Targeting Ornithine Decarboxylase for the Prevention of Nonmelanoma Skin Cancer in Humans

Abstract

Bailey et al. report in this issue of the journal (beginning on page 35) one of the first successful trials of basal cell carcinoma (BCC) prevention. Oral α-difluoromethyl-dl-ornithine (DFMO) reduced new BCCs in patients with a prior history of nonmelanoma skin cancer. DFMO is an inhibitor of ornithine decarboxylase, a key enzyme in the polyamine biosynthetic pathway. This perspective on Bailey et al. discusses our knowledge of the contribution of polyamines to BCC pathogenesis, how this knowledge advanced the development of a new method to prevent BCCs, and prospects for future studies of DFMO in BCC prevention. Cancer Prev Res; 3(1); 8–11. ©2010 AACR.

The nonmelanoma skin cancers (NMSC) basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common malignancies in whites worldwide. It is estimated that 1.0 to 1.3 million new NMSCs are diagnosed in the United States each year, only slightly fewer than the number of all other cancers combined. Although rarely lethal, these lesions are locally destructive and are a tremendous economic burden to the health care system. In 2004, the estimated cost of treating NMSCs in the United States was about $1.5 billion; adding actinic keratoses, premalignant lesions that can progress to SCCs, would increase the estimated cost to over $2.3 billion (1). The vast majority of NMSCs are caused by excessive exposure to UV radiation. In contrast to the stabilized or declined incidences of most other cancers, the rate of NMSCs continues to increase (2, 3). The reasons for this increase relate, at least in part, to increased time people have for outdoor recreational activities, more frequent use of artificial light sources by the lay public for cosmetic purposes, and the increasing proportion of aging individuals in the general population. NMSCs are becoming more frequent in younger people as well. A population-based retrospective study found that the incidence of BCCs and SCCs in patients younger than 40 years of age increased significantly between 1976 and 2003 (4).

Experts usually group BCCs and SCCs together because both occur on exposed areas of the skin, have a low mortality rate, and are frequently caused by chronic exposure to UV radiation. Despite these similarities, however, they also have distinguishing clinical and histologic characteristics and biochemical and molecular differences. Consider mutations in p53, for example, which occur in most cutaneous SCCs. Inactivation of p53-dependent tumor suppressor functions related to apoptosis induction and other critical processes are considered to be important in the pathogenesis of SCC (5). Although ~50% of BCCs have p53 mutations, 90% of BCCs are associated with unrepaired UV-induced mutations in patched or smoothened genes (5), which belong to the sonic hedgehog pathway. Mutations in the sonic hedgehog pathway are thought to be the sine qua non of BCCs. Therefore, nonsurgical treatment and prevention approaches for BCCs may differ from those for SCCs.

BCC and SCC prevention has focused mainly on limiting the amount of UV radiation that reaches the skin. Reducing UV exposure has been accomplished chiefly through public awareness campaigns that warn people about the adverse effects of sun exposure and have influenced the public to protect themselves from sun exposure during peak hours of UV intensity (i.e., 10:00 a.m. to 4:00 p.m.), use protective hats and clothing, avoid artificial UV radiation sources (e.g., tanning beds), and regularly apply sunscreens.

It is important to note that the efficacy of sunscreens is determined by their ability to protect against UV-induced sunburns, and the SPF number on sunscreen labels represents its “sunburn protection factor.” The value of sunscreens for protecting humans against NMSCs, melanoma, photoaging, and UV-induced immune suppression remains largely undetermined. Although sunscreens may play an important role in preventing skin cancer, it should be noted that they also have several limitations. There is inconsistent compliance in the use of most sunscreens because they are greasy and messy and stain clothing. Although large amounts of sunscreen are generally required to achieve the full SPF value displayed on the label, most people apply only ~25% of this...
COX-2 is found in the stroma surrounding islands of BCC, where its distribution differs from that of SCCs. Exposure to UVB (18) and is overexpressed in the epithelia COX-2 can be induced in such tissue by acute and chronic genesis. Not expressed in undamaged normal epidermis, angiogenesis during the progression stage of skin carcinogenesis, inhibits tumor cell apoptosis, and stimulates mesenchymal transition, suppresses host antitumor defense mechanisms tightly control the expression of ODC in normal cells, ODC regulation is altered in neoplastic cells, yielding constitutively high levels of ODC expression and activity (reviewed in ref. 24). Furthermore, a polymorphism in ODC is associated with colon adenoma recurrence and the survival of colon cancer patients, and modulates the preventive effect of aspirin in colorectal adenoma patients (25, 26).

ODC is transiently induced by a variety of stimuli including mitogens and tumor promoters such as 12-O-tetradecanoyl phorbol-13-acetate (TPA), UVB, and hormones and is dramatically elevated in human SCC and BCC (compared with levels in adjacent normal skin tissue). Several transgenic mouse model studies have shown the essential role of polyamines in the early promotion of skin tumorigenesis. Elevated levels of ODC activity are sufficient to promote skin tumor formation, without the addition of tumor-promoting agents, in the carcinogen-exposed skin of K6/ODC transgenic mice, where ODC is constitutively targeted to the skin with a keratin 6 or keratin 5 promoter (27). In addition, doses of UVB radiation that are insufficient to produce tumors in SKH-1 hairless mice will induce both premalignant papillomas and SCCs in K6/ODC transgenic mice. De novo induction of ODC activity in suprabasal epidermal cells causes increased epidermal proliferation, neovascularization, and increased synthesis of extracellular matrix proteins in a manner similar to that of skin responding to a wound. Of interest, ODC overexpression in the suprabasal layer of normal epidermis seems to affect other cell subpopulations in the skin, resulting in increased proliferation of basal cells of the epidermis and increased angiogenesis in the dermis (reviewed in ref. 23).

Experimental evidence of the contribution of ODC to the development of BCC is convincing (27). The growth of BCCs is augmented in pch−/− mice over-expressing ODC in the outer root sheath cells of hair follicles (Pch−/−/ODC TgN). These Pch−/−/ODC TgN mice mimic the phenotype of basal cell nevus syndrome,
which predisposes patients to BCC. The characteristic histologic features of BCC, including palisading basaloid cells in the periphery of tumor nests, the appearance of retraction spaces, the lack of keratinizing centers, and the characteristic expression pattern of keratin 17, Gli1, Gli13, Pch1, and Pch2, closely resemble characteristics of human BCC (27).

\(\alpha\)-Difluoromethyl-dl-ornithine (DFMO) is an ornithine analogue that irreversibly inhibits ODC activity (28). The mechanism of this inhibition involves enzymatic decarboxylation of DFMO to a carbonionic intermediate, which, following the loss of fluorine, alkylates a nucleophilic residue near or at the active site of ODC. This covalent modification of the active site of ODC leads to its suicidal inactivation. DFMO depletes polyamines in various organs including the skin. ODC inhibition reduces phosphorylation of the retinoblastoma tumor suppressor protein and invokes G1 arrest through upregulation of p21 and/or abolition of p27Kip1 repression (29). DFMO treatment inhibits tumorigenesis in various murine organ models, effectively reducing tumor development in a two-stage, initiation-promotion murine model of chemically induced skin carcinogenesis. This work has also been found to reduce UVB-induced tumorigenesis in BALB/c (30) and K5/ODC transgenic mice (31), to reduce UVB-induced immune suppression in BALB/c mice (30), and to inhibit epidermal carcinogenesis in ODC/Ras transgenic mice (32).

DFMO is a relatively nontoxic compound and thus has strong promise for cancer chemoprevention in humans. As reported by Bailey et al. in this issue of the journal, a randomized, double-blind, placebo-controlled phase III trial of DFMO (0.5 g/m²/day) versus placebo for up to 5 years produced promising results in men and women with a previous history of skin cancer (33). The study arms were well matched for all other important categories including use of sunscreen and nonsteroidal anti-inflammatory drugs (NSAID). Although DFMO did not achieve the primary objective of a statistically significant reduction in new NMSC (260 versus 363 cancers, P = 0.069) or inhibit the development of SCC, it decreased BCCs by 30%. The BCC result was significant not only from a statistical standpoint (P = 0.03), but also because it is the first time that a chemopreventive agent other than sunscreens has prevented BCCs in subjects who do not have conditions that predispose them to develop this cancer (e.g., xeroderma pigmentosum and organ transplantation). Daily oral DFMO at the dose used in this study (0.5 g/m²/day) was quite safe and well tolerated except for mild, reversible otoxicity, which is one of the major toxicities noted in other human clinical trials with the drug (34). Wang et al. (35) recently showed that polyamines regulate Kir channels that maintain the endochondral potential, which is necessary for adequate hearing, and that a deficiency of spermine synthase is otoxic.

The study of Bailey et al. provides evidence that ODC inhibition represents an important molecular target-based approach for preventing skin cancer and validates the utility of DFMO as a cancer chemopreventive agent in another human organ system besides the colon. Meyskens et al. (36) showed that DFMO plus the NSAID sulindac reduced advanced or multiple adenomatous polyps by >90%.

This important trial raises issues that will serve as the basis for future studies. First, it will be important to determine the mechanisms by which DFMO exerts its chemopreventive effects against BCC. The current trial showed that DFMO at the dose used effectively inhibited ODC activity and putrescine concentration, but DFMO effects on the expression of sonic hedgehog signaling–related proteins and on the antitumor immune response are also relevant and need to be explored. Second, Fischer et al. (37) showed that treatment with a combination of DFMO and the NSAID celecoxib was more effective in diminishing UVB-induced SCCs in murine skin than was treatment with either agent alone. These findings coincide nicely with the findings of Meyskens et al. (36) in colorectal adenomatous polyps. Therefore, adding an oral COX inhibitor to oral DFMO may have additive or synergistic effects in BCC and may allow chemopreventive efficacy with a lower dose of DFMO and/or the COX inhibitor, thus potentially reducing the toxicity either single agent might cause. Last, a topical formulation of DFMO (13.9%) has been approved by the U.S. Food and Drug Administration for the removal of unwanted hair. Topical DFMO also reduced the number of actinic keratoses in a small, randomized controlled trial (38). This medication is applied chronically, and clinical studies have shown that it has a favorable human dermal safety profile with no adverse side effects (39). A topical formulation of the NSAID diclofenac is also Food and Drug Administration approved for the treatment of actinic keratoses. Therefore, topical DFMO alone or with topical diclofenac could be investigated for chemopreventive effects against BCCs.

By identifying BCCs as a clinically relevant target for DFMO, the analyses by Bailey et al. (33) are a positive step forward for cancer chemoprevention. These investigators have taken basic observations about the pathogenesis of BCC and transformed them into something that has clinical applicability for individuals who are at risk for this too-common neoplasm.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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