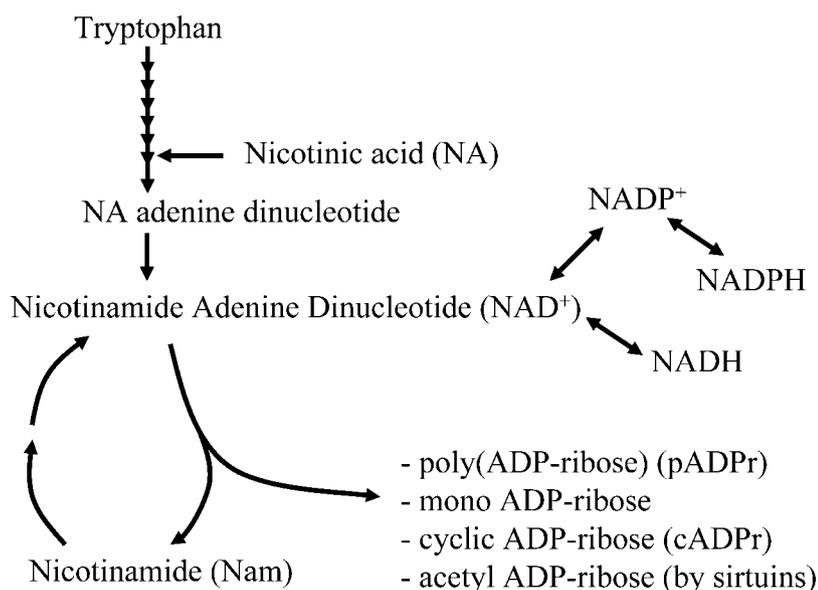- acetyl ADP-ribose (by sirtuins)

Figure 1. Niacin (vitamin B$_3$) is obtained from the diet in the form of tryptophan, nicotinic acid, and nicotinamide. NAD$^+$ can be used to generate NADP$^+$, participate in redox metabolism, or be cleaved, releasing nicotinamide and participating in a variety of ADP-ribosylation reactions.

reactions cycle pyridine nucleotides between oxidized and reduced forms, ADP-ribosylation reactions cleave NAD$^+$, releasing nicotinamide and using the ADP- ribose in poly (ADP-ribose) synthesis, mono ADP-ribosylation, cyclic ADP-ribose formation, and NAD-dependent deacetylation reactions (sirtuins; Fig. 1).

Poly(ADP-ribose) Polymerase Enzymes

In the last few years rapid progress has been made in the study of poly(ADP-ribose) metabolism (18–20). It is now recognized that 17 genes in humans have active site homology with poly(ADP-ribose) polymerase (PARP)-1, and catalytic activity has been proven in eight of these (18). PARP-1 has been recognized for several decades and makes the majority of cellular poly(ADP-ribose). It is a nuclear protein that binds to and is catalytically activated by DNA strand breaks, creating one of the earliest metabolic signals at a site of DNA damage (21). PARP-2 has functional similarities to PARP-1; animals with either gene deleted experience genomic instability, whereas deletion of both genes seems to be lethal (22). PARP-3 associates with the daughter centriole during cell division (18). Tankyrases 1 and 2 synthesize poly(ADP-ribose) at the telomere, opening the structure and allowing telomerase to maintain the length and stability of the chromosome terminus (23).

Although various individual functions have been described, it is also clear that PARP genes function together in the maintenance of genomic stability. PARP-1 and 2 have clear interactive roles in base excision repair of DNA, and likely function in other forms of DNA repair (21). PARP-1 and 3, tankyrase-1, and vPARP localize to centrosomes and mitotic spindle apparatus, whereas PARP-1 and 2 localize to centromeres, demonstrating an integrated role of poly (ADP-ribose) metabolism in chromosome segregation (18).

There is a rapidly growing literature describing specific reactions and regulatory impacts of the PARP family of proteins, but these can be divided functionally into three groups:

(1) Poly(ADP-ribose) is negatively charged, as is DNA, and these two molecules repel one another. When histones are poly(ADP-ribosyl)ated they lose their affinity for DNA, which leads to a local chromatin relaxation. PARP-1 and 2 become automodified, and this eventually pushes them away from the site of damage, allowing repair to finish. Also, clouds of poly(ADP-ribose) around sites of DNA damage likely repel other free ends of DNA and prevent nonhomologous translocation events.

(2) Proteins have specific high-affinity binding sites for poly(ADP-ribose), which draws them to sites of DNA damage, where they may participate in repair reactions or initiate signaling pathways for inflammatory or apoptotic responses (24). This also contributes to local chromosome relaxation, as histones have high affinity sites, and are pulled out of chromatin onto the polymer bound to automodified PARP-1/2. Other proteins involved in DNA repair, cell cycle arrest, apoptosis, and inflammation (topoisomerases, DNAPK, NF-kB, XRCC1, p53) are drawn to the site of injury through high-affinity poly(ADP-ribose) binding (24).

(3) Covalent poly(ADP-ribosyl)ation of enzymes, transcription factors, and signaling molecules can increase or decrease their activities, controlling the complex stress response of the cell, directing repair activities and survival decisions. Acceptor proteins for poly(ADP-ribose) addition include DNA topoisomerase, polymerase, and ligase enzymes (25).

Sirtuins

There has been great interest in the sirtuin gene family since the finding that SIRT1 is central to the extension of

lifespan in response to caloric restriction and that lifespan extension can be mimicked by the sirtuin activator resveratrol (26). SIRT1 is an NAD-dependent deacetylase, which removes acetyl groups from key proteins like histones and p53, leading to changes in chromatin structure and the cellular stress response. The deacetylation is an ADP-ribosylation reaction, producing acetyl-ADP-ribose as an end product. The sirtuins provide a mechanistic connection between cellular energy status, regulation of DNA structure and metabolism, and genomic stability and lifespan. Sir2 and PARP-1/2 may have close interactions, based on competition for NAD^+ and inhibition of Sir2 by nicotinamide. It has been suggested that cell survival is dependent on the balance of PARP versus sirtuin activity, with PARP directing apoptotic signals and sirtuins promoting survival (26).

Mono ADP-Ribosyltransferases and ADP-Ribosyl Cyclases

Whereas PARP enzymes and sirtuins provide the most plausible links between niacin status and genomic stability, there are also potential effects of mono ADP-ribosylation reactions and cyclic ADP-ribose metabolism. Mono ADP-ribosylation is known to control the activity of a variety of GTP-binding proteins (27). Cyclic ADP-ribose causes release of intracellular calcium stores, controlling functions in all cell types, from nerve conductance, to muscle contraction, to insulin secretion (28). There is potential for alterations in mono ADP-ribosylation and cyclic ADP-ribose metabolism to impact on genomic stability, though control of cell cycle and other signaling pathways (29).

Niacin Deficiency in a Whole Animal Model

In our work on niacin deficiency in rats, we found that bone marrow is the most sensitive tissue that we have characterized in our model, with decreases in NAD^+ of 80%, an almost complete loss of basal poly(ADP-ribose) (Fig. 2A) and a large inhibition of nitrosourea-induced poly(ADP-ribose) formation (30). Bone marrow poly(ADP-ribose) is also very sensitive to high niacin intake, as basal and damage induced poly(ADP-ribose) levels are much higher when rats are fed 4,000 mg nicotinic acid/kg diet compared with the 30-mg/kg diet found in the control diet (Fig. 2A) (ref. 31). In total, bone marrow NAD^+ and poly(ADP-ribose) concentrations vary 30- and 65-fold, respectively, going from niacin deficient to pharmacologically supplemented status (31). The majority of polymer seems to be bound to the 116-kDa PARP-1 and its 97-kDa apoptotic fragment (30).

The next question to be addressed was whether the diet-induced changes in NAD^+ and poly(ADP-ribose) were associated with pathological endpoints associated with genomic instability. From a human clinical perspective, bone marrow progenitors experience the critical side effects of most types of cancer chemotherapy, leading to dose-limiting bone marrow suppression in the short term, and the development of secondary leukemias over time (32). We set out to model the stress of chemotherapy on the bone marrow by chronically treating Long-Evans rats with ethylnitrosourea (ENU). ENU is not an effective chemotherapeutic compound, but it does mimic the alkylation component of bifunctional agents like BCNU, and it is this alkylation aspect that is thought to be responsible for bone marrow injury and leukemogenesis (33). This outcome is probably due in part to the low expression of alkyltransferase in the bone marrow (34). Long-Evans rats were selected as they tend to develop nonlymphocytic leukemias in response to alkylating agents (35), similar to human cancer patients (32), and unlike the
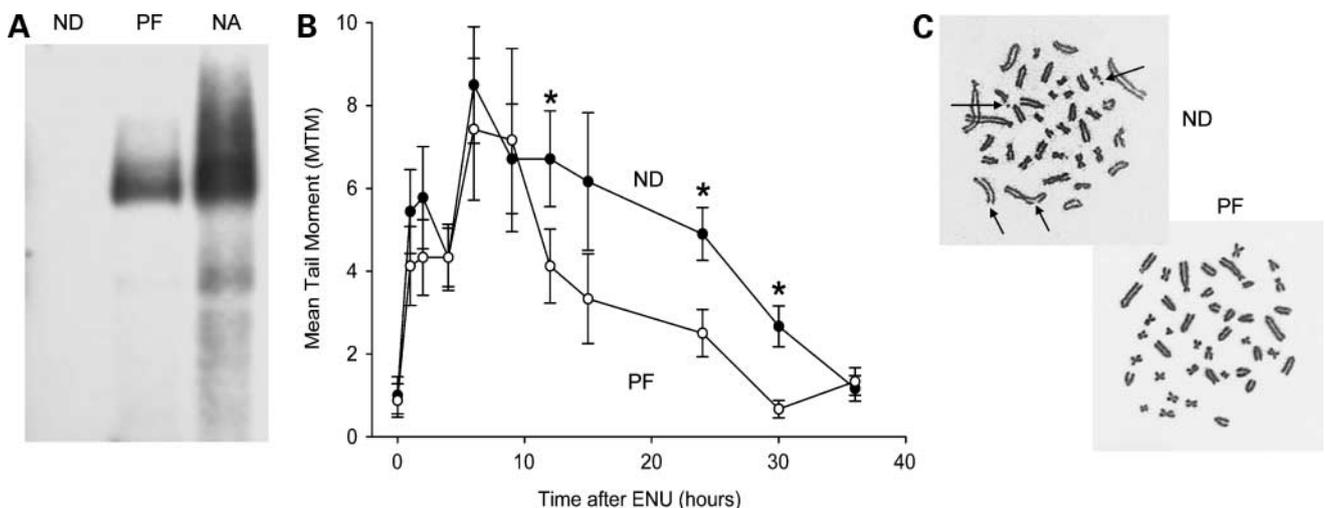

Figure 2. **A,** the effect of niacin status on bone marrow poly(ADP-ribose) levels. ND, niacin deficient (0 mg added dietary niacin); PF, pair-fed control (30 mg nicotinic acid/kg diet); NA, high niacin diet (4,000 mg nicotinic acid/kg diet). Cellular proteins are run using SDS PAGE, transferred, and blotted with anti-poly(ADP-ribose) antibody. **B,** the effect of niacin deficiency and ENU treatment on DNA strand breaks in bone marrow cells. Weanling Long-Evans rats were fed niacin deficient (ND) or pair-fed niacin replete control diet (PF) for 3 wk. Rats were gavaged with ENU (30 mg/kg body weight), and the bone marrow cells from the femurs were blindly analyzed by the alkaline comet assay. *ND, significantly greater than PF ($P < 0.05$, t test). **C,** the effect of niacin deficiency on chromosome breaks (arrows), indicative of double strand break accumulation.
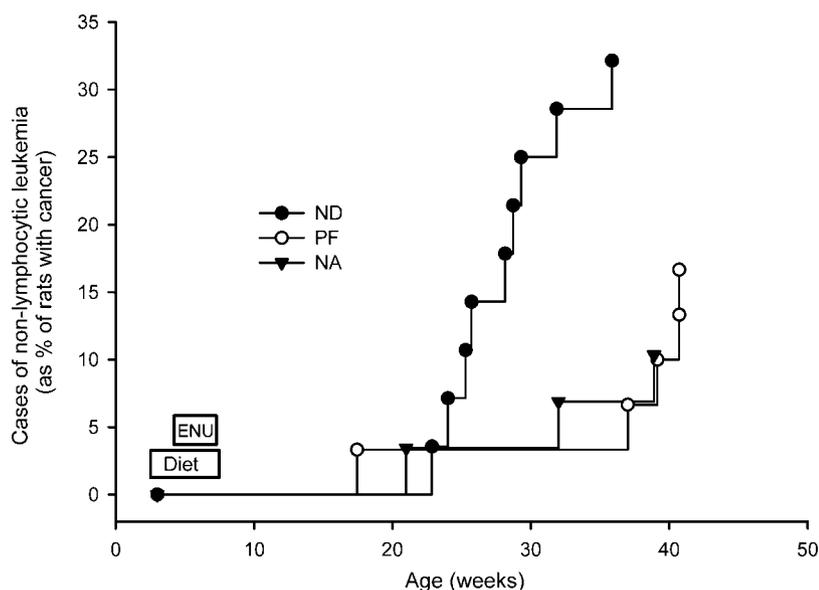
Figure 3. The effect of niacin status during exposure to ENU on the long term development of non-lymphocytic leukemias in Long-Evans rats. ND, niacin deficient (0 mg added dietary niacin); PF, pair-fed control (30 mg nicotinic acid/kg diet); NA, high niacin diet (4,000 mg nicotinic acid/kg diet). ENU is used to induce alkylation of DNA. Rats consumed experimental diets and were exposed to ENU between 3 and 7 weeks of age, after which all three groups consumed control diet (AIN93M) and were observed for development of cancer.

high proportion of lymphoblastic malignancies observed in most rodent models.

Long-Evans rats that were niacin deficient during ENU treatment displayed more severe short term bone marrow suppression. Niacin deficiency caused a synergistic effect on hematocrit and sensitization of circulating lymphocyte and neutrophil populations (36). ENU-induced depression of bone marrow populations of erythrocytes, lymphocytes, and monocytes were all enhanced by dietary niacin deficiency (37). Clinically, these endpoints are often the dose-limiting side effects during chemotherapy.

We then conducted a long term experiment in which young rats were fed niacin deficient, adequate, or pharmacologically supplemented diets while being treated every other day with ENU. Several days after the last ENU dose, all of the rats were placed on a standard AIN93 diet and monitored for the development of neoplasms. This model of altered nutritional status was implemented only during the period of chemotherapy, as one might expect during the treatment of childhood cancer. We found that niacin status had a significant impact on nitrosourea-induced leukemogenesis (Fig. 3; ref. 38). Although nonleukemia cancers were not affected by diet, the incidence of total and nonlymphocytic leukemias was very sensitive to niacin status. Pharmacological niacin intake provided the greatest degree of protection against leukemia (38). We initiated a larger experiment to test this dietary model using etoposide as a more clinically relevant chemotherapeutic agent, but commercially available Long-Evans rats are not especially pathogen-free, and etoposide treatment caused immune suppression and a premature end to this protocol.

Given the close connection between PARP-1/2 function and base excision repair (BER) (ref. 24), we sought to characterize the impact of niacin deficiency on the repair of alkylation injury in our model of niacin and leukemogenesis. ENU was an ideal compound to initiate the damage response because it decomposes rapidly and spontaneously to produce reactive ethyl ions that damage DNA in an even pattern across tissues, independently of phase I or II xenobiotic metabolism. These small ethyl adducts are then mainly resolved by BER. DNA excision repair pathways involve incision, excision, repair synthesis, and ligation (39). During BER, the removal of altered bases is initiated by DNA glycosylases, creating an abasic (AB) site, but not a strand break. The phosphate group 5′ to the AB site is incised by endonuclease, or the 3′ site is cleaved by lyase. This process creates the strand break that is recognized by PARP-1 and 2, initiating the synthesis of poly(ADP-ribose), leading to changes in local chromatin structure, and the protein-protein and protein-poly(ADP-ribose) interactions that help to organize the repair process. The deoxyribose phosphate is excised by phophodiesterase, and DNA polymerases fill the resulting gap. The final nick is sealed by DNA ligase. At some point, the synthesis of poly(ADP-ribose) on PARP enzymes becomes extensive enough that anionic repulsion allows it to leave the strand break to allow completion of repair. The ability of catalytically inactive PARP-1 to block excision repair has been shown through NAD^+ removal (40, 41), competitive inhibitor treatment, and mutagenesis of the catalytic domain (25). We examined repair kinetics using the alkaline comet assay during the 36 hours following a single dose of ENU (30 mg/kg body weight). The comet assay uses carefully isolated bone marrow cells, which are suspended in soft agar and incubated at alkaline pH. The slides are then electrophoresed, causing loose strands of DNA to migrate out of the nucleus, forming a comet-like image. Single strand breaks cause a loss of supercoiling between sites of attachment to the nuclear matrix, allowing loops of DNA to migrate with the electrical current. The alkaline assay is fully sensitive to existing single strand breaks, but is also partially sensitive to AB sites and some other DNA lesions. The digital comet images

generate a proportionate index of tail versus nuclear DNA, referred to as mean tail moment (MTM). In our time course, there was no effect of niacin deficiency on MTM before ENU treatment, or on the development of strand breaks between 0 and 8 hours after ENU (Fig. 2B; ref. 42). This indicates that the ENU is causing similar levels of DNA alkylation, and that subsequent differences are due to changes in DNA repair processes. The peaks at 4 and 9 hours likely represent formation of AB sites and strand breaks, respectively, through the action of glycosylases and endonucleases. These processes are not affected by niacin deficiency. In contrast, repair kinetics between 12 and 30 hours were significantly delayed by niacin deficiency, with a doubling of area under the MTM curve during this period (Fig. 2B; ref. 42).

It is logical to look at the lack of basal and damage-induced poly(ADP-ribose) synthesis in Fig. 2A and postulate that the observed delay in repair kinetics (Fig. 2B) represents the effect of PARP-1 and/or 2 binding to strand breaks and blocking the completion of the repair process due to the lack of automodification. This mechanism has been shown in many *in vitro* systems using NAD deprivation, competitive inhibitors, or catalytically inactive mutants to produce dominant-negative forms of PARP-1 that block the later stages of BER (25). This blocking may well be occurring in our *in vivo* model, but PARP enzymes play other roles in the BER process that should be considered. The local chromatin relaxation induced by poly(ADP-ribose) formation around strand breaks is likely decreased, and this may delay the completion of repair. PARP-1/2 activity draws XRCC1 to DNA strand breaks, where it acts as a scaffold for the repair machinery (24). PARP-1 also attaches poly(ADP-ribose) covalently to DNA protein kinase, topoisomerases, polymerases, and ligase (25), and these may all suffer functionally during niacin deficiency, leading to delayed excision repair.

Chromosome breaks and translocations are key players in carcinogenesis, and they are dependent on the formation of double strand breaks in DNA. However, these lesions are increased by many forms of DNA damage that are known to cause single strand breaks. In this model of simple alkylation damage, double strand breaks could form by several mechanisms, including multiple nearby single strand breaks, stalled replication forks (43), and the blockage of strand break repair by catalytically inactive PARP-1 or 2. Double strand breaks can be measured using the neutral comet assay. Neutral MTM was nearly doubled in niacin deficient bone marrow cells 24 hours following ENU treatment, indicating an accumulation of double strand breaks (42). PARP-1 has been shown to be required for efficient resolution of stalled replication forks (44). We have also shown that niacin deficiency impairs damage-induced cell cycle arrest in our model (45). Poorly resolved replication forks proceeding into DNA replication are likely to produce double strand breaks (43). Double strand breaks may also accumulate because of a lack of repair, and PARP enzymes have been shown to participate in various forms of double strand break repair (46, 47).

Double strand breaks are also revealed in traditional metaphase spreads by chromosome breaks, and these are much more frequent in niacin-deficient bone marrow cells (Fig. 2C; ref. 42). Double strand breaks can also lead to non-homologous translocations, which are responsible for most chemotherapy-induced leukemias. Clouds of negatively charged poly(ADP-ribose) around strand breaks are thought to help prevent translocation events; niacin deficiency will likely favor the formation of these deleterious lesions. Sister chromatid exchanges are homologous recombination events that seem to reflect the risk of nonhomologous events, and niacin deficiency increased these threefold (48). The micronucleus assay is sensitive to both DNA damage and chromosome sorting, and these lesions were increased sixfold by niacin deficiency (42).

There are many aspects to genomic stability beyond the correct replication and repair of DNA and the sorting of chromosomes. These processes can be disrupted indirectly by improper control of the cell cycle. A failure to maintain genomic stability is also mitigated by the process of apoptosis, and defects in these pathways allow damaged cells to survive and progress to leukemias. One protein that plays a key role in coordinating DNA repair, cell cycle arrest, and apoptosis is p53. This protein plays a strong role in tumor suppression and is mutated or downregulated in most human cancers. p53 is regulated by several NAD-dependent processes. It has been reported as a covalent acceptor of poly(ADP-ribose), via PARP-1 activation (49). It also has a high-affinity binding site for noncovalent interactions with poly(ADP-ribose; ref. 24), and it is deacetylated by Sir2 (50). The end result of these interactions is uncertain, and there is a lack of consensus on the role of ADP-ribosylation in the regulation of p53 function. We have examined p53 expression in bone marrow cells in our model and have found that niacin deficiency causes accumulation of two slow mobility forms of p53 (45). We have determined that they are not due to alternate splicing of the mRNA (45).

If p53 function is disrupted there can be impairment of cell cycle arrest and apoptotic signaling. We found that niacin-deficient bone marrow cells displayed an altered response to etoposide-induced DNA damage, with a blunting of the G1 arrest, and a greater portion of cells in S-phase. In addition, there was an impaired apoptotic response in niacin deficient cells. Of interest, this is one of the few biomarkers that we have found to be altered by pharmacological supplementation of niacin relative to adequate niacin intake. The progressive increase in apoptotic frequency from niacin deficient through adequate to pharmacological intake correlates with cellular NAD^+ and poly(ADP-ribose) content in these groups (45). This relationship is also reflected by the eventual development of ENU-induced leukemias (38). There are a number of possible connections between niacin status and apoptosis, but the most compelling of these involves the activation of apoptosis-inducing factor (AIF). AIF is a 67-kDa flavoprotein that seems to play important roles in mitochondrial metabolism of normal cells and in apoptosis of injured cells (similar to cytochrome c; ref. 51). Following cell injury,

AIF may be released from the mitochondria after PARP-1 is activated in the nucleus. It can then translocate to the nucleus and initiate or contribute to apoptotic cell death. Although the mechanisms are not well characterized, the synthesis of poly(ADP-ribose) by PARP-1 is required for the translocation of AIF and the induction of caspase-independent apoptosis (51).

Current Use of Niacin and PARP Modifiers in Cancer Therapy

Niacin Supplementation of Cancer Patients

There are a limited number of studies on niacin status and supplementation in cancer patients, and very little data on side effects or efficacy. Inculet found that essentially all of the patients in a small cohort of cancer patients were niacin deficient prior to nutritional support (12). They found that supplementation with standard quantities of intravenous B vitamins only corrected niacin status in 40% of patients, whereas most responded effectively to twice the recommended level (12). Predictably, chemotherapy can worsen nutritional status, and niacin deficiency has been observed in several studies (13, 14). In a recent study, breast cancer patients receiving tamoxifen were randomized to control or a combination of coenzyme Q_{10}, riboflavin, and niacin (52), but it is not clear what the changes in serum PARP-1 levels or circulating leukocyte parameters signify.

Nicotinamide and Microcirculation

High doses of nicotinamide have been used to enhance the impact of radiation or chemotherapy on solid tumors (53) by enhancing microvascular flow within the tumor (54). The clinical protocol involves oral doses of around 3 to 6 g nicotinamide, designed to raise systemic blood levels to 700 μM or higher. This administration is combined with the breathing of 95% oxygen/5% carbon dioxide, leading to improved tumor blood flow and oxygenation, which increase the killing potential of both radiation and chemotherapy treatments. The impact of nicotinamide seems to be related to an inhibition of myosin light chain kinase, as suggested by decreased phosphorylation of the regulatory myosin light chain, which impairs vascular smooth muscle contraction, leading to vasodilation (55). The microvascular effects of high dose nicotinamide do not seem to be related to its normal metabolic functions as a source of vitamin B_3. Of interest, Rojas showed in mouse tumors that the radiation sensitivity lasted beyond the drop in blood nicotinamide levels, suggesting that intracellular nicotinamide may remain elevated, or that the effect is due to a downstream effect, such as enhanced NAD levels (56), which may favor poly(ADP-ribose) accumulation and DNA damage-induced apoptosis (51). Nicotinamide and carbogen are being used in clinical trials with some promise in conjunction with radiation (57) and chemotherapy (58). Although these high doses of nicotinamide are likely to improve tissue NAD levels, there haven't been any direct attempts to measure niacin status in patients or to characterize the bone marrow responses.

PARP-1 Inhibitors and Cancer Treatment

Of interest, an exciting new direction in chemotherapy is the inhibition of PARP-1 activity (59, 60). This will have many effects that are opposite to those described in this review. The basic idea is to block the repair of chemotherapy-induced DNA lesions with catalytically inactive PARP-1, leading to gross genomic instability and the induction of apoptosis and tumor cell death (59). The most promise for this approach is in cancers, such as breast or ovarian, with BRCA mutations. These mutations create a deficit in double strand break repair, which is exacerbated by PARP-1 inhibition, leading to a more specific targeting of cancer cells (60).

Whereas PARP-1 inhibitors combined with genotoxic drugs may enhance killing of other types of cancer cells, it is not certain if this will be at the expense of increased risk of acute damage and secondary malignancies in normal tissues like the bone marrow. Most tumor tissues have already adjusted to some degree of genomic instability and have downregulated apoptotic signaling. Bone marrow cells may be more susceptible to this treatment than some types of cancer cells.

Summary

For the cancer patient, the critical relationship is between toxicity and efficacy of the chemotherapy treatment. Correcting niacin status may not be clinically beneficial if tumor cells are also protected from the toxicity of the chemotherapy drugs. Optimally, niacin supplementation could protect the bone marrow and increase tumor cell killing, and there are several indications that this could be true. Most tumor cells downregulate apoptosis signaling and these changes also protect them from chemotherapy drugs. When a cancer patient is niacin deficient, it is likely that the tumor cells will have decreased NAD levels and experience some of the physiological changes that we observe in the bone marrow, including depression of apoptosis, decreased control over the cell cycle, and increased genomic instability. These are effects that can increase the malignant potential of a tumor, and/or make it more resistant to chemotherapy. One intriguing possibility is that pharmacological niacin intake could increase poly(ADP-ribose) synthesis in tumor cells, activating the AIF-dependent apoptotic pathway and increasing treatment efficacy (51). In addition, tumors tend to display decreased mitochondrial metabolism and become more dependent on anaerobic glycolysis (61). These tendencies have been shown to inhibit apoptosis and contribute to chemoresistance. Dichloroacetate activates pyruvate dehydrogenase, increasing mitochondrial metabolism and sensitizing cancer cells and tumors *in vivo* to chemotherapy-induced apoptosis (61). Niacin supplementation could cause an additive effect by increasing tumor cell NAD, supporting the increase in mitochondrial metabolism and driving up the poly(ADP-ribose)-dependent activation of AIF. These mechanisms for enhancing the apoptotic response in tumors would not be occurring at the cost of genomic instability in normal tissues. Further research should be conducted to determine the impact of niacin supplementation in more complex tumor-bearing animal models.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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