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

Article published online: 18 July 2015

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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

http://dx.doi.org/10.1016/j.cmi.2015.07.009

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.