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Hot Topic

Papillomavirus-associated squamous skin cancers following transplant immunosuppression: one Notch closer to control

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ABSTRACT

The frequent occurrence of cutaneous squamous cell carcinomas (SCCs) containing weakly tumorigenic human papillomaviruses (HPVs) following iatrogenic immunosuppression for organ transplantation remains incompletely understood. Here we address this problem in the light of recent insights into (1) the association of low-risk β-HPVs with skin SCCs in the rare genetic syndromes of epidermodysplasia verruciformis and xeroderma pigmentosum, (2) the frequent recovery of post-transplant tumor control on substituting calcineurin-inhibitory with mTOR-inhibitory immunosuppression, (3) the unexpectedly favorable prognosis of node-positive SCCs containing high-risk α-HPVs originating in the activated immune niche of the oropharynx, (4) the rapid occurrence of HPV-negative SCCs in ultraviolet (UV)-damaged skin of melanoma patients receiving Raf-inhibitory drugs, and (5) the selective ability of β-HPV E6 oncoproteins to inhibit Notch tumor-suppressive signaling in cutaneous and mesenchymal tissues. The crosstalk so implied between oncogenic UV-induced mutations, defective host immunity, and β-HPV-dependent stromal-epithelial signaling suggests that immunosuppressants such as calcineurin inhibitors intensify mitogenic signalling in *TP53*-mutant keratinocytes while also abrogating immune-dependent Notch-mediated tumor repression. This emerging interplay between solar damage, viral homeostasis and immune control makes it timely to reappraise strategies for managing skin SCCs in transplant patients.

Introduction

Viruses are both genetically derived from, and replicatively dependent upon, eukaryotic cells. A balance between viral infectivity (host pathogenicity) and host response (viral killing) is maintained in part by the host immune system which initiates antigen-dependent responses that control both viral infections per se and virally-transformed cells [1]. The latter notion of tumor immunity has gained support from many clinical observations, including spontaneous tumor regression [2]; response to cytokine therapies [3]; correlations between patient survival and immune response, whether measured by tumor-infiltrating lymphocytes [4] or circulating antitumor antibodies [5]; and heightened cancer-specific host responses in autoimmune diseases [6]. Controlled trials have confirmed survival benefits using several immunotherapies including sipuleucel-T (autologous mononuclear cells pulsed ex vivo with a fusion protein) in prostate cancer [7], ipilimumab (a CTLA4-blocking antibody that overcomes T cell inhibition) in melanoma [8], and anti-PD1 (which blocks T cell apoptosis) in renal cell carcinoma [9]. Here we examine the diverse roles of human papillomaviruses (HPVs) in squamous cell cancers (SCCs) of at-risk patients, including those with iatrogenic immune defects following solid organ transplantation.

Cancer and the immune system

Cancer in hereditary immunodeficiencies

Genetic immunodeficiency syndromes

Severe combined immunodeficiency (SCID) is caused by a lack of T-lymphocytes and, in some cases, NK- or B-cells. Most SCID patients, including those with *JAK3* or γ-cytokine receptor subunit mutations, develop cutaneous HPV lesions similar to those in

Abbreviations: AIDS, acquired immunodeficiency syndrome; BCC, basal cell carcinoma; CNI, calcineurin inhibitor; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; EV, epidermodysplasia verruciformis; HIV, human immunodeficiency virus; HPV, human papillomavirus; IFN, interferon; mTOR, mammalian target of rapamycin; SCC, squamous cell carcinoma; SCID, severe combined immunodeficiency; UV, ultraviolet light; XP, xeroderma pigmentosum.

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recipients of solid organ transplants. In human and animal SCID, these chronic HPV infections cause skin SCCs, as they do in SCID-like immunodeficiencies such as WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis, caused by mutations of the CXCR4 receptor) [10] and Netherton's syndrome.

Epidermodysplasia verruciformis (EV)

EV is an autosomal recessive disease caused by truncating mutations disrupting the EVER1 and EVER2 zinc-transporting gene products in the endoplasmic reticulum (ER; hence, EVER). This defect disrupts zinc transport between cell compartments [11], inhibiting Jnk (Jun kinase) and thereby increasing expression of the immediate-early transcription factor Jun which drives keratinocyte proliferation in EV patients via the mitogenic AP1 (Fos/Jun) heterodimer. This genetically determined mitotic trigger in turn drives HPV oncoprotein expression in infected keratinocytes.

EV- or zinc-related immune dysfunctions such as secondary T cell defects are also implicated in the skin cancer susceptibility of EV patients, while primary T cell disorders can mimic the EV phenotype in the absence of EVER gene mutations [12]. The high risk of post-radiotherapy skin cancer in EV patients could thus reflect a carcinogenic synergy between multiple factors: primary EV-dependent Jun activation, secondary radiation-induced tumor suppressor gene dysfunction(s), and an environmental interplay between EV-related immune dysfunction and a tumorigenic infectious agent endemic in skin.

Xeroderma pigmentosum (XP)

Solar ultraviolet (UV) radiation causes DNA damage in human skin as the result of a photochemical reaction in which DNA bases absorb UV light energy to form signature photolesions such as cyclobutane pyrimidine dimers (which preferentially affect methyl-CpG sites) in addition to reactive oxygen species, producing mutagenic base damage such as 8-hydroxyguanine [13]. XP is a genetically heterogeneous recessive defect of DNA repair in which nucleotide excision repair enzyme activity is impaired, leading to unrepaired UV-induced thymine dimers that cause early-onset cancers, especially skin SCCs. XP repair defects also increase T cell apoptosis, however, consistent with the immune dysfunction noted in these patients [14], while defective UV-inducible cytokine induction is also demonstrable.

Cancer in acquired immunodeficiencies

HIV/AIDS

The human immunodeficiency virus (HIV) abrogates immunity by parasitizing and eliminating CD4+ helper T cells, leading to increased tumor incidence, AIDS-defining or otherwise (Table 1). Estimates as to the immunodeficiency-dependence of HIV-associated malignancies are confounded by the common sexual transmission of HIV and other viruses; for example, HPV-associated cancers of the cervix and anus occur more often in HIV-infected patients than in the post-transplant setting [15], but this difference could partly reflect less sexual activity (and hence less HPV transmission) in transplant patients. In general, HPV-related tumors in HIV-positive patients tend to occur at a younger age and at a more advanced stage than in HIV-negative patients, consistent with HIV-related reductions in HPV clearance that prolong HPV persistence.

Chronic lymphocytic leukemia (CLL)

CLL is an age-dependent neoplastic syndrome associated with immune defects; the incidence, aggressiveness and mortality of second cancers, especially skin cancers, is increased in CLL patients [16]. Moreover, the growth rate of skin cancers accelerates after initiation of DNA-damaging antileukemic drug therapy, which may relate in part to the frequent presence of mutations affecting DNA repair genes such as *ATM* [17]. Given the identification of HPV in CLL-associated cancers [18], these findings suggest a tumor-promoting feedback loop between defective immunity, DNA damage, genetic instability, and as-yet-unidentified HPV co-factors.

Ultraviolet (UV) irradiation

Cell-mediated immunity, including tumor immunity, is locally and systemically impaired by UV radiation. Although there may be physiological benefits from UV-induced immunosuppression – including incidence reductions for multiple sclerosis, asthma and photosensitivity – such immunosuppression may also contribute to skin cancer independent of UV-induced keratinocyte DNA damage. For example, solar UV reduces skin production of tumorilytic Th1 cytokines while also stimulating IL-10-releasing regulatory T cells [19].

Post-transplant immunosuppression

Over 30 different tumor types increase in incidence following organ transplantation. Transplant recipients remain at more than double the risk of cancer compared to the general population [20], and the natural history of cancer in these patients tends to be more aggressive than usual. Such immunosuppression-associated solid tumors are a major cause of death in transplant recipients, raising health-economic issues [21].

Both the duration and dose-intensity of immunosuppressive drug therapy are risk factors for tumors in transplant recipients. Although the most obvious mechanism of post-transplant tumorigenesis is that immunosuppression unmasks the transforming activity of an infectious agent, plausible alternative mechanisms include suppression of T-cell-mediated tumor surveillance, development of chromosomal abnormalities due to reduced DNA repair, and/or neoplastic selection via chronic inflammation [22].

Not all immunosuppressant drugs exert the same post-transplant oncogenicity. Most potent in this regard are the calcineurin inhibitors (CNIs: e.g., cyclosporin A, tacrolimus) and, to a lesser extent, antimetabolites such as azathioprine [23]. CNIs directly promote keratinocyte transformation and skin carcinogenesis via inhibitory effects on p53 and E-cadherin tumor-suppressive activity that permit tumorigenic upregulation of pro-inflammatory and mitogenic NF-κB, ERK and AP1 signaling [24] reminiscent of that seen in cancer-prone EV-mutant skin tissues (see above).

Prednisolone, mycophenolate mofetil and mTOR inhibitors (e.g., sirolimus, everolimus) are of weaker tumorigenicity than CNIs: indeed, mTOR inhibitors induce remissions of certain sporadic tumors in immunocompetent patients via non-immunolytic signal-blocking effects [25]. Both mTOR inhibitors and mycophenolate exert anti-angiogenic effects that may suppress UV-induced skin SCCs and perhaps account for the reported lower tumorigenicity of calcineurin/mTOR inhibitor combinations. Moreover, regression of post-transplant tumors, particularly Kaposi sarcoma, has been noted when mTOR inhibitors are substituted for CNIs [26]. However, the most typical effect of such substitutions has been the prevention of new skin SCCs and a halving of the ratio of SCCs to basal cell carcinomas (BCCs) due to reversion of field cancerization [27]. Since sublethal UV damage causes more BCCs than SCCs in immunocompetent individuals, CNI-induced skin SCCs may occur in part via a UV-independent mechanism involving HPVs or direct inhibition of p53 function [28].

Immunosuppression is not the sole pathway of CNI-induced carcinogenesis. DNA repair is also inhibited by cyclosporin and tacrolimus, whereas it is only affected at the highest doses by sirolimus [29]. UV-induced DNA damage in skin is exacerbated by cyclosporin-dependent inhibition of the repair enzyme XPC in vitro and in vivo, impairing nucleotide excision repair and implying CNI-dependent oncogenic synergy between UV skin damage and immunosuppression.