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New Agents for Prevention of Ultraviolet-Induced Nonmelanoma Skin Cancer

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With the incidence of nonmelanoma skin cancer on the rise, current prevention methods, such as the use of sunscreens, have yet to prove adequate to reverse this trend. There has been considerable interest in identifying compounds that will inhibit or reverse the biochemical changes required for skin cancers to develop, either by pharmacologic intervention or by dietary manipulation. By targeting different pathways identified as important in the pathogenesis of nonmelanoma skin cancers, a combination approach with multiple agents or the addition of chemopreventative agents to topical sunscreens may offer the potential for novel and synergistic therapies in treating nonmelanoma skin cancer.
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Nonmelanoma skin cancer is the most common human malignancy. In the United States alone, an estimated 3.5 million new cases of cutaneous squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) are diagnosed each year in more than 2 million people. This number is greater than the combined incidence of malignancies in all other organs.[1] It is estimated that 1 in 5 Americans will develop at least 1 nonmelanoma skin cancer (NMSC) during their lifetime.[2] In contrast to most other tumor types, the incidence of NMSC is increasing at an alarming rate. In Minnesota, there was a 53% increase in cutaneous SCCs in male and 115% increase in female patients during a 6-year interval,[3] and the number of women younger than age 40 diagnosed with BCC has more than doubled in the past 30 years.[4] Similarly in Denmark, NMSC has continually increased from 1978 to 2007, particularly in women and in persons younger than 40 years of age.[5] The direct cost for treatment of NMSC in the United States in 2004 was estimated to be approximately $1.5 billion, and if actinic keratoses (AK) are included, this increases to more than $2.3 billion.[6] The majority of NMSC are caused by exposure to ultraviolet radiation.[7]

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Potential Explanations for the Increasing Incidence Of Skin Cancer

There are several potential explanations for the increasing incidence in skin cancers. First, because people have more time for leisure activities and much of that time is spent outdoors, exposure to ultraviolet radiation has increased. Second, as evidenced by the indoor tanning industry's annual estimated revenue of $5 billion,[8] there is increased use of artificial ultraviolet radiation sources. Third, there is concern that the reduction in stratospheric ozone, which provides the beneficial effect of filtering solar Ultraviolet B (UVB) radiation, is contributing to the increased incidence of skin cancer. For every 1% decline in stratospheric ozone, mathematical models suggest that there will be a 1.4% increase in BCC and a 1.3%-1.7% increase in SCC.[9] Finally, because the incidence of NMSC increases with increasing age, greater numbers of NMSC cases are occurring as the population of our country ages.

Most Nonmelanoma Skin Cancers are Caused by Overexposure to Ultraviolet Radiation

Based primarily on studies in animal models, most NMSCs are thought to be caused by overexposure to UVB radiation.[10] Ultraviolet A (UVA) radiation can also cause NMSC, but it takes larger doses and the latency period is longer. Despite

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this, there is growing concern about the role that UVA may play in skin cancer development. Epidemiologic studies and studies in animal models suggest that UVA and even visible light are major contributors to melanoma development, although there are other studies that contradict this view.[11-13] Another reason for concern about the relationship between UVA and skin cancer relates to the increasing use of tanning salons for cosmetic purposes. The light sources in most tanning beds emit large amounts of UVA radiation. Epidemiologic studies have suggested that heavy users of tanning beds are at increased risk for the development of skin cancer, melanoma in particular,[14] and the International Agency for Research on Cancer of the World Health Organization has concluded that tanning beds are carcinogenic.[15] Recent studies have shown that UVA produces mutagenic lesions in DNA similar to those produced by UVB.[16-18] The third reason for concern about the role of UVA and skin cancer relates to the fact that many people are, on an ongoing basis, taking drugs, such as diuretics, which have photosensitizing properties.[19-21] These compounds all absorb significant amounts of UVA radiation. There is epidemiologic evidence to support the theory that chronic exposure to at least some photosensitizing medications may predispose individuals to the development of skin cancer.[22,23]

Photocarcinogenesis

NMSC develops over long periods through the orderly accumulation of UV-induced molecular and biochemical changes in target keratinocytes. In the first stage of photocarcinogenesis, termed initiation, UV radiation produces DNA damage through pyrimidine dimers and (6-4) photoproducts.[24] DNA repair processes are activated and reduce the number of mutations present after UV exposure, but do not eliminate them completely. Those that persist in the *p53* and *PTCH1* genes lead to the development of mutant cells that can eventually become skin cancers.[25] The mutant cells cannot be detected clinically but serve as targets for events that occur during the second stage of photocarcinogenesis, called promotion. In this stage, repeated exposure to UV radiation results in biochemical changes that facilitate the development of some mutant cells into premalignant AK.[24,26] The biochemical events that occur during the promotion stage include a UV-induced generation of reactive oxygen intermediates,[24] which activate signal transduction pathways that lead to the synthesis of a variety of new proteins. One of these proteins is the enzyme cyclooxygenase-2 (COX-2), which is responsible for the production of prostaglandin E_2. Prostaglandin E_2, in turn, is known to cause inflammation, cellular proliferation, and immunosuppression, all of which are important events in skin cancer development.[27-31] Another protein is the enzyme ornithine decarboxylase (ODC). ODC is the rate-limiting step in the polyamine biosynthetic pathway. Polyamines are known to regulate cellular proliferation, and therefore activation of this enzyme increases the division of mutant cells.[32] During the progression stage, some AK acquire the ability to become invasive NMSC. Molecular and biochemical changes associated with the progression stage include increased angiogenesis, epithelial-mesenchymal transition and the increased activity of myeloid suppressor cells. In addition to its effects during the promotion stage, cyclooxygenase-2 has been implicated in many of the changes that occur in the progression stage as well. Transforming growth factor-β has also been shown to be involved in the progression stage through its ability to stimulate tumor invasion.[33]

Ultraviolet radiation also has immunomodulatory effects that contribute to tumor development.[34,35] In animal models, UV-induced immunosuppression facilitates tumor growth and development. Studies into the mechanisms by which UV radiation exerts its immunosuppressive effects have shown that it depletes the skin of dendritic cells, augments the production of the cytokine interleukin-10, and preferentially supports the development of regulatory T cells.[34-36] There is evidence that UV-induced immunosuppression is a risk factor for humans as well,[37] and immunosuppressed organ transplant recipients are at increased risk of development of cutaneous SCCs and to some extent BCCs.[38]

Chemoprevention

The studies into the mechanisms by which UV radiation causes skin cancer have served as the basis for the identification of new agents for the prevention of NMSC. Chemoprevention refers to the inhibition or reversal of the development of cancer, either by pharmacologic intervention or dietary manipulation, such as the consumption of natural botanicals or adoption of a low-fat diet. Among the chemopreventive agents that were or are studied in humans include retinoids, DNA repair enzymes, small molecular inhibitors of the sonic hedgehog signaling pathway, difluoromethylornithine (DFMO), COX-2 inhibitors, green tea polyphenols, lycopene, low-fat diets, and photodynamic therapy (PDT). These various chemopreventive agents work at different stages of photocarcinogenesis (Fig. 1) and, when used in combination with traditional sunscreens, have the potential to provide a diverse armamentarium for the prevention of NMSC.

Sunscreens

Sunscreens block the interaction of UV radiation with the skin and thereby limit the amount of UV damage that occurs. Although not approved by the Food and Drug Administration for prevention of skin cancer, the available data do suggest that sunscreens reduce the incidence of AK and UV-induced SCC in humans. Thompson et al[39] reported in patients who previously had AK, sunscreens reduced the incidence of new AK when applied regularly during a 7-month period of time compared to subjects who were given the base cream without sunscreens. Green et al[40] compared patients who regularly applied sunscreen with those who used them sporadically during a 5-year period. There was a 35% reduction in cutaneous SCC among the regular users but no reduction in the incidence of BCC, although observation of these patients over a longer period has suggested sunscreens may be of some benefit for these tumors as well.[41]

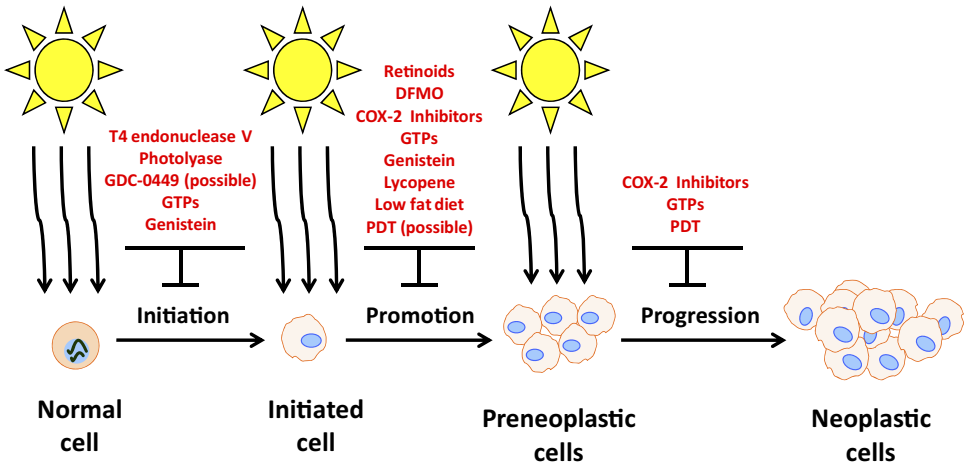

Figure 1 Chemopreventative agents inhibit different stages of photocarcinogenesis.

Although sunscreens are most certainly essential in skin cancer prevention, several factors limit their efficacy. These include poor patient compliance,[42] the large amount of sunscreen required to achieve the full sunburn protection factor (ie, SPF) value on a sunscreen product label,[43] concern (largely theoretic) about the effect of rigorous use of sunscreen in vitamin D-deficient individuals,[44,45] and the lack of any effect on prior UV damage.

Retinoids

Retinoids are vitamin A derivatives that activate nuclear retinoid receptors, influencing epithelial maturation, cellular differentiation, growth arrest and apoptosis. Systemic retinoids have proven to be effective in the chemoprevention of NMSC in several randomized controlled trials in psoriasis patients with a history of extensive psoralen UV therapy, organ transplant patients, and xeroderma pigmentosum (XP) patients.[46-52] However, oral retinoids have not been effective for chemoprevention of skin cancer in the general population.[53] The use of topical retinoids as chemopreventative agents has yielded variable results, with the authors of some studies demonstrating efficacy,[54,55] whereas others have found they produce no statistically significant improvement.[56,57] The most extensive examination of the efficacy of topical retinoids was the Department of Veterans Affairs Tretinoin Chemoprevention Trial. 1131 veterans were randomized to receive tretinoin cream 0.1% or placebo applied to the face and ears twice daily for up to 6 years. The primary end point was the chemopreventive effect of topical tretinoin on the development of NMSCs. However, the study was terminated 6 months early because of an excessive number of deaths in the group treated with tretinoin 0.1% cream applied to the face and ears twice daily (hazard ratio 1.54, $P = 0.01$).[58] The main reported differences in mortality were attributed to pulmonary disease and nonsmall cell lung cancer.

DNA Repair Enzymes

T4 Endonuclease V (Dimericine)

T4 endonuclease V (T4N5), or dimericine, is a bacterial enzyme isolated from *Escherichia coli* infected with T4 bacteriophage. In contrast to the slower nucleotide excision repair enzymes activated in human cells, T4N5 increases DNA repair by removing cyclobutane pyrimidine dimers via the faster base excision repair system in a 2-step process involving a β-elimination catalyst reaction.[59,60] T4N5 thus prevents mutations during the initiation stage. There is also evidence from animal models that it reverses UV-induced immunosuppression.[61] When applied topically to the skin in liposomes, T4N5 is readily absorbed in epidermal keratinocytes.[62,63] In a prospective, randomized, placebo-controlled study involving 30 XP patients, there was a 68% reduction in the development of new AK and a 30% reduction in BCC. This reduction persisted for at least 6 months after completion of treatment without any significant adverse effects.[64] It should be noted that XP patients have a defect in UV-induced DNA repair[13,65,66] and, as a result, it might be expected that administration of a DNA repair enzyme would protect against skin cancer in patients with BCC. It is of great interest to determine whether T4N5 is an effective chemopreventive agent in non-XP patients at risk for the development of NMSC.

Photolyase

Photolyase is a DNA repair enzyme derived from the algae, *Anacystis nidulans*. It binds to UV-induced cyclobutane pyrimidine dimers and pyrimidine-pyrimidone (6-4) photoproducts. Following exposure to photoreactivating light (300-500 nm), it converts them back to their monomeric form via photoinduced electron transfer. Similar to T4N5, photolyase has been encapsulated into a liposomal lotion that penetrates the stratum corneum and is absorbed by epidermal cells.[67] In UVB-irradiated human skin, the application of liposomal photolyase lotion plus photoreactivating light re-

sulted in a 40%-45% reduction in cyclobutane pyrimidine dimers and restored IFN-γ–induced keratinocyte ICAM-1 expression, thereby diminishing UV-induced immunosuppression.[68]

GDC-0449

The hedgehog pathway is an important regulator of cell growth and differentiation during embryogenesis.[69] Mutations activating this pathway in the skin of patients with basal cell nevus syndrome (BCNS)[70,71] and in chronically UV-irradiated skin of healthy individuals are responsible for BCCs.[70,71] GDC-0449 is an oral antagonist of the hedgehog pathway that selectively interrupts activation of downstream hedgehog genes[72] and thus acts during the initiation stage of photocarcinogenesis. In a phase 1 clinical trial, 33 patients with metastatic (n = 18) or locally advanced (n = 15) BCC received GDC-0449 at doses of 150, 270, or 540 mg per day. The response rate was 50% with metastatic disease and 60% with locally advanced disease.[73,74] Although the authors of this study investigated GDC-0449 as a therapeutic agent, it is interesting to speculate that an oral or topical formulation of this molecule or one with similar properties could be an effective chemopreventive agent for BCCs.

Difluoromethylornithine

Increased levels of polyamines have been implicated in the promotion stage of skin carcinogenesis. The rate-limiting enzyme in that pathway is ODC. Acute UV radiation induces ODC activity and elevated levels of ODC have been observed in skin cancers and in chronic UV irradiated skin.[75-77] In animal models, DFMO, a selective inhibitor of ODC, has been shown to inhibit UV-induced SCC and BCC.[76] In a double-blind placebo-controlled phase 3 clinical trial of oral DFMO (0.5 g/m^2/d) or placebo, 291 subjects were randomized to receive DFMO for up to 4 years.[78] Although the percentage reduction in total NMSC and SCC was not statistically significant, individuals given DFMO had 33% fewer BCCs than the control group, which was statistically significant. Thus, DFMO may be an effective chemopreventive agent for patients at risk for development of BCCs. Topical DFMO has been evaluated in the past for chemoprevention of AK, but in that study, several of the treated individuals experienced moderate or severe inflammatory reactions.[79]

Cyclooxygenase Inhibitors

Ultraviolet radiation is also a potent stimulus for the synthesis of the enzyme COX-2. Only trace amounts of COX-2 are produced in normal skin; however, large amounts can be found in UV-induced AK and SCCs.[80] COX-2 is expressed in tumors from basal cell nevus syndrome patients and in sporadic BCCs.[81,82] COX-2 stimulates the production of prostaglandin E_2, which causes inflammation, cellular proliferation, and immunosuppression.[83] COX-2 has been associated with epithelial-mesenchymal transition, angiogenesis, and the activity of myeloid suppressor cells.[84] UV-induced skin tumors are reduced in mice with a genetic deficiency of COX-2.[85] Celecoxib is an oral medication that inhibits COX-2 activity and has been approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, osteoarthritis, and familial adenomatous polyposis of the colon. This medication blocks UV-induced skin carcinogenesis in mice.[28,80,86,87] In a multicenter, double-blind, randomized phase 2 trial of 60 patients, celecoxib was shown to reduce the number of new BCCs in BCNS. Subjects received either celecoxib or placebo for 24 months with a follow-up interval of 36 months. In subjects with <15 BCCs at baseline, those receiving celecoxib displayed a 54% reduction in the number of new BCCs.[88]

Green Tea Polyphenols

Green tea, produced from the leaves of the plant *Camellia sinensis*, contains polyphenols which are potent antioxidants and, based on studies in preclinical models, have several photoprotective properties.[89-92] The most active constituents are polyphenolic catechins, of which epigallocatechin-3-gallate is the most potent. The rationale for using green tea as a chemopreventive agent in cancer derives from epidemiologic studies. For example, the areas of China with the highest esophageal cancer mortality rates are areas where tea is consumed the least.[93] Moreover, in postmenopausal women in Iowa, studies have shown that there is an inverse association between tea consumption and oral pharyngeal and esophageal cancers. Daily consumption of green tea was associated with more than a 50% decrease in risk of developing these malignancies.[94]

The first indication that green tea polyphenols might protect against UV-induced skin cancer came from animal studies in which progressively increasing doses of green tea administered in the drinking water prolonged the mean time of tumor development in mice subjected to a photocarcinogenesis protocol.[95] In subsequent studies, it was shown that the major chemopreventative agent was epigallocatechin-3-gallate and that a similar effect could be achieved when green tea was applied topically.[96,97] Consistent with the effects on UV-induced skin cancer, administration of green tea polyphenols reduced the acute UVB-induced sunburn reaction in mice and reversed the immunosuppressive effects of ultraviolet radiation.[91]

Preliminary studies suggest that green tea may have a protective effect on the adverse effects of UV radiation in humans.[89,98] When green tea is applied to the skin before UV exposure, the erythema response does not develop. Similar preventive effects of green tea are found histologically. Not only does green tea reduce the inflammatory response, it diminishes the formation of sunburn cells. Moreover, green tea polyphenols prevents UV-induced DNA damage and the generation of reactive oxygen intermediates, inhibits the adverse effects on epidermal Langerhans cells, and protects against UVA-induced erythema.[89]

Genistein

Genistein, an isoflavone isolated from soybeans, is a potent antioxidant with both antiproliferative and anti-inflammatory effects.[99-103] Diets high in soybean products are associated with reduced incidence of cardiovascular disease, osteoporosis, and certain cancers.[104] Animal studies show genistein suppresses activation of tyrosine phosphorylation as well as prostaglandin production.[100,104] These actions block acute UV inflammation, inhibit UV-induced skin cancer, and reduce photoaging.[100,104] Topical genistein also inhibits UV erythema in humans[104] and CPD formation in human reconstituted skin.[105]

Lycopene

Lycopene is a bright red carotenoid and phytochemical that lacks provitamin A activity but possesses potent antioxidant and anticancer properties.[106,107] It occurs naturally in many commonly consumed fruits and vegetables, including tomatoes, watermelon, pink grapefruit, guava, papaya, rosehips, and gac, the South-East Asian fruit (*Momordica cochinchinensis*).[108,109] The processing of tomatoes into tomato paste actually increases the concentration of bioavailable lycopene by up to 4-fold.[110,111] Epidemiologic studies indicate an inverse correlation between the consumption of tomato-based products and the incidence and mortality of certain cancers, including prostate, breast, lung, and colon.[112] Chemoprevention against photocarcinogenesis with topically applied lycopene has been demonstrated in murine models.[107] Furthermore, the consumption of tomato paste rich in lycopene has been shown to protect against cutaneous photodamage in humans. In a randomized, double-blinded, placebo-controlled trial, investigators demonstrated that dietary lycopene in the form of tomato paste produced significant reductions in UV-induced skin erythema, in matrix metalloproteinase-1, a biochemical marker of extracellular matrix damage, and in mitochondrial DNA 3895bp, a reliable marker of UV-induced DNA damage.[113]

Low-Fat Diet

Although an association between high dietary fat intake and increased occurrence of UV-induced skin cancers in experimental animals has been known since 1939, it was not until the 1990s that researchers began to address the effect of a low-fat diet in human skin cancer development. In a randomized, controlled clinical trial, those in the intervention arm, whose dietary fat intake was restricted to 20% of total calories consumed, developed significantly fewer new AK and NMSCs compared with those in the control group whose dietary fat intake was between 37% and 40% of total calories consumed.[114,115] More recent studies suggest that high dietary fat intake is associated with an increased risk of SCC[116] but not BCC.[116,117]

Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) combines the use of a photosensitizer, aminolevulinic acid or methylaminolevulinate and converts it to protoporphyrin IX. Protoporphyrin IX, in turn, can be activated by visible light to generate highly reactive oxygen species, predominantly singlet oxygen, that are selectively retained in and destroy rapidly dividing cells (eg, a tumor). Although PDT is currently approved for the treatment of AK, it has proven efficacy in the treatment of actinic cheilitis, BCCs, Bowen's disease, hidradenitis suppurativa, acne vulgaris, and photoaging. A number of studies demonstrate that topical PDT is efficacious in the chemoprevention of NMSCs in solid-organ transplant recipients.[118,119] However, one study did not find a significant difference in the development of new SCCs in the PDT group compared with the control group.[120] In a recent small, uncontrolled study, investigators specifically examined the efficacy of cyclic aminolevulinic acid PDT in the chemoprevention of new SCCs in solid-organ transplant recipients. Compared with baseline before PDT, the median reduction in SCCs was 79% at 12 months and 95% at 24 months.[121] Randomized controlled clinical trials will be required to establish the safety and efficacy of this modality as a preventive treatment.

Conclusions

There are several exciting new agents to use in the prevention of UV-induced skin cancer in the future. These agents will target the initiation, promotion and progression stages of skin cancer development, as well as reversing UV-induced immune suppression. The fact that these chemopreventive agents have mechanisms of action different from those in currently available sunscreens suggests that they have the potential, when used in conjunction with traditional sunscreens, to further protect the skin against the adverse effects of ultraviolet radiation. Furthermore, the combination of several chemopreventive agents, targeting different pathways in the development of skin cancers, may have additive or synergistic effects at doses that confer minimal side effects.

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