REVIEW

Immunodeficiency-associated viral oncogenesis

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Abstract

Several viruses with different replication mechanisms contribute to oncogenesis by both direct and indirect mechanisms in immunosuppressed subjects after solid organ transplantation, after allogeneic stem cell transplantation, or with human immunodeficiency virus (HIV) infection. Epstein–Barr virus (EBV), human papillomavirus (HPV), Kaposi sarcoma herpesvirus (KSHV), human T-cell lymphotropic virus type 1 (HTLV-1) and Merkel cell polyoma virus (MCV) are the main viruses associated with the development of cancer in immunosuppressed patients. Besides being a main cause of immunodeficiency, HIV1 has a direct pro-oncogenic effect. In this review, we provide an update on the association between the condition of acquired immunodeficiency and cancer risk, specifically addressing the contributions to oncogenesis of HPV, MCV, KSHV, HTLV-1, and EBV.

Keywords: Carcinogenesis, HIV, immunodeficiency, transplantation, viral oncogenesis
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Introduction

A large number of viruses have oncogenic potential in animals, but for only some of them has a clear association with the development of tumours in humans been demonstrated. It has been proposed that these viruses can contribute to carcinogenesis in humans by direct and/or indirect mechanisms: in one case, the virus is able to induce the expression of specific oncogenic protein(s) that then play a direct role in cell transformation; alternatively, the transformation is associated indirectly with the virus-induced chronic infection and inflammation. However, in several circumstances, it is not possible to precisely define whether the cancer development is the result of a direct or an indirect mechanism (e.g. in the case of hepatitis B virus (HBV), hepatitis C virus (HCV), or human T-cell lymphotropic virus type 1 (HTLV-I)) [1], and, more importantly, it is difficult to distinguish between the 'pro-oncogenic' immune/inflammatory mechanisms and the benign 'anti-oncogenic' mechanism of immunity [2]. Indeed, it is known that several viruses with different replication mechanisms contribute to oncogenesis in immunosuppressed subjects, both directly and indirectly. Among them, the main viruses are as follows: Epstein–Barr virus (EBV), HBV, HCV, human papillomavirus (HPV), Kaposi sarcoma herpesvirus (KSHV), HTLV-1, and Merkel cell polyoma virus (MCV). Besides being a main cause of immunodeficiency, human immunodeficiency virus (HIV) type 1 has a direct pro-oncogenic effect. In the limited space allowed for this minireview, we try to provide an update on the association between the condition of acquired immunodeficiency and cancer risk, specifically addressing the contributions to oncogenesis of HPV, MCV, human herpesvirus-8 (HHV-8)/KSHV, HTLV-1, and EBV (Table 1); HBV and HCV are addressed in a different article in this themed section.

EBV

In 1997, EBV was the first virus recognized to be a human carcinogen by the International Agency for Cancer Research (IARC) [3]; according to unadjusted estimates, approximately 3.7 million individuals developed EBV-associated cancers [4]. In 2009, the IARC confirmed this classification, given that

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TABLE 1. Human viruses in immunodeficiency-associated cancer (see text for details); primary immunodeficiencies were not considered

Settings	Association with viral infections (virus)	Level of evidence
Transplantation	Post-transplant lymphoproliferative disease	Strong
	Diffuse large B-cell lymphoma (EBV)	
	Kaposi sarcoma (HHV-8)	Strong
	Non-melanoma skin cancer (HPV)	Strong
	Non-melanoma skin cancer (MCV)	Moderate
AIDS	AIDS-related lymphoma:	
	Burkitt lymphoma (EBV)	Strong
	Diffuse large B-cell lymphoma (EBV)	Strong
	Hodgkin lymphoma (EBV)	Moderate
	Primary effusion lymphoma (HHV-8+/EBV±)	Strong
	Multicentric Castleman disease	Strong
Adult T-cell leukaemia/lymphoma	HTLV-1	Strong
Cervical cancer	HPV	Strong
Anal cancer	HPV	Strong
Oropharyngeal cancer	HPV	Moderate

EBV, Epstein–Barr virus; HHV-8, human herpesvirus-8; HPV, human papillomavirus; HTLV-1, human T-cell lymphotropic virus type 1; MCV, Merkel cell polyoma virus.

sufficient evidence for a causative role of EBV in nasopharyngeal cancer, endemic Burkitt's lymphoma (BL), immunosuppression-related non-Hodgkin lymphoma (NHL), extranodal natural killer/T-cell lymphoma (nasal type) and a subset of Hodgkin lymphoma (HL) was found [5].

In individuals with HIV, the incidence of NHL declined from approximately 100-fold to ten-fold higher than in the normal population during the antiretroviral therapy (ART) era [5,6]. The most frequent subtypes of NHL are BL and diffuse large B-cell lymphoma, and they may be either systemic or extranodal, like primary central nervous system lymphoma (reviewed in Pinzone *et al.* [7]). The incidence of NHL is approximately ten-fold higher in patients with more severe immunodeficiency than in patients with early stages of HIV infection [8]. Risk factors for HIV-associated lymphoma, other than the immunodeficiency, comprise biological markers of B-cell activation such as CD23, CD27, CD30, or CXCL13 [9], and prolonged periods of high-level HIV viraemia [10].

The post-transplant lymphoproliferative disorders (PTLDs) are lymphoid or plasmocytic life-threatening proliferations arising in the context of profound immunosuppression induced after solid organ or allogeneic stem cell transplantation (SCT). The incidence of PTLD is approximately eight-fold higher than in the general population [11,12]. It is particularly higher in children than in adults after solid organ transplantation, ranging from 1% to 20%, mainly after combined heart and lung transplantation; after SCT, the incidence ranges between 0.5% and 17% (reviewed in Quinlan *et al.* [13] and Nourse *et al.* [14]). The incidence of PTLD is bimodally distributed, with early (up to the first year after transplantation) and late peaks; risk factors and the frequency of EBV association differ between early and late PTLD, suggesting different mechanisms of lymphomagenesis [13]. Risk factors for PTLD include T-cell depletion, the use of antithymocyte globulin, acute and chronic graft-versus-host disease, patient age of >50 years, and the EBV serostatus of the donor (D) and recipient (R), D^+/R^- individuals being at higher risk [14,15]. HL, mainly the mixed cellularity and lymphocyte-depleted subtypes, is approximately ten-fold more frequent in individuals with HIV infection than in the general population [16]. The frequency of HL in the ART era has only slightly decreased [6]; however, a recent cohort study showed a slow but steady decline (approximately 20% per year of ART) of the incidence of HL in individuals with HIV infection after prolonged use of ART [17]. In transplant recipients, the incidence of HL is increased up to four-fold [11,12]. Risk factors for post-transplant HL are male gender, young age, and EBV seronegativity at the time of transplantation [18].

During latent infection in B-cells, the pattern of EBV gene expression might be heterogeneous, and three patterns of latency (I, II, and III) are known (reviewed in Cesarman [19]). Severe immunosuppression and dependence on EBV (the degree to which lymphoma cells depend on EBV correlates directly with the number of viral genes expressed within the tumor cells) which give rise to cancers are associated with higher latency patterns [20]. Latency pattern III involves the expression of nuclear proteins (EBV nuclear antigen (EBNA)-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-LP), non-structural membrane proteins (latent membrane protein (LMP)-1, LMP-2A, and LMP-2B), and untranslated RNAs (EBV-encoded small RNA (EBER)-1 and EBER-2). The infected B-cells, with latency pattern III, are susceptible to immune-mediated killing by EBV-specific cytotoxic T-lymphocytes (CTLs). After transplantation in the absence of CTLs, latency pattern III leads to the virus-driven transformation of EBV-infected B-cells, causing a polyclonal or oligoclonal lymphoproliferative disorder that can progress to monoclonal lymphoma with increased levels of circulating EBV DNA (reviewed in Nourse *et al.* [14]). PTLD is highly amenable to immunotherapy with *ex vivo* generation of autologous or allogeneic EBV-specific CTLs.

In AIDS-associated NHL, viral gene expression is variable, but the transforming EBV protein LMP, which has a crucial role in the transformation of B-cells, is frequently expressed (reviewed in Cesarman [19]). In AIDS/BL, EBV is found in 30–60% of cases, and adopts latency pattern I, expressing only EBNA-1 and EBER [19]. In HL, the malignant B-cell adopts latency pattern II, called the default programme, and expresses the transforming LMP-1 protein, as well as EBNA-1 and LMP-2 (reviewed in Cesarman [19]). Very recently, Arvey *et al.* [21], by using total RNA-sequencing technology (transcriptome sequencing) and the PathSeq analysis pipeline, found no virus other than EBV in patients with AIDS-related lymphomas treated with ART. Furthermore, a highly heterogeneous pattern of viral transcription was found, with many cancer samples showing the restricted type I viral latency, suggesting that EBV latency proteins are under high immunosurveillance [21].

EBV leads to the extensive methylation of both the host genome and the viral genome, and these changes facilitate cellular functions that promote viral persistence and propagation [22].

Recent evidence indicates that EBV is able to shape the microenvironment, making it more amenable to cell transformation. EBV regulates the production of soluble factors promoting the growth and/or the survival of lymphoid cells, and acts on a variety of mechanisms favouring escape from anticancer immune responses. In addition, EBV-infected B-lymphocytes actively secrete exosomes, which may contribute to the development and progression of tumour [23].

HHV-8/KSHV

The IARC classified HHV-8 as a group I carcinogen [16], based on data obtained from many cohort and case–control studies that showed a sufficient association between HHV-8 and Kaposi's sarcoma (KS) and primary effusion lymphoma (PEL); HHV-8 has been also associated with multicentric Castleman's disease (MCD), but with less evidence than for KS and PEL [16]. Most of this evidence has been obtained from studies performed on patients with long-term immunodeficiency, such as individuals with HIV infection and patients receiving solid organ transplants [11].

The occurrence of KS, a multicentric angioproliferative spindle cell tumour arising from HHV-8-infected endothelial cells, is increased up to 2000-fold in individuals with HIV infection, and it is related to the severity of the HIV-induced immunodeficiency, being 10–50-fold higher in patients with severe immunodeficiency than in those with HIV infection in the early stages [6]. The incidence of KS in patients with HIV receiving highly active ART has dramatically decreased (approximately 30% per year between 1996 and 2000, and 8% per year after 2000 [6]), but remains higher than in the general population [6]. Currently, KS can be diagnosed in individuals who are unaware of having HIV infection, in patients who have not yet received ART, and in patients during the first 6 months of ART (immune reconstitution) [24]. Iatrogenic KS occurs in patients treated with immunosuppressive drugs, such as cyclosporine, azathioprine, corticosteroids, and rituximab, most of whom are recipients of solid organ transplants [25]. The use of sirolimus, a mammalian target of rapomycin (mTOR) inhibitor, has been associated with regression of KS, suggesting a possible oncogenic effect of other immunosuppressive drugs [26]. The risk of KS in organ transplant recipients is increased up to 200-fold as compared with to general population [12]. In contrast, the occurrence of KS or other HHV-8-related malignancies such as PEL or MCD is exceptional in allogeneic SCT patients, and the reasons for this are still elusive [27]. Post-transplantation KS is usually induced by HHV-8 reactivation, and a few cases are derived from primary HHV-8 infection acquired from the donor organ (reviewed in Lebbe *et al.* [28]), with a higher risk of developing KS within the first 2 years after transplantation [28].

Two other forms of KS have been described: classic KS, which usually occurs in elderly people living in the Mediterranean area, and endemic KS, HIV unrelated, which affects people from sub-Saharan Africa. Detection of replicating HHV-8 in peripheral blood has been shown to be a stronger predictor of KS development [29]; however, cases of high and persistent HHV-8 replication in the absence of KS or any other HHV-8-associated neoplastic diseases have rarely been reported in SCT patients [30].

PEL is a rare, aggressive form of B-cell lymphoma, representing 1–4% of all AIDS-related lymphomas [31]. PEL occurs mainly in HIV-infected individuals, and it is occasionally diagnosed after solid organ transplantation (reviewed in Powles *et al.* [33]). PEL is composed of malignant, latently infected B-cells that affect pericardial, peritoneal and pleural body cavities (reviewed in Bhutani *et al.* [31] and Christenson *et al.* [32]). PEL is a monoclonal population of B-cells, and each tumour cell contains a high HHV-8 copy number, from 50 to 100 genomes per cell [31,32]. HHV-8 is universally associated with PEL, and in 70–80% of cases the lymphoma cells have coexisting latent infection with EBV, which adopts non-transforming EBV latency pattern I [31,32].

MCD is a disease of lymph nodes, and the plasmablastic variant has been associated with HHV-8 infection. HHV-8-associated MCD is usually observed in the setting of HIV infection, and rarely in non-HIV-infected immunocompromised patients (Bhutani *et al.* [31]). In contrast to KS, HHV-8-

associated MCD appears to be more frequent in the ART era [33], suggesting that, in MCD, altered immune responses and high levels of proinflammatory cytokines could represent relatively preserved immune functions. HHV-8 is observed in almost HIV-positive MCD cases, whereas HHV-8 is observed in <40% of HIV-negative cases. Concomitant KS is detectable in up to 70% of patients [31]. MCD is characterized by an abnormal, polyclonal IgMλ proliferation, and rare cases of monoclonal B-cell expansion have been observed. In HHV-8-positive MCD, expression of the viral interleukin (IL)-6 cytokine probably exacerbates inflammation and disease progression. Recently, a KSHV inflammatory cytokine syndrome, characterized by inflammatory symptoms, elevated cellular and viral cytokine levels, and high HHV-8 load, has been reported [31].

HHV-8 infects cells of the endothelial lineage, monocytes, and B-cells [33,34]. A characteristic of this virus is the expression of viral homologues of human regulatory proteins such as IL-6, BCL-2, and cyclin D (reviewed in Gramolelli and Schulz [34]). The HHV-8 genome encodes many proteins, several of which have immunological and angiogenic properties [34]. HHV-8 genome circularizes to form a closed extrachromosomal episome, which maintains its replication during host cell division. Recently, chromatin assembly, epigenetic modifications and factors acting on chromatin structures have been recognized to interact with the latent state cycle and mediate HHV-8 pathogenesis [35]; it is not known whether epigenetic modifications correlate with cancer development.

HHV-8 latent transcripts, such as latency-associated nuclear antigen, viral cyclin, viral FLIP, and virus-encoded microRNA, drive cell proliferation and prevent apoptosis, and are mainly expressed in B-cells and in neoplastic KS spindle cells [19,34]. HHV-8 lytic proteins, such as viral G-protein-coupled receptor, K1 and viral-encoded cytokines (IL-6 and chemokines), further contribute to the development of angioproliferative and inflammatory KS lesions [19,34,36]. HHV-8 lytic genes include those encoding viral IL-6, viral BCL-2, viral macrophage inflammatory protein (MIP), viral-G-protein coupled receptor, and viral interferon regulatory factor [19,34,36]. Lytic infection occurs in <3% of KS cells, and is more frequent in MCD [19,34,35].

HTLV-I

HTLV-I is an oncogenic retrovirus that has spread to many parts of the world, particularly in the tropics and subtropics (reviewed in Verdonck *et al.* [37], Ishitsuka and Tamura [38], and Gessain and Cassar [39]). It has been shown that, in some areas in Japan, sub-Saharan Africa, the Caribbean, and South America, >1% of the general population is infected with HTLV-1. The most recent estimate of the prevalence of HTLV-1 is 5–20 million persons worldwide [37–39]. In endemic areas, HTLV-1 is transmitted from mother to child (20% transmission rate) through prolonged breast-feeding, and also depending on HTLV-1 load. Transfusion of blood products containing HTLV-1 is the most efficient mode of transmission (15–60% risk of infection). However, other routes of spread of the virus, such as unprotected sex, intravenous drug use, and solid organ transplantation, have been reported [39,40].

HTLV-1 does not cause any disease in >90% of the carriers, but establishes latent infection in lymphocytes, which leads to lifelong persistence in the host. In approximately 10% of infected patients, HTLV-1 is associated with severe diseases, such as neoplastic diseases (adult T-cell leukaemia/lymphoma (ATL)), inflammatory syndromes (HTLV-1-associated myelopathy/tropical spastic paraparesis), and opportunistic infections (e.g. *Strongyloides stercoralis* hyperinfection) [37–39].

HTLV-1 integrates into host DNA, but it is not clear whether it integrates into $CD4^+$ or haematopoietic stem cells; subsequently, HTLV-1 establishes a persistent infection, usually characterized by a high proviral load (even >5% of peripheral blood mononuclear cells are infected), despite a chronic and strong activated cellular immune response ($CD8^+$ cytotoxic T-lymphocytes) (reviewed in Matsuoka and Jeang [40] and Cook *et al.* [41]). The HTLV-I genome encodes structural proteins, i.e. Gag, Pol, Pro, and Env, and complex regulatory proteins, such as Tax, Rex, HBZ, p12, p21, p13, and p30, encoded in the pX region of the genome. The oncogenic function of Tax lies in its ability to induce viral replication to increase genetic instability, to activate nuclear factor-κB and Akt signalling, and cyclin-dependent kinases, and to silence p53 function (reviewed in Verdonck *et al.* [37], Ishitsuka and Tamura [38], Cook *et al.* [41], and Ghezeldasht *et al.* [42]). Furthermore, Tax has a relevant role in the early phase of oncogenesis of ATL, immortalizing T-lymphocytes *in vitro* [43] and inducing mesenchymal tumours in transgenic mice [44], whereas HTLV-1 basic Zip factor plays a central role during all phases of oncogenesis of ATL, being involved in viral replication and T-cell proliferation [45]. HTLV-1 DNA provirus is clonally integrated into the DNA of ATL cells, and issues regarding the control of HTLV-1-infected T-cell clones *in vivo* are not yet resolved: antigen specificity, epigenetic modifications and genomic site of integration of the HTLV-1 provirus are believed to be relevant (reviewed in Bangham *et al.* [46]).

ATL is a malignancy of mature T-lymphocytes, with a heterogeneous clinical course. A peripheral T-cell lymphoma-unspecified with similar genomic alterations to lymphoma ATL has been reported, being characterized by the expression of CC chemochine receptor 4 (CXCR4), which is a

characteristics of ATL cells [47]. HTLV-I has been associated with ATL, but not with other haematological malignancies such as acute lymphatic leukaemia, chronic lymphatic leukaemia, and chronic myeloid leukaemia [48]. Risk factors for the development of ATL in HTLV-I carriers are high proviral load, advanced age, receipt of breast-feeding, family history of ATL, and having human leukocyte antigen alleles *A26*, *B4002*, *B4006*, and *B4801* (reviewed in Verdonck *et al.* [37], Ishitsuka and Tamura [38], Gessain and Cassar [39], and Iwanaga *et al.* [49]).

Whether ATL is more frequent in the immunosuppressed than in the immunocompetent population has not been evaluated systematically. The effect of immunosuppression on the natural history of HTLV-I is not well defined, as cases of ATL have been reported sporadically after transplantation [50–54]. The occurrence of post-transplant ATL suggests that HTLV-I-infected transplant (liver and renal) recipients who receive long-term immunosuppressive treatment may develop rapidly and aggressive forms of ATL, even if the overall survival is similar between HTLV-I-positive and HTLV-I-negative transplant recipients [50,51,53]. Given the importance of determining the safety of organ transplantation in HTLV-I-positive recipients, it is recommended to perform regular monitoring to diagnose ATL early [54].

HPV and cancers in immunosuppressed hosts

HPV is a small double-stranded DNA virus that infects epithelial tissues. Mucosal HPV genotypes are classified into low-risk types causing benign lesions, and high-risk types associated with anogenital squamous cell carcinoma (SCC) [55]; 12 high-risk HPVs are classified as type 1 carcinogens by the IARC [5]. Individuals with a depressed immune system are at an increased risk of developing HPV-associated malignancies in the anogenital and head and neck regions [56].

Cutaneous HPV genotypes progress into skin SCCs essentially in individuals with genetic defects, including those of the syndrome known as epidermodysplasia verruciformis (EV); HPV5 and HPV8 were classified by the IARC as possibly carcinogenic (type 2B) in EV patients [5]. Individuals with other primary immunodeficiencies and chronically immunosuppressed patients also frequently develop precancerous actinic keratoses and skin SCC [57].

HPV-associated cervical cancer

Mucosal HPV infection and associated diseases are more common and more likely to persist in HIV-positive than in HIV-negative individuals [58] and in transplanted patients [11]. The risk of anogenital SCC caused by high-risk HPVs is substantial, owing to the impact of cell-mediated immunity on HPV infection clearance and on tumour surveillance. Since 1993, SCC of the cervix has been considered to be an AIDS-defining cancer according to the CDC classification, owing to the frequent occurrence, estimated to be five times greater [59], among female AIDS patients. At the beginning of the ART era, when the incidence rates of the other AIDS-defining cancers (KS and NHL) were decreasing, owing to the better control of HIV replication and immune reconstitution, the incidence of cervical cancer was not influenced or even increased [59,60]. More recently, large cohort studies have shown a limited but constant trend for cervical cancer reduction among HIV-positive women, either treated or untreated [61–63]. Nevertheless, high-risk HPV positivity rates, persistence of infections, progression to high-grade lesions and cervical cancer risk are still elevated in HIV-positive women. Reasons for this are the common sexual risk factors for HIV and HPV transmission, the fact that HPV increases the efficiency of HIV sexual acquisition, and the impact of immunosuppression on HPV persistence. A complementary explanation for the elevated prevalence of HPV disease in immunosuppressed patients came from studies in animal models [58,64,65]. Given the ability of HPV DNA to persist in the long term in the absence of disease, mucosal immune dysfunction may cause latent HPV reactivation at local sites, despite general immune reconstitution in the patient [64,65]. Findings in HIV-positive patients [66], in older women [67] and in transplant patients [68] are in keeping with this hypothesis. In transplant patients with a lower rate of at-risk sexual behaviours, increased rates of HPV infection and high-grade lesions were recently reported [68], in contrast to previous studies.

Therefore, even in the absence of clinically evident lesions and of novel infections, undetected persistence and reactivation of past high-risk HPV infections would represent an additional risk in immunosuppressed women. Nonetheless, the direct effect of immunosuppression on invasive cancer risk is still debated [69–71]. Recent studies have suggested that there is no increased risk of SCC in HIV-positive women when adherence to the strict cervical cancer screening programmes is complete [72]. Accordingly, there is a need for improved awareness of the importance of cervical cancer screening, which is still partial in HIV-positive women [72], and probably even lower in female transplant patients.

HPV-associated anal cancer

HPV infection has also been strongly associated with the risk for SCC of the anal canal, which is relatively low in the general population but is substantially elevated for HIV-infected patients, especially men who have sex with men [73]. Anal carcinoma has been included in the non-AIDS-defining cancers, which cumulatively still represent a leading cause of death

among virologically suppressed individuals with high $CD4^+$ cell counts [74]. After initially increasing at the beginning of the ART era, anal cancer rates remained steady, with no trend for a decline in the recent period [62,75,76].

Anal HPV infection is common among HIV-positive individuals, and reaches prevalence rates as high as 90–95% in HIV-positive men who have sex with men [77]. Most precancerous HPV-associated anal lesions are asymptomatic but have a clear potential to progress to SCC; anal cancer precursors should be detected by digital anorectal examination and high-resolution anoscopy, during controlled follow-up visits [77]. Early ART initiation may reduce non-AIDS-defining cancer risk by reducing HIV replication, improving immune function, and limiting chronic inflammation [78,79]; moreover, a direct antineoplastic effect of certain nucleoside and non-nucleoside inhibitors of HIV reverse transcriptase and protease inhibitors (in particular nelfinavir) has been suggested [80]. On the other hand, particular ART regimens containing protease inhibitors have been associated with increased cancer risk, as they affect the cytochrome P450 enzyme system [81].

HPV-associated oropharyngeal cancer

Immunosuppression probably plays a role during the carcinogenesis process of the head and neck region, but its contribution is less clear, owing to the heterogeneous origins of these tumours. HPV has been recognized to be the cause of 40–80% of oropharyngeal SCCs, whose incidence has significantly increased in the last decade [56]. HPV-positive SCCs arise mostly in the tonsils and the base of the tongue, and have a different clinical, histological and molecular profile, and a significantly better prognosis [56]. HPV-positive oropharyngeal SCC is caused by oral HPV16 infection in 85% of cases, in contrast to the 60% found in cervical cancer. In HIV-positive individuals, the standardized incidence ratio for invasive oropharyngeal SCC was 1.6 (95% CI 1.2–2.1), the lowest value among all HPV-associated SCCs [59,61] (Table 1). The high burden of oral infections in HIV-positive individuals [82] suggests that oral subclinical HPV infections, especially those with high viral loads [83], cause an excess risk of precancerous changes in the oropharynx.

HPV-associated skin tumours

A role for HPV in human skin carcinogenesis was suggested earlier than for HPV in cervical cancer, because of the observation of verrucous lesions in EV patients developing in cutaneous SCC [84]. Cutaneous HPV types, most of which are included in the beta genus, are widely present in the skin of normal individuals, induce skin warts more frequently in immunosuppressed patients, and cause severe generalized verrucosis in certain primary immunodeficiencies [85], resulting in a 50–100-fold increased risk of developing skin cancer [86]. Different transforming mechanisms are employed by beta HPV than by mucosal high-risk HPV (reviewed in Howley and Pfister [86]): UV radiation and impairment of immune surveillance are essential cofactors; beta HPV E6 and E7 are less efficient than alpha HPV E6 and E7 in exerting tumour-promoting activities; beta HPV E6 is able to inhibit tumour-suppressive Notch pathway signalling; and HPV DNA is not necessary in the final stages of tumour development and, when present, is generally not integrated.

The fundamental role of the immune response in beta HPV carcinogenesis has to be further emphasized in the light of recent reports. Mutations in the genes called *EVER1* and *EVER2* are the major genetic defects in EV patients [87], conferring increased susceptibility to infection with beta HPVs. Initially found only in keratinocytes, in which they control zinc levels, EVER1 and EVER2 proteins seem to be involved in exogenous DNA sensing and the response to different viruses in immune cells [88].

In the rare autosomal dominant immunodeficiency named warts, hypogammaglobulinaemia, infections, and myelokathexis (WHIM), HPV-related disease is the predominant recurrent disease [89]. WHIM syndrome is caused by dominant heterozygous mutations in the chemokine receptor CXCR4 that impair desensitization to ligand stimulation, thus causing CXCR4 upregulation, ultimately resulting in myeloid hypercellularity and neutropenia [89]. HPV16 and HPV18 upregulate CXCR4 and its ligand CXCL12, in order to immortalize keratinocytes [90], and this could partly explain the elevated HPV infection and lesion progression rates in WHIM.

As seen in iatrogenic KS, immunosuppressive therapy with calcineurin inhibitors (e.g. cyclosporine A and tacrolimus) is associated with post-transplant oncogenicity. Calcineurin inhibitors directly promote keratinocyte transformation and skin carcinogenesis via inhibitory effects on tumour-suppressive genes that permit upregulation of proinflammatory and mitogenic pathways [91]. Greater use of mTOR inhibitors in post-transplant immunosuppression protocols could help to reduce the risk of cutaneous SCC development [91].

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is one of the most aggressive skin cancers; although relatively infrequent in the general population, it is the second most common cause of skin cancer death after melanoma [92]. A novel polyomavirus, named MCV, was identified in 2008 [93] as being clonally integrated into MCC cells. Further studies indicated that most MCCs are associated with a

deleted MCV genome, causing virus replication to be incompetent; MCV was recently classified as a 2A carcinogen [94]. Immunosuppression increases the risk of MCC, and appears to be associated with a worse prognosis [95]. For the first time among a large, population-based cohort, the occurrence of MCC was recently evaluated among US transplant recipients [96]. The main finding of the study was the sharply elevated risk resulting from long-term immunosuppressive regimens, mainly cyclosporine/azathioprine, but also mTOR inhibitors [96], that, conversely, decreased the risk of HPV-associated cutaneous SCC [91].

Although less elevated than in iatrogenic immune suppression, the risk of developing MCC and of having a worse clinical course is also elevated in patients with HIV/AIDS [95].

In these patients, MCC tumours do not arise only in the typical sun-exposed areas, indicating that UV exposure may not be an essential cofactor [95]. Moreover, in HIV-positive individuals, MCV DNA has been detected on the skin, on the oral and anogenital mucosa, and in plucked eyebrow hairs, and significantly higher cutaneous MCV DNA loads were found in those with severe immunosuppression [97].

Final considerations

This review has dealt with viruses that, directly or indirectly, are associated with cancer development in humans. The whole article is premised on the certainty that acquired immunodeficiency in humans is associated with increased cancer risk, thus indirectly validating the indication that virus-associated cancer immunosurveillance does exist.

Continuous epidemiological surveillance is therefore necessary to monitor the rates of infectious causes of cancer among immunosuppressed individuals, and to better understand the impact of specific medications (e.g. early ART initiation or adjuvant therapies) on the excess risk in this population.

It is our firm opinion that, for the above reasons, the role of preventive measures (i.e. screening programmes and/or vaccination) in reducing cancer risk and of virological characterization in determining specific therapies deserve further investigation.

Transparency declaration

The authors declare that they have no conflicts of interest.

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