Prospects for Skin Cancer Treatment and Prevention: The Potential Contribution of an Engineered Virus

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Nonmelanoma skin cancers are among the most common human malignancies. Although typically not lethal, they are responsible for tissue deformity and substantial morbidity, particularly in high-risk populations. Solar UVB radiation—a major etiologic factor for this kind of malignancy—produces DNA lesions such as cyclobutane pyrimidine dimers and 6-4 photoproducts in skin. These lesions are removed through nucleotide excision repair because humans lack a DNA glycosylase required to initiate base excision repair of pyrimidine–pyrimidine photoproducts but produce all the other proteins required for this process. In this issue, Johnson et al. show that a DNA glycosylase derived from Chlorella virus and engineered to enhance tissue penetration and nuclear localization can remove UVB-induced DNA lesions in a human skin equivalent model and that the protein can be incorporated into a topical formulation for the prevention and treatment of UVB-induced DNA damage. These results suggest that such an enzyme may be incorporated into regimens for the chemoprevention of skin cancers.


When UVR interacts with skin, it produces photochemical changes in DNA that can adversely affect the skin’s biological activities and produce disease. Two lesions most commonly result from UVR exposure: cyclobutane pyrimidine dimers (CPDs), in which adjacent pyrimidine rings are coupled through carbon–carbon double bonds at the 5 and 6 positions, and 6,4-pyrimidine pyrimidone photoproducts, in which adjacent pyrimidines are connected through a single bond between the 6 position of one molecule and the 4 position of the other. These alterations, if not restored to their original state, produce mutations that can ultimately lead to nonmelanoma skin cancers (NMSCs), including both squamous cell (SCCs) and basal cell carcinomas (BCCs) (Cleaver and Crowley, 2002). Fortunately, virtually all living organisms possess intricate repair mechanisms to mend damaged DNA. Bulky lesions such as CPDs are normally repaired by nucleotide excision repair, but they can also be restored by base excision repair (BER). Humans, however, can repair CPDs only through nucleotide excision repair (NER). Although human cells have most of the enzymes necessary to complete BER, they lack an important DNA glycosylase required to initiate the process (Cafardi and Elmets, 2008). The importance of DNA repair for protection from UV-induced skin cancers is evident if one examines individuals who suffer from xeroderma pigmen-tosum (XP), an inherited disease in which the NER pathway of DNA is deficient. These patients have a propensity to develop extensive photodamage, cutaneous SCCs, BCCs, and melanomas at an unusually early age.

Even in healthy individuals NMSCs are particularly common. In the United States alone, the estimated 1.5–3.5 million new NMSC diagnoses each year exceed those of all other types of cancer combined. Although rarely lethal, these lesions are locally destructive and the cost of their removal represents an economic burden to the healthcare system. The direct cost for treatment of NMSCs in the United States was estimated to be $1.5 billion in 2004, and if actinic keratoses—premalignant lesions that may progress to SCCs—were included, the direct cost would increase to over $2.3 billion (Bickers et al., 2006). In contrast to most other malignancies, in which the incidence has stabilized or declined, the rate of NMSCs continues to rise (Athas et al., 2003; Karagas et al., 1999). Moreover, in a population-based retrospective study from 1976 to 2003, the incidence of BCCs and SCCs in patients under 40 years old was found to be increasing significantly (Christenson et al., 2005).

Efforts to prevent actinic keratoses and NMSCs have been directed at counseling patients to limit the amount of UVR that reaches the skin, either through avoidance of sun exposure and tanning bed use or through the application of sunscreens. The American Academy of Dermatology, the American Cancer Society, and other organizations throughout the world have developed sophisticated educational programs to educate people on the importance of sun protection. While these strategies have certainly had an impact on patient behavior and awareness of the risks of skin cancer, it seems clear that an alternative approach is needed to address the continued rise in the incidence of these common malignancies.
Clinical Implications

- Cv-pdg-NLS-TAT is a genetically engineered glycosylase that enables human skin to perform base excision repair of UVR-damaged DNA.
- In contrast to other topically applied enzymes, Cv-pdg-NLS-TAT has greater nuclear localization, can penetrate into the lower levels of the epidermis without encapsulation into a delivery vehicle, is more stable, and may act against a wider variety of UVR-induced mutations.
- Cv-pdg-NLS-TAT shows promise as a topical preventive and therapeutic agent for patients at high risk for UVR-induced skin cancer.

These findings suggest that Cv-pdg-NLS-TAT may have both cancer preventive and therapeutic applications and therefore could be ideal for individuals at high risk for NMSCs, such as patients with XP, organ transplant recipients, and individuals with extensive photodamage. However, evidence of clinical efficacy and tolerability for Cv-pdg-NLS-TAT awaits clinical trials. That Cv-pdg-NLS-TAT did not require encapsulation into a delivery vehicle to reach basal keratinocytes is an advantage over both T4N5 and photolyase. The Cv-pdg-NLS-TAT topical enzyme also is more stable over a range of salt concentrations and temperature extremes than other topical formulations that accelerate the repair of UV-damaged DNA (McCullough, 1998). Furthermore, Cv-pdg-NLS-TAT showed favorable retention kinetics in skin cells, indicating that it may be ideal for developing a convenient dosing regimen for human application.

Although mutations in the Sonic hedgehog pathway (for BCCs) and in p53 (for both BCCs and SCCs) are responsible for most NMSCs, some of those tumors lack these mutations (Athar et al., 2006). Because Cv-pdg-NLS-TAT is able to repair a broad range of DNA mutations, Johnson et al. (2011) postulate it could have broad efficacy against a variety of UV-induced mutations and, in contrast to other potential chemopreventive agents (Hacker et al., 2010), may be effective for the small number of UV-induced tumors without CPDs. Cv-pdg-NLS-TAT may also be useful in melanoma prevention because it has broad substrate specificity and an improved nuclear concentration caused by the NLS component.

Even if Cv-pdg-NLS-TAT is found to be effective, additional properties remain to be evaluated for it to be acceptable for widespread application in humans, including examination of its irritancy following chronic application and its cosmetic elegance.

Another important issue is the effect of this enzyme on the repair of oxidative DNA lesions induced by the reactive oxygen species that arise following UV exposure. UVB and UVA radiation can lead to oxidative DNA damage, such as 8-hydroxyguanisine, which is mutagenic and may contribute to the development of skin cancers (Kunisada et al., 2005;...
Montaner et al., 2007). It would be interesting and important to determine whether Cv-pdg-NLS-TAT repaired this type of DNA damage as well. This enzyme may not have a direct effect on the repair of oxidative DNA damage, but it may contribute to an overall upregulation of repair mechanisms in the nuclear environment.

Because NMSCs continue to be a major health and economic issue, the development of new treatment and preventive modalities is crucial. In addition to standard recommendations such as sun avoidance and the application of sunscreen, there are promising treatments and preventive therapies on the horizon. Cv-pdg-NLS-TAT may be one such modality; future clinical studies will further define its efficacy and tolerability.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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Peeling Skin Syndrome: Genetic Defects in Late Terminal Differentiation of the Epidermis
Paul E. Bowden

In this issue, Israeli and colleagues confirm that homozygous mutations in corneodesmosin (CDSN) cause type B peeling skin syndrome (PSS), an autosomal recessive skin disorder. The deletion mutation described resulted in a frameshift, producing a downstream premature stop codon and early truncation of the protein. The recently described CDSN nonsense mutation in another PSS family also resulted in protein truncation and nonsense-mediated mRNA decay. Type B generalized PSS can now be clearly distinguished from acral PSS, caused by mutations in transglutaminase 5. This directly affects cornified envelope cross-linking rather than corneodesmosome adherence. These observations provide new insight into the molecular defects underlying two closely related forms of PSS.

PSS
Peeling skin syndrome (PSS), first described in the early twentieth century (Fox, 1921), is a rare cutaneous genodermatosis that is classified into two forms: acral PSS (APSS; OMIM 609796) and generalized PSS (OMIM 270300).

Although it has been suggested (Traque, 1989) that the generalized form can be further subdivided into noninflammatory (type A) and inflammatory (type B), other phenotypes including those with hair and nail abnormalities have also been described, further