

Review Article

Role of Nicotinamide in DNA Damage, Mutagenesis, and DNA Repair

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Nicotinamide is a water-soluble amide form of niacin (nicotinic acid or vitamin B3). Both niacin and nicotinamide are widely available in plant and animal foods, and niacin can also be endogenously synthesized in the liver from dietary tryptophan. Nicotinamide is also commercially available in vitamin supplements and in a range of cosmetic, hair, and skin preparations. Nicotinamide is the primary precursor of nicotinamide adenine dinucleotide (NAD⁺), an essential coenzyme in ATP production and the sole substrate of the nuclear enzyme poly-ADP-ribose polymerase-1 (PARP-1). Numerous *in vitro* and *in vivo* studies have clearly shown that PARP-1 and NAD⁺ status influence cellular responses to genotoxicity which can lead to mutagenesis and cancer formation. This paper will examine the role of nicotinamide in the protection from carcinogenesis, DNA repair, and maintenance of genomic stability.

1. Introduction

Nicotinamide (pyridine-3-carboxamide; Figure 1(a) is an amide active form of Vitamin B3 or niacin (pyridine-3-carboxylic acid; Figure 1(b). Both nicotinamide and niacin are precursors for the synthesis of nicotinamide adenine dinucleotide (NAD⁺) and the phosphorylated derivative NADP⁺ [1] (Figure 2). Nicotinamide and niacin are readily available from plant and animal foods, and niacin can be endogenously synthesized from the amino acid tryptophan [2], which constitutes ~1% of protein in the diet [1]. The main dietary sources of nicotinamide and niacin are various meats, liver, yeast, dairy products, legumes, beans, nuts, seeds, green leafy vegetables, fortified bread, cereals, coffee, and tea [1, 3]. Uncooked foods mostly contain NAD⁺ and NADP⁺, which can be enzymatically hydrolysed to nicotinamide in the process of cooking [1]. Studies in adult humans in the 1950s estimated that around 60 mg of tryptophan is hepatically converted to 1 mg of niacin, which is equal to 1 niacin equivalent (NE) [1]. Vitamins B2 (riboflavin) and B6 (pyridoxine) in addition to iron are needed as cofactors for conversion of tryptophan to niacin [1, 3]. The ability to convert tryptophan to niacin varies greatly between individuals and is enhanced by

protein and tryptophan deficiency, and it is depressed by excessive dietary leucine [1]. The adult recommended daily intake expressed as niacin equivalent is 16 NE/day for men, 14 NE/day for women and 18 NE/day and 17 NE/day for pregnant and lactating women, respectively [4]. In humans, dietary nicotinamide and niacin are absorbed from stomach and intestine via both sodium-dependent and passive diffusions [1]. Most tissues take up both forms of vitamins to synthesize NAD⁺ and NADP⁺, although nicotinamide is the preferable substrate [5]. Dietary NAD⁺ and NADP⁺ are hydrolyzed by intestinal mucosal and hepatic NAD glycohydrolases to release nicotinamides into the portal or systemic circulation [1]. Niacin is also endogenously synthesized from dietary tryptophan via kynurenine pathway and quinolinate (Figure 2), and this supplies most of the body's niacin requirements [1]. Niacin and quinolinate are further converted to nicotinic acid ribonucleotides and then into NAD⁺ [1]. Excess nicotinamide and niacin are methylated in the liver to form N¹-methylnicotinamide (NMN) and N¹-methylnicotinic acid (NMNA), respectively [1]. NMN is further oxidised into N¹-methyl-4-pyridone-3-carboxamide (4-pyr) and N¹-methyl-2-pyridone-5-carboxamide (2-pyr) [1]. Niacin is also metabolized in the liver into glycine conjugate and nicotinuric acid [6]. These metabolites are

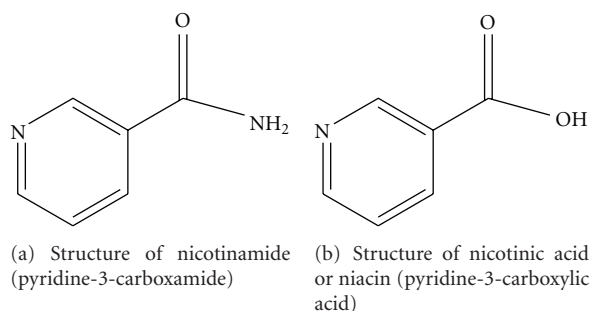


FIGURE 1

then renally excreted [1]. Some cosmetic preparations also contain nicotinamide. Systemic absorption of topical nicotinamide has been reported to be approximately 10% depending on the vehicle used [7]. Adverse effects of nicotinamide are rare and have occurred mainly with high oral doses (≥ 6 gram/day), which include nausea, vomiting, liver toxicity, headache, fatigue, and dizziness [8–10]. Unlike niacin, nicotinamide is not a vasodilator, thus it rarely causes flushing [11].

Severe nicotinamide deficiency in humans causes the disease pellagra (*Italian “pelle agra”; “rough skin”*), which is characterised by photosensitive dermatitis, diarrhoea, dementia, and death [3]. It was thought that the clinical manifestations of pellagra arise from the deficient NAD^+ and NADP^+ levels in maintaining energy for cellular functions [13]. However, understanding of these multiple symptoms has progressed with the finding of NAD^+ as a substrate for poly(ADP-ribose)polymerases (PARPs) [14]. PARP has been recognized to play multitude roles in DNA damage responses, including DNA repair, maintenance of genomic stability, transcriptional regulation, signaling pathways involving apoptosis, telomere functions, and other multiple cellular functions [15]. Several members of the PARP family have been identified, of which PARP-1 is the most reported and is the focus of this paper. NAD^+ has also been shown to be a free radical scavenger [16–20] and is directly used for the synthesis of cyclic ADP-ribose, which may be involved in calcium signaling pathways leading to apoptosis or necrosis [21, 22]. Cellular NAD^+ status has been increasingly demonstrated to alter the cell susceptibility to genotoxic damage [23], highlighting the crucial role of nicotinamide as a NAD^+ precursor in modulating pathways involved in carcinogenesis. This paper will first discuss nicotinamide and carcinogenesis in humans and whole animal models. Next, the roles of nicotinamide in relation to DNA repair, genomic stability, and mutagenesis will be examined.

2. Nicotinamide, Niacin, and Cancer in Humans

There are relatively few epidemiological studies on the association between nicotinamide intake and cancer in humans. Deficiency of nicotinamide and other micronutrients including riboflavin, zinc, and magnesium have been linked to the increased frequency of oesophageal cancer in certain

populations in China and Italy [24, 25]. Low dietary niacin has also been associated with an increased frequency of oral, gastric, and colon cancers, as well as oesophageal dysplasia [25–27]. In the Linxian trial in China, involving nearly 30,000 residents, 40 mg niacin and 3.2 mg riboflavin were supplemented in one of the treatment arms daily for over 5 years. It was shown that this combined supplementation decreased oesophageal cancer incidence and mortality by 14% and 10%, respectively [24]. Most human studies have examined the dietary intake or supplementation of niacin in combination with other micronutrients [24, 25, 28–32]. The impact of niacin on human carcinogenesis is therefore confounded by the effect of other micronutrients. Analysis from a large Western population within The Malmö Diet and Cancer Study in Sweden showed that approximately 15%–20% of individuals in this population were niacin deficient [33]. While severe niacin deficiency resulting in pellagra is uncommon in Western populations, suboptimal niacin intake may be relevant in populations at risk such as cancer patients and individuals with high occupational or environmental exposure to genotoxic agents including ionizing radiation, ultraviolet radiation (UVR), and alkylating agents. Limited studies indicate that cancer patients are at risk of niacin deficiency [34, 35]. In one trial involving 42 patients with various primary cancers, it was shown that 40% of these patients were niacin deficient as measured by abnormally low urine levels of the niacin metabolite N^1 -methylnicotinamide [34]. Chemotherapy may also depress NAD^+ levels [35] and precipitate pellagra by promoting anorexia and malabsorption. Some chemotherapeutic agents (e.g., 5-fluorouracil, 6-mercaptopurine) also interfere with tryptophan conversion to niacin [36]. Moreover, chemotherapeutic alkylating agents have been shown to cause miscoding lesions, chromosomal aberrations [37], and secondary cancer, particularly leukemia, which complicates chemotherapy in 10%–15% of cancer survivals [38]. More direct evidence comes from studies in rats, which showed that niacin deficiency significantly increases the risk of chemotherapeutic-induced secondary leukemia [39]. Niacin and NAD^+ levels are important determinants of genomic responses to genotoxic insults [23]. Maintaining an optimum nicotinamide level is therefore essential in cancer patients and individuals at risk of exposure to genotoxic agents.

3. Nicotinamide Supplementation and Animal Models of Carcinogenesis

Animal models show that nicotinamide supplements influence carcinogenesis in a dose-dependent and organ-specific manner (Table 1). Nicotinamide is not carcinogenic by itself at doses more than 300-fold above requirement, administered to mice throughout their life span [40]. Overall, low-dose nicotinamide (dose range of 150–200 μM , topical; 0.25%–2.5%, oral; 30 mg/kg body weight (bw) intraperitoneal) appears to be protective in various chemical- and UVR-induced carcinogenesis models in animals. Nicotinamide at dietary concentrations of 0.25%–2.5% is protective against urethane-induced pulmonary adenoma in

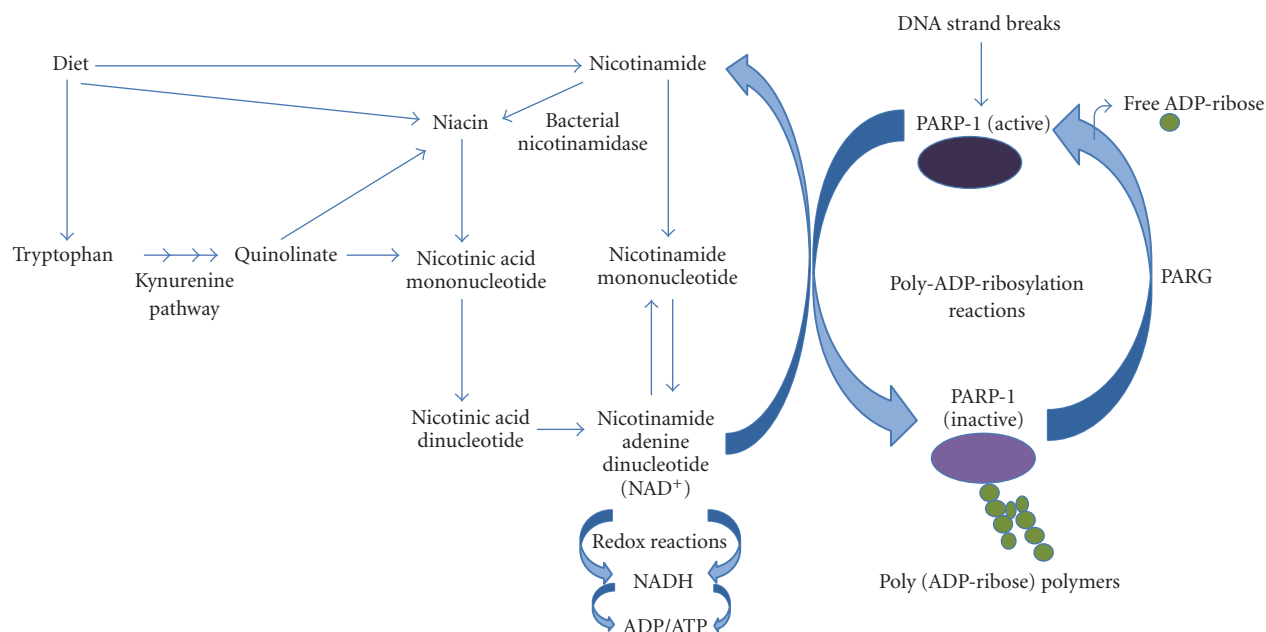


FIGURE 2: The simplified pathways for nicotinamide, niacin, NAD⁺, and PARP-1 metabolism. Dietary nicotinamide, niacin, and tryptophan are precursors for the synthesis of NAD⁺, essential in ATP production and PARP-1 activation. Nicotinamide can be converted to niacin by bacterial nicotinamidase in the intestinal lumen. PARP-1 is activated by DNA strand breaks, cleaving NAD⁺ into nicotinamide and ADP-ribose. Poly(ADP-ribose) glycohydrolase (PARG) reactivates PARP-1 by removing poly(ADP-ribose) polymers, allowing for continuous NAD⁺ utilization. Figure is adapted from Jacobson et al., in 1995 [6] and Meyer-Ficca et al., in 2004 [12].

mice, whereas 0.25% niacin did not show the same protection [41, 42]. However, higher concentrations of dietary niacin (0.4%) caused a 6% reduction in the incidence of nonlymphocytic leukemia induced by ethylnitrosourea in Weanling male Long-Evans rats [43]. Nicotinamide has also been shown to inhibit the growth of transplanted murine breast adenocarcinoma in mice, although the doses required are higher (2.5% and 5% diet; 1000 mg/kg bw intraperitoneal) than those needed to suppress carcinogen-induced cancers [44, 45]. The effect of nicotinamide on diethylnitrosamine (DEN)-, streptozotocin-, and heliotrine-induced carcinogenesis seems to be organ-specific. Massive doses of nicotinamide (350–500 mg/kg bw intraperitoneal, multiple dosing) inhibited DEN-induced liver tumours (34% reduction), but promoted DEN-induced kidney neoplasia (44% increase) in Wistar rats [46]. However, in another study of DEN-induced carcinogenesis, even low-dose nicotinamide (0.082% and 0.37% oral) increased the incidence of DEN-induced kidney tumours from 5% in controls (DEN only) to 28% and 59%, respectively, in male F344 rats [47]. 0.37% nicotinamide by itself had no effect on tumour formation [47], suggesting that the presence of carcinogen is required for the tumour promoting or inhibiting effect of nicotinamide.

Intraperitoneal nicotinamide (350 mg/kg) increased the incidence of streptozotocin-induced pancreatic islet-cell tumours in male Holtzman rats from 4% in controls (streptozotocin only) to 64% [48], but it decreased the incidence of renal adenomas from 77% to 18% [49]. Nicotinamide administered intraperitoneally at 500 mg/kg to

white male weanling rats before and after administration of pyrrolizidine alkaloid heliotrine increased pancreatic islet-cell tumours [50]. The varying effects of nicotinamide with different carcinogens and target organs may reflect the differential susceptibility of each organ to DNA damaging agents. Furthermore, it has been shown that PARP-1 protein expression is tissue- and/ or cell-type specific [51], and there are tissue and species differences in requirements for NAD⁺ precursors. Tissues with high cellular turnover including breast, lung, and skin have higher NAD⁺ requirements, and mice are relatively more resistant to niacin deficiency compared to rats or humans [23]. Hence, the breast, lung, and skin tissues of rats and humans likely required higher doses of NAD⁺ precursors in the face of genomic insults.

4. Nicotinamide: Photoimmunosuppression and Skin Cancer

The immune system is an important defense mechanism that prevents potentially cancerous cells from developing into tumors. In humans, the importance of immunity in preventing cancer is observed in renal transplant recipients on immunosuppressive medications. In this population, there is an increased incidence of all cancer type (13.7-fold increase), nonmelanoma skin cancer (33-fold increase), and melanoma (3.3-fold increase) compared to age-matched immune competent individuals [58]. Ultraviolet (UV) radiation in sunlight is the primary initiator of skin cancer by

TABLE 1: Animal models of nicotinamide or niacin effect on carcinogenesis.

Animal	Carcinogen	Form of nicotinamide (dose)	Organ	Effect on tumor	Ref.
Mouse	None	Oral	All	None	[40]
Mouse	UV	Topical(200 μ M)	Skin	Inhibition	[52]
Mouse	UVB	Oral (niacin)(0.5%; 1% diet)	Skin	Inhibition	[53]
Mouse	TPA	Topical (150 μ M)	Skin	Inhibition	[54]
Mouse	DMBA and Croton oil	Oral(0.2% diet)	Skin	None	[55]
Mouse	Urethane	Oral (0.25%; 0.4% diet)	Lung	Inhibition	[41]
		Oral (niacin) (0.25% diet)	Lung	None	
Mouse	Urethane	Oral (1%; 2.5% diet)	Lung	Inhibition	[42]
Rat	ENU	Oral (niacin) (0.4% diet)	Bone marrow (haemopoietic cells)	Inhibition	[43]
Rat	Bracken fern	Oral (0.5% diet)	Intestine	Inhibition	[56]
			Bladder	Inhibition	
Hamster	BOB	ip (30 mg/kg bw)	Pancreas	Inhibition	[57]
Rat	DEN	ip (350–500 mg/kg bw)	Kidney	Increase	[46]
			Liver	Inhibition	
Rat	DEN	Oral (0.082%; 0.37%)	Kidney	Increase	[47]
Rat	Streptozotocin	ip (350 mg/kg bw)	Pancreas	Increase	[48]
Rat	Streptozotocin	ip (350 mg/kg bw)	Kidney	Inhibition	[49]
Rat	Heliotrine	ip (500 mg/kg bw)	Pancreas	Increase	[50]
Mouse	Transplanted murine breast adenocarcinoma	Oral (2.5%; 5%)	Recipient subcutaneous tissue	Inhibition	[44]
Mouse	Transplanted murine breast adenocarcinoma	ip (1000 mg/kg bw)	Recipient subcutaneous tissue	Inhibition	[45]

causing DNA damage in the skin and also by suppressing cutaneous immunity, even at exposure doses 25% to 50% of those required to cause mild sunburn [59]. Both UVB (290–320 nm) and UVA (320–400 nm) in sunlight are immune suppressive [60, 61]. UV-induced DNA damage, particularly in the form of cyclobutane pyrimidine dimers (CPDs), is an important molecular trigger for UV-induced immunosuppression [62]. Agents that can modulate DNA repair and prevent UV-induced immunosuppression may thus reduce skin cancer.

In mice, 200 μ M topical nicotinamide [52] and 0.5% and 1% niacin-supplemented diets [53] have both been shown to markedly protect against UV-induced immunosuppression and significantly reduce the incidence of UV-induced skin tumours. In these studies, UV-induced immunosuppression was measured by passive transfer assay, whereby splenocytes from irradiated mice enhanced the growth of antigenic tumours in unirradiated, recipient mice [52, 53]. Topical nicotinamide also slowed down the rate of skin tumour development [52] and the effect of oral niacin on tumour inhibition was greater with increasing dose [53]. Oral niacin increased skin NAD⁺ levels, which were reduced by UVR in mice not receiving niacin, and this was thought to contribute to tumour prevention [52, 53]. It was also suggested that protection from photoimmunosuppression is a mechanism by which nicotinamide and niacin prevent UV-induced carcinogenesis [52, 53].

Using the Mantoux model of delayed-type hypersensitivity (DTH) in healthy volunteers, we have shown that nicotinamide protects from UV-induced immunosuppression in humans [63, 64]. 5% topical nicotinamide, applied 15 minutes before or after each of 3 daily exposures to low-dose solar-simulated (ss) UV (equivalent to less than \sim 8 minutes exposure to Sydney spring sunlight [65]), prevented UV-induced suppression of Mantoux reactions [63]. 5% topical nicotinamide, applied immediately after a single exposure to narrowband UVB (300 nm) or UVA (385 nm), protected against immunosuppression by both wavebands [66]. Using the same model, oral nicotinamide has also been shown to protect skin immunity in humans [64].

5. Nicotinamide, PARP-1 and DNA Repair

The role of nicotinamide in DNA repair and maintenance of genomic stability is tightly related to its functions as an NAD⁺ precursor and a substrate for PARP-1. PARP-1 is a nuclear enzyme which detects DNA damage, binds to DNA single or double strand breaks, and then uses NAD⁺ as a substrate to form nicotinamide and ADP-ribose. Subsequent enzymatic reactions lead to the formation of branched ADP-ribose polymers on a nuclear acceptor protein [67, 68] (Figure 2). Poly(ADP-ribosylation) of the acceptor protein has been hypothesized to function in DNA repair by modifying structural proteins proximal to DNA

strand breaks, facilitating the opening of the condensed chromatin structure, which is required for the recruitment of DNA repair complexes [69, 70]. The major acceptor proteins of poly(ADP-ribose) are PARP-1 itself, and auto-poly(ADP-ribosylation) results in downregulation of the enzyme [70]. Other major acceptor proteins reported are histone, topoisomerase I and II, DNA polymerase α and β , DNA ligase I and II, nuclear retinoid X receptor, nuclear factor (NF)- κ B, and p53 [70, 71]. Poly(ADP-ribose) glycohydrolase (PARG) is the main enzyme involved in catabolism of poly(ADP-ribose), cleaving it into free ADP-ribose monomers [70]. PARP-1 itself is also known to be part of chromatin structure and involved in maintaining a compact chromatin structure, preventing inadvertent transcription from occurring [72]. Unfolding of the compact chromatin structure allows DNA regulatory and repair processes access to the damaged sites as well as to replication and transcription initiation sites [73]. PARP-1 has been reported to play a key role in the nucleotide excision repair (NER) pathway used to remove bulky DNA adducts [74] and in the base excision repair (BER) pathway by interacting with BER protein XRCC1 (X-ray repair cross-complementing 1) [75–78]. PARP-1 is involved in maintaining chromosomal integrity by protecting broken DNA from inappropriate homologous recombination during DNA repair and replication [79, 80]. PARP knockout mice exhibited dramatically increased sensitivity to ionizing radiation and alkylating agents [81–83] and showed a 2–3-fold increase in spontaneous sister chromatid exchange (SCE) and amplified SCE and micronuclei (MN) formation induced by carcinogens [83, 84]. PARP-null mice also showed extreme sensitivity to nitrosamine-induced carcinogenesis [85], had shorter telomeres, and increased end-to-end chromosomal fusions, aneuploid cells, and chromosome fragments [86]. Thus, nicotinamide is involved in maintenance of genomic stability by providing a substrate for PARP-1, preserving a cellular energy reserve for ATP-dependent DNA repair [87] and enabling preservation of PARP-1 integrity [88].

6. The Influence of NAD⁺ Status on Genomic Stability and DNA Repair

6.1. In Vitro Studies. A large number of *in vitro* studies reported that NAD⁺ status influences genomic stability and sensitivity to cytotoxic effects of DNA-damaging agents. Nicotinamide (50–500 μ M) increased intracellular NAD⁺ and enhanced the repair of DNA damage induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in cultured primary human mammary epithelial cells [23]. Preincubation with 74 μ M nicotinamide prevented NAD⁺ depletion after dimethyl sulphate (DMS) exposure and increased strand break rejoining rate [89]. Increasing NAD⁺ status by the addition of nicotinamide thus improved the capacity of DNA repair. NAD⁺ is also an important determinant of skin cell survival following UV radiation. 0.1 and 33 μ M nicotinamide added to UV-irradiated cultured human skin fibroblasts increased cell survival 7 days post irradiation in a dose-dependent manner [90]. Even in the absence of genotoxic stress, NAD⁺ depletion increased spontaneous

DNA damage in human HaCaT keratinocytes, which was reversible with the addition of nicotinamide [91]. NAD⁺ status is therefore critical in preserving genomic function of skin cells. Furthermore, it was shown that skin NAD⁺ levels are negatively correlated with malignant phenotype in human skin cancers. Normal skin from patients with premalignant actinic keratoses had significantly higher NAD⁺ than normal skin from patients with cutaneous squamous cell cancers [23].

Exposure of *ex vivo* human lymphocytes to oxygen radicals [92], UVB [93, 94], γ -irradiation [95], N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) [93, 94], or dimethyl sulfate (DMS) [93] resulted in reduced intracellular NAD⁺, with numbers of DNA-strand breaks inversely correlated with NAD⁺ levels [92]. Addition of 2–5 mM nicotinamide prevented this lowering of NAD⁺ levels, stimulated unscheduled DNA synthesis (UDS), and increased DNA repair [93–95]. The ability of nicotinamide to enhance DNA repair depends on the presence of functional repair mechanisms. Xeroderma pigmentosum is an autosomal recessive genetic disorder of DNA repair, in which the ability to repair DNA damage caused by UVR is deficient. [96]. In the presence of 2 mM nicotinamide, lymphocytes from these patients exhibited increased UDS after MNNG treatment but failed to show increased UDS after UVB irradiation. Normal lymphocytes incubated with the same dose of nicotinamide, in contrast, showed increased UDS and enhancement of DNA repair after UVB or MNNG exposures [97].

In HaCaT cells (human keratinocyte cell line) NAD⁺ depletion upregulated NADPH oxidase activity with consequent increase in reactive oxygen species (ROS) production. NAD⁺ repletion with nicotinamide completely reversed the ROS accumulation [91]. In support of these findings, niacin deficiency, which results in intracellular NAD⁺ depletion in rats, also caused an increase in both protein carbonyls and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) in bone marrow [98]. Oxidative-induced DNA damage 8-oxo-dG is a miscoding lesion, which generates GC \rightarrow TA transversion mutations by pairing with an adenine instead of a cytosine during replication [99]. ROS also damages other cellular components including cell membranes by peroxidation of fatty acids within the phospholipid bilayer and proteins by forming carbonyl derivatives [100]. Lipid peroxidation increases production of prostaglandins (PG), including PGE₂, which is known to play an important role in inflammation. Inflammation in premalignant actinic keratoses has been reported to be a marker of progression to squamous cell carcinoma [101]. It was also postulated that ROS may cause gene mutations in actinic keratoses, driving their progression to squamous cell carcinoma [101]. Regulation of ROS levels by maintenance of intracellular NAD⁺ is therefore important in preventing oxidative DNA damage and gene mutation.

6.2. In Vivo Studies. Administration of 100 mg/day niacin to two volunteers for 8 weeks protected against *ex vivo* lymphocyte DNA strand breaks induced by hypoxanthine/xanthine oxidase. The supplementation increased NAD⁺ concentrations by nearly 5 times baseline levels and significantly

reduced oxygen radical-induced DNA strand breaks in the lymphocytes [92].

The impact of niacin deficiency in rats has been extensively studied by the Kirkland group [98, 102–106]. Wenling Long-Evans rats were kept niacin-deficient (ND) or were pair-fed (PF) either normal dietary niacin or supplemental 4 mg/gram niacin (NA) (0.4% of diet). The DNA-alkylating agent ethylnitrosurea (ENU) or the topoisomerase II inhibitor etoposide (ETO) was then administered to these rats orally. Bone marrow is a good indicator of niacin intake. ND diets caused 72%–80% [102, 104] reduction in bone marrow NAD⁺ content, whereas NA diets produced a 240% increase [103]. Basal poly(ADP-ribose) levels were also significantly lower in ND rats. After ENU- or ETO-treatment, poly(ADP-ribose) levels were not increased in bone marrow of ND rats whereas in PF and NA rats, the level of bone marrow poly(ADP-ribose) rose significantly [102, 104]. Adequate NAD⁺ is therefore essential for the increase in ADP-ribose polymer metabolism activated by DNA damage. Niacin deficiency alone causes increased micronuclei (MN) formation (6.2-fold), SCE frequency (2.8-fold) [103], chromosomes breaks (4-fold), and chromatid breaks (2-fold). With ENU- or ETO-treatment, there were much greater increases in MN formation, SCE, and chromosomal aberrations (CA) in bone marrow of ND rats [103, 105]. The increased genomic instability in ND rats is further evidenced by the reduction in latency and the increase in the incidence of developing ENU-induced leukemia [102]. Niacin deficiency significantly delayed DNA repair in bone marrow after ENU- or ETO-treatment [103, 105] and was shown to alter p53 expression and impair ETO-induced cell cycle arrest and apoptosis [104].

7. Nicotinamide, PARP-1, and Cellular Responses to DNA Damage

The activation of PARP-1 by DNA strand breaks can lead to three cellular pathways depending on the intensity of DNA-damaging stimuli [70] (Figure 3). In the case of relatively mild DNA damage, PARP-1 activation enhances DNA repair by interacting with p53 protein, signaling cell-cycle arrest, and facilitating DNA repair enzymes, including XRCC1 and DNA-dependent protein kinases to access damaged DNA [70]. When DNA damage is irreparable, PARP-1 activation induces apoptotic cell death by activating NF- κ B pathway and preventing ATP depletion and DNA repair through caspase-mediated PARP-1 cleavage [70, 107]. In contrast, extensive DNA damage leads to PARP-1 overactivation, depleting its substrate (NAD⁺). As cells consume ATP in an attempt to replenish NAD⁺, this leads to a cellular energy crisis, which precipitates necrotic cell death [70]. Apoptosis is an energy-dependent process [108–111] thus cells severely deficient in energy are unable to proceed through apoptotic cell death.

PARP-1 is inhibited by nicotinamide and its analogues such as 3-aminobenzamide and metoclopramide [112, 113]. PARP-1 inhibition by nicotinamide *in vitro* has been reported to delay the rejoining of DNA strand breaks [95, 114, 115],

induce UDS [95, 97, 116], and increase the frequency of spontaneous SCE [117, 118]. It has been suggested that high dose of nicotinamide (5 mM or more) inhibits DNA repair through PARP-1 inhibition while low dose nicotinamide enhances rejoining of DNA strand breaks through provision of NAD⁺ [114]. However, it is argued that nicotinamide is unlikely to inhibit PARP *in vivo* [119]. Rats fed nicotinamide 33 times above normal requirements exhibited 2-fold increases in basal poly(ADP-ribose). After exposure to a hepatocarcinogen, induction of poly(ADP-ribose) was only marginally higher in the nicotinamide supplemented rats [120], suggesting that a much higher dose of nicotinamide is required to possibly inhibit PARP-1 in the whole organism.

Excessive PARP activity is however detrimental to cells. Augmented PARP activity caused by reactive oxygen injury to cultured pulmonary-artery endothelial cells resulted in NAD⁺ and ATP depletion and necrotic cell death, which was prevented by the PARP-1 inhibitors nicotinamide and 3-aminobenzamide (3-AB) [121]. *Ex vivo* murine lung exposed to bleomycin, a DNA-cleaving antitumor antibiotic, caused acute lung injury through sustained PARP activation and NAD⁺ depletion. This injury was prevented in the presence of 3-AB [122]. The topical PARP inhibitor, BGP-15M (O-(3-piperidino-2-hydroxy-1-propyl) pyrimide-3-carboxylic acid amidoxime monohydrochloride) reduced UVB-induced DNA strand breaks in hairless mouse skin and prevented excessive production of poly(ADP-ribose) induced by moderate UV doses. These findings suggest that the inhibition of PARP-1 overactivation, and therefore of NAD⁺ and ATP depletion, can occur without negative consequence to DNA repair [123].

PARP-1 inhibition by nicotinamide has been shown to switch the mode of cell death from necrosis to apoptosis in *ex vivo* human lymphocytes treated with hydrogen peroxide [124]. In addition, it has been widely reported that in the cells exposed to oxidative stress, both ATP and NAD⁺ levels serve as crucial molecular switches between apoptosis and necrosis [125–133]. Nicotinamide as a precursor of NAD⁺, ATP, and as an endogenous inhibitor of PARP-1 therefore plays significant roles in cellular protection and in determining cellular fate in response to genotoxic DNA damage.

8. Nicotinamide, PARP-1, and Regulation of Gene Expression

PARP-1 has been reported to frequently associate with transcriptionally active regions of chromatin [134, 135]. PARP-1 is a transcription coactivator of nuclear factor- κ B (NF- κ B) [136], a transcription factor that plays a significant role in regulation of genes involved in a variety of cellular processes including immune and inflammatory responses, apoptosis, cell proliferation, and differentiation [137, 138]. There is a large amount of literature supporting the involvement of NF- κ B in cutaneous carcinogenesis [136, 139]. Epidermal inflammation promotes tumor progression [101] and NF- κ B is known to be one of the mediators involved [139]. PARP-1 knockout mice are much less sensitive to inflammatory stress [140, 141] and PARP-1 deficient mice exhibited

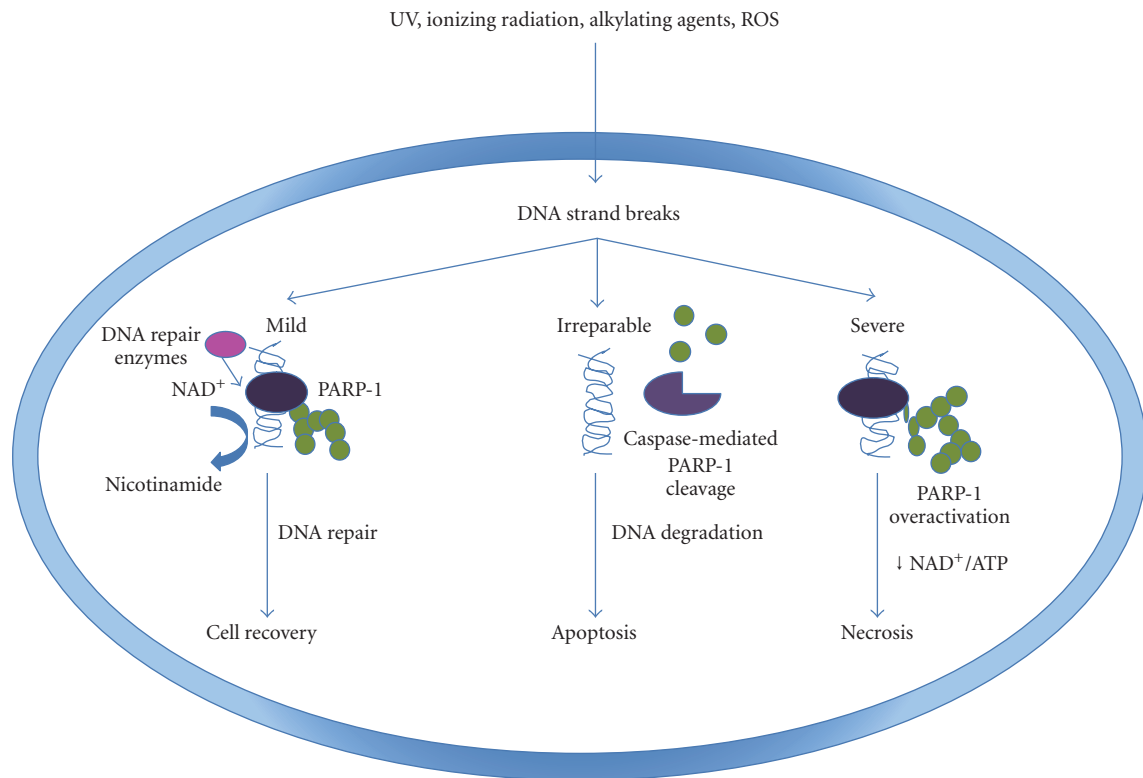


FIGURE 3: PARP-1 and cellular responses to DNA damage. The intensity of DNA damage determines cellular pathways: survival, apoptosis, or necrosis. In the case of mild DNA damage, poly(ADP-ribosylation) enhances DNA repair and thus cell survival. When the damage is beyond repair, PARP-1 facilitates apoptosis, preventing ATP depletion and DNA repair through PARP-1 caspase-mediated cleavage. Severe DNA damage leads to PARP-1 overactivation, cellular energy depletion, and necrotic cell death. Figure is adapted from Virág and Szabó, in 2002 [70].

substantially reduced sensitivity to the carcinogenic effect of DMBA and TPA on the skin [136]. In PARP-1 null (*parp-1*^{-/-}) mice, the development of skin papillomas induced by DMBA and TPA was significantly delayed and reduced in numbers compared to control (*parp-1*^{+/+}) mice. PARP-1 inhibition in mice with 3,4-dihydro-5-[4-(1-piperidinyl)butoxy]-1(2H)-isoquinoline (DPQ) also had the same effect [142]. PARP-1 inhibition with nicotinamide and benzamides was also shown to inhibit NF- κ B in vitro and suppress lipopolysaccharide-induced TNF- α production in mice [143]. Indirect inhibition of NF- κ B by elimination or inhibition of PARP-1 may prevent activation of κ B-target genes, leading to suppression of inflammation and expression of genes associated with tumor progression [136]. Although PARP-1 knockout mice as mentioned previously have increased genomic instability in response to alkylating agents and ionizing radiation [81–83] and were more recently shown to be more sensitive to nitrosamine- [85] and azoxymethane-induced cancers [144], it is thought that this controversy can be explained by the unique environmental and intrinsic factors involved in tumorigenesis of differing genotoxic agents and organs [136].

PARP-1 inhibition by DPQ or by genetic deletion of PARP-1 in mice was also found to normalize or downregulate some upregulated genes in DMBA/TPA-treated skin, including several tumor-associated genes in mouse and human

and genes involved in oxidative stress, inflammation, and the immune response. Of particular importance is the absence of induction of Hif (Hypoxia inducible factor)-1 α in the PARP-1 deficient and DPQ-treated murine skin [142]. The transcription factor Hif-1 α promotes the adaptation of tumour cells to hypoxia, including angiogenesis, vasodilation, glucose transport, and anaerobic metabolism [145]. It was also noted that in the tumours of DPQ-treated mice, there were increased apoptotic cells, suggesting that inhibition of Hif-1 α may contribute to tumour death through failure of these cells to adapt to hypoxia [142]. In our research group, topical nicotinamide was found to normalize subsets of apoptosis, energy metabolism, and immune function-related genes that are downregulated by UVR in human skin [63]. Low dose of ssUV was shown in this study to downregulate apoptotic genes BCL2, TP53, IGF1R, PRKCA, and AKT1, which are also involved in the regulation of telomerase activity, and thought to play important roles in the initiation of skin carcinogenesis [63, 146]. Normalisation of these subsets of genes by nicotinamide suggests its involvement in apoptosis and early events in skin carcinogenesis. The downregulation of genes for energy production in ssUV-treated skin supports evidence for the cellular energy decline known to be induced by UVR [90]. As previously mentioned, DNA repair requires ATP [87], and an adequate NAD⁺ level is critical in maintaining the genomic integrity of skin

cells during UV radiation [90]. Consistent with its role as an NAD⁺ and ATP precursor, nicotinamide protects the cell from UVR-induced energy depletion. Nicotinamide also normalized ssUV downregulation of TP53 genes. p53 is a key regulator of cell cycle arrest and apoptosis in response to DNA damage [147]. In response to genotoxic stress, p53 is stabilized and activated by posttranslational modifications, including poly(ADP-ribosyl)ation, phosphorylation, and acetylation [148, 149]. Niacin deficiency in rats [104] and nicotinamide depletion in cultured cells derived from breast, lung, and skin cells [23] caused decreased expression of the tumor suppressor protein, p53. PARP-1 inhibition has been shown to decrease basal p53 levels and impairs p53 stabilization after DNA damage [150]. In addition, PARP-1 deficient cell lines exhibit a significant reduction in both baseline p53 expression and its activity compared to normal wild type cells [150]. Diminished p53 function is highly associated with malignancy in breast, lungs, and skin [151]. Nicotinamide prevented UV-induced downregulation of p53, suggesting its mode of protection from genotoxic effect of UVR. The effect of nicotinamide on p53 regulation has also been reported to be independent of PARP [152].

9. Conclusion

Nicotinamide, which is the dietary precursor for NAD⁺, provides a substrate for PARP-1 activity. The activation of nuclear enzyme PARP-1 by DNA strand breaks during cellular genotoxic stress responses leads to complex signaling pathway that can enhance DNA repair, result in apoptotic cell death, or cause cellular energy loss leading to necrotic cell death. *In vivo* and *in vitro* studies showed that NAD⁺ content of the cells influences responses to DNA damaging agents. NAD⁺ depletion impairs ADP-ribose polymer metabolism and increases genomic instability in the face of genotoxic and oxidative stress challenges. Nicotinamide deficiency in humans may also contribute to increased frequency of gastrointestinal cancers in certain populations although other micronutrient deficiencies are likely to be involved as well. Nicotinamide supplementation in animal models has opposing effect on carcinogenesis, depending on the type of carcinogens and target organs. Nicotinamide protected against UV-induced immunosuppression in mice and humans and UV-induced carcinogenesis in mice. Limited study in humans indicates that skin NAD⁺ content is an important determinant of malignant phenotype. Thus, nicotinamide supplementation may influence the progression of premalignant actinic keratoses to malignant squamous cell cancers. PARP-1 plays a key role in regulation of genes involved in inflammation, apoptosis, and cellular differentiation. While PARP-1 inhibition could impair its role in DNA repair, PARP-1 overactivation is detrimental to the cells by depleting its substrate NAD⁺, which leads to cellular energy crisis and necrotic cell death. In various murine models, PARP-1 inhibition was shown to favor apoptotic cell death, reduce inflammatory response, and reduce genomic sensitivity to various carcinogens. However, extrapolation of these data to human, particularly when

physiological regimes involved in human carcinogenesis, should be done cautiously. Further studies are needed to determine the effect of high-dose nicotinamide on *in vivo* carcinogenesis and genomic stability of the cancer cells and the surrounding normal cells.

Abbreviations

BOB	N-nitrosobis(2-oxopropylamine)
DEN:	diethylnitrosamine
DMBA:	9,10-dimethyl-12-benzanthracene
DMS:	dimethyl sulphate
DTH:	delayed-type hypersensitivity
ETO:	etoposide; FBS, fetal bovine serum
MN:	micronuclei
MNNG:	N-methyl-N'-nitro-N-nitrosoguanidine
NAD ⁺ :	nicotinamide adenine dinucleotide
PARP:	poly-ADP-ribose polymerase
ROS:	reactive oxygen species
SCE:	sister chromatid exchange
ssUV:	solar-simulated ultraviolet
TPA:	12-O-tetradecanoylphorbol-13-acetate
UDS:	unscheduled DNA synthesis
UVR:	ultraviolet radiation.

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