

About the Authors

Daniel B. Yarosh, PhD, *Independent Technology Advisor*

Daniel B. Yarosh, PhD., is an independent advisor in cosmetics, beauty, dermatology, pharmaceuticals, biotechnology, and neuromarketing. He was the chief technology advisor and senior vice president, Basic Science Research, Estee Lauder Co., and was responsible for the company's worldwide basic research. Dr. Yarosh also served on the Board of Directors of Aceto Corp., a specialty chemical and generic drug company headquartered in Port Washington, NY.



Dr. Yarosh received his BA degree in biology from Macalester College, St. Paul, Minnesota, in 1976, and his doctorate in molecular biology from the University of Arizona College of Medicine in 1978. He served as a National Science Foundation fellow at Brookhaven National Laboratory, Upton, New York, and then a staff fellow and cancer expert at the National Cancer Institute of the National Institutes of Health, Bethesda, Maryland. In 1985, Dr. Yarosh founded the biotechnology company AGI Dermatics, with an emphasis on the commercial application of DNA repair. He is the inventor of Dimericine® (T4N5 liposome lotion), which is a liposomal DNA repair enzyme for the prevention of skin cancer. AGI Dermatics also supplied ingredients to many major worldwide cosmetic and personal care companies. In 2006, the company launched its own Remergent® brand of skincare products, including sunscreens and prescription drugs. In 2008, AGI Dermatics was acquired by Estee Lauder Co.

Dr. Yarosh is the author of more than 140 scientific articles and two dozen patents. He has been an active participant in the dermatology and New York biotechnology communities. In 2004, the International Union of Photobiology presented Dr. Yarosh with the Finsen Award, which is granted every 4 years at the International Congress for Photobiology for breakthrough research in the photobiology sciences. He was honored by the American Cancer Society, Nassau County, for his professional service in 2008. His book *The New Science of Perfect Skin*, about skincare technology in the cosmetic marketplace, was published by Random House in May 2008. Dr. Yarosh researches and writes about the evolutionary biology of beauty and neuromarketing on his website www.danyarosh.com.

Angela Tewari, *NHS Dermatology*

Consultant Angela Tewari is an NHS dermatology consultant at the prestigious King's College Hospital in London seeing a wide breadth of complex clinical adult and pediatric dermatology and performing skin surgery. Angela completed her dermatology training in London, presenting her clinical work at a number of national and international meetings, and won a number of prizes. Before this, she was awarded a competitive Medical Research Council (MRC)/British Association of Dermatology (BAD)/British Skin Foundation (BSF) fellowship to complete a PhD looking at the effects of UVA1 in sunshine and how it causes cellular and molecular damage in the skin. In particular, she examined for the presence of DNA damage markers—cyclobutane pyrimidine dimers (CPDs)—and showed that they are produced after UVA1 albeit much less than UVB and have a predilection for the basal epidermis. She has published her work in a number of high-impact journals including the *Journal of Investigative Dermatology*, and she has a small BSF grant to pursue further research into the effects of ultraviolet radiation on the skin.



Importance of DNA Repair: Recent Advances

DANIEL B. YAROSH and ANGELA TEWARI, *Daniel B. Yarosh, Inc., Merrick, NY (D.B.Y.), Department of Dermatology, Kings College Hospital, NHS Foundation Trust, London SE1 9RT, United Kingdom (A.T.)*

Synopsis

Our defense against solar ultraviolet (UV) damage to skin comprises endogenous mechanisms of DNA repair and pigmentation, and exogenous application of light-absorbing and reflecting sunscreens. Our most important endogenous defense, DNA repair, has been the focus of molecular and clinical research, and recent advances are summarized here. The approach of using microbial DNA repair enzymes to augment the natural DNA repair capacity of skin has gained acceptance in many commercial products, and clinical studies have supported their benefits.

INTRODUCTION

DNA repair is the most important endogenous protection against sunlight damage to skin. A deficiency in DNA repair causes the genetic disease xeroderma pigmentosum (XP) classic form, wherein one of seven genes is disabled by mutation, resulting in extreme sun sensitivity, skin cancer, and premature death (1). The symptoms of XP are as severe in people of color as in light-skinned patients, demonstrating that efficient DNA repair capacity is more important in providing protection from ultraviolet (UV)-induced precancerous cutaneous changes than is melanin pigmentation (1). Even the heavy melanin content of black skin affords a protection of only 20- to 60-fold against skin cancer (2), whereas XP patients younger than 20 years have a 10,000-fold increased risk of non-melanoma skin cancer and a 2,000-fold increased risk of melanoma (1).

Chemical and physical sunscreens are the most important exogenous systems of photoprotection. Despite their intrinsic ability to block DNA damage (3), sunscreens are often used at a fraction of the recommended application dose (4). The potential for systemic absorption and environmental damage (5) has led to a search for alternatives, and increasing the endogenous DNA repair system is an attractive goal.

Here, we will highlight recent advances in understanding DNA repair protection against solar radiation and review the support for the use of exogenous DNA repair enzymes for photoprotection.

Address all correspondence to Daniel B. Yarosh at dyarosh@danyarosh.com.

DNA DAMAGE

Sunlight, primarily the shorter wavelengths in the UV range, are absorbed by the DNA in living skin cells, producing a variety of direct chemical modifications as well as modifications by reactive molecules secondarily produced by sunlight (recently reviewed in ref. 6). The most common form is the cyclobutane pyrimidine dimer (CPD, fusion of adjacent DNA bases) followed by the (6-4) photoproduct (6-4PP, also a fusion of DNA bases) and oxidation of the DNA base guanine producing 8-oxo-guanine (8oGua). On a macroscopic level, the occurrence of CPDs is randomly distributed along the genome at dipyrimidine sites, but closer examination has revealed that nucleosomes influence DNA damage formation and repair (7), and hotspots adjacent to certain transcription-binding sites preferentially accumulate DNA damage.(8) Telomeres, the special tips of chromosomes, are especially susceptible to damage due to the high density of dipyrimidines (9). Long wave ultraviolet A (UVA) (UVA1 340–400 nm) produces CPD with a predilection for the basal epidermis where the actively dividing stem cells reside, and thus broad band photoprotection is important for reducing the DNA damage burden (10).

The predominant mutation in keratinocyte tumors is the ultraviolet radiation (UVR) signature mutation (11,12), and the CPD is of particular trepidation for skin health, as not only does its formation triggers erythema and the sunburn reaction (13) but also immune suppression that allows the outgrowth of skin tumors (14). Sunscreens are less efficient in preventing immunosuppression than blocking erythema, perhaps because only small amounts of the CPD are able to initiate it (15).

Recent research highlights the role of UVA in melanoma development, including DNA damage in melanocytes and inhibition of DNA repair (16). Of particular interest is a study showing that melanin by-products absorb UVA and continue to form CPDs even in the absence of UVA (17). Thus, pigmentation not only protects skin from UV damage but may, in some cases, also foster it. Pigmentation occurs after UV-induced stimulation of α -melanin stimulating hormone production which then binds to melanocortin 1 receptor, promoting tyrosinase activity and melanin formation, and may also stimulate DNA repair (16). On the other hand, another melanocyte-specific transcription regulator was shown to turn up pigmentation and turn down DNA repair, and *vice versa*, in a counterbalancing system (18).

DNA REPAIR

The broad outlines of nucleotide excision repair (NER) of UV-induced DNA damage were recently reviewed (19,20) A complex of proteins, many also involved in gene transcription, identify distortions in DNA produced by photoproducts, and phosphorylation of the xeroderma pigmentosum group C protein within this complex recruits the rest of the NER proteins to the damaged site (21). A length of single-stranded DNA containing the lesion is excised, and the opposite intact strand serves as a template to fill in the gap. When DNA replication uses a damaged template, an error-prone polymerase enables replication across the lesion, at the cost of somatic mutations, but with an overall reduction in skin cancer incidence (22).

Whereas the entire genome is surveilled for damage by a global repair system, (23) a special system of transcription-coupled repair focuses repair complexes at transcription sites (24,25). This interactive relationship between NER and gene expression was recently

reviewed (26). The physical relationship between transcription factor transcription factor IIH and the NER factor xeroderma pigmentosum group A was visualized, which explains how transcription factors are recruited to NER complexes (27). The complexity of repairing DNA bound in nucleosomes and chromatin (7) is solved by the binding of UV-DNA damage-binding protein to UV-damaged nucleosomes and the shifting of nucleosome structure to expose DNA damage (28).

An added complexity is the ability of cellular signaling pathways, such as those regulated by cytokines, to modify NER according to the state of the cell, organ, or body (29). Circadian rhythm and the molecular clock affect DNA repair and related responses such as pigmentation (30). One consequence of these DNA repair oversight functions is that low, chronic doses increase expression of DNA repair proteins and result in increased repair of CPD but not (6–4) PP (31).

Recruitment of DNA repair complexes to damaged sites starts in 1 h and peaks at 6 h (32). (6–4) PP are repaired much faster than the CPD because of their more efficient recognition and base flipping by XPC–Rad4 protein complex (33). Most cellular responses peak at around 6 h while inflammation, and antigen-specific immune suppression signals crest at 24 h. Overall, the half-life of CPDs in the human skin is about 11 h when the system is within its capacity (35), but it becomes saturated just at UV doses that produce a sunburn (36).

ENHANCING DNA REPAIR

The DNA repair capacity of the skin can be enhanced by delivering DNA repair enzymes. The first patent for a commercial method, using phospholipid liposomes encapsulating enzymes to deliver to skin, was granted in 1991 (37) and enables the delivery of a number of enzymes from a variety of microbial sources, including photolyase from *Anacystis nidulans*, UV endonuclease from *Micrococcus luteus*, bacteriophage T4 endonuclease V, and 8oGua glycosylase 1 from *Arabidopsis thaliana*. Recently, others have encapsulated the UV DNA damage endonuclease from yeast and the pyrimidine dimer glycosylase from *Paramecium bursaria chlorella virus-1* (38). In each case, the liposome–enzyme composition increased the repair of UV-induced DNA damage.

Today, more than 75 skincare products are available that contain DNA repair enzymes, and dozens of clinical studies have reported prevention and enhanced regression of actinic keratosis, nonmelanoma skin cancers, and photoaging (reviewed in ref. 39,40). Indeed, adding DNA repair enzymes to sunscreens provides additive protection (41). The benefits appear in a few months, suggesting that enhanced DNA repair reduces short-term cancer-promoting signaling and long-term mutagenic events.

Another approach uses nicotinamide (vitamin B3) to overcome UV-induced energy depletion and subsequent inhibition of DNA repair (42), and this also reduces the erythral response to a given dose of UV. Studies show that daily ingestion of nicotinamide reduces the number of nonmelanoma skin cancers over a 1-year period in Caucasian skin (42). An intriguing advance was the demonstration that secreted proteins from amnion-derived multipotent progenitor cells applied topically on the human skin immediately after UV irradiation reduced erythema, increased XPA DNA repair protein, and decreased DNA damage (43). Similarly, extracellular vesicles derived from human adipose-derived stem cells, which contain a mixture of miRNAs and proteins, mitigated many effects of UVB irradiation (44).

CONCLUSION

DNA repair is our primary endogenous defense against sunlight damage to skin, and recent advances have highlighted its complexity and limitations. The speed and efficiency of recognition and incision of UV-induced DNA lesions can be enhanced by the delivery of exogenous DNA repair enzymes, in a variety of forms. Clinical studies have confirmed an improved repair of damage and skin health in as little as a few weeks or months of use. This technology is a valuable addition to our primary exogenous defense using sunscreens.

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