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Impact on Epidermal Cells of Narrow Band UVB (311 nm) Irradiation

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Abstract: One of the most significant environmental risks affecting the skin is ultraviolet radiation (UVR). Chronic UVR exposure has been shown to cause immunosuppression, speed up skin aging, and increase the risk of developing skin cancer. However, UVR has been shown to be successful in treating a wide range of skin conditions, leading to the development of different phototherapy techniques. One of the most often used phototherapy devices today is narrow-band ultraviolet B (NB-UVB), which emits light with a peak at around 311 nm. It has been shown to be beneficial in treating a variety of skin conditions. Even though NB-UVB was created over thirty years ago, nothing is known about the precise mechanism of its therapeutic activity. Although the majority of NB-UVB effects have so far been linked to its impact on immune cells, the epidermis absorbs about 90% of NB-UVB radiation, and keratinocytes seem to play a significant role in mediating NB-UVB biological activity. Here, we have examined the available information about NB-UVB's effects on epidermal cells, with a focus on cell death and proliferation.

Keywords: cell death; epidermis; keratinocytes; NB-UVB; phototherapy

1. Introduction

One of the most significant environmental risks affecting the skin is ultraviolet radiation (UVR). Chronic UVR exposure has been shown to accelerate skin aging, cause systemic and local immunosuppression, and increase the risk of developing melanoma and non-melanoma skin malignancies [1,2]. Beginning with the absorption of UVR energy by endogenous chromophores, such as nuclear DNA, trans-urocanic acid, and components of cell membranes, a series of processes initiates the immunomodulatory capabilities of UVR [3]. Owing to very powerful photons, UVB more effectively alters the skin than UVA, resulting in numerous epigenetic consequences and carcinogenic DNA damage [2,4]. Single-stranded DNA breakage and intra-stranded DNA base-crosslinkings via the creation of cyclobutane pyrimidine dimers and 6-4 pyrimidine-pyrimidone photoproducts are examples of DNA alterations after UVB exposure [5,6]. Furthermore, since UVB produces reactive oxygen species, it may cause cell damage much as UVA.

Human skin has many defense mechanisms to reduce the harmful effects of UVR, such as cell-cycle arrest, DNA repair, and programmed cell death for circumstances in which DNA damage cannot be repaired [4,7–14]. Skin cancer growth and carcinogenesis may result from any of these pathways failing

UVR has been demonstrated to be useful in treating a variety of skin conditions, despite the risks noted above. Early in the 1980s, it was noted that UVB's favorable effects were mostly associated with wavelengths between 295 and 313 nm, with a range between 310 and 313 nm seeming to have the greatest safety profile [9,10]. Thus, a lamp that emits UVB irradiation with a peak at 311–312 nm (sometimes referred to as narrow-band ultraviolet B, or NB-UVB) and blocks out shorter, more hazardous wavelengths for photobiological reasons has been created. Plaque psoriasis, primary cutaneous T-cell lymphomas, atopic dermatitis, seborrheic dermatitis, pityriasis rubra pilaris, lichen planus, prurigo nodularis, uremic pruritus, and even vitiligo have all been shown to respond well to NB-UVB therapy

[11,12]. The combination of NB-UVB's therapeutic effectiveness and favorable safety profile with respect to acute adverse events has encouraged its usage from its inception. Concerns about long-term effects, however, have not yet been addressed [13,14].

Surprisingly, little is known about the precise mechanism of NB-UVB therapeutic activity; it's even uncertain if the systemic or local effects are more significant [12,15–18]. Although the majority of NB-UVB action has so far been ascribed to its impact on immune cells, the epidermis absorbs almost 90% of NB-UVB irradiation, and it is likely that keratinocytes, a significant cellular component of the epidermis, may also be impacted by NB-UVB to some extent and contribute to the phototherapy's therapeutic efficacy. Here, we have examined recent findings about NB-UVB's impact on epidermal cells, paying particular attention to cell division and death.

2. Narrow Band UVB (311 nm) and Keratinocyte Proliferation

Numerous investigations have shown that NB-UVB may cause apoptosis and suppress proliferation in human keratinocytes both in vitro and in vivo [19–25]. According to Luo et al. [21,23], a single low dosage of NB-UVB irradiation (dose below or equal to 100 mJ/cm2) combined with retinoids (acitretin or tazarotene) substantially reduces cell growth in vitro compared to treatment with these medications alone. According to the authors [21,23], heparin-binding epidermal growth factor-like growth factor (HB-EGF), which was up-regulated after both NB-UVB irradiation and retinoid therapy [21], may be at least partly responsible for this synergistic impact. In contrast to other members of the epidermal growth factor family, HB-EGF stimulates keratinocyte migration while slowing their proliferation, a characteristic that may be crucial for wound healing [26]. GATA3-mediated pathways may potentially be involved in the inhibition of cell proliferation that occurs following repeated NB-UVB therapy [27]. The six-nucleotide sequence (A/T)GATA(A/G) is bound by the transcription factor GATA3, which has two zinc finger motifs [28]. It is necessary for proper desquamation, epidermal differentiation control, and epidermal barrier development [29, 30]. Kallikrein 1 activation mediates the latter impact [30]. Patients with psoriasis, a chronic inflammatory skin condition marked by a high rate of keratinocyte proliferation, have been shown to have downregulated GATA3 [27]. GATA3 mRNA expression in psoriatic skin was raised by standard NB-UVB treatment to levels comparable to those in healthy controls, and the improvement of psoriasis was associated with the restoration of GATA3 expression [27]. Additionally, compared to the skin of control animals, NB-UVB-treated mouse skin with psoriasiform dermatitis had considerably fewer proliferative cells, enhanced epidermal differentiation, and lower epidermal thickness [27]. GATA3 downregulation was linked to lower expression of genes regulating epidermal differentiation, such as the transcription factor AP2-α (TFAP2A) and the apoptosis-inducing FAS ligand, as well as other transcription factors, such as the psoriasis susceptibility gene TNFAIP3 and the Notch ligand jagged 2, which both function as negative regulators of inflammation. Generally speaking, aberrant expression of genes related to cell differentiation, proliferation, and apoptosis was associated with decreased GATA3 expression in human psoriatic and GATA3-deficient mouse epidermis [27]. Crucially, NB-UVB therapy reversed these changes and improved psoriatic lesions in both clinical and histological ways [27]. Furthermore, psoriatic epidermis in vivo showed reduced levels of survivin, an anti-apoptotic protein, after multiple NB-UVB exposures, allowing epidermal cells to undergo apoptosis [31].

In the case of single NB-UVB irradiation, epidermal cell proliferation was shown to be inhibited in vivo with a dosage of at least 200 mJ/cm2 [21,22]. Higher dosages of NB-UVB seem to cause DNA damage that results in cell-cycle arrest, giving cells time to fix DNA mutations. Following a single NB-UVB treatment, the suppression of keratinocyte growth often lasted less than 48 hours [22]. However, keratinocytes (HaCaT cell line) showed signs of death if the treatment exceeded 400 mJ/cm2.

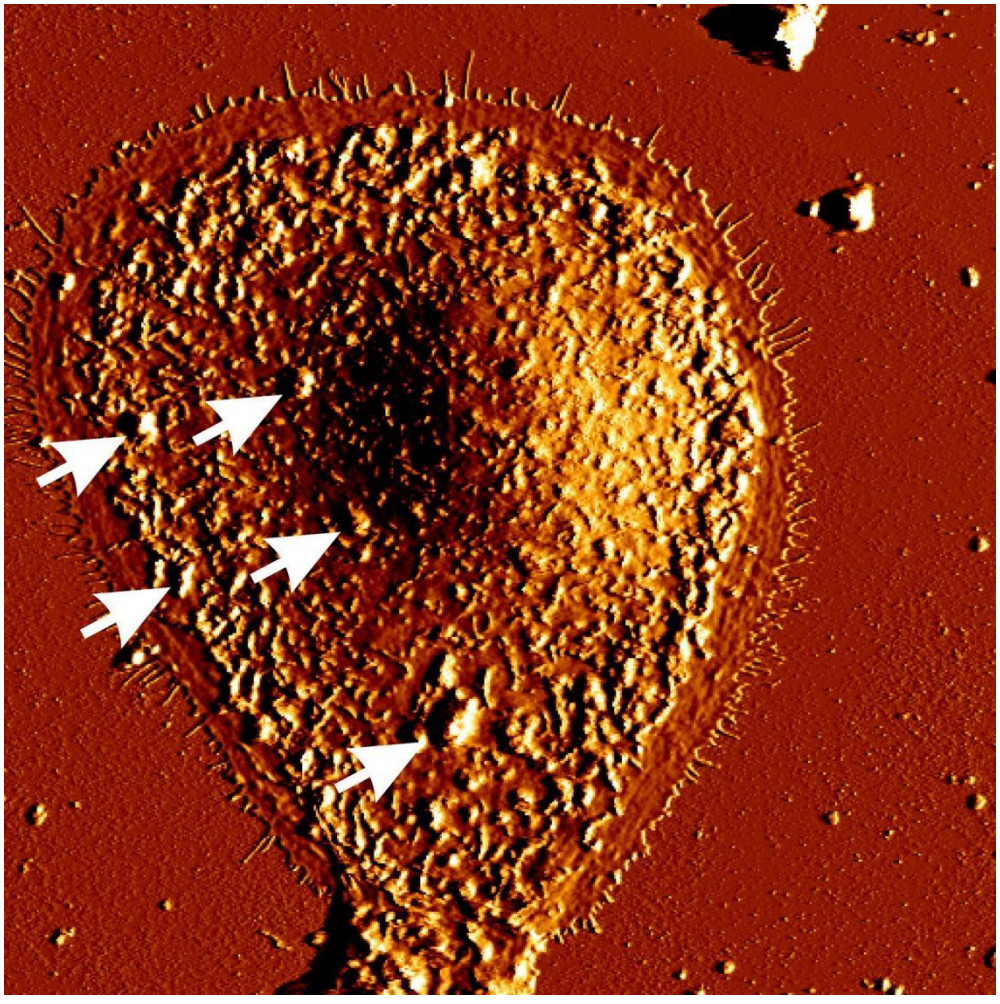
3. Narrow Band UVB (311 nm) and Apoptosis of Keratinocytes

Similar to broad-band UVB, NB-UVB may induce apoptosis in epidermal cells. However, five to ten times more dosage is needed to cause the same level of apoptosis and cell death as in the cells treated with broad-band UVB [19]. Schindl et al. [19] demonstrated that a dose of 2048 mJ/cm2 of NB-UVB was

necessary to achieve 50% to 60% of cells positive for propidium iodide, which identifies cells with the loss of membrane integrity that is typical of later stages of cell death, using a human squamous cell carcinoma-derived cell line. Nevertheless, depending on the cell types under study and the irradiation settings, a considerable amount of apoptosis was already seen at doses of around 800–1000 mJ/cm2 [20,22]. Crucially, the minimal erythema dose (MED) of NB-UVB observed by Gloor and Scherotzke [32] in Caucasian subjects is very similar to an apoptotic dose of NB-UVB. This suggests that UV-induced erythema may, in fact, be an inflammatory reaction to the appearance of "sunburn cells" (i.e., apoptotic cells) in native human

skin. In healthy individuals, p53 and p16 expression and apoptosis were both strongly induced by broad-band UVB and NB-UVB at identical MED dosages [33]. Aufiero et al. [20] shown that caspase 3 activation was a direct reaction to in vitro NB-UVB-mediated apoptosis. Keratinocyte apoptosis is a key indicator of NB-UVB's therapeutic effect in psoriasis, according to a recent research by Weatherhead et al. [34]. Apoptosis of lesional epidermal cells was shown to be greatly enhanced by NB-UVB irradiation, but not by similarly erythemogenic dosages of 290 nm [34]. The number of apoptotic cells peaked at 16–24 hours. They were found in the suprabasal and basal layers of the epidermis. Additionally, a computational model of psoriatic epidermis showed that inducing keratinocyte apoptosis (but not inhibiting keratinocyte proliferation) in psoriatic lesions is sufficient to explain the clearance of psoriatic plaques within the clinical timeframes observed during NB-UVB therapy [34, 35]. It was also shown that apoptosis occurs in vivo during routine clinical therapy with NB-UVB. This research suggests that the primary target of NB-UVB therapeutic effectiveness is, in fact, keratinocytes.

Figure 1. Morphology of a single keratinocyte 48 h after irradiation with 800 mJ/cm^2 of narrow-band UVB showing numerous bleb-like protrusions on the cell surface (arrows) (AFM micrograph, retrace deflection image, image size: 85 × 85 µm)



Irradiation with apoptosis-inducing NB-UVB doses strongly altered cultured keratinocyte morphology, both on the cell surfaces as well as intracellulary. NB-UVB irradiation led to disintegration of nuclear and cell membranes as well as to severe cytoplasmic vacuolization [20,22]. Using atomic force microscopy (AFM) which enables to study cell morphology at a high resolution in the physiologically relevant, aqueous environment it was shown that one of the most prominent morphological alterations on surfaces of NB-UVB irradiated cells was the formation of irregularly distributed, bleb-like protrusions (Figure 1) [22]. Similar structures were observed by other authors on the keratinocytes irradiated with broad band UVB, but not with UVA, and were found to contain nuclear ribonucleoproteins [36–39]. They were also shown to contain nuclear antigens recognized by antinuclear antibodies like Ro/SS-A or La/SS-B from patients suffering from lupus erythematosus, a common autoimmune multi-organ disease [24,39]. These observations further supported the damage of cell nucleus by NB-UVB irradiation and underlined a possible explanation of photosensitivity in patients with autoimmune connective tissue disorders having antinuclear antibodies. NB-UVB irradiation also provoked significant rearrangement of the cytoskeleton, causing thinning of microfilaments and their redistribution to the cell periphery [22].

Disruption of cellular membranes of cultured cells upon NB-UVB irradiation was accompanied by significant changes in the cellular lipid content [25]. Irradiation with NB-UVB resulted in the increased production of ceramides—*i.e.*, lipid species which are considered to be signal transducers of a variety of cell stressors, including reactive oxygen species, cytokines, exposure to chemotherapeutic agents, irradiation or exogenous lipopolysaccharides [40]. Increased ceramide level was able to provoked cell cycle arrest and/or apoptosis in a variety of cell types [40], suggesting that overproduction of ceramides after NB-UVB exposure may be another mechanism of apoptosis induction in heavily irradiated cells. Interestingly, the content of some PC- and PE-ethers (1-alkyl,2-acylglycerophosphocholines and 1-alkyl,2-acylglycerophosphoethanolamines) also increased in irradiated cells [25]. Although their role in response to irradiation remains unclear, it is likely that they were also associated with ongoing apoptosis, as they changed similarly to ceramides. Their highest level was achieved 12 h post irradiation and dropped later down to the baseline concentration. It seems probable that formation of PC- and PE-ethers might be a consequence of lipid peroxidation caused by NB-UVB irradiation and these lipid species might be toxic for epidermal cells as it was previously reported that synthetic ether phospholipids (e.g., 1 *O*-octadecyl-2-Omethyl-rac-glycero-3-phosphocholine) were able to induce apoptosis in a number of cell lines [41,42]. In addition, cells irradiated with 800 mJ/cm^2 of NB-UVB were found to accumulate triacylglycerols (TAG), which peaked at the later stages of apoptosis [25]. Several previous studies also reported accumulation of TAGs in various cell types upon different apoptotic stimuli [43–48]. This was observed in cells stimulated by free fatty acids and FAS pathway activation. Increased TAG content is a widely recognized apoptosis marker, unrelated to the factors inducing this process. Al-Saffar *et al.* [44] suggested that TAG accumulation in Jurkat T cells might be a result of altered PC metabolism. It was found that PC biosynthesis was inhibited during apoptosis at the level of cytidine diphosphate-choline: 1,2-DAG choline phosphotransferase and that the accumulation of PC substrates activated TAG production [44,49,50]. It was speculated that TAG accumulation in non-adipose cells might constitute a protective mechanism against apoptosis, due to increased ability to incorporate free fatty acids into TAGs, a phenomenon which decreases the apoptosis ratio. In addition, the magnitude of TAG accumulation correlates with cell survival upon

exposure to palmitate [45,47]. However, the exact mechanism remains controversial, as other authors suggested that TAG accumulation enhanced ceramide synthesis and reactive oxygen species production, eventually causing cell death [51,52]. In conclusion, NB-UVB altered the lipidome of keratinocytes in a pattern of changes consisting with unfolding apoptosis. It is still unclear, whether these observations have clinical relevance, however, one may speculate that increased synthesis of ceramides and TAGs after NB-UVB irradiation in apoptosis-undergoing cells may help in restoration of abnormal epidermal lipid composition in patients suffering from atopic dermatitis or psoriasis, an idea which has been already suggested by Wefers *et al.* [53]. Despite single NB-UVB irradiation increased ceramide content in epidermis for a short time only, it seems probable that repetitive therapy with NB-UVB, as it is usually applied, may lead to durable increase of ceramides and TAGs in the skin. Therefore, this unwanted effect from the point of view of single cells might be beneficial for patients suffering from certain skin disorders.

4. Narrow Band UVB (311 nm) Action on Other Cell Types

NB-UVB is also able to induce apoptosis of skin cells other than keratinocytes. Lymphocytes seems to be more sensitive to NB-UVB irradiation as compared to keratinocytes, as slightly lower doses were required to induce apoptosis of former cells [20]. It was also shown that NB-UVB evoked apoptosis in T lymphocytes infiltrating epidermis more efficiently than broad band UVB [54]. Besides inducing apoptosis, NB-UVB treatment lowered production of proinflammatory cytokines such as IL-1α, IL-2, IL-5 and IL-6, whereas the synthesis of anti-inflammatory IL-10 was significantly augmented [55]. Furthermore, NB-UVB also decreased number of epidermal Langerhans cells from 4 h up to 48 h post irradiation and multiple exposures of NB-UVB reduced the density of Langerhans cells in epidermis by about 20% [33,56]. However, the reduction of the density and function of Langerhans cells in the skin and their migration to the draining lymph node upon NB-UVB irradiation was less pronounced than after broad-band UVB exposure [57]. On the other hand, NB-UVB evoked greater depletion of T lymphocytes in psoriatic plaques than broad-band UVB [58]. Due to the depth of NB-UVB penetration [59], these observations mostly apply for immune cells present in the epidermis and papillary dermis.

NB-UVB also acts on the epidermal pigment cells. NB-UVB remains a gold standard in the treatment of vitiligo, an immune-driven disease with loss of melanocytes [60]. It was shown, that NB-UVB irradiation with a dose of 25 mJ/cm^2 increased proliferation rate of NCCmelan5 cells, a melanoblast cell line [61]. Interestingly, other study did not show a direct stimulatory effect of NB-UVB on melanocyte growth, a difference that could be explained by different cell line (*i.e.*, cultured primary human melanocytes) studied [62]. However, the melanocyte proliferation was stimulated by supernatant of NB-UVB irradiated keratinocytes, an effect that seems to be mediated via endothelin-1 [62]. On the other hand, NB-UVB directly increased the melanocyte migration [62]. NB-UVB was also shown to directly stimulate hair follicle-derived neural crest stem cells to differentiate into melanocyte lineage. NB-UVB enhanced the mobility of NCCmelan5 cells via upregulation of pp125FAK (a protein known to be involved in cell mobility after phosphorylation) as well as increased melanin formation and tyrosinase expression [61,63]. Remarkably, irradiation with higher NB-UVB dose (50 mJ/cm^2) decreased the viability of NCCmelan5 cells by about 30% [61].

5. Conclusions

In conclusion, NB-UVB may cause apoptosis in a variety of cell types and suppress cell growth. Its therapeutic impact in conditions like psoriasis that have a high rate of proliferation may be due to this action. However, the activation of apoptosis with NB-UVB irradiation may result in nuclear antigens being expressed on the surface, which may further exacerbate autoimmune connective tissue illnesses caused by antinuclear antibodies. Although fresh information on NB-UVB's mode of action has emerged in the last ten years, the precise mechanism behind its therapeutic effectiveness is still unclear. For example, it is unclear why some psoriasis patients react to NB-UVB treatment while others do not exhibit any discernible improvement. Additionally, it's still unclear which cells—keratinocytes, lymphocytes, or even Langerhans cells—are the main targets of NB-UVB activity. It's also unclear whether NB-UVB may have a systemic immunomodulatory impact or if it simply affects the irradiated skin region. Furthermore, the majority of research on the NB-UVB mechanism to far has focused mostly on psoriasis; however, these findings may not accurately represent the NB-UVB action in other conditions that NB-UVB is effective in treating. Thus, further research is required to fully comprehend the biological action of NB-UVB irradiation.

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