Int. J. Cancer: **000,** 000–000 (2009)

SPECIAL SECTION PAPER

Cancer and viral infections in immunocompromised individuals

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Over the last 30 years, the increasing use of organ and stem cell transplantation and the AIDS epidemic have led to the realization that some, but not all, human cancers occur more frequently in immunosuppressed individuals. With the notable exception of non-melanoma skin cancer (NMSC), most tumors that show strongly increased incidence rates in both transplant recipients and AIDS patients have been found to have a viral etiology. Among these are Kaposi sarcoma, diffuse large cell B-cell lymphoma, cervical cancer, liver cancer, Merkel cell carcinoma and a subset of Hodgkin's disease. A viral etiology for NMSC, *i.e.*, β- and γ-subtypes of human papillomavirus, has been suggested and investigated for many years, but remains controversial. In addition, the moderately increased incidence rates of several other cancers in immunosuppressed individuals (*e.g.*, Vajdic and van Leeuwen, Int J Cancer, in press) could indicate that additional infectious causes for at least some human cancers remain to be discovered. The controversy surrounding the role of cutaneous papillomavirus subtypes in the pathogenesis of NMSC illustrates the difficulties encountered when weighing the epidemiological and molecular biology evidence arguing for an involvement of highly prevalent viruses in certain types of cancer.

Key words: cancer; infection; virus; immune suppression

The accompanying review by Vajdic and van Leeuwen[1] summarizes our current knowledge on cancer in transplant recipients. Although both AIDS and organ transplantation have provided epidemiological data on cancers that are more common in immune suppression, each of these clinical settings also contributes its own bias. Thus, the prevalence of infections with oncogenic viruses in AIDS patients may not be the same as in the general population. This is, for example, the case for KSHV/HHV8, which in Western countries is more common in men who have sex with men (MSM) and also for HCV and HBV, whose transmission is associated with intravenous drug use. Similarly, certain causes of organ failure necessitating organ transplantation may have introduced a bias. However, a comparison of cancer rates in both AIDS patients and organ transplant recipients has identified several cancers that are noticeably more common in both patient groups than in the general population, strongly suggesting a contributory role of immune suppression in their development.

A recent meta-analysis[2] of 7 studies[3–9] covering 444,172 people with AIDS and 5 studies comprising 31,977 transplant recipients[10–14] found increased standardized incidence rates (SIRs) for Hodgkin's lymphoma (HL), Non-Hodgkin's lymphoma (NHL), Kaposi's sarcoma (KS), cancer of the liver, stomach, cervix, vagina/vulva, penis, anus, oral cavity and pharynx, skin (mainly non-melanoma skin cancer), lip, esophagus, larynx, trachea/bronchus/lung, eye and kidney in both patient groups (refer to Figs. 1 and 2 and Fig. 1 in the accompanying review[1]). Incidence rates for cancer of the bladder, thyroid colon and rectum were only increased in transplant recipients, whereas brain tumors and cancer of the testis were increased moderately only in HIV/AIDS patients.[1,2] In contrast, breast and prostate cancer were not more common in these 2 patient groups than in the general population, with prostate cancer being even slightly rarer in people with HIV/AIDS than expected (for a more detailed review refer to the accompanying review[1]).

Among cancers with a known viral or bacterial cause (refer to below), the meta-analysis, and several individual studies, found the highest standardized incidence rates in the case of Kaposi sarcoma, NHL, Hodgkin's disease, cervical cancer, cancers of the vulva, vagina, penis and anus, oral cavity, oropharynx and liver cancer (refer to Figs. 1 and 2 and Refs. 3–14). The meta-analysis found also a significantly increased risk for gastric cancer (due to *H. pylori*) in people with HIV/AIDS (SIR 1.9) and transplant recipients (SIR 2.0); this association was seen in 3/3 studies on transplant recipients, but only in 1/7 studies on HIV/AIDS patients.[2]

Although very rare, and therefore, not addressed in these 12 studies, Merkel cell carcinoma is also much more frequent in AIDS patients than in the general population[15] and has recently been found to be caused by a new polyomavirus, MCV.[16]

Among cancers with no established infectious etiology, non-melanoma skin cancer and cancer of the lip stand out as generally showing higher SIRs in transplant recipients compared to people with HIV/AIDS[1,2] (Fig. 2). Smaller, but significant increases in incidence were also noted for cancer of the esophagus, larynx and eye[1,2] (refer to Fig. 2).

All human oncogenic viruses identified so far have the ability to establish persistent infections in their host. Their replication is controlled by the immune system and the increase of these virus-associated cancers in the context of immune suppression is therefore most likely due to the inability of the host to limit viral replication and/or expansion of infected cells. Where the expression of viral proteins occurs in tumor cells, immune effector cells may recognize these viral proteins and play a role in curbing tumor cell growth, as predicted by the immune surveillance hypothesis of Burnet and Thomas.[17]

Role of established human tumor viruses in immunodeficiency-associated cancer

Epstein-Barr virus

A recent IARC (International Agency for Research on Cancer) working party confirmed the classification of EBV as a Group 1 carcinogen and concluded that there is sufficient evidence for a causative role of EBV in nasopharyngeal cancer, endemic Burkitt's lymphoma, immune suppression-related NHL, extranodal NK/T-cell lymphoma (nasal type) and a subset of HL. In addition, there is limited evidence for a role of EBV in gastric carcinoma and lympho-epithelioma-like carcinoma.[18]

Of these EBV-associated cancers, 2, immune suppression-related NHL and HL, are more frequent in immunosuppressed individuals than in the general population (refer to previous paragraph).

EBV-associated NHL in the immunosuppressed, in particular AIDS patients, include Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL) with immunoblastic morphology, primary central nervous system lymphoma (PCNSL), KSHV+/EBV+ primary effusion lymphoma (PEL) and plasmablastic lymphoma of the oral cavity type (for a recent review, see Ref. 19). The

Grant sponsor: Deutsche Forschungsgemeinschaft; Grant sponsor: EU Integrated Project INCA; Grant number: LSHC-CT-2005 018704.

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Received 22 May 2009; Accepted after revision 3 July 2009
DOI 10.1002/ijc.24741
Published online 8 July 2009 in Wiley InterScience (www.interscience.wiley.com).

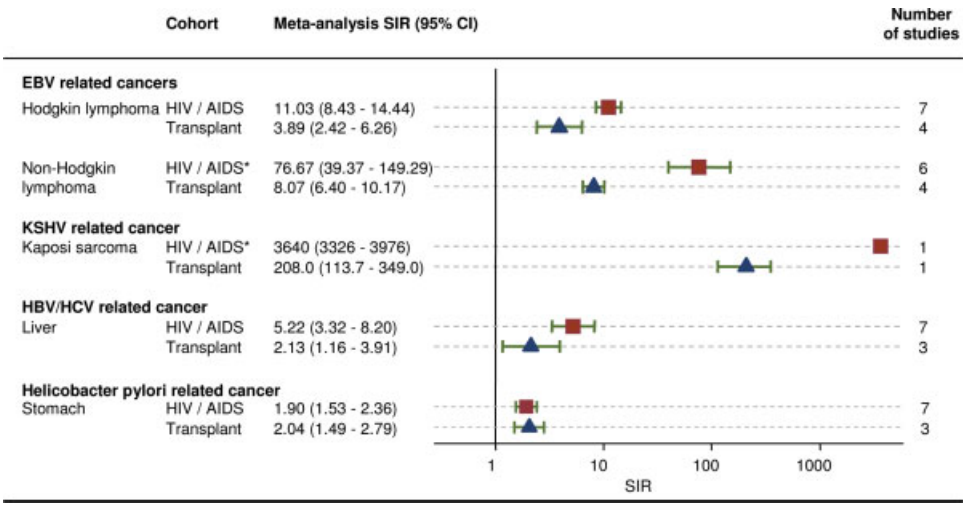

Figure 1 – Standardized incidence ratios, reported in a meta-analysis of up to 7 studies,[2] for cancers related to infection with Epstein-Barr virus, Kaposi sarcoma herpesvirus/human herpesvirus 8, hepatitis B virus, hepatitis C virus and *Helicobacter pylori* in people with HIV/AIDS and in transplant recipients. (Adapted from Ref. 2).

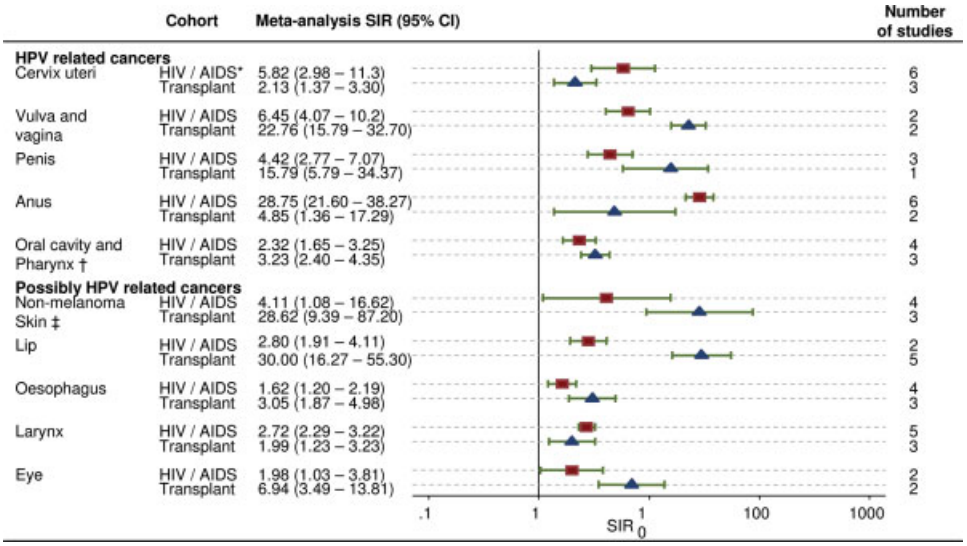

Figure 2 – Standardized incidence ratios, reported in a meta-analysis of up to 7 studies,[2] for cancers related to infection with human papillomavirus infection, and cancers of uncertain viral etiology, in people with HIV/AIDS and in transplant recipients. (Adapted from Ref. 2).

proportion of tumors associated with EBV varies from 40 to 100%, depending on the histological entity.

It is thought that the contribution of EBV to tumor development varies among different categories of NHL. In normal B-cells EBV can adopt 4 different latent gene expression programs, depending on the B-cell differentiation stage and reflecting the needs for its persistence in these different environments. Thus, the "growth" or "latency III" program, involving the expression of 6 nuclear proteins (EBNA-1, -2, -3A, -3B, -3C, -LP), 3 non-structural membrane proteins (LMP-1, -2A, -2B) and 2 untranslated RNAs (EBER-1, -2) is normally employed in naïve B-cells to drive their proliferation. *In vitro*, the latency III program is sufficient to induce B-cell immortalisation. Since several of the "latency III" proteins are good targets for cytotoxic T-lymphocytes (CTLs), B-cells expressing this program *in vivo* are normally quickly eliminated. However, in immunocompromised individuals, particularly in transplant recipients, expression of this "growth" program becomes possible and leads to the virus-driven transformation of B-cells and development of poly- or oligoclonal B-cell proliferation, which can progress to monoclonal lymphoma (reviewed in Ref. 20). This group of lymphoproliferations is referred to as post-transplant lymphoproliferative disease (PTLD) and is classified histologically as DLBCL. These tumors can respond to therapy with adoptively transferred EBV-specific CTLs, indicating that EBV is the main driving force for their development (reviewed in Ref. 21). EBV-associated DLBCL have therefore been considered as EBV-driven lymphoproliferations occurring in the context of defective T-cell immunity against EBV.[22]

In AIDS-associated DLBCL, viral gene expression patterns are more variable but the transforming EBV protein LMP1 (latent membrane protein 1) is frequently expressed.[23,24] LMP1 plays a crucial role in the transformation of B-cells by EBV (reviewed in Ref. 20). Knockdown of LMP1 in EBV-transformed B-cell lines results in apoptosis, suggesting a requirement of LMP1 for their survival.[25] In DLBCL, expression of LMP1 correlates inversely with the expression of BCL-6, a marker for germinal center B-cells, suggesting that, among DLBCL, the impact of LMP1 is

likely to be strongest in tumors representing a post-germinal center plasmacytic differentiation profile.[26] In contrast to PTLD, AIDS-associated DLBCL is always a monoclonal tumor.

Burkitt lymphoma (BL) occurs about 100 times more frequently in people with HIV/AIDS than in the general population of industrialized countries.[18,27,28] About 30–60% of AIDS-BL are EBV positive.[19] In BL EBV adopts, the "latency I" program, which involves only the expression of EBNA-1 and EBERs; it thus provides only the viral functions required to maintain the circular viral genome in dividing B-cells (EBNA-1) without expressing the classical EBV transforming proteins such as LMP-1 (reviewed in Ref. 20). The absence of EBV from the majority of sporadic or AIDS-associated BL indicates that it is not essential in the pathogenesis of this tumor. The key pathogenic event in BL is thought to be the Ig/*c-myc* translocation found in all BL tumors, which maintains BL cells, displaying a post-germinalcenter phenotype, in proliferation (reviewed in Refs. 20 and 29). However, EBV is likely to contribute to the survival of continuously c-mc expressing B-cells by protecting them against apoptosis[30] and EBNA-1 may contribute to DNA damage in these cells.[31]

In AIDS patients, HL is more frequently associated with EBV infection (80–100% of cases) than in the general population; in these cases the Hodgkin Reed-Sternberg (HRS) cells, the malignant component of this tumor, show evidence of the EBV "latency II" or "default" program, which involves expression of the transforming EBV protein LMP1, as well as EBNA-1 and LMP2A.[19,32–35] Since the "default" program is physiologically expressed in normal germinal center B-cells (reviewed in Ref. 36) and HL HRS cells show evidence of deleterious mutations in the hypermuted Ig variable regions,[37,38] the majority of HL in HIV-infected persons are therefore thought to be derived from post-germinal center B-cell clones that escaped physiological apoptosis by virtue of the anti-apoptotic effects of EBV LMP1. The role of EBV in the pathogenesis of HL is discussed in more detail in the accompanying review by R. Jarrett.[39]

While in many PEL cases the lymphoma cells harbor both EBV and KSHV, some are only positive for KSHV (reviewed in Ref. 19). This, and the fact that the (non-transforming) EBV latency I program is expressed in dually positive PEL cells, suggests that KSHV, rather than EBV, is the driving force behind the development of PEL.

Kaposi sarcoma herpesvirus/human herpesvirus 8

A recent evaluation of the available epidemiological and molecular mechanistic evidence by an IARC working group resulted in the classification of KSHV as a Group 1 carcinogen.[18] In the case of Kaposi's sarcoma (KS) and primary effusion lymphoma (PEL) the evidence supporting a causative role for KSHV was considered sufficient; KSHV is also associated with the plasma cell variant of Multicentric Castleman's disease (MCD).[18]

The epidemiological evidence supporting a causative role for KSHV in the pathogenesis of Kaposi's sarcoma is now compelling. Not only is the virus found in virtually all KS tumors, irrespective of the clinical form ("classic," African-endemic, HIV-associated, post-transplant), data from more than 20 cohort studies and 80 case-control studies show an association between KSHV and Kaposi's sarcoma, with relative risks higher than 10. In transplant recipients and people with HIV/AIDS, the risk of Kaposi sarcoma increases with the increasing titre of antibodies directed against KSHV, which are markers of the viral load.[40–43] Detection of KSHV in the peripheral blood of asymptomatic individuals predicts the subsequent progression to Kaposi sarcoma.[44]

In immunosuppressed individuals, KS can often regress as a result of a reduced immunosuppressive therapy (in transplant recipients) or anti-HIV therapy (HAART). As assessed by clonality of the viral episome, KS can be oligo- as well as monoclonal.[45] In the context of immunosuppression, at least some cases of KS may therefore represent virus-driven, oligoclonal proliferations that are still susceptible to immune surveillance. In experimental *in vitro* systems, KSHV has been shown to induce the formation of spindle cells in primary endothelial cell cultures (endothelial cells of a spindle cell morphology are thought to represent the neoplastic component in the KS tumor) and to reduce their dependence on growth factors[46,47]; in primary endothelial cells, it also induces a partial re-differentiation of lymphatic endothelial cells towards vascular endothelial cells and vice versa by modulating the expression of Prox-1, a transcription factor determining lymphatic endothelial cell differentiation, followed by the increased expression of podoplanin and VEGFR-3—markers for the lymphatic endothelial cell lineage.[48–50] In HPV E6/E7 immortalized endothelial cells, KSHV leads to extended survival, growth-factor independence, evidence of loss of contact inhibition and growth of infected cells in soft agar (*i.e.*, signs of transformation).[47,48,51,52] The outgrowth of fully tumorigenic clones was also noted.[53] KSHV establishes a latent gene expression program in the majority of infected endothelial spindle cells in KS tumors; however, a small proportion of infected cells in these tumors show evidence of productive infection. Several (latent and lytic) KSHV proteins have been shown experimentally to have transforming or tumorigenic potential. Among these are the latency-associated nuclear antigen LANA, the D-type cyclin homologue vcyc, the FLIP (caspase inhibitor) homologue vFLIP (mRNA expression for these latent genes has been observed in tumor cells *in vivo*), as well as the lytic cycle proteins K1, vIRF1/K9, the viral chemokine receptor vGPCR and kaposin A (reviewed in Ref. 54). The exact contribution of these individual viral proteins to the development of KS has not yet been established.

PEL is a very rare lymphoma, encountered in AIDS patients and transplant recipients. Because of its rarity, only case reports and no systematic case-control or cohort studies are available and the epidemiological argument in favor of a causative involvement of KSHV is therefore limited to the fact that KSHV is consistently found in this lymphoma. From an experimental point of view, the same latent viral proteins (LANA, vcyc, vFLIP, kaposin) found in KS (refer to previous section) are also expressed in PEL; in addition, one of the KSHV interferon regulatory factor homologues, vIRF-3, shows a latent gene expression pattern in B-lymphoma cells and there is also substantial expression of an interleukin 6 homologue, vIL6. Knockdown of vIRF-3 and vFLIP have been shown to induce cell death in PEL cell lines, suggesting that the continuous expression of these viral proteins is required for PEL cell survival.[55–57]

MCD is a polyclonal lymphoproliferative disease that can be a precursor to frank lymphoma. In KSHV-associated MCD, LANA, v-myc, vFLIP, vIL6 and vIRF3 are expressed in MCD B-cells (refer to previous section). Since vIL6 is a potent stimulator of B-cell growth, it is likely that this protein plays an important role in the B-cell proliferation seen in MCD. In addition, the role of vFLIP and vIRF3 in protecting against apoptosis in B-cells[56,57] is likely to contribute to B-cell survival. KSHV has also been detected in occasional solid plasmablastic lymphomas in people with AIDS.[19]

Human papillomavirus

The recent IARC evaluation[18] of biological carcinogenic agents confirmed the classification as Group 1 carcinogens of several human papillomavirus types belonging to a few phylogenetically related mucosotropic "high-risk" species (alpha-5, 6, 7, 9, 11).[18,58,59] These include the types most frequently found in cervical cancer (HPV-16, 18, 31, 33, 35, 45, 52, 58) and 4 less frequently encountered types (HPV-39, 51, 56, 59). Of these, HPV-16 carries by far the highest risk of cancer. Other types were classified as probably or possibly carcinogenic to humans.[18] A detailed review of the epidemiological evidence linking these HPV types to cervical cancer can be found in previous IARC evaluations.[59,60] Since then, several comprehensive studies have confirmed that these high-risk HPV types cause virtually all cases of cervical cancer worldwide.[61,62] HPV-16 is also the most important

cause of anal cancer.[18] Figure 2 shows standardized incidence rates of HPV-related cancers (cervical, anal, vulva, vaginal, penile, oropharynx) in immunocompromised individuals. Whereas EBV-associated NHL and KSHV-associated KS show standardized incidence rates of 100–1000 in AIDS patients (Fig. 1), these rates are lower (5–10-fold) for most HPV-related cancers, with the exception of anal cancer (~30-fold; refer to Fig. 2). This may reflect differences in the biology of the oncogenic viruses involved in these different malignancies and/or the susceptibility of their target cells to virus-induced transformation. Epidemiological data also provide clues to the role of immune suppression in the development of HIV-associated cancers. Many EBV- and KSHV-related malignancies, in particular DLBCL, primary CNS lymphoma and KS have become much rarer after the widespread introduction of highly active antiretroviral therapy (HAART) in 1995, illustrating the role of immune suppression in their pathogenesis.[9,63] Likewise, the detection of HPV and the incidence of squameous intraepithelial lesions (SILs) in cervical smears of HIV-infected women is strongly linked to a low CD count or high viral load.[64,65] However, cervical cancer does not appear to have decreased after the introduction of HAART.[9,63] Therefore, the early stages of HPV replication and/or persistence, but not, or less so, the progression to cervical cancer may be influenced by HIV-associated immune deficiency.[3]

Experimental evidence for the oncogenic potential of some of these high-risk HPVs (in particular HPV-16 and -18) and some of their proteins (particularly their E6 and E7 proteins) comes from many studies using transformation assays in rodent cell lines such as NIH 3T3, Rat1 or oncogene cooperation assays in primary baby rat kidney or mouse kidney cell cultures co-transfected with E6 or E7 and a cellular oncogene such as activated ras or fos. In addition, human keratinocyte cultures could be immortalized by joint expression of high-risk E6 and E7 proteins. Furthermore, silencing of the expression of E6/E7 in cervical carcinoma cell lines has been shown to induce senescence or apoptosis, providing a clear indication that the continued expression of these proteins is required for the proliferation of cervical carcinoma cell lines. A detailed review of these studies can be found in IARC monographs volumes 64 and 90.[59,60]

An important biochemical property of the E6 protein of many HPV types is its ability to target cellular binding partners for degradation through the combined activity of a cellular ubiquitin ligase, E6AP and the cellular ubiquitin proteasome pathway.[66] There are many cellular binding partners targeted by E6 in this way and their precise contribution to the overall activity of E6 has been difficult to disentangle.[67] Of particular importance for the transforming potential of mucosal HPV types appears to be the E6-mediated degradation of the tumor suppressor protein p53.[68] Another important mechanism appears to be the ability to induce telomerase activity[69–71] and to inhibit both p53-dependent and -independent apoptosis.[72–74]

HPV E7 also recruits a cellular ubiquitin ligase, the multi-protein Cullin ubiquitin ligase complex, to target a range of cellular interaction partners for proteasomal degradation. Most important among them are the Rb tumor suppressor protein and the related p107 and p130 pocket proteins, whose removal allows progression through S-phase.[75,76] Other key regulators of cell cycle that are known interacting partners of E7 include the p21/p27 cdk inhibitors and a subset of cyclins and E7 also associates with the AP1 family of transcription factors, HDACs and MPP2.[76,77]

One important consequence of E6 and E7 targeting, respectively, p53 and pRB as well as the p21/p27 cdk inhibitors is its ability to abrogate normal DNA damage responses, and this is hypothesized to contribute to the accumulation of genetic alterations in HPV-positive cells including those that might contribute to HPV-associated cancers. One of the hallmarks of E6- and E7-expressing keratinocytes, therefore, is genomic instability resulting in multiple chromosomal abnormalities.[76] The role of E7 in genomic instability may also involve pRB-independent mechanisms, such as an effect on centrosome biogenesis, and the consequent defects in segregation of daughter chromosomes during cell division.[78–80]

Hepatitis B and C virus

Hepatitis B and hepatitis C virus infect, respectively, over 300 million and 170 million people world wide. Extensive epidemiological evidence shows a strong association of HBV with hepatocellular carcinoma in immunocompetent persons (relative risks in prospective studies in the range of 10–60). References 81–84 serve as examples. The earlier literature is reviewed in IARC monograph vol. 59.[85] Likewise, many cohort and case-control studies have established an association of HCV with hepatocellular carcinoma, with relative risks in studies that controlled for confounding factors, including chronic HBV infection, ranging from 2.5–88. References 86–88 serve as examples for more recent studies, while case-control studies and the earlier literature is reviewed in IARC monograph 59.[85] On the basis of this substantial body of evidence, both HBV and HCV continue to be classified a Group 1 carcinogens.[18]

The pathogenesis of HBV-induced hepatocellular carcinoma (HCC) is thought to involve both direct (virus-mediated) and indirect mechanisms. The latter are thought to be the result of hepatocellular regeneration in chronic hepatitis and cirrhosis and involve a loss of proliferation control, reactivation of telomerase activity, oxygen radical-induced DNA damage. The former are thought to involve the HBV x protein, a truncated form of the HBsAg envelope protein and the consequences of integration of the HBV genome into cellular DNA. The HB x protein has been shown to activate a number of genes involved in cell cycle control and progression, DNA repair, apoptotic cell death and cellular adhesion and to disturb the function of p53 and the DNA damage specific DNA-binding protein DDB-1.[89,90] The HB x protein binds to specific sequences in the C-terminal end of p53, preventing its entry into the nucleus, abrogating its sequence-specific DNA-binding and transcriptional activity and inhibiting the interaction of p53 with the DNA repair proteins XBP and XPD, thereby compromising the role of p53 in the DNA damage response and DNA repair.[91,92] The truncated preS/S protein modulates protein kinase C signal transduction and affects several cellular transcription factors such as NFkB and AP-1.[93]

Although chronic HCV infection is a major risk factor for hepatocellular carcinoma (refer to previous section), it remains uncertain how HCV causes this tumor.[94] Chronic ER stress in HCV-infected hepatocytes, destruction of infected hepatocytes by virus-specific T-cells and the accompanying inflammatory damage and oxidative stress may lead to the accumulation of genomic damage[95,96]; HCV-induced changes in MAPK signaling, which regulates both cell metabolism and growth may also contribute.[97] In addition, several HCV proteins affect intracellular signaling, metabolism and cellular growth control, by, *e.g.*, modulating the function of p53 or p73 family members in the case of the HCV core protein.[98–100] The HCV core protein, NS3, NS4B and NS5A have all been shown to have transforming properties when transfected in tissue culture, or expressed in transgenic mice carrying individual viral proteins or an HCV polyprotein.[98,101–103] However, these findings need to be substantiated in the context of a viral infection, which is currently difficult, given the lack of a suitable *in vivo* experimental system. Overall, the current view is that synergistic effects between the consequences of chronic inflammation and direct virus–host cell interactions represent the most likely mechanisms of pathogenesis.

Although HCC is more frequent in HIV-infected persons and transplant recipients than in the general population, the exact role of HIV and/or immune suppression in HCC development is not clear. HIV-related immune deficiency worsens the risk of cirrhosis in HCV-infected individuals.[104–106] In a meta-analysis[105] of several studies, the increased risk of HIV on HCV-related cirrhosis was found to be ~2-fold. One study[106] observed an increased risk for cirrhosis in HIV/HCV-co-infected individuals only in the pre-HAART era (prior to 1996), which would underline the role of

HIV-induced immune suppression in the accelerated progression towards cirrhosis. However, a direct link of HIV-related immune suppression to HCC risk has not yet been demonstrated: when adjusted for HCV infection and/or alcohol use, 2 studies[106,107] found no independent association of HIV-infection with the rate of HCC.

Merkel cell carcinoma virus

Although Merkel cell carcinoma (MCC) is very rare, and therefore, not covered by most large cohort studies, it has been noted to be much more frequent in people with AIDS.[15] This observation stimulated the search for an infectious cause, which resulted in the discovery of Merkel cell carcinoma virus.[16] About 70–80% of MCC cases appear to harbor clonally integrated MCV genomes,[16,108–110] although this may vary depending on the geographic region studied.[111] Using PCR, MCV genomes have also frequently been detected in uninvolved skin and other body sites/fluids.[16,108,109,112] Interestingly, mutations have been observed in the MCV genomes integrated into the cellular genome of MCC tumor cells: these lead to premature truncations of their large T (LT) proteins, which consequently lack their helicase domain and are no longer able to replicate an episomal MCV genome.[112] In contrast, MCV genomes derived from other body sites possess full-length, replication competent, LT proteins.[112] Mutations observed in the MCV genomes obtained from MCC samples often involve pyrimidine dimers, suggesting that exposure to UV light, a known risk factor for MCC, could have contributed to their accumulation.[112] Since the monoclonal integration pattern of MCV genomes in tumor samples suggests that integration preceded tumor development,[16] and since LT-catalyzed replication of an integrated viral genome would be expected to induce a cellular DNA damage response, the loss of replication competence, caused by UV-induced mutations, could provide a key step in the survival of MCV containing tumor cell precursors.[112] The role of immune suppression in MCC development is likely to be linked to the fact that several other polyomaviruses are known to show increased replication in immunosuppressed individuals. The mechanism of tumourigenicity proposed for MCV could therefore serve as a precedent for other skin cancers, in particular SCC, where UV-exposure and immune suppression are also recognized as major risk factors (refer to below).

Human T-cell lymphoma virus I

Whether adult T-cell leukemia/lymphoma (ATL), the malignancy associated with HTLV-I, is more common in immune suppressed individuals relative to the general population has so far not been addressed systematically. However, case reports suggest that HTLV-I infected transplant recipients may progress more quickly to ATL.[113]

Disputed human tumor viruses in immunodeficiency-associated human cancer

As discussed earlier and in the accompanying review,[1] non-melanoma skin cancer—this entity comprises squameous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin—as well as cancer of the lip, are markedly more frequent in both transplant recipients and in people with HIV/AIDS. Of note, the incidence appears to be higher in transplant recipients than in HIV-infected individuals (refer to Fig. 2). Also, while BCC is about 5-fold more common than SCC in immunocompetent persons, this ratio is reversed after immune suppression, with SCC reported to be between 18-fold and 250-fold more common in transplant recipients than in the general population, compared to an increase of BCC bin the order of 1.2-fold to 16-fold.[114–117]

The question whether the marked increase in SCC could reflect a viral etiology of this tumor, and whether cutaneous (β, γ) types of human papillomaviruses could be the cause, has been investigated intensely over many years. Multiple studies have shown that cutaneous HPV types are frequently found on the skin, in plucked hair follicles and in SCC tissue; however, in SCC tissue the viral load is generally much lower than 1 copy per cell and the role of the cutaneous HPV types in SCC pathogenesis, if any, must therefore be fundamentally different from that of all other known human DNA tumor viruses, whose genomes are always found, and at least a few viral genes expressed, in each tumor cell. In addition, unlike the situation in cervical or anal cancer (refer to previous section), where a few mucosal HPV types such as HPV-16 or HPV-18 account for most human cervical and anal cancers, a plethora of cutaneous HPV types has been found in SCC, mostly by PCR techniques, with only HPV-5 and HPV-8 being perhaps more frequently encountered. Recent PCR-based studies have not provided consistent evidence of an etiological role for any viral type or groups of types.[118–120]

Recent serological case-control studies have also not come to consistent conclusions. While some studies[121–123] suggested an association of skin cancer with beta-1 or beta-2 papillomaviruses, in particular HPV-5 or HPV-8, another report observed associations with SCC for other types (beta-15, -17, -38; gamma-50, -95).[124]

In addition, one strong risk factor for SCC, previous exposure to UV light, could have led to confounding in some studies, if HPV replication were enhanced in UV-damaged skin. Heavily light-exposed areas were reported be much more likely to test HPV positive, raising the important possibility of confounding playing a role in the reported weak associations between SCC and HPV detection.[119] In another study,[123] individuals with tumors on chronically sun-exposed sites were more frequently seropositive for beta HPV types than individuals with SCC at other anatomic sites. A small cohort study[125] found no association between the presence of antibodies to β-type HPVs and the subsequent emergence of SCC, but did note a (not-significant) higher rate of HPV antibodies in SCC cases after the tumors were diagnosed. The possibility of "reverse causality," *i.e.*, the more frequent detection (at low copy number) of many HPV types in SCC samples compared to normal skin being the consequence, rather than the cause, of UV-damage or increased HPV replication in premalignant or malignant tissue, cannot therefore be categorically excluded at present. In a recent study in transplant recipients,[126] no association between HPV antibodies and SCC was found, although the expected significant associations between HPV-16 antibodies and a self-reported abnormal PAP smear, as well as between HPV-6 antibodies and a history of genital warts, was observed.

How strong is the experimental evidence that links cutaneous HPV types to skin cancer? Some cutaneous beta HPV types show transforming activity in rodent cell transformation assays[127,128] (*e.g.*, HPV-5, -8 and -47) or primary rodent cell co-transformation assays (*e.g.*, HPV-12, -14, -15, -24, -36 and -49).[129] HPV-8 and -38 show immortalizing activity in primary human keratinocyte assays.[128,130] HPV-38 induces the p53 repressor, ΔNp73, to inhibit p53 responsive pathways[131] and activates telomerase.[132,133] A property common to the E6 proteins of several mucosal high risk and cutaneous HPV types (HPV-16, -18, -11, -5, -8, -20, -22, -38, -76, -92 and -96) appears to be the interaction with, and inhibition of, the pro-apoptotic protein Bak.[134–136] The E7 proteins of some cutaneous β-type HPVs can target pRB.[130] Transgenic mice expressing the HPV8 early genes in the epidermis are prone to benign and malignant skin cancers[137] and HPV38E6E7 mice developed skin cancers following treatment with chemical carcinogens.[138]

Although these experimental data support the carcinogenic potential of at least some beta HPV types, the currently available inconsistent epidemiological evidence does not permit the firm conclusion that these HPV types play a causative role in SCC in immunosuppressed individuals. The recent IARC working group considered the available epidemiological evidence as inconclusive; in the context of epidermodyplasia verruciformis, a genetically determined susceptibility to HPV-induced skin cancer, the beta types HPV-5 and HPV-8 were considered an exception and classified as "possibly carcinogenic" (group 2B).[18]

Following the recent discovery of MCV (refer to previous section), a few studies have examined an association of this virus with SCC and BCC. Although MCV appears to be detected more frequently in SCC and BCC of immunosuppressed compared to immune competent individuals,[109] no evidence of clonal integration in these tumors has been so far reported and it is currently unclear, if MCV plays a role in the pathogenesis if these tumors.

An infectious cause for other cancers associated with immune suppression?

Among common epithelial cancers not yet linked to a viral cause, only cancers of the trachea, bronchus and lung show a noticeable and consistent (at least in transplant recipients) increase during immune suppression (refer to Fig. 2 in this review and Fig. 1 in the accompanying review[1]). In kidney transplant recipients, the increase in lung cancer rates is much higher after transplantation than during dialysis suggesting a role of immune suppression.[13] Several studies have shown lung cancer to be more frequent in AIDS patients than in the general population, in particular after the widespread use of highly active antiretroviral therapy (HAART). However, the recent IARC working group felt that residual confounding by smoking, a very strong risk factor for lung cancer, could not be ruled out[18] (exemplary Refs. 9,139–141).

In kidney transplant recipients, the increased incidence rates for myeloma, kidney and bladder cancer are already seen during and before dialysis, suggesting that the increase of these tumors in transplant recipients may not be genuinely linked to immune suppression.[1,13] The involvement of an infectious agent in leukemia has been the subject of speculation for some time.[142]

Outlook

The availability of large scale cohort data on cancer incidence in transplant recipients as well as people with HIV/AIDS now indicates that several, but by no means all, human cancers appear to increase in frequency in the absence of an intact immune system. With the notable exception of NMSC, the cancers showing the most dramatically increased incidence rates are now known to have a viral cause. The role of the incriminated viruses in the development of their associated tumors varies and ranges from a directly transforming effect to a facilitating mode of action. Consequently, in these cases, the immune system may exert its protective effect against tumor development either by limiting the outgrowth of virus-transformed cells or tumor cells that require the continued expression of viral proteins for their survival, or by curbing viral replication at an earlier stage, thus reducing the likelihood of a "tumourigenic hit." A protective effect of the immune system appears to also apply in the case of liver and gastric cancer, where immune-mediated destruction of virus-infected liver cells and subsequent hepatocellular regeneration, or inflammation in response to bacterial persistence, are thought to play an important role in cancer development and where a "weakened" immune system could have been expected to be beneficial. In the case of liver cancer, this may be due to increased viral replication during immune suppression and there is limited evidence for increased *H. pylori* colonization rates in transplant recipients.[143]

Given the marked increase of NMSC, in particular SCC, in both transplant recipients and people with HIV/AIDS, and the recently proposed model of how UV-induced mutations could enhance the tumourigenicity of a possibly widespread polyomavirus,[112] a (yet to be identified) viral cause for SCC would not be surprising.

Where do these findings leave the concept of immunological tumor surveillance, proposed by Macfarlane Burnet and Thomas nearly a half century ago? It would appear that the examples of several common tumors, in particular of the breast, prostate, ovary, which appear not to be linked to immune suppression (refer to previous section), indicate that there is probably no "general" recognition of tumor cells as "non-self." In virus-associated cancers there will be recognition of tumor cells as long as they express immunogenic viral proteins recognized by effector T-cells. If some of the human cancers occurring more frequently in immunosuppressed individuals are not caused by an infectious agent, this might after all point to the existence of antigenic determinants on some tumor cells that are indeed recognized by the adaptive immune system.

Acknowledgements

The author thanks Dr. Andrew Grulich for granting permission to use and modify the diagrams shown in Figures 1 and 2 (originally from Ref. 2) and all members of the IARC monograph working group (see Ref. 18) for illuminating discussions on the infectious origins of cancers covered in this review.

References

1. Vajdic CM, van Leeuwen MT. Cancer incidence and risk factors affecting solid organ transplantation. Int J Cancer. DOI: 10.1002/ijc.24439 .
2. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370:59–67.
3. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 2000;92: 1500–10.
4. Grulich AE, Li Y, McDonald A, Correll PK, Law MG, Kaldor JM. Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. AIDS 2002;16:1155–61.
5. Dal Maso L, Franceschi S, Polesel J, Braga C, Piselli P, Crocetti E, Falcini F, Guzzinati S, Zanetti R, Vercelli M, Rezza G. Risk of cancer in persons with AIDS in Italy, 1985–1998. Br J Cancer 2003;89:94–100.
6. Allardice GM, Hole DJ, Brewster DH, Boyd J, Goldberg DJ. Incidence of malignant neoplasms among HIV-infected persons in Scotland. Br J Cancer 2003;89:505–7.
7. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, Bordoni A, De Weck D, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005;97:425–32.
8. Newnham A, Harris J, Evans HS, Evans BG, Moller H. The risk of cancer in HIV-infected people in southeast England: a cohort study. Br J Cancer 2005;92:194–200.
9. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 2006;20:1645–54.
10. Kyllonen L, Salmela K, Pukkala E. Cancer incidence in a kidney-transplanted population. Transpl Int 2000;13(Suppl 1): S394–S398.
11. Birkeland SA, Lokkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. Lancet 2000;355:1886–7.
12. Adami J, Gabel H, Lindelof B, Ekstrom K, Rydh B, Glimelius B, Ekbom A, Adami HO, Granath F. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2003; 89:1221–7.
13. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor JM, Grulich AE. Cancer incidence before and after kidney transplantation. JAMA 2006;296:2823–31.
14. Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant 2007;7:941–8.
15. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. Lancet 2002;359:497–8.
16. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096–100.
17. Burnet M. Cancer: a biological approach. III. Viruses associated with neoplastic conditions. IV. Practical applications. Br Med J 1957;1: 41–7.
18. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens. Part B: Biological agents. Lancet Oncol 2009;10:321–2.

19. Carbone A, Cesarman E, Spina M, Gloghini A, Schulz TF. HIV-associated lymphomas and gamma-herpesviruses. Blood 2009;113:1213–24.
20. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer 2004;4:757–68.
21. Gottschalk S, Heslop HE, Rooney CM. Adoptive immunotherapy for EBV-associated malignancies. Leuk Lymphoma 2005;46:1–10.
22. Rowe M, Young LS, Crocker J, Stokes H, Henderson S, Rickinson AB. Epstein-Barr virus (EBV)-associated lymphoproliferative disease in the SCID mouse model: implications for the pathogenesis of EBV-positive lymphomas in man. J Exp Med 1991;173:147–58.
23. Carbone A, Tirelli U, Gloghini A, Volpe R, Boiocchi M. Human immunodeficiency virus-associated systemic lymphomas may be subdivided into two main groups according to Epstein-Barr viral latent gene expression. J Clin Oncol 1993;11:1674–81.
24. Hamilton-Dutoit SJ, Rea D, Raphael M, Sandvej K, Delecluse HJ, Gisselbrecht C, Marelle L, van Krieken HJ, Pallesen G. Epstein-Barr virus-latent gene expression and tumor cell phenotype in acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. Correlation of lymphoma phenotype with three distinct patterns of viral latency. Am J Pathol 1993;143:1072–85.
25. Guasparri I, Bubman D, Cesarman E. EBV LMP2A affects LMP1-mediated NF-kappaB signaling and survival of lymphoma cells by regulating TRAF2 expression. Blood 2008;111:3813–20.
26. Gaidano G, Carbone A, Dalla-Favera R. Pathogenesis of AIDS-related lymphomas: molecular and histogenetic heterogeneity. Am J Pathol 1998;152:623–30.
27. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123:187–94.
28. Stein L, Urban MI, O'Connell D, Yu XQ, Beral V, Newton R, Ruff P, Donde B, Hale M, Patel M, Sitas F. The spectrum of human immunodeficiency virus-associated cancers in a South African black population: results from a case-control study, 1995–2004. Int J Cancer 2008;122:2260–5.
29. Klein E, Kis LL, Klein G. Epstein-Barr virus infection in humans: from harmless to life endangering virus-lymphocyte interactions. Oncogene 2007;26:1297–305.
30. Kelly GL, Milner AE, Baldwin GS, Bell AI, Rickinson AB. Three restricted forms of Epstein-Barr virus latency counteracting apoptosis in c-myc-expressing Burkitt lymphoma cells. Proc Natl Acad Sci USA 2006;103:14935–40.
31. Gruhne B, Sompallae R, Marescotti D, Kamranvar SA, Gastaldello S, Masucci MG. The Epstein-Barr virus nuclear antigen-1 promotes genomic instability via induction of reactive oxygen species. Proc Natl Acad Sci USA 2009;106:2313–8.
32. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006;108:3786–91.
33. Grogg KL, Miller RF, Dogan A. HIV infection and lymphoma. J Clin Pathol 2007;60:1365–72.
34. Tirelli U, Errante D, Dolcetti R, Gloghini A, Serraino D, Vaccher E, Franceschi S, Boiocchi M, Carbone A. Hodgkin's disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and Tumors. J Clin Oncol 1995;13:1758–67.
35. Carbone A, Gloghini A, Larocca LM, Antinori A, Falini B, Tirelli U, Dalla-Favera R, Gaidano G. Human immunodeficiency virus-associated Hodgkin's disease derives from post-germinal center B cells. Blood 1999;93:2319–26.
36. Thorley-Lawson DA. EBV the prototypical human tumor virus: just how bad is it? J Allergy Clin Immunol 2005;116:251–61; quiz 62.
37. Kuppers R, Rajewsky K, Zhao M, Simons G, Laumann R, Fischer R, Hansmann ML. Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development. Proc Natl Acad Sci USA 1994;91:10962–6.
38. Kanzler H, Kuppers R, Hansmann ML, Rajewsky K. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. J Exp Med 1996;184:1495–505.
39. Jarrett R. EBV and Hodgkin's disease, review in this issue. Int J Cancer, in press.
40. Sitas F, Carrara H, Beral V, Newton R, Reeves G, Bull D, Jentsch U, Pacella-Norman R, Bourboulia D, Whitby D, Boshoff C, Weiss R. Antibodies against human herpesvirus 8 in black South African patients with cancer. N Engl J Med 1999;340:1863–71.
41. Newton R, Ziegler J, Bourboulia D, Casabonne D, Beral V, Mbidde E, Carpenter L, Parkin DM, Wabinga H, Mbulaiteye S, Jaffe H, Weiss R, et al. Infection with Kaposi's sarcoma-associated herpesvirus (KSHV) and human immunodeficiency virus (HIV) in relation to the risk and clinical presentation of Kaposi's sarcoma in Uganda. Br J Cancer 2003;89:502–4.
42. Ziegler J, Newton R, Bourboulia D, Casabonne D, Beral V, Mbidde E, Carpenter L, Reeves G, Parkin DM, Wabinga H, Mbulaiteye S, Jaffe H, et al. Risk factors for Kaposi's sarcoma: a case-control study of HIV-seronegative people in Uganda. Int J Cancer 2003;103:233–40.
43. Dedicoat M, Newton R, Alkharsah KR, Sheldon J, Szabados I, Ndlovu B, Page T, Casabonne D, Gilks CF, Cassol SA, Whitby D, Schulz TF. Mother-to-child transmission of human herpesvirus-8 in South Africa. J Infect Dis 2004;190:1068–75.
44. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, Hatzioannou T, Suggett FE, Aldam DM, Denton AS, Tedder RA, Schulz TF, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet 1995;346:799–802.
45. Judde JG, Lacoste V, Briere J, Kassa-Kelembho E, Clyti E, Couppie P, Buchrieser C, Tulliez M, Morvan J, Gessain A, Tedder RA, Schulz TF. Monoclonality or oligoclonality of human herpesvirus 8 terminal repeat sequences in Kaposi's sarcoma and other diseases. J Natl Cancer Inst 2000; 92:729–36.
46. Ciufo DM, Cannon JS, Poole LJ, Wu FY, Murray P, Ambinder RF, Hayward GS. Spindle cell conversion by Kaposi's sarcoma-associated herpesvirus: formation of colonies and plaques with mixed lytic and latent gene expression in infected primary dermal microvascular endothelial cell cultures. J Virol 2001;75:5614–26.
47. Flore O, Rafii S, Ely S, O'Leary JJ, Hyjek EM, Cesarman E. Transformation of primary human endothelial cells by Kaposi's sarcoma-associated herpesvirus. Nature 1998;394:588–92.
48. Carroll PA, Brazeau E, Lagunoff M. Kaposi's sarcoma-associated herpesvirus infection of blood endothelial cells induces lymphatic differentiation. Virology 2004;328:7–18.
49. Hong YK, Foreman K, Shin JW, Hirakawa S, Curry CL, Sage DR, Libermann T, Dezube BJ, Fingeroth JD, Detmar M. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet 2004;36:683–5.
50. Wang HW, Trotter MW, Lagos D, Bourboulia D, Henderson S, Makinen T, Elliman S, Flanagan AM, Alitalo K, Boshoff C. Kaposi sarcoma herpesvirus-induced cellular reprogramming contributes to the lymphatic endothelial gene expression in Kaposi sarcoma. Nat Genet 2004;36:687–93.
51. Moses AV, Fish KN, Ruhl R, Smith PP, Strussenberg JG, Zhu L, Chandran B, Nelson JA. Long-term infection and transformation of dermal microvascular endothelial cells by human herpesvirus 8. J Virol 1999;73:6892–902.
52. Wang L, Damania B. Kaposi's sarcoma-associated herpesvirus confers a survival advantage to endothelial cells. Cancer Res 2008; 68:4640–8.
53. An FQ, Folarin HM, Compitello N, Roth J, Gerson SL, McCrae KR, Fakhari FD, Dittmer DP, Renne R. Long-term-infected telomerase-immortalized endothelial cells: a model for Kaposi's sarcoma-associated herpesvirus latency in vitro and in vivo. J Virol 2006;80:4833–46.
54. Schulz TF. The pleiotropic effects of Kaposi's sarcoma herpesvirus. J Pathol 2006;208:187–98.
55. Godfrey A, Anderson J, Papanastasiou A, Takeuchi Y, Boshoff C. Inhibiting primary effusion lymphoma by lentiviral vectors encoding short hairpin RNA. Blood 2005;105:2510–8.
56. Guasparri I, Keller SA, Cesarman E. KSHV vFLIP is essential for the survival of infected lymphoma cells. J Exp Med 2004;199:993–1003.
57. Wies E, Mori Y, Hahn A, Kremmer E, Sturzl M, Fleckenstein B, Neipel F. The viral interferon-regulatory factor-3 is required for the survival of KSHV-infected primary effusion lymphoma cells. Blood 2008;111:320–7.
58. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology 2004;324:17–27.
59. IARC. Monograph on the evaluation of carcinogenic risks to humans, Vol. 90. WHO, 2007.
60. IARC. Monograph on the evaluation of carcionogenic risks to humans, Vol. 64. WHO, 1995.
61. Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, Tortolero-Luna G, Kjaer SK, Munoz N. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine 2008;26(Suppl 10):K1–K16.
62. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, Clifford GM. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer 2007;121:621–32.
63. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst 2007;99:962–72.
64. Harris TG, Burk RD, Palefsky JM, Massad LS, Bang JY, Anastos K, Minkoff H, Hall CB, Bacon MC, Levine AM, Watts DH, Silverberg MJ, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. JAMA 2005;293:1471–6.

65. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, Hall C, Bacon M, Levine AM, Watts DH, Silverberg MJ, Xue X, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. J Natl Cancer Inst 2005;97:577–86.
66. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell 1993;75:495–505.
67. Nomine Y, Masson M, Charbonnier S, Zanier K, Ristriani T, Deryckere F, Sibler AP, Desplancq D, Atkinson RA, Weiss E, Orfanoudakis G, Kieffer B, et al. Structural and functional analysis of E6 oncoprotein: insights in the molecular pathways of human papillomavirus-mediated pathogenesis. Mol Cell 2006;21:665–78.
68. Hiller T, Poppelreuther S, Stubenrauch F, Iftner T. Comparative analysis of 19 genital human papillomavirus types with regard to p53 degradation, immortalization, phylogeny, and epidemiologic risk classification. Cancer Epidemiol Biomarkers Prev 2006;15:1262–7.
69. James MA, Lee JH, Klingelhutz AJ. HPV16-E6 associated hTERT promoter acetylation is E6AP dependent, increased in later passage cells and enhanced by loss of p300. Int J Cancer 2006;119:1878–85.
70. Sekaric P, Cherry JJ, Androphy EJ. Binding of human papillomavirus type 16 E6 to E6AP is not required for activation of hTERT. J Virol 2008;82:71–6.
71. Liu X, Dakic A, Chen R, Disbrow GL, Zhang Y, Dai Y, Schlegel R. Cell-restricted immortalization by human papillomavirus correlates with telomerase activation and engagement of the hTERT promoter by Myc. J Virol 2008;82:11568–76.
72. Pan H, Griep AE. Altered cell cycle regulation in the lens of HPV-16 E6 or E7 transgenic mice: implications for tumor suppressor gene function in development. Genes Dev 1994;8:1285–99.
73. Filippova M, Song H, Connolly JL, Dermody TS, Duerksen-Hughes PJ. The human papillomavirus 16 E6 protein binds to tumor necrosis factor (TNF) R1 and protects cells from TNF-induced apoptosis. J Biol Chem 2002;277:21730–9.
74. Filippova M, Parkhurst L, Duerksen-Hughes PJ. The human papillomavirus 16 E6 protein binds to Fas-associated death domain and protects cells from Fas-triggered apoptosis. J Biol Chem 2004;279: 25729–44.
75. Huh K, Zhou X, Hayakawa H, Cho JY, Libermann TA, Jin J, Harper JW, Munger K. Human papillomavirus type 16 E7 oncoprotein associates with the cullin 2 ubiquitin ligase complex, which contributes to degradation of the retinoblastoma tumor suppressor. J Virol 2007;81: 737–47.
76. Munger K, Basile JR, Duensing S, Eichten A, Gonzalez SL, Grace M, Zacny VL. Biological activities and molecular targets of the human papillomavirus E7 oncoprotein. Oncogene 2001;20:7888–98.
77. Longworth MS, Wilson R, Laimins LA. HPV31 E7 facilitates replication by activating E2F2 transcription through its interaction with HDACs. EMBO J 2005;24:1821–30.
78. Duensing S, Munger K. Human papillomavirus type 16 E7 oncoprotein can induce abnormal centrosome duplication through a mechanism independent of inactivation of retinoblastoma protein family members. J Virol 2003;77:12331–5.
79. Duensing S, Munger K. The human papillomavirus type 16 E6 and E7 oncoproteins independently induce numerical and structural chromosome instability. Cancer Res 2002;62:7075–82.
80. Duensing S, Duensing A, Lee DC, Edwards KM, Piboonniyom SO, Manuel E, Skaltsounis L, Meijer L, Munger K. Cyclin-dependent kinase inhibitor indirubin-3′-oxime selectively inhibits human papillomavirus type 16 E7-induced numerical centrosome anomalies. Oncogene 2004;23:8206–15.
81. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–74.
82. Evans AA, Chen G, Ross EA, Shen FM, Lin WY, London WT. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. Cancer Epidemiol Biomarkers Prev 2002;11:369–76.
83. Amin J, Dore GJ, O'Connell DL, Bartlett M, Tracey E, Kaldor JM, Law MG. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol 2006;45:197–203.
84. Ribes J, Cleries R, Rubio A, Hernandez JM, Mazzara R, Madoz P, Casanovas T, Casanova A, Gallen M, Rodriguez C, Moreno V, Bosch FX. Cofactors associated with liver disease mortality in an HBsAg-positive Mediterranean cohort: 20 years of follow-up. Int J Cancer 2006;119:687–94.
85. IARC. Monograph on the evaluation of carcinogenic risks to humans, Vol. 59. 1994.
86. Sun CA, Wu DM, Lin CC, Lu SN, You SL, Wang LY, Wu MH, Chen CJ. Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. Am J Epidemiol 2003;157:674–82.
87. Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S, Mabuchi K. Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. Int J Cancer 2003;103:531–7.
88. Chang CC, Yu MW, Lu CF, Yang CS, Chen CJ. A nested case-control study on association between hepatitis C virus antibodies and primary liver cancer in a cohort of 9,775 men in Taiwan. J Med Virol 1994;43:276–80.
89. Murakami S. Hepatitis B virus X protein: structure, function and biology. Intervirology 1999;42:81–99.
90. Feitelson MA. Parallel epigenetic and genetic changes in the pathogenesis of hepatitis virus-associated hepatocellular carcinoma. Cancer Lett 2006;239:10–20.
91. Shimamura A, Fisher DE. p53 in life and death. Clin Cancer Res 1996;2:435–40.
92. Becker SA, Lee TH, Butel JS, Slagle BL. Hepatitis B virus X protein interferes with cellular DNA repair. J Virol 1998;72:266–72.
93. Hildt E, Saher G, Bruss V, Hofschneider PH. The hepatitis B virus large surface protein (LHBs) is a transcriptional activator. Virology 1996;225:235–9.
94. McGivern DR, Lemon SM. Tumor suppressors, chromosomal instability, and hepatitis C virus-associated liver cancer. Annu Rev Pathol 2009;4:399–415.
95. Sumida Y, Nakashima T, Yoh T, Nakajima Y, Ishikawa H, Mitsuyoshi H, Sakamoto Y, Okanoue T, Kashima K, Nakamura H, Yodoi J. Serum thioredoxin levels as an indicator of oxidative stress in patients with hepatitis C virus infection. J Hepatol 2000;33:616–22.
96. Shimoda R, Nagashima M, Sakamoto M, Yamaguchi N, Hirohashi S, Yokota J, Kasai H. Increased formation of oxidative DNA damage, 8-hydroxydeoxyguanosine, in human livers with chronic hepatitis. Cancer Res 1994;54:3171–2.
97. Tardif KD, Waris G, Siddiqui A. Hepatitis C virus, ER stress, and oxidative stress. Trends Microbiol 2005;13:159–63.
98. Ray RB, Lagging LM, Meyer K, Ray R. Hepatitis C virus core protein cooperates with ras and transforms primary rat embryo fibroblasts to tumorigenic phenotype. J Virol 1996;70:4438–43.
99. Alisi A, Giambartolomei S, Cupelli F, Merlo P, Fontemaggi G, Spaziani A, Balsano C. Physical and functional interaction between HCV core protein and the different p73 isoforms. Oncogene 2003;22:2573–80.
100. Ray RB, Steele R, Meyer K, Ray R. Transcriptional repression of p53 promoter by hepatitis C virus core protein. J Biol Chem 1997;272: 10983–6.
101. Sakamuro D, Furukawa T, Takegami T. Hepatitis C virus nonstructural protein NS3 transforms NIH 3T3 cells. J Virol 1995;69:3893–6.
102. Gale M, Jr, Kwieciszewski B, Dossett M, Nakao H, Katze MG. Antiapoptotic and oncogenic potentials of hepatitis C virus are linked to interferon resistance by viral repression of the PKR protein kinase. J Virol 1999;73:6506–16.
103. Park JS, Yang JM, Min MK. Hepatitis C virus nonstructural protein NS4B transforms NIH3T3 cells in cooperation with the Ha-ras oncogene. Biochem Biophys Res Commun 2000;267:581–7.
104. Di Martino V, Rufat P, Boyer N, Renard P, Degos F, Martinot-Peignoux M, Matheron S, Le Moing V, Vachon F, Degott C, Valla D, Marcellin P. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology 2001;34:1193–9.
105. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33:562–9.
106. Kramer JR, Giordano TP, Souchek J, Richardson P, Hwang LY, El-Serag HB. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. Am J Gastroenterol 2005;100:56–63.
107. McGinnis KA, Fultz SL, Skanderson M, Conigliaro J, Bryant K, Justice AC. Hepatocellular carcinoma and non-Hodgkin's lymphoma: the roles of HIV, hepatitis C infection, and alcohol abuse. J Clin Oncol 2006;24:5005–9.
108. Kassem A, Schopflin A, Diaz C, Weyers W, Stickeler E, Werner M, Zur Hausen A. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the VP1 gene. Cancer Res 2008;68:5009–13.
109. Kassem A, Technau K, Kurz AK, Pantulu D, Loning M, Kayser G, Stickeler E, Weyers W, Diaz C, Werner M, Nashan D, Zur Hausen A. Merkel cell polyomavirus sequences are frequently detected in non-melanoma skin cancer of immunosuppressed patients. Int J Cancer 2009;125:356–61.
110. Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. J Invest Dermatol 2009;129:248–50.
111. Garneski KM, Warcola AH, Feng Q, Kiviat NB, Leonard JH, Nghiem P. Merkel cell polyomavirus is more frequently present in North

American than Australian Merkel cell carcinoma tumors. J Invest Dermatol 2009;129:246–8.
112. Shuda M, Feng H, Kwun HJ, Rosen ST, Gjoerup O, Moore PS, Chang Y. T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. Proc Natl Acad Sci USA 2008;105:16272–7.
113. Kawano N, Shimoda K, Ishikawa F, Taketomi A, Yoshizumi T, Shimoda S, Yoshida S, Uozumi K, Suzuki S, Maehara Y, Harada M. Adult T-cell leukemia development from a human T-cell leukemia virus type I carrier after a living-donor liver transplantation. Transplantation 2006;82:840–3.
114. Gupta AK, Cardella CJ, Haberman HF. Cutaneous malignant neoplasms in patients with renal transplants. Arch Dermatol 1986;122: 1288–93.
115. Kinlen LJ, Sheil AG, Peto J, Doll R. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. Br Med J 1979;2:1461–6.
116. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 1990;49:506–9.
117. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol 2006;154:498–504.
118. Patel AS, Karagas MR, Perry AE, Nelson HH. Exposure profiles and human papillomavirus infection in skin cancer: an analysis of 25 genus beta-types in a population-based study. J Invest Dermatol 2008; 128:2888–93.
119. Forslund O, Iftner T, Andersson K, Lindelof B, Hradil E, Nordin P, Stenquist B, Kirnbauer R, Dillner J, de Villiers EM. Cutaneous human papillomaviruses found in sun-exposed skin: beta-papillomavirus species 2 predominates in squamous cell carcinoma. J Infect Dis 2007;196:876–83.
120. Alotaibi L, Provost N, Gagnon S, Franco EL, Coutlee F. Diversity of cutaneous human papillomavirus types in individuals with and without skin lesion. J Clin Virol 2006;36:133–40.
121. Feltkamp MC, Broer R, di Summa FM, Struijk L, van der Meijden E, Verlaan BP, Westendorp RG, ter Schegget J, Spaan WJ, Bouwes Bavinck JN. Seroreactivity to epidermodysplasia verruciformis-related human papillomavirus types is associated with nonmelanoma skin cancer. Cancer Res 2003;63:2695–700.
122. Masini C, Fuchs PG, Gabrielli F, Stark S, Sera F, Ploner M, Melchi CF, Primavera G, Pirchio G, Picconi O, Petasecca P, Cattaruzza MS, et al. Evidence for the association of human papillomavirus infection and cutaneous squamous cell carcinoma in immunocompetent individuals. Arch Dermatol 2003;139:890–4.
123. Karagas MR, Nelson HH, Sehr P, Waterboer T, Stukel TA, Andrew A, Green AC, Bavinck JN, Perry A, Spencer S, Rees JR, Mott LA, et al. Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. J Natl Cancer Inst 2006;98:389–95.
124. Waterboer T, Abeni D, Sampogna F, Rother A, Masini C, Sehr P, Michael KM, Pawlita M. Serological association of beta and gamma human papillomaviruses with squamous cell carcinoma of the skin. Br J Dermatol 2008;159:457–9.
125. Casabonne D, Michael KM, Waterboer T, Pawlita M, Forslund O, Burk RD, Travis RC, Key TJ, Newton R. A prospective pilot study of antibodies against human papillomaviruses and cutaneous squamous cell carcinoma nested in the Oxford component of the European prospective investigation into cancer and nutrition. Int J Cancer 2007; 121:1862–8.
126. Casabonne D, Lally A, Mitchell L, Michael KM, Waterboer T, Pawlita M, Imko-Walczuk B, Wojnarowska F, Proby C, Harwood C, Newton R. A case-control study of cutaneous squameous cell carcinoma among Caucasian organ transplant recipients: the role of antibodies against human papillomavirus (HPV) and other risk factors. Int J Cancer, in press.
127. Hiraiwa A, Kiyono T, Segawa K, Utsumi KR, Ohashi M, Ishibashi M. Comparative study on E6 and E7 genes of some cutaneous and genital papillomaviruses of human origin for their ability to transform 3Y1 cells. Virology 1993;192:102–11.
128. Schmitt A, Harry JB, Rapp B, Wettstein FO, Iftner T. Comparison of the properties of the E6 and E7 genes of low- and high-risk cutaneous papillomaviruses reveals strongly transforming and high Rb-binding activity for the E7 protein of the low-risk human papillomavirus type 1. J Virol 1994;68:7051–9.
129. Massimi P, Thomas M, Bouvard V, Ruberto I, Campo MS, Tommasino M, Banks L. Comparative transforming potential of different human papillomaviruses associated with non-melanoma skin cancer. Virology 2008;371:374–9.
130. Caldeira S, Zehbe I, Accardi R, Malanchi I, Dong W, Giarre M, de Villiers EM, Filotico R, Boukamp P, Tommasino M. The E6 and E7 proteins of the cutaneous human papillomavirus type 38 display transforming properties. J Virol 2003;77:2195–206.
131. Accardi R, Dong W, Smet A, Cui R, Hautefeuille A, Gabet AS, Sylla BS, Gissmann L, Hainaut P, Tommasino M. Skin human papillomavirus type 38 alters p53 functions by accumulation of deltaNp73. EMBO Rep 2006;7:334–40.
132. Gabet AS, Accardi R, Bellopede A, Popp S, Boukamp P, Sylla BS, Londono-Vallejo JA, Tommasino M. Impairment of the telomere/telomerase system and genomic instability are associated with keratinocyte immortalization induced by the skin human papillomavirus type 38. FASEB J 2008;22:622–32.
133. Bedard KM, Underbrink MP, Howie HL, Galloway DA. The E6 oncoproteins from human betapapillomaviruses differentially activate telomerase through an E6AP-dependent mechanism and prolong the lifespan of primary keratinocytes. J Virol 2008;82:3894–902.
134. Thomas M, Banks L. Inhibition of Bak-induced apoptosis by HPV-18 E6. Oncogene 1998;17:2943–54.
135. Jackson S, Harwood C, Thomas M, Banks L, Storey A. Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. Genes Dev 2000;14:3065–73.
136. Underbrink MP, Howie HL, Bedard KM, Koop JI, Galloway DA. E6 proteins from multiple human betapapillomavirus types degrade Bak and protect keratinocytes from apoptosis after UVB irradiation. J Virol 2008;82:10408–17.
137. Schaper ID, Marcuzzi GP, Weissenborn SJ, Kasper HU, Dries V, Smyth N, Fuchs P, Pfister H. Development of skin tumors in mice transgenic for early genes of human papillomavirus type 8. Cancer Res 2005;65:1394–400.
138. Dong W, Kloz U, Accardi R, Caldeira S, Tong WM, Wang ZQ, Jansen L, Durst M, Sylla BS, Gissmann L, Tommasino M. Skin hyperproliferation and susceptibility to chemical carcinogenesis in transgenic mice expressing E6 and E7 of human papillomavirus type 38. J Virol 2005;79:14899–908.
139. Kirk GD, Merlo C, P OD, Mehta SH, Galai N, Vlahov D, Samet J, Engels EA. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis 2007;45:103–10.
140. Phelps RM, Smith DK, Heilig CM, Gardner LI, Carpenter CC, Klein RS, Jamieson DJ, Vlahov D, Schuman P, Holmberg SD. Cancer incidence in women with or at risk for HIV. Int J Cancer 2001;94:753–7.
141. Serraino D, Boschini A, Carrieri P, Pradier C, Dorrucci M, Dal Maso L, Ballarini P, Pezzotti P, Smacchia C, Pesce A, Ippolito G, Franceschi S, et al. Cancer risk among men with, or at risk of, HIV infection in southern Europe. AIDS 2000;14:553–9.
142. Kinlen L. Infections and immune factors in cancer: the role of epidemiology. Oncogene 2004;23:6341–8.
143. Hruby Z, Myszka-Bijak K, Gosciniak G, Blaszczuk J, Czyz W, Kowalski P, Falkiewicz K, Szymanska G, Przondo-Mordarska A. Helicobacter pylori in kidney allograft recipients: high prevalence of colonization and low incidence of active inflammatory lesions. Nephron 1997;75:25–9.