Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in human keratinocytes and ex vivo skin

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Nicotinamide (vitamin B3) protects from ultraviolet (UV) radiation-induced carcinogenesis in mice and from UV-induced immunosuppression in mice and humans. Recent double-blind randomized controlled Phase 2 studies in heavily sun-damaged individuals have shown that oral nicotinamide significantly reduces premalignant actinic keratoses, and may reduce new non-melanoma skin cancers. Nicotinamide is a precursor of nicotinamide adenine dinucleotide (NAD+), an essential coenzyme in adenosine triphosphate (ATP) production. Previously, we showed that nicotinamide prevents UV-induced ATP decline in HaCaT keratinocytes. Energy-dependent DNA repair is a key determinant of cellular survival after exposure to DNA-damaging agents such as UV radiation. Hence, in this study we investigated whether nicotinamide protection from cellular energy loss influences DNA repair. We treated HaCaT keratinocytes with nicotinamide and exposed them to low-dose solar-simulated UV (ssUV). Excision repair was quantified using an assay of unscheduled DNA synthesis (UDS). Nicotinamide increased both the proportion of cells undergoing excision repair and the repair rate in each cell. We then investigated ssUV-induced cyclobutane pyrimidine dimers (CPDs) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8oxoG) formation and repair by comet assay in keratinocytes and with immunohistochemistry in human skin. Nicotinamide reduced CPDs and 8oxoG in both models and the reduction appeared to be due to enhancement of DNA repair. These results show that nicotinamide enhances different pathways for repair of UV-induced photolesions, supporting nicotinamide’s potential as an inexpensive, convenient and non-toxic agent for skin cancer chemoprevention.

Introduction

Non-melanoma skin cancers, comprising mostly basal cell carcinomas and squamous cell carcinomas, are the most common malignancies in light-skinned populations, with worldwide skin cancer incidence continuing to increase (1). Ultraviolet (UV) radiation is the major cause of skin cancer (2). UVB (290–320 nm) damages DNA directly resulting in the formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidone photoproducts (6-4PPs). CPDs give rise to UV-signature C to T and CC to TT transition (CPDs) and pyrimidine (6-4) pyrimidone photoproducts (6-4PPs). Non-melanoma skin cancer incidence increases with age (6), and age-associated decreases in nucleotide excision repair (NER) of CPDs in ex vivo human skin (7) and in oxidative repair of 8oxoG by human 8-oxoguanine-DNA glycosylase 1 (hOGG1) in ex vivo human lymphocytes (8) have been reported. There is some evidence that DNA repair is deficient in patients with basal cell carcinoma (9). Unrepaired CPDs have been found in actinic keratoses and squamous cell carcinomas (10), and recently it has been shown that basal cell carcinomas are deficient in hOGG1 and have a correspondingly high level of unrepaired 8oxoG (11).

Nicotinamide, an amide form of vitamin B3, prevents UV-induced immune suppression and tumor formation in mice (12). In humans, nicotinamide prevents UV-induced immune suppression (13,14) and oral nicotinamide reduced precancerous actinic keratoses by ~30% relative to placebo within 2–4 months in our heavily sun-damaged Australian patients. In these recent Phase 2 studies, numbers of new non-melanoma skin cancers were also significantly reduced in patients randomized to receive nicotinamide (15). Nicotinamide is a precursor of nicotinamide adenine dinucleotide (NAD+), a key coenzyme in cellular metabolism and energy production, and the sole substrate for the DNA repair enzyme poly-ADP-ribose polymerase (PARP) (16,17). Recently, we showed that nicotinamide prevents UV-induced cellular energy loss in human keratinocytes (18). DNA damage is a key trigger of photoinmunosuppression (19), and agents that enhance DNA repair, such as liposomal DNA repair enzymes, have been shown to reduce the immune suppressive effects of UV exposure (20). In this study, we present data showing that nicotinamide increases DNA excision repair activity in HaCaT human keratinocytes and enhances repair of CPDs and 8oxoG following exposure of human keratinocytes and ex vivo human skin to solar-simulated UV (ssUV; UVB + UVA). This enhancement of DNA repair may contribute to nicotinamide’s apparent immune protective and chemopreventive effects against skin cancer.

Materials and methods

HaCaT cells, ex vivo human skin, nicotinamide treatment and ssUV irradiation

The HaCaT human keratinocyte cell line was grown in Dulbecco’s modified Eagle’s medium (Invitrogen, Calsbad, CA) supplemented with 10% (vol/vol) fetal bovine serum (FBS) (Hyclone, Logan, UT). The concentration of FBS was reduced to 0.5% (vol/vol) 24 h before irradiation, in order to minimize the number of cells in replicative DNA synthesis (21). Three healthy volunteers who underwent abdominoplasty (n = 2) and breast reduction (n = 1) gave written informed consent prior to surgery for the use of their skin in the study (approved by the Human Ethics Committee of the University of Sydney according to Declaration of Helsinki principles). The skin was cut into 4 mm² pieces and incubated in RPMI 1640 medium (Invitrogen) supplemented with 10% (vol/vol) fetal bovine serum and 100 U/ml penicillin, 0.1 mg/ml streptomycin and 250 ng/ml amphotericin B (Invitrogen). Nicotinamide (Sigma–Aldrich, St Louis, MO) at a final concentration of 50 μM was added to the media and the cells and skin sections were incubated in their respective media for 24 h in a 37°C humidified atmosphere containing 5% CO₂. Semiconfluent cells (70%) and skin pieces were washed twice with phosphate-buffered saline and then irradiated in phosphate-buffered saline with 4 J/cm² ssUV using a 1000W xenon-arc Oriel solar simulator (Newport, Stratford, CT). The ssUV spectrum comprised 9.5% UVB and 90.5% UVA, closely matching the spectrum of natural sunlight (22). UV irradiance was measured before each irradiation using an IL-1700 broadband radiometer (International Light, Newburyport, MA) calibrated against the source with an OL-754 scanning spectroradiometer (Optronic Laboratories, Orlando, FL).

Unscheduled DNA synthesis

Following irradiation, HaCaT cells were further incubated for 45 min at 37°C in 10 μM of BrDU (BD Pharmingen, San Diego, CA) with or without 50 μM nicotinamide. The cells were fixed in cold methanol/glacial acetic acid (3:1) for 20 min at 4°C, washed with 100% ethanol and stored at -20°C.

Abbreviations: 8oxoG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; ANOVA, analysis of variance; ATP, adenosine triphosphate; BrDU, bromodeoxyuridine; CPDs, cyclobutane pyrimidine dimers; FBS, fetal bovine serum; hOGG1, 8-oxoguanine-DNA glycosylase 1; NAD+, nicotinamide adenine dinucleotide; NER, nucleotide excision repair; PARP, poly(ADP)-ribose polymerase; ssUV, solar-simulated UV; T4N5, T4-endonuclease V; UDS, unscheduled DNA synthesis; UV, ultraviolet.

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Nicotinamide and DNA repair

Nicotinamide stimulates unscheduled DNA repair, but not cell division, in HaCaT keratinocytes

HaCaT cells were pretreated with 50 μM nicotinamide for 24 h and then exposed to a single dose of 4 J/cm² ssUV. The cells were incubated with BrdU, a thymidine analogue that is incorporated into newly synthesized DNA strands at sites of excision of damaged DNA strands, and into newly synthesized DNA in dividing cells. BrdU was detected by immunofluorescent labeling with anti-BrdU antibody and alexa-fluor-594-conjugated secondary antibody (red fluorescence). Nuclei were visualized by counterstaining with 4′,6-diamidino-2-phenylindole (blue fluorescence). In contrast to uniformly BrdU-labeled nuclei in cells undergoing replicative S-phase scheduled DNA synthesis, unscheduled DNA synthesis (UDS) occurs in discrete foci throughout the nuclei (punctate nuclear pattern) (23) (Supplementary Figures S1 and S2, available at Carcinogenesis Online). As expected, ssUV increased the percentage of UDS nuclei (unirradiated (no UV), 6.9% vs UV-irradiated (UV), 20.5%; P = 0.0001) (Figure 1a) as it causes genetic damage, initiating DNA repair. Nicotinamide treatment alone did not cause DNA damage as indicated by a lack of effect on UDS. However, it stimulated a further significant increase in the percentage of UDS in ssUV-irradiated cells (UV, 20.5% versus UV + nicotinamide, 25.2%; P = 0.01), suggesting an enhancement of DNA repair.

There was no significant difference in the percentage of S-phase cells in any treatment group showing that this low dose of ssUV was not sufficient to cause cell cycle arrest and that nicotinamide did not affect cell division under these conditions (Figure 1b). The number of grains per nucleus, representing sites of excision repair in each individual cell (27) was also increased by ssUV (no UV, 46.3 grains/nucleus versus UV, 53.7 grains/nucleus; P = 0.0089) (Figure 1c). Nicotinamide further significantly increased the number of grains per nuclei (UV, 53.7 grains/nucleus versus UV + nicotinamide, 62.1 grains/nucleus; P = 0.049), consistent with nicotinamide increasing not only the number of cells undergoing repair of UV-induced DNA damage but also the rate of repair in each cell.

Low-dose ssUV and nicotinamide did not affect HaCaT cell viability

To determine whether the low dose of ssUV (4 J/cm²) used in these studies and incubation with 50 μM nicotinamide affected HaCaT cell survival, cell viability was assessed for 15, 45, 75, 105 and 135 min after ssUV irradiation. There were no differences in viability between groups treated with and without ssUV or nicotinamide at any time points after ssUV irradiation (repeated measures ANOVA). Viability exceeded 85% in all groups at all times (Supplementary Table S1, available at Carcinogenesis Online) indicating that this dose of ssUV was too low to cause substantial cell death and nicotinamide did not influence viability with or without ssUV.

Nicotinamide enhanced repair of CPDs and 8oxoG in HaCaT keratinocytes

Comet assays using T4-endonuclease V (T4N5) and hOGG1 DNA excision enzymes were used to detect CPDs and 8oxoG, respectively, in HaCaT cells. Following 24 h incubation with or without 50 μM nicotinamide, cells were exposed to 4 J/cm² ssUV. Immediately after irradiation, cells were further incubated with or without nicotinamide for 0, 30, 60, 90 and 120 min. Due to the 15 min additional time taken to detach the cells from culture plates, the comet assay time course was reported as 15, 45, 75, 105 and 135 min following irradiation. A T4N5 comet assay detected CPDs and abasic sites (apurinic or apyrimidinic sites), observed as increased comet length and fluorescence intensity (tail moment). Unirradiated cells with or without nicotinamide did not have a detectable tail moment (Supplementary Figure S3a, available at Carcinogenesis Online), consistent with the UDS data that nicotinamide alone did not cause DNA damage. Exposure to 4 J/cm² ssUV induced formation of T4N5-sensitive sites (CPDs and abasic sites). At 45 and 75 min, respectively, after irradiation, there were 19.9 and 38.6% relative reductions in T4N5-tail moment in UV + nicotinamide-treated cells compared with UV-treated cells (Figure 2a). Using repeated measures ANOVA to compare tail moment values over the repair time course, nicotinamide was found to significantly enhance the repair of CPDs (P = 0.0001), consistent with the UDS data on nicotinamide stimulation of DNA excision repair. A hOGG1 comet assay measured cleaved 8oxoG and DNA-containing formamidopyrimidine moieties. 8oxoG is a ubiquitous oxidative DNA damage formed by various endogenous and exogenous biochemical processes (28) and was therefore found as expected in unirradiated keratinocytes (Supplementary Figure S3b, available at Carcinogenesis Online and Figure 2b). 8oxoG was significantly increased by 4 J/cm² ssUV, detected at 15 and 45 min after irradiation. In UV-irradiated cells, a 45.6% relative reduction in 8oxoG at 45 min after irradiation was observed in cells pretreated with
Nicotinamide increased repair of DNA photolesions induced by 4 J/cm² ssUV in HaCaT keratinocyte cells as measured by comet assay. HaCaT cells were irradiated with 4 J/cm² ssUV (‘UV’), further incubated for various time points, and finally detached for quantification of detectable photolesions using comet assay. Fig. 2a and b) hOGG1 tail moments (tail length × fluorescent intensity) were measured in at least 50 cells in each treatment group using image analysis. Each time point tail moment represents mean ± SEM from three independent experiments. Nicotinamide (‘Nic’), significantly enhanced repair of both T4N5- and hOGG1-sensitive sites in irradiated HaCaT keratinocytes [P = 0.0001 (a) and P < 0.0001 (b), respectively; repeated measures ANOVA].

Nicotinamide enhanced repair of CPDs and 8oxoG in ex vivo human skin

Exposure of ex vivo skin to 4 J/cm² ssUV resulted in significant formation of CPDs and a significant increase in 8oxoG above baseline levels in the epidermis (Figure 3a and b). Nicotinamide alone did not increase levels of either CPDs or 8oxoG in unirradiated skin (repeated measures ANOVA) consistent with previous findings that it did not cause DNA damage. CPDs were first detected at 15 min after irradiation and nicotinamide pretreatment did not affect the initial formation of CPDs in the epidermis (Figure 4a). Nicotinamide caused 26.5 and 34.9% relative reductions in the number of epidermal cells containing detectable CPDs in irradiated HaCaT keratinocytes [P = 0.0001 (a) and P < 0.0001 (b), respectively; repeated measures ANOVA], showing that nicotinamide increased repair of this photolesion.

Nicotinamide enhanced repair of 8oxoG in irradiated keratinocytes

Nicotinamide significantly reduced the number of 8oxoG photolesions over the time course studied ([P < 0.0001; repeated measures ANOVA]), showing that nicotinamide increased repair of this photolesion. At 75 min after ssUV, most 8oxoG had been removed by excision repair. Nicotinamide significantly reduced the number of 8oxoG photolesions over the time course studied (P < 0.0001; repeated measures ANOVA), showing that nicotinamide increased repair of this photolesion.
Nicotinamide and DNA repair

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Nicotinamide enhancement of 8oxoG repair is not mediated by an increase in hOGG1 expression

We investigated whether nicotinamide influenced the expression of the 8oxoG repair enzyme, hOGG1 by protein staining. At 45 min after irradiation, there was no difference in hOGG1 expression in any groups (Supplementary Figures S4 and 5, available at Carcinogenesis Online), suggesting that enhancement of 8oxoG repair by nicotinamide is not due to increased levels of hOGG1.

Discussion

Using the UDS assay in irradiated HaCaT human keratinocytes, we demonstrated an increase in DNA excision repair in cells treated with nicotinamide. UDS is a direct measure of DNA excision repair, a pathway that not only repairs most forms of base damage but also DNA strand breaks and DNA cross links (29). Our ssUV radiation was delivered at a low dose, found to be suberythemal in our previous in vivo studies in humans, and equivalent to about 15 min exposure to noon spring sunlight in Sydney (13). This UV dose thus models routine daily sunlight exposure rather than high dose erythemal recreational exposure. We assessed cell viability after 4 J/cm² ssUV at various time points up to 135 min, the time over which DNA repair was assessed. Cell survival was not affected by the doses of nicotinamide and ssUV used in this study, consistent with our previous findings at similar UV doses (18). The ssUV dose used was too low to reduce cell viability or cause cell cycle arrest as shown by the lack of effect on cells entering division. Therefore, these issues of loss of UV damaged cells or arrest of cell division did not interfere with our assays for detection of DNA repair. This low-dose irradiation, however, resulted in an almost 3-fold increase in the proportion of the cells undergoing UDS within 45 min of irradiation, showing that it did damage DNA and initiate DNA repair. Treatment of HaCaT cells with 50 μM nicotinamide for 24 h before ssUV ('UV') significantly enhanced repair of both CPD and 8oxoG photolesions in human skin (mean ± SEM from three independent experiments; P = 0.0496 and P = 0.0023, respectively; repeated measures ANOVA).

Fig. 3. Nicotinamide reduced (a) CPDs and (b) 8oxoG in ex vivo human skin exposed to 4 J/cm² ssUV. After irradiation, ex vivo human skin pieces were further incubated at various time points and then sectioned and stained for CPDs and 8oxoG (red chromogen staining) by immunohistochemistry (bar = 200 μm).

Fig. 4. Nicotinamide enhanced repair of (a) CPDs and (b) 8oxoG in ex vivo human skin exposed to 4 J/cm² ssUV. Ex vivo skin was treated with 50 μM nicotinamide ('Nic') for 24 h before ssUV ('UV'). The skin was further incubated with nicotinamide for various time points before being snap-frozen for immunostaining. Determination of percentage epidermal cells positive for photolesions was performed using image analysis. Nicotinamide significantly enhanced repair of both CPD and 8oxoG photolesions in human skin (mean ± SEM from three independent experiments; P = 0.0496 and P = 0.0023, respectively; repeated measures ANOVA).

(P = 0.0023; repeated measures ANOVA), showing that nicotinamide also enhances repair of 8oxoG photolesions in human skin.

Nicotinamide enhancement of 8oxoG repair is not mediated by an increase in hOGG1 expression

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In human lymphocytes treated with UV radiation, 2 mM nicotinamide prevented lowering of NAD+ and stimulated a 2-fold increase in UDS compared with control cells treated with UV alone (30). Interestingly, nicotinamide has a more dramatic effect in stimulating UDS in irradiated lymphocytes derived from young mice, suggesting NAD+ level as a critical factor in regulating DNA repair in old mice (31).

Using HaCaT cells and ex vivo human skin, we also investigated the effect of nicotinamide on the two most commonly studied UV-induced DNA photolesions, CPDs and 8oxoG. A single dose of 4 J/cm² ssUV induced formation of CPDs and 8oxoG in both HaCaT cells and human epidermis. There was no reduction with nicotinamide in CPDs detected by either system or 8oxoG photolesions detected by the comet assay at 15 min after irradiation, indicating that nicotinamide did not reduce the formation of these photolesions. This excluded any UV filtering effect of nicotinamide, as we reported previously (13). In HaCaT cells, detectable T4N4 and hOGG1-sensitive sites reached maximum levels at 45 min post ssUV, with >80% of T4N5 and all hOGG1-sensitive sites repaired by 135 and 75 min, respectively. Repair was slower in whole human skin than in HaCaT cells, with a decrease of 60.9% in CPDs and 70.4% in 8oxoG from the maximum levels at 135 min after irradiation. Mouret et al. (32) similarly reported slower repair of DNA photoproducts in skin biopsies than in cultured primary human keratinocytes and fibroblasts. Delayed formation of CPDs and 8oxoG after UV, as observed in this study, has also been reported previously (33). Peak levels of detected photolesions using the comet assay technique were observed at 45 min after irradiation, probably reflecting changes in the targeted substrate, such as DNA relaxation and increasing accessibility in the context of repair (25,34). Others have observed similar repair time courses to our study for CPDs (25,35,36) and 8oxoG (25,37). Hence, the kinetics of formation and repair of these photolesions, which are likely to vary in different studies depending on UV dose and subsequent damage to repair processes, are similar to previous reported studies with similar UV doses to ours.

Although UDS measures the amount of DNA excision repair, its correlation with specific repair of DNA photolesions is not completely understood. Two enzyme systems were utilized in our in vitro comet assay studies, T4N5 which recognizes CPDs and abasic sites, and hOGG1 which cleaves 8oxoG and DNA-containing formamidopyrimidine moieties. Our data showed that nicotinamide enhances excision repair of both T4N5- and hOGG1-sensitive sites. This specificity issue with the enzymes was addressed, along with confirmation of repair enhancing capacity of nicotinamide in human skin rather than a cell line, by immunostaining of whole human skin with specific anti-thymine dimer (38) and anti-8oxoG monoclonal antibodies (39). Immunostaining of whole human skin also allowed localization of CPDs and 8oxoG photolesions in the epidermis and reduced the potential artefactual DNA damage induced during cell harvesting and lysis during DNA isolation in the comet assay. The use of normal human skin also demonstrates that nicotinamide enhances repair occurs in normal keratinocytes in their usual physiological and architectural relationship to other cells. The comet assay is, however, a better quantitative method than immunohistochemistry as used in whole human skin. The combination of the in vitro and ex vivo systems used in these studies gives confidence to our evidence that nicotinamide enhances repair of different UV-induced photolesions and therefore acts on a number of pathways.

It is unclear as to how nicotinamide stimulates an increase in at least two pathways of DNA excision repair after UV irradiation. However, nicotinamide is a primary precursor for the synthesis of NAD, NAD+ and NADP+ (40). NAD+, NADP+ and their reduced forms, NADH and NADPH, play major roles in cellular metabolism and energy production. Nicotinamide supplementation increases intracellular NAD+ (41) and ATP levels in HaCaT human keratinocytes (18). NAD+ is also utilized in ADP-ribosyl transferase reactions by three major classes of enzymes: poly(ADP-ribose) polymerases (PARPs), cADP-ribose synthases and sirtuins; thus, linking NAD+ metabolism to cellular processes involved in DNA-damage responses, control of gene expression, cellular homeostasis, cell death and aging (16). NAD+ is the sole substrate for the DNA repair enzyme PARP, and both NAD+ and PARP are essential for effective DNA repair, in particular during damage-excision steps (42).

NAD+ is an essential co-factor in glycolysis and NAD+ depletion inhibits glycolysis and in effect ATP production (43). We found previously that 4 J/cm² ssUV radiation caused significant intracellular ATP depletion within 2 h (18). DNA repair is highly energy dependent. Both nNER and double-strand break repair involves remodeling of the chromatin structure to allow access of DNA repair enzymes. This chromatin modification is highly ATP dependent (44). Our previous studies showed that 50 μM nicotinamide prevented ssUV-induced depletion of intracellular ATP and glycolytic blockade in HaCaT cells (18). It is likely that the nicotinamide stimulation of DNA excision repair shown in this study is mediated by its ability to prevent UV-induced ATP decline, making higher amounts of ATP available for DNA repair and other cellular processes. Hence, our study also highlights the importance of cellular energy in the DNA repair process.

We found that nicotinamide enhances DNA repair after UV radiation. This may be a key mechanism of nicotinamide’s demonstrated protective effects against photoinmunosuppression and skin carcinogenesis. Nicotinamide is non-toxic (45), inexpensive and already widely available. It is a promising agent for skin cancer chemoprevention. Phase 3 clinical trials of its effectiveness are now needed.

Supplementary material

Supplementary Figures S1–S4 and Table 1 can be found at http://carcin.oxfordjournals.org/

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References

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