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REVIEW ARTICLE

ORNITHINE DECARBOXYLASE: AS A TARGET FOR PREVENTION OF NONMELANOMA SKIN CANCER

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ABSTRACT

Elevated levels of polyamines have long been associated with skin tumorigenesis. Tightly regulated metabolism of polyamines is critical for cell survival and normal skin homeostasis, and these controls are dysregulated in skin tumorigenesis. A key enzyme in polyamine biosynthesis, ornithine decarboxylase [ODC] is up regulated in skin tumors compared to normal skin. Use of transgenic mouse models has demonstrated that polyamines play an essential role in the early promotional phase of skin tumorigenesis. The formation of skin tumors in these transgenic mice is dependent upon polyamine biosynthesis, especially putrescine, since treatment with inhibitors of ODC activity blocks the formation of skin tumors and causes the rapid regression of existing tumors. Although the mechanism by which polyamines promote skin tumorigenesis are not well understood, elevated levels of polyamines have been shown to stimulate epidermal proliferation, alter keratinocyte differentiation status, increase neovascularization, and increase synthesis of extracellular matrix proteins in a manner similar to that seen in wound healing. It is becoming increasingly apparent that elevated polyamine levels activate not only epidermal cells but also underlying stromal cells in the skin to promote the development and progression of skin tumors. The inhibition of polyamine biosynthesis has potential to be an effective chemoprevention strategy for nonmelanoma skin cancer.

INTRODUCTION

Skin cancer is by far the most common type of cancer, with tremendous impact on health and morbidity. The three main types of skin carcinomas are basal cell carcinomas [BCCs], squamous cell carcinomas [SCCs] and cutaneous melanomas [CMs]. Non-melanoma skin cancers [NMSCs] are the most frequently diagnosed malignancies in the USA, accounting for approximately 40% of all cancer cases. It is estimated that more than 1,000,000 new cases of NMSCs diagnosed in the USA in 2003 resulted in 2200 deaths.[1] UV radiation is considered to be the major carcinogenic factor for all types of skin cancers.

However, many other factors contribute to the initiation and promotion of skin carcinogenesis.[1,2] For instance, occupational exposures to chemical pollutants [e.g. polycyclic aromatic hydrocarbons], volatile organic compounds [e.g. benzene], and heavy metals [e.g. arsenic, cadmium and lead] considered very potent genotoxic factors for some population groups such as steel, agriculture, petrochemical, textile and pesticide industry workers.[2, 3] UVR and chemical agents can initiate damages to biomolecules either by direct photochemical reactions or/and via oxidative mechanisms generated by reactive oxygen species [ROS].[4, 5, 6, 7, 8] Skin spontaneously responds to increased ROS levels, induced by ultraviolet radiation [UVR] or chemical agents, by detoxifying enzymes such as superoxide dismutase, catalase, thioredoxin reductase and low-molecular mass antioxidant molecules such as glutathione, a-tocopherol and ascorbic acid.

However, this response may not be sufficient to prevent the oxidative damage of cutaneous cells after excessive or repetitive exposure to carcinogenic agents. [9] Thus, ROS may oxidize lipids, proteins and DNA leading to formation of oxidized products such as lipid hydroperoxide, protein carbonyls and 8-oxo-gouanosine.[5] If these alterations occur to genes involved in normal homeostatic mechanisms that control proliferation and cell death, significant abnormalities are observed in the cell cycle, leading to the first cancer stage,

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initiation.[10,11] It is thought that many epidermal genetic lesions are caused by exposure to solar irradiation early in life.[12,13] However, cells harboring these mutations often remain dormant for many years until triggered to form tumors later in life. The induction of ornithine decarboxylase [ODC] activity with subsequent increased levels of polyamines has been shown to play a causal role in skin tumor development in a variety of animal models. Moreover, inhibitors of polyamine synthesis have been shown to effectively suppress skin tumor incidence and severity in both UV and chemically induced experimental models and in cancer chemoprevention trials in high-risk human populations.

The polyamines putrescine, spermidine and spermine are some of the major cations present in eukaryotic cells. The majority of polyamine molecules are bound to polyanionic macromolecules such as DNA, RNA, and phospholipids [14], resulting in far-reaching effects upon cellular processes including DNA replication, transcription, and translation. It is not surprising that numerous studies using specific inhibitors of polyamine biosynthesis have documented that these small ubiquitous molecules are absolutely required for all cell growth and differentiation. Although a vast number of studies have shown that polyamines are crucial to the growth and proliferation of cells, the cellular functions of polyamines and their interactions with cellular components that play a key role in promoting tumorigenesis remain largely unknown. This review will focus on our current understanding of the relationship between polyamines and nonmelanoma skin tumorigenesis.

Mammalian metabolism of polyamines

Polyamine levels are tightly controlled by a complex array of biosynthetic and catabolic pathways and a multitude of compensatory mechanisms, all of which attest to the essential role of polyamines in cell survival. [15, 16, 17] In mammalian cells, polyamines are synthesized from the amino acids L-methionine and L-arginine. L-arginine is metabolized to L-ornithine through the action of arginase. Polyamine biosynthesis begins with the decarboxylation of ornithine by ornithine decarboxylase [ODC] to produce putrescine. Spermidine and spermine are synthesized by the sequential additions of aminopropyl groups provided by L-methionine after its conversion into S-adenosylmethionine [SAM] by methionine adenosyltransferase [MAT]. Decarboxylation of S-adenosylmethionine [SAM] by S-adenosylmethionine decarboxylase [SAMDC] generates decarboxylated SAM which donates its propyl amine moiety to the formation of spermidine and spermine by spermidine synthase and spermine synthase, respectively. Both ODC and SAMDC are rate-limiting enzymes in the biosynthesis of polyamines.

Intracellular levels of polyamines are also controlled by catabolic pathways that permit the conversion of spermine back to putrescine. In this retroconversion process, spermine and spermidine are acetylated by spermidine/spermine acetyltransferase [SSAT] using acetyl-CoA to form N1-acetylspermine and N1-acetylspermidine. These acetylated polyamines are substrates for a peroxisomal, FAD-dependent polyamine oxidase [PAO] which catalyzes their conversion back to spermidine and putrescine. In a second pathway, putrescine and N1-acetylspermidine can be exported by the transporter, diamine exporter [DAX] [18] and then eliminated in the urine. As a consequence of this export system, acetylated polyamines are rarely found in normal cells, but are found in high concentrations in some cancer cells that demonstrate altered polyamine catabolism.[19, 16] In addition, a second polyamine catabolic pathway has recently been characterized. The inducible, cytosolic spermine oxidase [SMO] oxidizes nonacetylated spermine to spermidine, H2O2, and aldehyde 3-aminopropanol.[20] Polyamine levels are controlled not only by these highly regulated biosynthetic and catabolic pathways, but are also fine-tuned by an energy dependent and carrier-mediated polyamine uptake system that is important in maintaining cellular polyamine homeostasis.

This alternative supply of polyamines is upregulated in response to polyamine depletion, and the polyamine uptake system can provide a major method of resistance to chemotherapeutic treatments that rely on inhibition of polyamine biosynthesis. Additional regulation of polyamine homeostasis is provided by the protein antizyme [AZ] that binds noncovalently to the ODC monomer to inhibit ODC activity and to target ODC for proteasomal degradation in an ubiquitin-independent manner.[21, 22] In addition, AZ inhibits the uptake of exogenous polyamines and promotes polyamine excretion. Thus, whereas AZ is upregulated by high levels of polyamines, it functions to suppress polyamine accumulation via multiple mechanisms.

Nonmelanoma skin tumorigenesis in humans and animals

Malignant skin tumors in humans include malignant melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).(23,24) BCCs are the most common human cutaneous malignancy and they are typically slow-growing, locally invasive tumors that rarely metastasize. Although SCCs only represent about 20% of nonmelanoma skin cancers in humans, SCCs are generally more aggressive than the more common basal cell carcinomas (BCC) and can be lethal. SCCs are usually very well differentiated tumors with massive production of horny material, which progressively invade surrounding tissue and can eventually metastasize to distant sites. Approximately 60% of SCCs arise from preexisting benign actinic keratoses.(25) While most actinic keratoses do not progress to SCC, actinic keratoses represent SCC in situ at its earliest stages.(26) One of the most frequently used animal models for studying carcinogenesis in a lining epithelium is the initiation–promotion model of tumorigenesis in mouse skin.

Whereas actinic keratoses are thought to be the benign precursor for human SCCs, papillomas have been identified as benign precursors for murine SCCs. Papillomas are benign epidermal tumors seen very frequently after chemical carcinogen exposure, especially in two-stage carcinogenesis protocols in mouse skin.(23) Murine papillomas are cauliflower-like structures with a series of folds consisting of a central vascularized, connective tissue core covered by a proliferative, stratified squamous epithelium and an abundant, orthokeratotic horny layer. Some papillomas regress, but others can progress to malignancy. Squamous cell carcinomas (SCC) can be

induced in animals using UV light, ionizing radiation, or chemical carcinogens. In contrast to humans, mice have a strong predisposition to developing squamous cell carcinomas and appear to be relatively resistant to the development of BCCs. Following exposure to UV light or complete carcinogens, mice can also develop Keratoacanthomas (KA), which have a cup shaped form with a horny central crater and epidermal edges that appear to be a continuation of the upper third of hair follicles. Unlike human KA, murine KA rarely regresses and often converts to squamous carcinomas.[23]

ODC and nonmelanoma skin tumorigenesis

Polyamines have long been known to be associated with cell proliferation in both normal and neoplastic tissues.[27, 28, 29] Elevated levels of ODC and increased polyamines were initially suspected to play a causal role in skin tumorigenesis largely due to the early induction of ODC by tumor promoters [30, 31, 32] and to studies using inhibitors of ODC.[33, 34, 35, 36] For instance, α-difluoromethylornithine (DFMO), which is a specific and irreversible inhibitor of ODC enzyme activity, inhibits the development of skin tumors in carcinogen treated mice when it is given during the promotion phase. [35, 36] Although cellular mechanisms exist to tightly control the expression of ODC in normal cells, the regulation of ODC is altered in tumor cells, yielding constitutively high levels of ODC expression [30, 31, 32, 37] and subsequent increased levels of polyamines.[38] ODC activity and polyamine levels are dramatically elevated in human squamous cell carcinomas compared to adjacent normal skin tissue.[39, 40] This can result from the upregulation of ODC expression by oncogenes such as c-myc [41,42], v-src [43], v-raf, or an activated Ras or RhoA.[44] In fact, c-Myc has been shown to transactivate ODC.[41, 42] However, although some oncogenes can increase ODC activity, ODC is also transiently induced in the skin by a variety of stimuli including mitogens, tumor promoters such as 12-O-tetradecanoylphorbol ester (TPA), and hormones.

Use of transgenic mouse models has demonstrated that polyamines play an essential role in the early promotional phase of skin tumorigenesis. [45, 17] Elevated ODC activity in K6/ODC and K5 ODC transgenic mice has been constitutively targeted to either the outer root sheath of hair follicles or the basal epidermal layer in the skin with a keratin 6 or keratin 5 promoters, respectively, to yield increases in polyamine pools, especially putrescine levels. [46, 47]

These sustained high levels of putrescine lead to alopecia, the development of follicular dermal cysts, increased nail growth, and skin wrinkling. With regard to tumor development, the targeted expression of ODC to the skin also increases the susceptibility of these mice to skin tumor formation following a variety of initiating events including carcinogens [47, 48], UV irradiation [49], and oncogenes. [50, 51, 52] The treatment of newborn or adult K6/ODC transgenic mice with a single topical application of the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) yields papilloma formation 6 to 8 weeks later without the use of tumor promoting agents. [47, 53] Likewise, single treatment with other carcinogens from different chemical classes also induces skin tumors in K6/ODC transgenic mice. [48] With particular relevance to human skin tumorigenesis, K6/ODC transgenic mice develop more papillomas following UVB irradiation compared to wild type littermates. [49]

Expression of specific oncogenes in the skin of K6/ODC transgenic mice is sufficient to lead to spontaneous and differential skin tumor outcomes without the need of additional chemical carcinogens or tumor promoters. Bi-transgenic mice expressing both skin-targeted ODC and the v-Ha-ras Oncogene develop spontaneous Keratoacanthomas and squamous cell carcinomas, whereas no tumors develop in the mono-transgenic mice. [50, 52] On the other hand, basal cell carcinomas develop in mice that are both heterozygous null for the patched tumor suppressor gene and over expressing ODC in follicular cells. [51] The formation of skin tumors in these transgenic mice is dependent upon polyamine biosynthesis, especially putrescine, since treatment with the specific inhibitor of ODC activity, α-difluoromethylornithine (DFMO) blocks the formation of skin tumors and causes the rapid regression of existing tumors. [50] Furthermore, over expression of AZ in the skin of transgenic mice leads to decreased ODC activity following tumor promoter treatment and also suppresses tumor growth in the classic DMBA/TPA skin tumorigenesis model [54] and in the UV carcinogenesis model using the Ptch+/− heterozygous mouse model. [51] Both DFMO and AZ inhibition of skin tumor development primarily inhibit the accumulation of putrescine, whose levels correlate very closely with tumor development in the skin. [53] Even modest reductions in ODC expression reduce skin tumor susceptibility as demonstrated by the reduced skin tumor yield in Odc+/− haploin sufficient mice subjected to a two-stage initiation–promotion protocol. [55]

The association between increased levels of putrescine and skin tumorigenesis is also seen in transgenic mice in which SSAT is targeted to the skin with a keratin 6 promoter (K6/SSAT). [56] Although increased expression of a key regulatory enzyme in the catabolism of polyamines would be expected to suppress skin tumorigenesis, expression of SSAT in K6/SSAT transgenic mice increases the incidence of skin papillomas and their progression to carcinomas in response to a two-stage carcinogenesis protocol. [56] On the other hand, transgenic mice that express SSAT under the control of its own promoter (line UKU 165b) or a metallothionein I promoter (line UKU 181) have been reported to be resistant to the development of papillomas during two-stage skin carcinogenesis. [57] UKU 165b transgenic mice over accumulate putrescine in their skin, lose their hair by 3 weeks of age, and develop large dermal cysts as do transgenic mice in which ODC is constitutively targeted to the skin. In contrast, K6/SSAT transgenic mice have a normal skin phenotype and normal hair cycle since the keratin 6-driven SSAT expression is only increased in skin tumors. [56] It is likely that the different skin tumor responses of the UKU 165b and the K6/SSAT transgenic mice to a two-stage carcinogenesis protocol is due to the use of different transgene promoters which have dissimilar regulation in different subpopulations of the skin.

Moreover, unlike the normal skin phenotype of K6/SSAT transgenic mice, UKU 165b transgenic mice exhibit dramatic changes in their skin morphology which may alter their responses to carcinogens and tumor promoters. Indeed, ODC

activity and spermidine levels are higher in nontransgenic littermates following tumor promoter treatment and in subsequent skin tumors compared to that seen in UKU 165b transgenic mice. [57] It has been hypothesized that the changes in tumor development may arise from a greatly accelerated polyamine metabolic flux which is driven by decreased spermidine and spermine pools that in turn trigger a sustained increase in polyamine biosynthetic activity and a sustained release of reactive by-products. [58, 59] Further studies are obviously needed to better understand the role of SSAT in skin carcinogenesis.

Accumulating reports in the literature suggest a strong link between Oncogene activation and increased polyamine biosynthesis in skin tumorigenesis. ODC is induced by activation of Ras and its downstream effectors pathways Raf/MEK/ERK and PI 3-kinase in NIH 3T3 cells [60] and in skin tumors that spontaneously develop in transgenic mice that express an activated MEK protein in the basal layer of the epidermis. [61] Moreover, skin tumorigenesis in response to Ras activation requires increased polyamine biosynthesis since DFMO and AZ expression can block the spontaneous development of skin papillomas in transgenic mice that express an activated MEK mutant in the basal layer of the epidermis. [61, 62] However, activation of Raf or MEK in normal transgenic mouse skin or in primary cultures of keratinocytes does not increase ODC activity and is not sufficient to convert normal keratinocytes to an invasive phenotype. [61, 63] Indeed, conversion of normal keratinocytes to invasive, malignant cells minimally requires activation of the Raf/MEK/ERK signaling pathway and a threshold level of increased ODC activity. [64, 63] Another requirement may involve a selective susceptibility of a targeted subpopulation of keratinocytes or stem cells within the skin. In order to promote invasiveness in keratinocytes, increased ODC activity may cooperate with Raf/ERK signaling by activation of the AKt/mTOR and/or Rho/Rac signaling pathways. [63]

Effects of polyamines in skin

High levels of polyamines are usually correlated with rapid proliferation, and induction of ODC enzyme activity is one of the classic characteristics of tumor promoter activity in the skin.[65] Studies using transgenic mice have shown that proliferation and differentiation of keratinocytes are regulated by changes in their cellular polyamine content. The epithelial cells lining the follicular cysts of K6/ODC transgenic mice express high levels of ODC and demonstrate a high proliferative index. [66] Since it is not known how the abnormal skin phenotype of the K6/ODC transgenic mouse may contribute to changes in proliferation and tumorigenesis, a transgenic mouse model with a normal skin phenotype in which an inducible form of ODC is targeted to Suprabasal epidermal cells by an involucrin promoter was generated. De novo induction of Suprabasal epidermal ODC activity in ODCER transgenic mice increases both proliferations in the basal layer of the epidermis as well as epidermal differentiation. [52] Suprabasal cells in intact, normal adult skin are no longer proliferating and are committed to terminally differentiate. This proliferation control is disrupted in skin tumorigenesis, and cycling cells that express high levels of ODC can be found also in Suprabasal layers of skin tumors. [31, 50] However, induction of only ODC activity without any Oncogene activation does not rescue primary epidermal keratinocyte cultures isolated from ODCER mice from a calcium-triggered DNA synthesis block in cells committed to terminally differentiate. [52] Altered keratinocyte differentiation and an increased proliferation index have also been reported with SSAT overexpression and increased putrescine levels in UKU 165b transgenic mice. [67]

One mechanism by which elevated levels of polyamines affect cell cycling and differentiation status in the skin is through their effects on gene expression. [68, 69, 70, 71] Polyamines regulate gene expression by altering DNA structure [72] and by modulating the binding of transcription factors to response elements in target genes. [15] In addition, polyamines have been shown to affect chromatin remodeling in the skin, in part, via elevated intrinsic histone acetyltransferase (HAT) activity that has a pronounced specificity preference for histone H4. [73, 74] Both p300/CBP-associated HAT activity and the Tip60 HAT enzyme are elevated following ODC overexpression in transgenic mouse skin. [75] The polyamine-stimulation of these HAT enzymes in the skin may alter the recruitment of a subset of transcription factors to the regulatory regions of genes to influence their expression. Interestingly, ODC overexpression targeted to the Suprabasal layer of non tumor-bearing ODCER transgenic epidermis appears to affect other cell subpopulations in the skin, resulting in increased proliferation in the basal cells of the epidermis and activation of the underlying stromal layer with neovascularization and increased synthesis of extracellular matrix proteins in a manner similar to wound repair in skin. [52] Increased vascularization of the skin has been reported in K6/ODC transgenic mice as well. Moreover, there is a positive correlation of DFMO-induced regression of ODC/Ras tumors with decreased vascularization and increased apoptosis of both tumor epithelial and stromal cells. In this study, there was no effect of DFMO inhibition on the epithelial proliferation index in the regressed ODC/Ras skin tumors. [76] However, DFMO-induced tumor regression in DMBA-initiated papillomas in K6/ODC transgenic mice is associated with a selective decreased proliferation in tumor epithelial cells and no effect on the proliferation index in normal keratinocytes. [53]

It remains to be determined what essential survival factors and/or angiogenic factors are regulated by polyamines that play a key role in the maintenance of these skin tumors. These studies suggest that polyamine-activation of keratinocytes and underlying stromal cells is an early event in the tumor process that creates a more permissive microenvironment for tumor development. An under-explored area of research in this field is the molecular pathways impinged upon by elevated levels of polyamines that are responsible for promoting skin tumorigenesis.

Polyamine-based therapy in skin cancer

The dysregulation of polyamine metabolism in skin cancer provides a rational target for therapeutic intervention in human patients. The premier drug used to target polyamines in human

skin cancer is DFMO since it has been shown to inhibit skin tumor incidence in animals following induction with either chemical carcinogens [35, 36] or UVB irradiation. [77] In addition, DFMO causes rapid regression of murine squamous cell carcinomas, with the exception of resistant spindle cell carcinomas. [78] Currently DFMO has been used in skin cancer chemoprevention trials that focus on the patients with precancerous lesions such as actinic keratoses. Topical DFMO ointment (10% w/w) significantly reduces the numbers of actinic keratoses, spermidine levels, and epidermal p53 expression with no change in the proliferation or apoptotic rate. [79, 80] These trials appear promising since topical application of DFMO has shown no adverse side effects and systemic DFMO treatment is associated with reversible autotoxicity only at high doses. [79] O'Brien *et al*. have reported a positive association between an ODC polymorphism (associated with higher ODC activity) and increased prostate cancer risk in men who smoke or have high risk alleles of the androgen receptor gene. [81] Although there is no data in humans to suggest that some individuals may be at an elevated risk for nonmelanoma skin cancer based on the presence of ODC polymorphic variants, an area for future studies is whether chemoprevention using DFMO is more efficacious if combined with screening for ODC polymorphic variants that may be associated with greater potential for ODC induction and increased cancer risk. [82] In addition, future studies using mouse strains with varying tumor responses may identify human genetic loci that modify ODC-dependent enhanced susceptibility to skin tumorigenesis. [83, 84]

Despite these promising results in clinical trials for cancer prevention, there have been no published reports of polyamine based chemotherapeutic trials for basal cell carcinomas or squamous cell carcinomas. In part, this may be due to the lack of success of DFMO as a global antitumor agent in other tissue types since ODC inhibition leads to a compensatory increased cellular uptake of polyamines from the circulation which neutralizes the cytostatic effect of DFMO. [85] However, murine squamous cell carcinomas, with the exception of aggressive spindle cell carcinomas, show rapid tumor regression following treatment with high doses of DFMO. [78] In addition, an attempt to achieve sufficient depletion of polyamines by inhibiting not only polyamine biosynthesis but also polyamine uptake has recently been reported to be significantly more effective in causing regression of murine squamous cell carcinomas compared to DFMO alone. Use of a polyamine uptake inhibitor in this study also permitted the use of lower doses of DFMO to achieve tumor regression and led to a greater decline in tumor polyamine levels compared to that seen using higher doses of DFMO alone. [86] Thus, the effects of DFMO in combination chemotherapy for squamous cell carcinomas remain to be more fully investigated, especially in recurrent or inoperable skin cancer.

Skin tumor development involves not only genetic alterations in the epithelium that are well documented in the literature, but also less-well-understood epigenetic contributions from surrounding supportive stromal cells. Recent studies suggest that elevated ODC activity and polyamines stimulate modifier genes acting in critical metabolic pathways that ultimately determine the fate of genetically altered epithelial cells and the actual development of a tumor. However, the molecular pathways modulated by polyamines that play a key role in promoting tumorigenesis are not well characterized and is an understudied area of research. In addition, polyamines themselves are strong biological modifiers that promote skin tumorigenesis by altering the regulation of multiple genes. Since elevated levels of ODC and polyamines are common to skin tumors, it is important to characterize cells that are targeted by polyamines as well as nodal signaling pathways that mediate the tumor promoting effects of polyamines. The identification of mechanisms by which elevated levels of polyamines alter environmental signals to trigger the proliferation of latent epidermal stem cells possessing genetic lesions will lead to the development of better chemopreventive and chemotherapeutic strategies for cutaneous neoplasia.

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