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Cancer processes in immunodeficient populations: an introduction

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Infection has been linked to cancers since the 19th century. Viral infection was once thought to be responsible for most malignancies, but the lack of evidence linking a virus to a specific human cancer led to the dismissal of this hypothesis during the first half of the 20th century. The emergence of the acquired immune deficiency syndrome (AIDS) has refocused attention on the interplay between infection and malignancy (reviewed in [1]) (Table 1).

Cancer development is a multifactorial and multistep process [2]. In almost all solid cancers, with the exception of certain germ cell tumours and malignancies with inherited predisposition, a sequential accumulation of somatic mutations over many years is necessary before a clonal expansion of transformed cells emerges. Cumulative mutational load, telomere dysfunction and altered stromal milieu are all required before a solid tumour presents itself [3]. Initial genetic mutations lead to the uncontrolled growth of cells. When these preneoplastic cells have undergone a limited number of divisions, the cells undergo an 'angiogenic switch', providing the necessary growth factors and nutrients for accelerated growth; activation of matrix-degrading enzymes then leads to vascular and stromal invasion and this is followed by distant seeding of micrometastases. This sequential progression of genetic mutations was first shown in human colorectal carcinomas [4]. The multistep process of carcinogenesis was confirmed in various transgenic models (reviewed in Ref. [5]): in transgenic mice expressing the simian virus-40 T antigen (SV40-T), early cellular nodules expressing the *SV40-T* oncogene are not angiogenic and the switch appears as a discrete, separate step in a multistage pathway to tumour invasion. In a model of squamous cell carcinoma induced by human papillomavirus (HPV) type 16, a hyperplastic stage with weak angiogenic activity is followed by a dysplastic stage with pronounced angiogenesis and eventually squamous cell invasion with highly vascular cancers.

Somatic mutations, increased epigenetic gene silencing, telomere dysfunction and marked cytogenetic abnormalities distinguish adult epithelial malignancies from most paediatric solid tumours and many mouse cancers. Viral-induced epithelial cancers therefore develop many years, or even decades, after the initial infectious event and the implicated viruses can trigger many of the aberrant cellular changes, although other inherited or exposing factors are usually also involved. Classic examples include HPV-induced cervical cancer, and Epstein–Barr virus (EBV)-associated nasopharyngeal carcinoma (NPC). EBV latent proteins are thought to provide some of the cellular proliferation and anti-apoptotic signals, and the latent membrane protein-I (LMP-1) has been shown to activate matrix metalloproteinase-9 (MMP-9) which is implicated in invasion and in the angiogenic switch [6,7].

In the beginning of the AIDS epidemic, the incidence of virus-driven epithelial cancers like HPV-associated squamous ano-genital and skin carcinomas was not noticeably increased. However, longer survival and increased surveillance indicate that the incidence of some of these tumours is indeed significantly increased. In particular, in Africa, ultraviolet (UV)-induced DNA damage with HPV oncogene expression, and loss of antiviral immunity result in a marked increase in the incidence of squamous carcinoma of the conjunctiva [8].

Kaposi's sarcoma (KS) is the most common cancer seen in HIV-1-infected individuals. Molecular epidemiological and serological surveys have confirmed the association of KS with the human KS associated herpesvirus (KSHV or HHV-8) (reviewed in [9]). KSHV is latently present in tumour cells [10] and KSHV latent proteins like the latent nuclear antigen (LNA-1) interfere with the functions of the p53 and retinoblastoma pathways to prevent cellular apoptosis, and driving cells into uncontrolled proliferation [11,12]. The virus also encodes a number of cellular homologues that may

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Table 1
Tumours increased in patients with AIDS

Cancer type	Relative risk[a]	Viral link
KS	310	KSHV
NHL	113	EBV
Angiosarcoma	36.7	?
Anal cancer[b]	31.7	HPV
Leukaemias other than lymphoid and myeloid	11.0	?
HD	7.6	?EBV
Leiomyosarcoma and other soft tissue sarcomas[c]	7.2	?EBV
Multiple myeloma	4.5	?
Primary brain cancer[d]	3.5	Polyomoviruses
Testicular seminoma or malignant germinoma	2.9	?

NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; KSHV, Kaposi's sarcoma-associated herpesvirus; HPV, human papillomavirus.

[a] Adapted from Ref. [39].

[b] Anal carcinoma is increased in gay men, even prior to HIV.

[c] EBV sequences described in smooth-muscle tumours from children with AIDS, including monoclonal EBV episomes in some cases.

[d] Predominantly malignant glioma or astrocytoma. The detection of papovavirus sequences in brain tumours remains unconfirmed.

perturb cell growth including a viral cyclin, interferon regulatory proteins and a FLICE-inhibitory protein (FLIP) [13–15]. Other KSHV proteins interfere with the functions of cytotoxic T-cells and natural killer cells, preventing elimination of KSHV-infected cells by the immune system [16–18] (Fig. 1).

The KS tumour (spindle) cells infected by KSHV belong to the endothelial lineage of cells and probably represent endothelial progenitor cells [10]. Haematopoietic, vascular and lymphatic endothelial and smooth muscle cells all derive from progenitor haemangioblasts present in the lateral mesoderm during embryonal development. The vascular endothelial growth factor receptor Flk1 (or VEGFR-2) which appears on embryonic stem (ES) cells, is one of the first markers of endothelial cell differentiation. Circulating Flk1+ stem cells are present in the adult, and these cells have the ability to differentiate into distinct endothelial lineages. Circulating KS spindle cells have been identified and spindle cells express Flk1 and VEGFR-3, markers of precursor and immature endothelium, respectively. Infection of these endothelial precursor cells by KSHV may lead to uncontrolled cell growth, block of differentiation, angiogenesis and invasion. KSHV also encodes for proteins that have the ability, at least in experimental systems, to directly induce angiogenesis. These include the viral chemokine homologues (vMIP-I, II and III) and the virally-encoded G-protein coupled receptor (GPCR) [19,20]. Although these proteins are only expressed by a fraction of KS spindle cells at a specific time-point, their angiogenic ability is potent and KSHV GPCR transgenic mice develop histological lesions very similar to KS [21]. Highly active antiretroviral therapy (HAART) has led to a decrease in the incidence of KS (Fig. 2), and also to the resolution of established KS lesions. We believe that this is the result of a partial restoration of cellular (CD4+ and CD8+ lymphocytes) immunity against KSHV proteins.

Lymphoproliferative disorders are the next most common cancers seen in HIV-infected individuals. The γ-herpesviruses, EBV and KSHV, play a role in over 50% of these tumours. An unidentified virus(es) may account for some of the others.

EBV is the prototype of γ-herpesviruses. *In vitro,* EBV infection of primary B lymphocytes efficiently induces continuous proliferation and transformation into permanent cell lines (called lymphoblastoid cell lines or LCLs). These LCLs normally contain multiple episomal copies of the EBV genome [22]. Of the approximately 100 viral genes, only thirteen genes are expressed in LCLs including the six nuclear proteins (EBNAs 1–6), three membrane proteins (LMP-3), and two non-translated RNAs (EBER 1 and 2) (reviewed in Ref. [23]). These transformation-associated viral proteins regulate the maintenance of episomal viral DNA and viral gene expression, drive cellular proliferation directly, activate cellular oncogenes, and block apoptosis.

EBV-infected B lymphocytes are highly immunogenic and elicit powerful cytotoxic T-cell (CTL) responses [24]. EBV-specific CTLs are targeted against human leucocyte antigen (HLA) class 1-associated peptides derived from the EBNAs and the LMPs (latent membrane proteins), with the notable exception of EBNA-1. The choice of the viral target depends on the HLA phenotype of the responder [25]. A sufficient variety of immunogenic peptides can be presented by the HLA spectrum to provide immunosurveillance against uncontrolled growth of virally-transformed immunoblasts.

Although EBV is a highly transforming virus, only a fraction of EBV-infected individuals will ever develop EBV-associated tumours, and despite the interactions between autologous EBV-infected B cells and CD8+ T lymphocytes, EBV persists in B lymphocytes. These two apparent paradoxes are explained by the down-regulation of all growth transforming-associated viral proteins, which include those known to elicit CTL responses, in persistently infected B lymphocytes [26]. Only EBNA-1 (EBV nuclear antigen 1) is expressed in these cells. EBNA-1 is essential to maintain the stability and proliferation of the viral episome (unintegrated viral DNA) [27] and does not evoke an immune response. EBV-driven lymphoproliferations seen in immunosuppressed individuals include posttransplant lymphoproliferative disorder (PTLD), AIDS-related lymphoma and Hodgkin's disease (HD).

PTLDs represent one of the most common complications of immunosuppression following organ transplan-

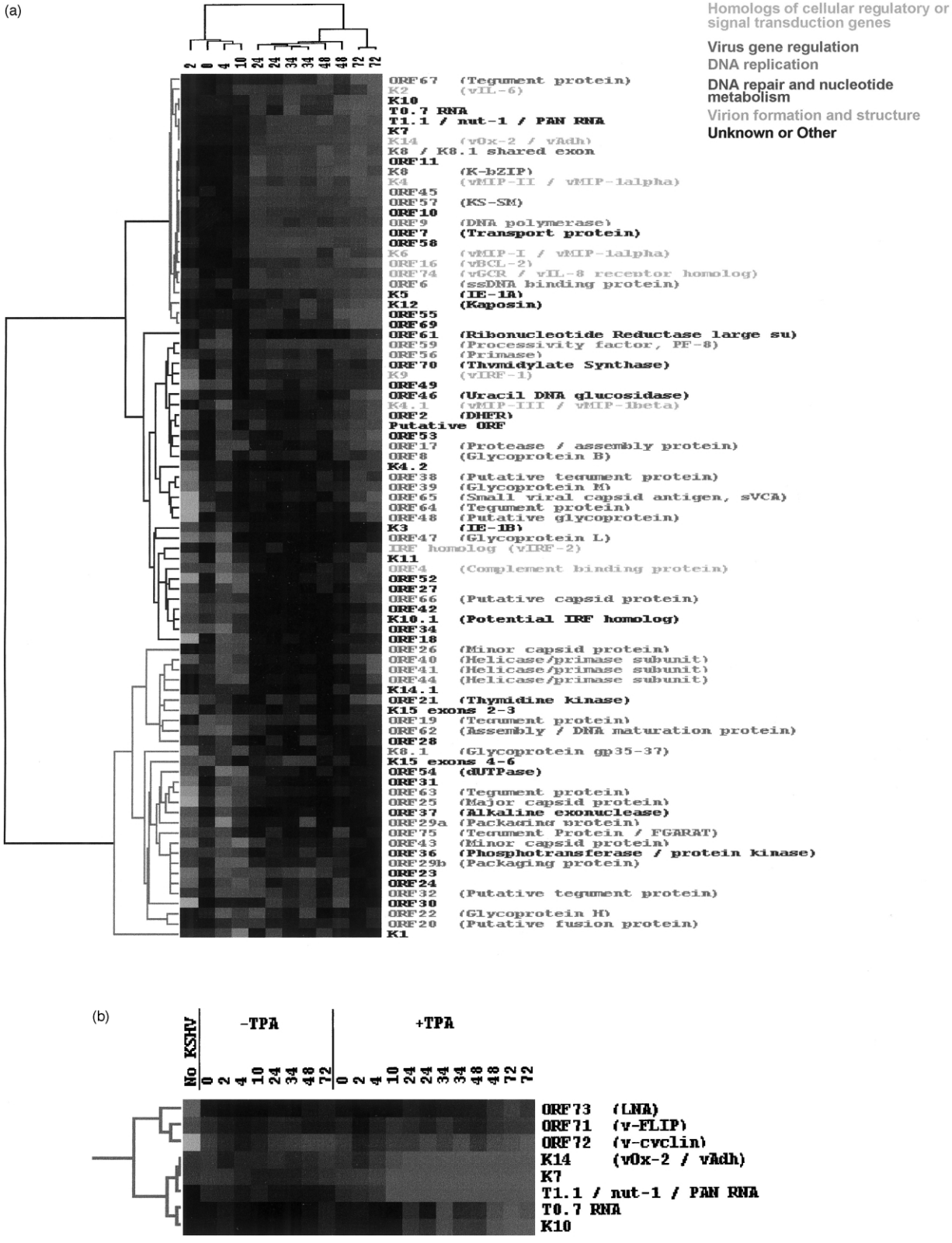

Fig. 1. Kaposi's sarcoma herpesvirus (KSHV) gene expression as determined by array technology and hierarchical clustering from Ref. [40]. (a) Hierarchical clustering of the genes and samples after the induction of lytic replication with phorbol 12-myristate 13-acetate (TPA). The open reading frames and corresponding gene names are listed on the right-hand side and are colour-coded according to their putative function; (b) expanded view of the cluster of genes whose expression is detectable in uninduced primary effusion lymphoma (PEL) cells (latently infected).

tation and occurs in approximately 1–10% of cases. Predisposing factors include high cumulative doses of immunosuppressive drugs and primary EBV infection at, or post-dating, transplantation. In heart and lung transplant recipients the risk of PTLD is ~10-fold higher in those who are EBV-seronegative at the time of transplant compared with those who are seropositive. PTLD in EBV-seronegative patients often presents as a polyclonal lymphadenopathy (infectious mononucleosis-like primary infection), whereas EBV-seropositive patients present with monoclonal lymphomas in extranodal sites like gut, brain and the engrafted organ. Similar lymphoproliferative disorders also occur in some congenital immunodeficiencies, e.g. X-linked lymphoproliferative syndrome. Phenotypically, PTLDs resemble B-lymphocytes transformed by EBV *in vitro,* where tumour cells express all the latent viral genes (Table 2). These cells are able to proliferate in PTLD because of a lack of CTL responses in the immunodeficient host and may regress when immunosuppression is discontinued [24]. The treatment of PTLD remains unsatisfactory and current studies are evaluating adoptive immunotherapies. One approach is to infuse EBV-specific cytotoxic T lymphocytes [28,29]. In bone-marrow transplant recipients, the healthy donor can act as a source of CTL. However, in solid organ transplant recipients either autologous CTLs must be grown from a stored pretransplant blood sample or allogeneic HLA-matched CTLs from a suitable donor must be used. CD20 is frequently expressed on the tumour cells and immunotherapy against this antigen, using rituximab (anti-CD20 antibody) is an effective and well-tolerated treatment option [30,31].

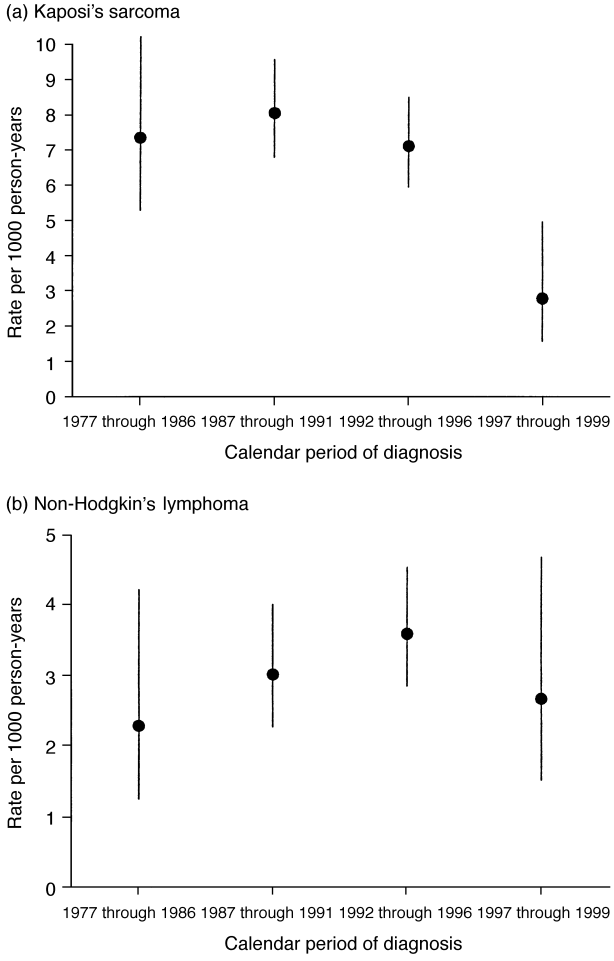

Fig. 2. Incidence rates (99% confidence intervals [CIs] for Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL), by calendar period in subjects with well known dates of seroconversion to human immunodeficiency virus-1 (HIV) (data from Ref. [41]).

Both PTLD-like lymphoma and Burkitt's-type lymphoma (BL) occur in HIV-infected patients. The overall incidence is approximately 3%. AIDS-BL occurs relatively early in HIV-infection and shows a peak at age 10–19 years. BL accounts for ~20% of all HIV-related lymphomas. However, only some of these contain EBV DNA. Non-BL AIDS lymphoma is referred to as large cell lymphoma and >50% of such tumours contain EBV DNA. Nearly 100% of AIDS-associated central nervous system (CNS) lymphomas contain EBV and PCR detection of EBV in the cerebrospinal fluid can help in the differential diagnosis of CNS lesions in HIV-infected patients [32,33].

Castleman's disease (CD) is a lymphoproliferative disorder [34] more often diagnosed in HIV-infected patients. A systemic variant of CD is associated with multiple organ involvement, especially spleen and lymph nodes with systemic symptoms such as weight loss and fever. This is called multicentric Castleman's disease (MCD).

KSHV is present in plasmablasts in MCD (Fig. 3) and these plasmablasts are not present in KSHV-negative MCD [10,35]. KSHV-positive plasmablasts belong to the B cell lineage. Although these KSHV latently infected cells phenotypically look like plasmablasts, they have germ-line immunoglobulin genes indicating that they are pregerminal centre naïve B cells. It is expected

Table 2
Neoplasms associated with EBV infection and expressed EBV latent gene

Tumour	EBV gene expression
Burkitt's lymphoma	*EBNA-1*
Nasopharyngeal carcinoma (NPC)	*EBNA-1*
	LMP-1
	LMP-2A[b]
Hodgkin's disease	*EBNA-1*
	LMP-1, *2A* and *2B*
PTLD[a]	*EBNA-1* to *6*
	LMP-1, *2A* and *2B*

[a] Posttransplant lymphoproliferative disease: EBV gene expression pattern is similar to that seen in *in vitro* EBV-transformed B lymphoblastoid cell lines.

[b] Not always expressed in NPC.

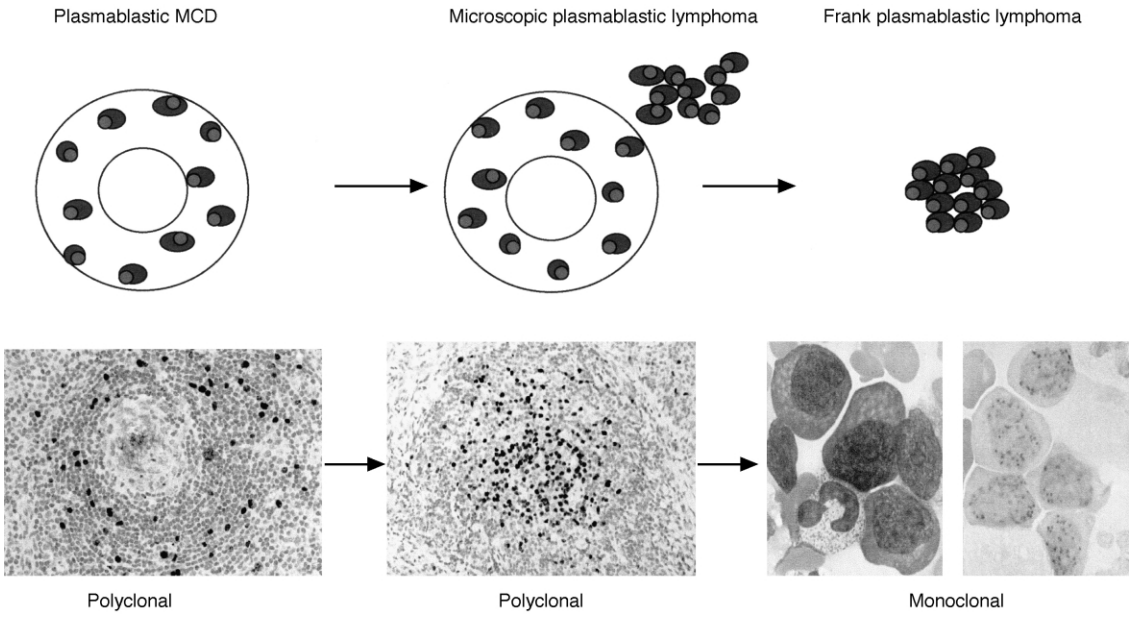

Fig. 3. Model of the role of KSHV in plasmablastic Castleman's disease and associated lymphoproliferations. KSHV latent nuclear staining is shown in the bottom panels.

that the virally-encoded interleukin-6 (IL-6) and cellular IL-6 drive these cells to differentiate and mature, without having to go through the germinal centre. These plasmablasts also exclusively express the lambda light chain, although they are not always a monoclonal population, suggesting a specific role for the lambda light chain in their pathogenesis [36,37]. KSHV is also present in all tumour cells of plasmablastic lymphoma that develop in a few patients with the KSHV-positive plasmablastic variant of MCD [36]. Unlike KSHV-positive primary effusion lymphoma (PEL) cells [38], the plasmablasts in MCD are only positive for KSHV, and not for EBV (Table 3).

In contrast to KS lesions that may resolve following partial restoration of the immune system (e.g. by highly active antiretroviral treatment (HAART) for HIV-positive patients), KSHV-positive MCD often continues to progress. Anti-IL-6 or anti-CD2O antibody therapies are currently being investigated as alternative therapies to cytotoxic drugs in the management of AIDS-associated MCD.

Hepatitis B virus (HBV) and hepatitis C virus (HCV)-associated liver cancers are the result of chronic necro-inflammatory disease, where massive liver necrosis is followed by extensive regeneration leading to an accumulative mutation load above the threshold that prevents cellular transformation. However, direct cellular growth-promotion by viral proteins probably also plays a role in hepatocellular carcinoma (HCC) pathogenesis: transgenic mice expressing HBV X protein or HCV core protein develop HCC. HCC very seldom develops in the absence of liver cirrhosis. The lack of inflammatory

Table 3
Comparison of KSHV-infected PEL cells and plasmablasts in MCD

	PEL	Plasmablastic[a] MCD
Site	Body cavity, extranodal	Lymph nodes, spleen
Morphology	Immunoblastic	Plasmablastic
KSHV	Positive	Positive
EBV	Positive in majority	Negative
Cytoplasmic Ig expression	Absent	High level of IgM
Ig light chain	Monotypic κ or λ mRNA	Monotypic λ Ig
CD30	Positive	Weakly positive
B-cell antigens	Absent	Weak or absent
Mutation in Ig genes	Hypermutated in majority	Absent
Cellular origin	Germinal centre or post germinal centre B-cells	Naïve IgMλ expressing B-cells

KSHV, Kaposi's sarcoma herpesvirus; EBV, Epstein–Barr virus; PEL, primary effusion lymphoma; MCD, multicentric Castleman's disease.

[a] The term plasmablast is used to denote a medium sized cell with a moderate amount of amphophilic cytoplasm and a large vesicular nucleus containing up to three prominent nucleoli. In contrast to an immunoblast, the cytoplasm contains abundant immunoglobulin (Ig).

responses in late HIV-1 infection was thought to partly explain the lack of an increased incidence of HBV- and HCV-induced HCC. Indeed, this hypothesis is also put forward to explain the apparent decrease in the incidence of breast cancer in HIV-1-infected women. However, it now seems that HIV-1-infected patients with haemophilia do develop HCV-associated HCC. HCV induced liver cirrhosis is usually micronodular and therefore similar to that seen with alcohol abuse, whereas HBV cirrhosis is usually macronodular. The differences in immunopathology associated with liver regeneration caused by HBV and HCV, respectively, may explain the apparent lack of an increased incidence of HCC in HIV-positive gay men, despite the high prevalence of HBV in this population.

Viruses now account for 15% of the global cancer burden, and immunosuppressed populations are at a significant increased risk to develop virally-driven neoplasms. Improved survival following organ transplantation and antiretroviral therapies may still lead to an increased risk to develop other solid cancers. Studying the mechanisms of how these viruses cause cancer will continue to elucidate carcinogenesis in general.

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