



## Viruses associated with skin and mucosal cancers

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### In this issue

*Viruses associated with skin and mucosal cancers*  
 Pierre Coursaget, Tours, France

*Merkel cell carcinoma: the first human cancer shown to be associated with a polyomavirus*  
 Mahtab Samimi et al., Tours, France

*Origin and immunoescape of uterine cervical cancer*  
 Dorien van Hede et al., Liège, Belgium

*HPV in genital cancers (at the exception of cervical cancer) and anal cancers*  
 Silvia de Sanjosé et al., Barcelona, Spain

*Human papillomavirus (HPV) and oropharyngeal squamous cell carcinoma*  
 Tina Dalianis, Stockholm, Sweden

*Cutaneous HPV and skin cancer*  
 Rosita Accardi et al., Lyon, France

In the last 20–30 years it has been recognized that a high proportion of human cancers are due to viruses, and that viral flora, like bacterial flora, is present on normal skin and mucosa. Many commensal viruses have now been identified.

The link between infection and cancer is now uncontested and infectious agents, mostly viruses, have been recognized as the etiological agents of more than 20% of cancers worldwide. On the basis of epidemiological and biological studies, 22 viruses have been classified as carcinogenic in humans. Epstein-Barr virus (EBV) is associated with Burkitt lymphoma, Hodgkin lymphoma, AIDS-related lymphomas, and nasopharyngeal carcinoma; hepatitis B and hepatitis C viruses (HBV and HCV) with liver cancer; human herpes virus 8 (HHV8 or KSHV) with Kaposi sarcoma and primary effusion lymphoma; human T-cell lymphotropic virus type 1 (HTLV-1) with adult T-cell leukemia (ATL). Moreover, 13 genital human papillomaviruses (HPVs) are associated with cancers of the cervix, vulva, vagina, penis, anus and oropharynx. In addition, two cutaneous HPV types are reported to be associated with the development of a skin lesion called epidermodysplasia verruciformis (EV), observed in patients with a rare genetic disorder. These lesions frequently develop into squamous cell carcinoma. Merkel cell polyomavirus (MCPyV) has recently been recognized to be associated with a relatively rare skin tumor, Merkel cell carcinoma. In addition, although not a direct causal agent of cancer, human immunodeficiency virus-1 (HIV-1) dramatically increases the frequency of virus-associated cancers. The main mechanism by which HIV induces cancer is by impairment of the immune system, thereby favoring the development of both oncogenic viruses and virus-associated cancers. It should be noted that most of these oncogenic viruses ( $n = 17$ ) are causative agents of skin and mucosal cancers.

The reviews published in this special issue will help to update and disseminate virological and medical knowledge about the etiological role of viruses in skin and mucosal cancers.

Healthy human skin and mucosa harbor resident or transient viruses, and a growing body of evidence suggest the emerging concept of viral skin flora. Innovative molecular screening techniques have led to the surprising identification of many unknown viruses on the skin and/or mucosa of every person tested. The viruses detected mainly include polyomaviruses (MCPyV, HPyV6, HPyV7 and possibly HPyV9) and papillomaviruses (hundreds of different viruses). However, herpes viruses (HHV6, HHV7, HSV1 and 2, HHV8, VZV) and a poxvirus (moluscum contagiosum virus) have also been detected. A human gyrovirus has recently been identified on the skin surface, although the specificity of its detection on the skin remains to be established [1]. Most of these viruses can be considered resident symbiotic organisms on normal skin, but some of them are associated with skin and mucosal cancers.

The development of cancers induced by infectious agents is a consequence of their persistence in the host. The observation that the risk of cancer increases dramatically with immunosuppression,

suggests an infectious etiology for these cancers. Viruses associated with skin and mucosal cancers are DNA viruses and include one herpes virus (HHV8), one polyomavirus (MCPyV), and 13 papillomaviruses. It should be noted that the laboratory of Yuan Chang and Patrick Moore separately identified two of these viruses, at an interval of 14 years [2,3]. MCPyV is today recognized as the etiologic agent of Merkel cell carcinoma, a rare skin cancer (the molecular biology and pathogenesis of MCPyV are described in the article by Samimi et al. [4]). The association of HPV and cervical cancer was recognized in 1983 by the Zur Hausen laboratory [5,6]. Thirteen papillomaviruses of the alpha species (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) are today known to be associated with cancers of the cervix (see article by Van Hede et al. [7]), vagina, vulva, penis and anus (see article by de Sanjosé et al. [8]). It was also recently shown that high-risk HPVs are associated with around half of all oropharynx cancers, as reported in the article by Dalianis [9].

Detection of several HPV types in the beta species is higher in squamous cell carcinoma (SCC) than in either healthy subjects or in basal cell carcinoma (BCC) [10]. However, the role of cutaneous HPVs in skin cancers is still not completely understood, and further studies on the biological and epidemiological association of these gamma HPVs in SCC are needed (see article by Accardi et al. [11]). Because skin cancers regularly appear on sun-exposed areas, UV radiation is regarded as a major risk factor. UV radiation can induce multiple types of DNA damage, with as a consequence either cell cycle arrest and then DNA repair or apoptosis resulting in cell death. It is also believed that UV and viruses act synergistically to transform cells [12].

Epidemiological studies indicate that many more people are infected with oncogenic viruses than those developing the corresponding virus-associated cancer. Cancer development is a multi-step process and oncogenic viruses enable only some of the steps necessary to progress from a normal cell to a malignant one. DNA viruses (papillomaviruses and polyomaviruses) are known to induce cancer through direct mechanisms at the cell genome level. The viral DNA is frequently integrated into the host cell DNA in transformed cells. Several viral proteins expressed early during the cycle of DNA viruses facilitate viral replication. After integration of the viral DNA into the host cell DNA, these proteins are over expressed or modified and can promote cancer development by modifying the activities of cellular regulation proteins. Binding to viral oncoproteins leads either to functional inactivation or to degradation of key cell proteins. Oncoproteins can promote cellular transformation by interfering with the regulation of cell cycles, apoptosis, and other cellular pathways. In contrast to papillomaviruses and polyomaviruses, the transforming properties of HHV8 are due to the production of viral proteins homologous to host cell proteins or proteins with immunomodulatory functions, which then act on cell cytokine production, cell cycle control and apoptosis.

It is also evident that immunosuppression is involved in the development of these virus-associated cancers and clearly predispose to reactivation of latent viral infections. These viruses have the ability to exploit a number of immune evasion strategies, and impairment of the innate and adaptive immune system pathways thus helps to initiate or maintain cancer development (see article by van Hede et al. [7]). This immune evasion enables these viruses to persist during a latent phase within host cells, and then to reactivate under immunosuppression or UV irradiation. Recent evidence also supports the hypothesis that Langerhans cells (LCs), a specific subset of dendritic cells detected in skin and mucosal epithelium, participate in this immune evasion by promoting tolerance to oncogenic viruses through the induction of regulatory T-cells at steady state.

## Future prospects

The future perspectives for research on viruses associated with skin and mucosal cancers include clarification of the still incompletely understood role of beta papillomaviruses in SCC, the discovery of other virus-associated cancers and the development of specific therapies.

It is evident that epidemiological studies to demonstrate the link between beta papillomaviruses and SCC are warranted to clarify the role of these viruses in this skin cancer. In addition, a new animal model that may assist the study of skin cancer is that of the soft furred multimammate rat (*Mastomys coucha*), which is infected with a persistent papillomavirus (MnPV) and develops benign tumors. MnPV persists without evidence of integration, as observed for HPV 5 and 8, and can evolve to SCC in conjunction with tumor-promoting agents. In addition, the induction of cancer without integration of the viral DNA was recently reported for the raccoon polyomavirus that induces brain cancers in raccoons [13].

Given today's technology, including PCR amplification and deep sequencing, it is expected that new viruses will be identified in the near future on skin and mucosal surfaces. In addition, since the incidence of skin and mucosal cancers other than those reported here is increased in immunosuppressed patients [14], we can expect the discovery of new viral agents related to cancer. Among these cancers, non-melanoma skin cancers and SCCs of the conjunctiva (SCCCs) are also likely to be virus-related.

Understanding viral infections associated with cancers, including the discovery of cells in which these viruses replicate, will open the way for therapeutic intervention and prevention. Prevention of virus-induced cancers is focused mainly on developing preventive vaccines against viral infections. The first great success in the area of cancer control was the dramatic reduction of the HBV chronic carrier state in many endemic countries after implementation of mass immunization against HBV, although this goal was not reached until 30 years after the

discovery of the vaccine [15]. The efficacy of the HBV vaccine in reducing hepatocellular carcinoma was also demonstrated in infants in Taiwan [16]. The second success in prophylactic immunization against virus-associated cancers has come against genital papillomaviruses, with the demonstration of the vaccine's efficacy against premalignant genital lesions [17] and genital warts [18]. It is expected that HPV vaccination will also successfully decrease genital and anal cancers, as well as oropharyngeal cancers in the future. It is expected that mass immunization with HBV and HPV vaccines will eventually prevent 1 million cancers per year worldwide. Prophylactic vaccines developed against HHV8, on the other hand, like those against EBV, have not yet demonstrated their efficacy in preventing these infections. In contrast, a vaccine against MCPyV would be easy to produce with the same technology used for HPVs. However, it is unlikely that such a vaccine would be applied because

prevention of a small number of MCCs occurring late in life would not be justified in view of the high cost of implementing a mass immunization program early in life.

Another option is the development of therapeutic vaccines against established viral tumors or against the chronic viral infections and premalignant lesions that precede tumor development. Current therapeutic vaccines against the different virus-associated cancers so far have no or limited efficacy. These vaccines remain under development, and it is not expected that they will be available in the near future. The viral proteins necessary for the maintenance of a tumor, such as E6/E7 proteins of HPVs and T antigens of polyomaviruses, may provide specific therapeutic targets for the future, for example, the development of new types of therapy by silencing these viral proteins.

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