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Reduced ultraviolet-induced DNA damage and apoptosis in human skin with topical application of a photolyase-containing DNA repair enzyme cream: Clues to skin cancer prevention

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Abstract. The exposure of human skin to ultraviolet radia- tion (UVR) results in the formation of DNA photolesions that give rise to photoaging, mutations, cell death and the onset of carcinogenic events. Photolyase (EC 4.1.99.3) is a DNA repair enzyme that reverses damage caused by exposure to UVR. We sought to investigate whether addition of photolyase enhances the protection provided by a traditional sunscreen (SS), by reducing the *in vivo* formation of cyclobutane-type pyrimidine dimers (CPDs) and UVR-induced apoptosis in human skin. Ten volunteers (Fitzpatrick skin type II) were exposed to solar-simulated (ss) UVR at a three times minimal erythema dose for 4 consecutive days. Thirty minutes prior to each exposure, the test materials [vehicle, SS (sun protection factor 50) alone, and SS plus photolyase from *Anacystis nidulans*] were applied topically to three different sites. One additional site was left untreated and one received ssUVR only. Biopsy specimens were taken 72 h after the last irradiation. The amount of CPDs and the extent of apoptosis were measured by ELISA. Photolyase plus SS was superior to SS alone in reducing both the formation of CPDs and apoptotic cell death (both $P<0.001$). In conclusion, the addition of photolyase to a traditional SS contributes signi cantly to the prevention of UVR-induced DNA damage and apoptosis when applied topi- cally to human skin.

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REVIEW

Six critical questions for DNA repair enzymes in skincare products: a review in dialog

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Clinical, Cosmetic and Investigational Dermatology

Abstract: Concerns over existing sunscreen filters have reinforced the need to examine supplemental sun protection or repair of sun damage. Technology to enhance DNA repair has been available in

skincare and sunscreen products for several decades, but skepticism and lack of familiarity with the supporting data remain prevalent. Here, we address six of the main questions raised by medical professionals regarding the efficacy of DNA repair enzymes in sun protection. These include the mode of delivery and mechanism of action, the effect on cellular responses and the amelioration of pre-cancers, cancers and photoaging. The conclusions are that topical DNA repair enzymes do enhance removal of DNA damage and reduce the appearance of new actinic keratoses as well as increase regression of existing lesions. Support for prevention of photoaging and skin cancer is significant but could be strengthened or disproven with additional research. Keywords: DNA repair, skin cancer, T4 endonuclease V, photolyase, UV endonuclease, actinic keratosis

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REVIEW

New Vision in Photoprotection and Photorepair

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ABSTRACT

Chronic exposure to solar radiation is associated with an increased incidence of skin cancer worldwide and more specifically with non-me- lanoma skin cancers and actinic keratosis. At the cellular level DNA damage is the main event following ultraviolet (UV) exposure. The kind of lesions produced depends on the wavelength and the energy profile of the radiation, with different photoproducts being formed as a result. Although endogenous DNA repair mechanisms are somewhat effective in repairing DNA, some DNA damage persists and can accumulate with chronic exposure. UV protec- tion strategies, such as sunscreen use, are important in limiting further DNA damage. Several published studies have demonstrated the protective effect that regular use of sun- screen can have against the development of skin cancers. Newer options that aim to help repair damaged DNA may have an important role in reducing the incidence of chronic sun exposure-related photoaging and non-me-lanoma skin cancers. Photolyase, which is cap- able of repairing cyclobutane dimers formed as a result of DNA irradiation, is one such novel ingredient. In the first part of this paper we review the rationale for a combined treatment approach of photoprotection and photorepair with photolyase. In the second part we evaluate several published clinical studies, which suggest a beneficial effect in preventing new skin lesions in photodamaged skin. A strategy of photoprotection plus photorepair appears to be relevant for all persons with a high level of solar exposure and those at a higher risk for devel- oping skin cancers.

Mechanisms of DNA Repair by Photolyase and Excision Nuclease

Nobel Lecture, December 8, 2015

by Aziz Sancar

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Summary

e ultraviolet (UV) wavelengths in sunlight damage DNA by converting two adjacent thymines into a thymine dimer (T<>T) which is potentially mutagenic, carcinogenic, or lethal to the organism (Fig. 1). is damage is repaired by pho- tolyase in *E. coli* and by the nucleotide excision repair system in *E. coli* and in humans. In this lecture I will present our work on photolyase and nucleotide excision repair, and I will conclude my talk by describing how our research on photolyase led to the discovery of an essential circadian clock protein, called cryptochrome, that links these two research subjects to one another and thus completes the circle.

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Photolyase: Dynamics and Mechanisms of Repair of Sun-Induced DNA Damage

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Abstract

Photolyase, a photomachine discovered half a century ago for repair of sun-induced DNA damage of cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts (6-4PPs), has been characterized extensively in biochemistry (function), structure and dynamics since 1980s. The molecular mechanism and repair photocycle have been revealed at the most fundamental level. Using femtosecond spectroscopy, we have mapped out the entire dynamical evolution and determined all actual timescales of the catalytic processes. Here, we review our recent efforts in studies of the dynamics of DNA repair by photolyases. The repair of CPDs in three life kingdoms includes seven

electron-transfer (ET) reactions among ten elementary steps through initial bifurcating ET pathways, a direct tunneling route and a two-step hopping path both through an intervening adenine from the cofactor to CPD, with a conserved folded structure at the active site. The repair of 6-4PPs is challenging and requires similar ET reactions and a new cyclic proton transfer with a conserved histidine residue at the active site of (6-4) photolyases. Finally, we also summarize our efforts on multiple intraprotein ET of photolyases in different redox states and such mechanistic studies are critical to the functional mechanism of homologous cryptochromes of blue-light photoreceptors.

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Fluorescently-labelled CPD and 6-4PP photolyases: new tools for live- cell DNA damage quantification and laser-assisted repair

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The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors. Received 2018 Jun 22; Revised 2018 Nov 29; Accepted 2019 Jan 15.

ABSTRACT

UV light induces cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone (6-4) photoproducts (6-4PPs), which can result in carcinogenesis and aging, if not properly repaired by nucleotide excision repair (NER). Assays to determine DNA damage load and repair rates are invaluable tools for fundamental and clinical NER research. However, most current assays to quantify DNA damage and repair cannot be performed in real time. To overcome this limitation, we made use of the damage recognition characteristics of CPD and 6-4PP photolyases (PLs). Fluorescently-tagged PLs efficiently recognize UV-induced DNA damage without blocking NER activity, and therefore can be used as sensitive live-cell damage sensors. Importantly, FRAP-based assays showed that PLs bind to damaged DNA in a highly sensitive and dose-dependent manner, and can be used to quantify DNA

damage load and to determine repair kinetics in real time. Additionally, PLs can instantly reverse DNA damage by 405 nm laser-assisted photo-reactivation during live-cell imaging, opening new possibilities to study lesion-specific NER dynamics and cellular responses to damage removal. Our results show that fluorescently-tagged PLs can be used as a versatile tool to sense, quantify and repair DNA damage, and to study NER kinetics and UV-induced DNA damage response in living cells.

Understanding the Role of Photolyases: Photoprotection and Beyond

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ORIGINAL ARTICLE

The limitations of photoprotection modalities have been the inability to arrest the progression of photodamage. Chemoprevention strategies involving a sunscreen has been incomplete because of the need to induce sustained repair of mutations and slow carcino- genesis. Photolyases, or photoreactivation enzymes, serve the role of repairing mutations and damage to DNA induced by ultraviolet (UV) radiation and therefore in uence the initiation phases of carcinogenesis. As these enzymes are absent in humans, exogenous forms have been manufactured and are now utilized in topical agents to supplement and augment the innate repair mechanisms that are mostly inef cient.

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