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Advancing Skin Cancer Prevention: Nicotinamide and DNA Repair Enzymes

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Abstract

Historically, the public has looked to sunscreen as the primary method for prevention of skin cancer. However, fortunately there have been advancements in chemopreventative care for both precancerous lesion progression of Actinic Keratoses (AKs) and Non-Melanoma Skin Cancers (NMSCs) that have potential to be more patient-friendly for consistent at home use. These measures can be adjunctive therapies to daily broad-spectrum sunscreen or as well as in office procedures. As a whole, the advantage of these newer therapeutics is that they have dual mechanisms of action in that they promote repair of past damage and prevent future

incidence of NMSCs by 23% over the 12-month survey period, with a specific decrease in basal cell carcinomas in squamous cell carcinoma by 20% and 30%respectively [3]. This effect was more pronounced in those participants who had a higher number of prior NMSCs at baseline. Additionally, their study found an overall decrease in the incidence of AKs over the course of the survey period. The mechanism by which nicotinamide is able to exert these anti-neoplastic effects is through prevention of ATP depletion and promotion of DNA repair in cells that have been damaged by UV rays [3]. Ultraviolet Radiation (UVR) also leads to immunosuppression in the cell secondary to DNA damage. These beneficial effects did not last after treatment was discontinued, which could be slightly disheartening to some patients [3]. Yet, the positive effects while taking the medication are undeniable.

Another exciting chemopreventive class of agents are DNA repair enzymes. They hold particular appeal because they are typically used in topical formulation. When applied to the skin, T4 endonuclease (T4N5), a bacterial DNA repair enzyme, can penetrate the stratum corneum and repair DNA by removing Cyclobutane Pyrimidine Dimers (CPDs) that are introduced into cells by photo damage [2]. The safety and efficacy of topical T4N5 is well established, with studies dating back to 19754. In a 2001 study investigating chemoprevention with topical T4N5 in Xeroderma Pigmentosum patients, the rate of new AK formation decreased by 68%, and the rate of BCC development decreased by 30% when compared to placebo [4]. Unlike many chemopreventive therapies, treatment with T4N5 produced lasting positive effects in these high-risk patients even after the treatment was discontinued [4].

An additional enzyme that is involved with DNA repair process is photolyase, another bacterial repair enzyme that, similar to T4N5, targets CPDs that result from UV radiation of cells [2-5]. A 2013 pilot study examined its photo-protective effects featured three treatment groups-those who used sunscreen alone, those who used sunscreen and topical endonuclease post-radiation, and those who used sunscreen with photolyase and topical endonuclease post radiation [6]. This study focused on telomere shortening and excessive c-FOS expression as endpoints as measures of UV damage. Both have been implicated in carcinogenesis process for NMSCs [6]. While un-enhanced sunscreen +T4N5 group displayed mildly lessened telomere shortening and cFOS expression, the photolyase enriched-sunscreen +T4N5 group produced superior results-the longest telomere length and lowest cFOS expression post-irradiation [6].

Researchers posited that since the T4N5 was applied after UV exposure it was a contributor to chemoprevention and could be used at any point after sun exposure and still exert the DNA repair effects [6]. Carducci, et al. built upon this work by investigating the efficacy of sunscreen alone followed by T4N5 application versus a combination product of sunscreen with T4N5 and endonuclease. Their outcomes were in line with the Emanuele, et al. study, confirming that sunscreen with added DNA repair enzymes can significantly prevent progression of precancerous to cancerous lesions (AKs to SCC)[7]. In this study, UV damage was quantified with field cancerization imaging, presence of hyperkeratosis, and amount of CPDs (known target of both T4N5 and photolyase) [7]. In addition to these enzymes, other studies have also included 8-oxoguanine glycosylase 1, an enzyme that reduces the oxidative stress in DNA.

When a topical medication containing T4N5, photolyase, and OGG1 was applied to the skin, it was shown to decrease signs of UV damage (CPDs and expression of p53) [8,9].

Conclusion

As demonstrated by the studies, some of the genetic targets that contribute to photo-carcinogenesis in the skin have been established. With targeted therapies such as T4N5, photolyase, and OGG1 available to complement traditional prevention methods like sunscreen, there is a greater potential to both actively prevent and reverse malignant changes within the skin. Looking forward, DNA repair enzymes seem to be the future standard of comprehensive UV radiation protection. Researchers are constantly searching for new genetic targets to prevent and further delay the progression of cancerous lesions. New discoveries in this arena already show promise. A recent 2023 article investigating acute UVB associated changes in the skin identified multiple new gene families that show acute up or down-regulation following UV exposure, indicating there are many more potential targets for novel therapeutics as well.

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