Human Papillomaviruses and Non-melanoma Skin Cancer

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Human papillomaviruses (HPVs) infect the squamous epithelium and can induce benign and malignant lesions. To date, more than 200 different HPV types have been identified and classified into five genera, α, β, γ, μ, and ν. While high-risk α mucosal HPVs have a well-established role in cervical carcinoma and a significant percentage of other anogenital tract and oral carcinomas, the biology of the cutaneous β HPVs and their contribution to non-melanoma skin cancer (NMSC) has been less studied. Although the association of β HPV infection with NMSC in patients with a rare, genetically determined condition, epidermodysplasia verruciformis has been well established, the role of β HPV infection with NMSC in the normal population remains controversial. In stark contrast to α HPV-associated cancers, the presence of the β HPV genome does not appear to be mandatory for the maintenance of the malignant phenotype. Moreover, the mechanism of action of the β HPV E6 and E7 oncoproteins differs from the β HPV oncoproteins.
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Non-melanoma skin cancers (NMSCs), including basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), are the most common malignancies in the United States with over 1.3 million cases annually.[1] While ultraviolet (UV) radiation, immunosuppression, and host genetic constitution are known risk factors for the development of NMSC,[2,3] increasing evidence suggests that a link also exists between human papillomavirus (HPV) infection and skin cancer.[4–9]

Papillomaviruses (PVs) are small, non-enveloped, double-stranded DNA tumor viruses that have a circular, approximately 8-kb genome. PV genotypes are classified into five genera, α, β, γ, μ, and ν, based on the degree of sequence similarity. PVs infect the squamous epithelium of a number of species and cause epithelial hyperplastic lesions that range from benign to malignant. To date, at least 200 HPV types have been described. Much of our knowledge on the contribution of HPVs to carcinogenesis stems from studies with α HPVs, which infect the mucosal epithelium; these HPVs can be subdivided into low- and high-risk, depending on the malignant progression potential of the associated lesion. High-risk mucosal HPVs cause almost all cases of cervical cancer, and also are associated with a significant fraction of other anogenital tract, as well as oropharyngeal, cancers.[10]

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HUMAN PAPILLOMAVIRUS AND EPIDERMODYSPLASIA VERRUCIFORMIS

It has been proposed that the β HPVs may also be classified into low- and high-risk groups. The first evidence for the involvement of β HPVs with cancer was their association with a rare, genetically determined condition, epidermodysplasia verruciformis (EV). EV was first described in 1922 by Felix Lewandowsky and William Lutz.[11] Patients with EV develop warts and macular lesions that usually persist throughout life.[12] By the fourth decade of life 30%–60% of patients with EV develop carcinoma in situ or SCC at sun-exposed areas of the body.[13] Autoinoculation and heteroinoculation experiments by Stefania Jablonska and Gerard Orth linked infection with HPV with lesions and cancers in EV patients.[14,15] The most frequently detected β HPV genomes in benign EV lesions are HPVs 5, 8, 9, 12, 14, 15, 17, and 19–25[16]; HPV5 and 8 have been detected in 90% of cutaneous SCCs in EV patients.[17] The association of HPVs 5 and 8 with SCC in EV patients led to their classification as "possibly carcinogenic."[18]

Immunology of Epidermodysplasia Verruciformis

Although EV patients are unable to effectively clear β HPV infections, they do not appear to be at a

higher risk for infections with bacteria and other viruses, including α HPVs.[19–21] Moreover, the risk for cancers other than NMSCs does not appear to be elevated in EV patients.[22] While humoral immunity is preserved,[23] cell-mediated immunity (CMI) is impaired in EV patients.[24,25] HPV-associated lesions usually regress spontaneously; however, the complete regression of EV lesions has never been observed, and the immune responses toward β HPV-infected keratinocytes are still poorly understood. The increased expression of tumor necrosis factor alpha (TNF-α) and transforming growth factor-beta (TGF-β) that has been observed in keratinocytes from EV lesions may play a role in impaired local immunosurveillance.[26] Further studies are needed to elucidate the immune response in EV patients.

Genetic Basis of Epidermodysplasia Verruciformis

An estimated 10% of EV patients are born from consanguineous parents, and there is more than one affected sibling in about 10% of EV families. The sex ratio of EV is close to one, and the proportion of EV siblings is approximately 25%, indicating that EV is an autosomal recessive disease.[22] Genome-wide linkage analysis was used to map the first susceptibility locus for EV (*EV1*) on chromosome 17q25[27–29]; subsequently, a second locus was mapped on chromosome 2p21-p24, indicating that non-allelic heterogeneity exists in EV.[29]

Approximately 75% of EV patients have mutations in one of two human susceptibility genes contained in the EV1 region, *transmembrane cochlear (TMC)6* and *TMC8*.[28] *TMC6* and *TMC8* encode for the transmembrane proteins EVER1 and 2. EVER1 and EVER2 are expressed in keratinocytes and leukocytes and localize to the endoplasmic reticulum, where they form a complex with the zinc transporter ZnT-1. ZnT-1 is involved in zinc efflux and the resistance to zinc toxicity,[30] leading to the possibility that unbalanced intracellular zinc levels affect the viral life cycle.[31] In addition, EVER2 also may be involved in skin homeostasis.[31] It has been hypothesized that EVER1 and 2 act as restriction factors for EV-specific HPVs in keratinocytes, and also function in the regulation of the immune system.[32] However, the exact function of EVER1 and 2 in the development of persistent HPV infections remains unclear. Additionally, because not all EV patients have mutations in EVER1 and 2, it is likely that more genes and loci are involved in the development of EV.[33]

UV and Epidermodysplasia Verruciformis

UV radiation is a co-factor for carcinogenesis in the general population as well as in EV patients. A number of EV patients develop NMSC at sun-exposed sites. Upon UV-exposure, UV-mediated immunosuppression occurs.[34] During UV-mediated immunosuppression Langerhans cells leave the epidermis; normally the epidermis is then re-populated with Langerhans precursor cells migrating along a CCL20 gradient.[35–37] C/EBPβ is a key regulator of *CCL20* expression in keratinocytes. EV lesions that lack Langerhans cells express low to no CCL20 protein[38] Interestingly, HPV8 E7 interacts with C/EBPβ in the nucleus and interferes with the binding of C/EBPβ to the CCL20 promoter in vivo and suppresses *CCL20* expression.[38] Keratinocytes that express the HPV8 E7 protein produce low amounts of the chemokine CCL20 and have reduced chemotactic activity toward Langerhans cells.[38] Therefore, Langerhans cells may not properly repopulate EV lesions upon UV exposure.

β HUMAN PAPILLOMAVIRUSES AND NMSCs IN IMMUNOSUPPRESSED PATIENTS

β HPVs also are the likely etiologic agent of NMSCs that arise in chronically immunosuppressed patients. NMSC is the most common cancer among solid organ transplant recipients (OTRs), and causes significant morbidity and mortality in these patients.[3,39] Immunosuppressed OTRs have a higher risk of developing NMSC than the general population, with a reversal of the usual BCC:SCC ratio.[40–42] In fact, within 15 years of transplantation, up to 90% of OTRs develop skin warts and 40% develop NMSC.[43] The SCCs that develop in OTRs have characteristic clinical and morphological features of HPV-induced warts.[44] SCC often co-localize with β HPV-induced warts in OTRs, indicating that persistent warts may progress to skin cancer.[45] Moreover, the prevalence rate of β HPV DNA in precursor lesions, actinic keratoses (AKs), and SCCs from organ transplant recipients is higher than in the general population.[46–48]

β HUMAN PAPILLOMAVIRUSES AND NMSCs IN THE GENERAL POPULATION

While it has been established that β HPV infections are the etiologic agents of SCC in EV patients, and likely in immunocompromised patients, the contribution of β HPV infections to NMSCs in the general population is still an area of debate.[49,50] While β HPV genomes are frequently detected in NMSC, they also are often found on healthy skin of non-EV individuals.[51,52] However, epidemiological studies have shown that patients with a history SCC are more likely to be positive for β HPV infections than normal individuals.[8,53–59] The prevalence of β HPV in AK, the SCC precursor lesion, is