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Viral Carcinogenesis in Skin Cancer

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Abstract

The skin is an organ in which direct contact with viruses, solar UV irradiation and increased susceptibility to immune suppression gather to support viral tumorigenesis. Viruses transform keratinocytes by activation of cancer-promoting genes. Viral proteins may directly act as oncogenes that drive cells to proliferate or generate inflammatory responses and cause regeneration of injured cells that eventually lead to malignant transformation. Accelerated viral carcinogenesis is observed in the immune-deficient host. Decreased T-cell reactivity and lower number of antigen-presenting cells in the skin assist in viral escape and emergence of skin tumors. Three pathogenic human viruses associated with skin neoplasms are described: human papilloma virus (HPV), Kaposi's sarcoma (KS)-associated herpesvirus and human T-cell leukemia virus type 1. HPV was linked to squamous cell carcinoma (SCC) of the skin after its role in SCC of the cervix has been discovered. In the rare autosomal recessive epidermodysplasia verruciformis, an increased susceptibility to specific HPV strains initially results in widespread wart infection and later in life in the development of SCC over the sun-exposed skin. The role of HPV in nonmelanoma skin cancer of immune competent hosts is more difficult to prove. The discovery of human herpesvirus 8 as the causative pathogen of KS was made following the AIDS epidemic, and its role in all clinical variants of this tumor was confirmed. KS-associated herpesvirus exerts its tumorigenic effect through a wide repertoire of genes that regulate angiogenesis, inflammation, and cell cycle. Human T-cell leukemia virus type 1 causes adult T-cell leukemia and is often associated with skin eruptions that share common features with cutaneous T-cell lymphoma. In summary, studies of oncogenic viruses shed light on molecular mechanisms leading to tumor formation and aid in recognition of new pathways of carcinogenesis.

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Virus-Induced Tumorigenesis

Viruses were initially incriminated in the induction of cancer as early as 1908, when the infectivity of avian leukemia was demonstrated and later with

the discovery of Rous sarcoma virus as the transmissible agent [1]. The notion that viral oncogenicity is not restricted to animal tumors but also to human cancers was gathered through the establishment of the role of Epstein-Barr virus in Burkitt's lymphoma, hepatitis B virus in hepatocellular carcinoma and later of hepatitis C [2, 3]. Human papilloma virus (HPV) was linked to genital cancer only in the early 80s [4]. It took so long to realize that viruses take an etiological role in carcinogenesis because cancer development is a rare and delayed outcome of active infection. At its early stages, the virological research was dependent on circumstantial evidence and on direct visualization of viral particles and cytopathic effects. The development of recombinant DNA technology has enabled direct detection of nucleotide sequences of viral genome. It is now possible to detect the presence of a viral agent within the infected cell using in situ hybridization and the highly sensitive polymerase chain reaction techniques.

The skin is a natural target of virus-induced carcinogenesis. While viruses may create the initiating event that leads to cancer, they may still need the mediating effect of other cofactors. The skin is an organ where UV irradiation, direct contact with viruses and increased susceptibility to immune suppression gather to promote the formation of tumors.

There are several direct mechanisms by which viruses transform the host cell. Insertion of viral genome into human DNA can be mutagenic or can activate tumor-promoting genes, called oncogenes. Mutated proto-oncogenes or viral protein homologues to transcription factors induce uncontrolled cell proliferation. Viral proteins may activate cell growth through a variety of transduction signal pathways.

Tumorigenic Effect of Inflammation

Viral infections are associated with reactive inflammation. The role of inflammation as a driving carcinogenic force is gaining increased attention. Cytokine secretion by effector cells of the immune system may create a growth signal for other cells. Tumor necrosis factor- α (TNF- α) secreted by adjacent endothelial cells triggers NF- κ B and induces malignant transformation [5]. Granulocyte-macrophage colony stimulating factor is secreted by keratinocytes shortly after injury and mediates epidermal cell proliferation in an autocrine manner [6]. TNF- α , interferon- γ and interleukin-2 (IL-2) may suppress synthesis of viral proteins and thus prevent recognition and destruction of infected cells [7, 8]. The regeneration processes of cellular damage caused by the cytopathic effect of viral invasion can trigger neoplastic transformation of the regenerating tissue [reviewed in 9].

Viral Carcinogenesis and Immunity

Immune deficiency states established the relation between viral infection and cancer. Increased susceptibility to viruses is a common outcome of

impaired immunity. Immunosuppressed organ transplant recipients have up to hundredfold increased risk of squamous cell carcinoma (SCC) and a tenfold increased risk of basal cell carcinoma (BCC), resulting in a reversal of the normal ratio of SCC to BCC [10–12]. Duration of immunosuppression and past sun exposure are important confounders [13, 14] but the contributing role of HPV cannot be overlooked. Immunosuppressive agents are directly targeted against T lymphocytes, thus reducing T cell cytotoxic effect against cellular targets. Cytotoxic T cells are the critical effectors that mediate cell destruction in viral infections. T cells recognize specific peptides of degraded viral proteins when presented on cell surface [15, 16]. Upon triggering of the T cell receptor, proteolytic enzymes including perforins and granzyme B are secreted and destroy target cell. Viruses betray their presence to the immune system once they have entered cells and started synthesis of their viral proteins. Effective antigen presentation is required for T cell responses. By suppressing the expression of molecules associated with antigen processing and presentation, viruses abrogate the major immune mechanism that deals with the elimination of infected and tumor cells. This is accomplished either by downregulation of MHC class I molecule synthesis and by interfering with transport of class I molecules to the cell surface. In some cases herpes simplex and other viruses shut off the expression of most viral proteins during latency or express mainly nonimmunogenic or antagonistic peptide epitopes [17, 18]. In the skin, the main cells to be damaged by immune suppression are antigen-presenting cells. A decrease in skin dendritic cell numbers and function reduces antigen presentation capacity, and assists latent viruses to persist.

Human Papilloma Virus and Squamous Cell Carcinoma

HPVs are small DNA viruses infecting keratinocytes in various locations. Over 120 different types of HPV have been identified to date. The most frequent manifestation of cutaneous HPV infection is the development of cutaneous warts, self-limiting epithelial proliferations. HPV has also been recognized to have a role in the development of SCC of the genital tract, but the role in the development of cutaneous malignancy is less clear [19].

The difficulty in elucidating the extent and mechanism of HPVs involvement in skin cancer arises from their propensity to infect in practice everyone sometime throughout life, the low copy number of viral DNA and its presence in only a proportion of tumor cells. Absence of virus in tumor cells suggests a role of HPV at tumor initiation rather than in the maintenance of the malignant phenotype. The mechanisms by which HPV induces neoplastic transformation are probably various, and in fact, in vitro models demonstrate only a weak transforming

potential. The E6 and E7 genes of HPV seem to be the dominant oncogenes, leading to morphologic transformation and anchorage-independent growth but not to tumorigenicity [20]. E6 and E7 exert a direct effect on cell cycle regulators p53 and Rb proteins by binding to these proteins and enhancing their proteolysis [21]. This effect by itself is not enough to transform cells [22]. UV exposure is an important cofactor in HPV carcinogenesis. It may be then, that the contribution of HPV infection to cancer is via inhibition of apoptosis of UV-damaged cells, which should have otherwise gone to senescence and disintegration. Unrepaired DNA damage was observed in UVB-irradiated cells expressing the E6 protein, and inactivation of the retinoblastoma protein with HPV-16 E7 resulted in significant inhibition of the ability to recover mRNA synthesis and increased levels of apoptosis following UV radiation [23, 24].

Human Papilloma Virus and Squamous Cell Carcinoma in Epidermodysplasia Verruciformis

The paradigm for HPV involvement in human skin cancer was based on patients with epidermodysplasia verruciformis (EV). This is a rare autosomal recessive hereditary disease, characterized by disseminated, persistent, flat warts and pityriasis versicolor-like macular lesions arising during childhood. Later in life patients tend to develop cutaneous SCC most frequently localized in sun-exposed areas of the skin. The HPV types found in patients with EV are referred to as EV-HPV types, and include, among others, HPV types 5, 8, 9, 12, 14, 15, 17, and 19–25 [25, 26]. In SCC lesions of EV patients, HPV DNA usually persists extra chromosomally in high copy numbers and is actively transcribed. In contrast to multiple HPV types found in benign lesions, mostly HPV types 5 or 8 and sometimes HPV types 14, 17, 20, or 47 are found in SCC of EV. These are regarded as high-risk HPV types. The persistence of HPV infection in EV has been suggested to be due to the inability of the patient's immune system to reject EV-HPV-harboring keratinocytes by a still unknown immunogenetic defect and is probably also influenced by environmental factors, particularly ultraviolet radiation [27]. EV has been linked to two susceptibility loci on chromosome 17p25, where two EV sensitivity genes (EVER1 and EVER2) have been discovered [28, 29]. The gene products EVER1 and EVER2 have features of integral membrane proteins and are localized in the endoplasmic reticulum. At present, it is still unclear how these genes are involved in the immune response to control EV-HPV infection in epidermal keratinocytes [30].

Human Papilloma Virus and Skin Cancer in the General Population

EV-HPVs have also been found in normal skin and in nonmelanoma skin cancers in the immunocompetent general population, with detection rates of about 30% for SCC and BCC. A high prevalence (85%) of EV-HPV DNA has

also been found in actinic keratoses, which are precursor lesions of SCC in the immunocompetent population [19]. HPV DNA was also detected in normal skin but at a much lower prevalence compared to cancer tissue.

Human Papilloma Virus and Squamous Cell Carcinoma in Immunosuppressed Patients

Historically, the second model of HPV-induced SCC was that of skin cancer occurring in the context of immune suppression, particularly organ transplantation. Renal transplant recipients are highly susceptible to extensive cutaneous warts and have a 200-fold increased incidence of cutaneous SCC, arising on sun-exposed body sites [31]. Up to 90% of SCCs in immunosuppressed patients contain HPV DNA. A diverse spectrum of HPV types was detected, mostly EV-associated types. Multiple infections of individual tumors were frequently noted in immunosuppressed patients.

Human Papilloma Virus and Verrucous Carcinoma

HPV has also been associated with certain unique subtypes of SCC. Verrucous carcinoma is a form of SCC characterized by slow-growing exophytic tumors with cauliflower-like appearance that develop at sites of chronic irritation. It is considered a locally aggressive, low-grade SCC with little metastatic potential. In their early stages, tumors may be mistaken for warts; however, they are unresponsive to locally destructive procedures and slowly, over months or years, increase in size and deeply penetrate the dermis. Verrucous carcinoma typically occurs at three sites: epithelioma cuniculatum in the plantar surface of the foot, giant condylomata of Buschke-Löwenstein in the perineum and oral florid papillomatosis in the oral mucosa of elderly male tobacco chewers [32, 33]. Verrucous carcinomas are thought to be caused by HPV and are most often associated with HPV types 6 and 11 [34].

Human Papilloma Virus and Periungual Squamous Cell Carcinoma

SCC of the distal digit and periungual skin is strongly associated with genital oncogenic types, especially HPV16, indicating a genital-digital mode of transmission. HPV16 RNA transcripts have been detected in these cancers, suggesting that HPV has a role in their pathogenesis [35].

Treatment of Human Papilloma Virus-Induced Skin Disease with Immunomodulators

HPV infection is difficult to treat due to the evasive properties of the virus. It infects basal keratinocytes and lies relatively dormant, not eliciting an effective immune response. Langerhans cells are not induced to present viral antigens and HPV-specific T cells are probably inadequate in mounting necessary

cytokines or recruiting effector cells to fight the infection. Imiquimod, an imidazoquinolone amine, is an immunomodulating agent which has been approved by the US Food and Drugs Administration for the treatment of genital HPV warts. Imiquimod does not possess a direct antiviral activity. Through activation of Toll-like receptors (TLR), particularly TLR-7, imiquimod is capable of inducing the lacking inflammatory signals needed to recruit effective antiviral response against HPV. TLRs consist of human pathogen-recognition receptors which allow cytokine synthesis in response to various classes of microbial products, regulating both innate and acquired immune responses. Through activation of TLR-7, imiquimod stimulates the immune system. It activates the innate immune response through induction, synthesis and release of cytokines, including INF- α , IL-6 and TNF- α . These cytokines are maturation signals that activate several types of antigen-presenting cells: dendritic cells, Langerhans cells, macrophages and B lymphocytes. The result is enhancement of the immune response against the virus [36]. The immune response-modifying properties of imiquimod extended its therapeutic uses beyond the treatment of HPV infections. Imiquimod has been studied as a therapy for a variety of premalignant and malignant skin disorders and has recently been approved for the treatment of superficial BCC and actinic keratosis [37].

Human Herpesvirus 8 and Kaposi's Sarcoma

Clinical Variants of Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a vascular neoplasm consisting of spindle-shaped endothelial cells expressing endothelial and macrophage markers, mainly localized in the skin. The classical variant was recognized in 1872, affecting elderly people of Mediterranean and eastern European origin. Classical KS is usually very slowly progressive indolent neoplasm of the lower legs consisting of bluish macules that slowly coalesce to larger plaques and may develop protruding nodules, sometimes accompanied by nonpitting leg edema. Upper body and mucosal involvement, mainly the palate, is less frequent. Extracutaneous lesions uncommonly affect lymph nodes, stomach and duodenum [38].

The endemic form of KS develops in residents of equatorial Africa. It may have a benign nonaggressive course, a lymphadenopathic form or a florid aggressive variant [39]. Retrospectively, the florid variant may be linked to HIV positivity whereas HIV-negative patients display the more classical features of KS [40].

Post-transplant KS shed light on the crucial role of immune surveillance in KS development [41]. The correlation between KS progression and the depth of immune suppression is markedly demonstrated in these patients. Withdrawal of immunosuppressive agents can lead to complete clearance of the disease.

It takes a median interval of 29–31 months for KS to develop from time of transplantation [42].

In the late 1970s, clusters of KS were first observed in HIV-infected individuals, and from here the way to unveil the role of herpesvirus 8 in the etiology of KS was short. The epidemic variant of KS involves skin, mucosa, lymph nodes and viscera and may frequently be fatal. Its propensity to affect homosexual men with AIDS 20 times as frequently as it did other male patients who had similar degrees of immunosuppression drew attention to the option of a different causing pathogen [43].

Tumorigenic Effect of Kaposi's Sarcoma-Associated Herpesvirus

In 1994, Chang et al. [44] identified DNA fragments of a previously unrecognized γ 2-herpesvirus, herpesvirus 8 or KS-associated herpesvirus (KSHV), in a KS skin lesion from a patient with AIDS, that later was found in over 95% of KS lesions and in all clinical variants [45]. KSHV is involved in the pathogenesis of KS, primary effusion lymphoma and the plasma cell variant of multicentric Castleman's disease. KSHV has also been linked to other, nonmalignant disorders such as bone marrow failure in transplant recipients and hemophagocytic syndrome [46].

Current data suggest that KSHV, acquired exogenously, initially most likely infects a B lymphoid precursor, or alternatively a KS precursor cell, integrates and subsequently enters a latent phase of infection. Immunosuppression, genetic predisposition, environmental and other unknown stimuli enable activation and transcription of viral genes. In a slow evolutionary course, KSHV has pirated many human genes whose products regulate angiogenesis, inflammation, and the cell cycle [41]. NF- κ B is activated by the virus and induces vascular epithelial growth factor production. KSHV encodes four interferon regulatory factor (IRF) homologues. Interferon signaling is an early event initiated rapidly upon virus infection, independent of protein synthesis and triggers antiviral responses. KSHV vIRF products presumably contradict interferon-protective effects and promote KSHV infection [47]. Another KSHV product encodes for a mutated G protein-coupled receptor, one of the largest family of signaling molecules that respond to a wide array of ligands, induces constant signaling activity independent of ligand binding [48] and generates many mitogenic and angiogenic cytokines that are vital to the biology of KS.

Overall, KSHV protein products shed light on new cellular mechanisms of oncogenesis.

Therapy

KS is radiosensitive and responds to several chemotherapeutic agents including vinblastin [49], etoposide and liposomal doxorubicin that is less toxic

than the nonliposomal drug [50]. Biologic treatment with interferon- α is a first-line treatment for younger patients with epidemic KS and can be administered systemically or intralesionally. Primary prevention of KS in individuals who were to undergo organ transplantation has been successful with oral cidofovir [51]. The systemic side effects of antiviral drugs make them unsuitable for long-term administration. Reversal of the immune suppressed status is often associated with significant regressions of KS lesions.

Human T-Cell Leukemia Virus Type 1

Human T-cell leukemia virus 1 (HTLV-1) is a member of the deltaretrovirus genus of the retrovirus family, which includes the bovine leukemia virus as well as the primate T-cell leukemia viruses [52]. HTLV-1 infection is endemic in Japan, the Caribbean basin, central Africa, parts of South America, Melanesia, Papua New Guinea, and the Solomon Islands [53, 54]. It is estimated that there are 15–20 million carriers of the virus worldwide. In other parts of the world, HTLV-1 is mainly detected in immigrants from endemic areas and in intravenous drug abusers [53]. HTLV-1 is a highly cell-associated virus and efficient transmission requires transfer of infected cells and cell-to-cell contact. The major route of transmission is via infected cells in breast milk but transmission through infected blood products and sexual transmission also occur [55, 56].

Clinical Spectrum of Human T-Cell Leukemia Virus Type 1

More than 90% of infected individuals remain asymptomatic carriers. However, those who develop a clinical disease may present with varied clinical manifestations.

Adult T-Cell Leukemia

The cumulative incidence rate of adult T-cell leukemia (ATL) in HTLV-1 carriers approximates 2–5% with a latent period from infection to outbreak of leukemia of 20 years or more. ATL is a fatal malignancy with a multiorgan invasion by leukemic infiltrate and refractory hypercalcemia complicating more than 70% of cases during clinical course [57]. Skin involvement may occur at any time point and is polymorphic, with uncharacteristic macular eruption, plaques or nodules formed by monoclonal T cells. Although the virus infects T cell subsets that display either CD4 or CD8 cell surface markers, the leukemic cell is exclusively of the CD4+ subtype [58].

The prognosis of ATL is poor. Most patients die within 1 or 2 years of diagnosis, usually of infections or hypercalcemia [59]. The course of smoldering and chronic ATL is less dramatic and involvement of inner organs and hypercalcemia

are observed less frequently than in ATL lymphoma and acute ATL and patients have a better prognosis [60].

Neurological Disease

HTLV-1 infection is associated with chronic progressive myelopathies, referred to as tropical spastic paraparesis in the Caribbean and HTLV-1-associated myelopathy in Japan. Patients suffering from TSP/HAM are generally younger than ATL patients with a shorter latency between infection and clinical onset. The lifetime risk to develop HAM/TSP has been estimated at 1% [61].

Infective Dermatitis

An exudative, chronic, relapsing eczema in children has been associated with a difficult to control infection by *Staphylococcus aureus* and β -hemolytic streptococcus [62]. The characteristic clinical picture, the recalcitrant course, and HTLV-1 seropositivity differentiate infective dermatitis from other forms of recurrent eczema [63]. Immunosuppression in HTLV-1 carriers is assumed to play a role in the pathogenesis of infective dermatitis. Infective dermatitis has been rarely reported from regions outside the Caribbean; therefore, regional, cultural, or genetic factors probably participate in the pathogenesis of infective dermatitis [64].

Human T-Cell Leukemia Virus Type 1 Mechanism of Action

Following infection of a cell with HTLV-1, the RNA genome is transcribed into DNA and integrates into host cell chromosomal DNA [52]. Infection of the infected cell is therefore life-long and the viral genome is passed on to daughter cells. Infection of T lymphocytes by HTLV-1 in vitro leads to their continuous growth in tissue culture and the development of cell lines with growth characteristics of transformed cells. In infected patients, HTLV-1 is mainly present in CD4+ T cells, but it has also been found in dendritic cells of blood and cells from the synovial lining of arthritic joints [65].

HTLV-1 encodes an oncoprotein, Tax, which induces persistent activation of NF- κ B, and of a large array of cellular genes that contribute to T cell transformation and elicit host's inflammatory responses [66]. NF- κ B activation leads to increased expression of many cytokines and their receptors, including IL-2 and the IL-2-R α , which leads to polyclonal proliferation of HTLV-1-infected cells by autocrine and paracrine mechanisms. In addition, NF- κ B stimulation causes increased expression of proteins with antiapoptotic function [67].

Tax also causes dysregulation of cellular genes involved in cell cycle control, apoptosis, and DNA repair, such as p53, cyclin D and CDKs 4 and 6 [68]. In the majority of ATL cases, there is no evidence of expression of Tax [59]. The current model of ATL pathogenesis is therefore one in which initial infection by

HTLV-1 leads to Tax expression and polyclonal expansion of infected CD4+ cells. Over time, proliferation and Tax expression lead to genetic and epigenetic changes in the host genome and to the outgrowth of a leukemic clone that no longer expresses Tax [69].

In summary, the interest in oncogenic viruses is twofold: clinical and mechanistic. Their clinical manifestation shed light on the important role of host defense, genotoxic exposures and new options of therapy. The growing understanding of molecular mechanisms utilized by viruses for tumor formation reveals new pathways of carcinogenesis and points at critical genes which in the future may be the basis of new therapies.

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