8.5.26 Viruses and cancer 945

8.5.26 Viruses and cancer 945

8.5.26 Viruses and cancer 945 8.5.26 Viruses and cancer Robin A. Weiss ESSENTIALS Viruses are important in cancer for three main reasons: (1) As a cause of cancer—about 15% of the worldwide cancer burden is due to vir- uses. (2) In understanding of the biology of cancer-through the dis- covery and characterization of oncogenes and tumour suppressor genes. (3) In the treatment of cancer—some viruses selectively rep- licate in and destroy proliferating cells, viruses as foreign antigens may aid the recognition of cancer cells by the host’s immune system (‘xenogenization’), and viruses can also be used as vectors for im- munization and for gene therapy. Viral cancers are prevented by early screening for tumours, screening for the virus in order to pre- vent transmission, and immunization as in the cases of hepatitis B virus and human papilloma virus. Viruses as aetiological agents of cancer Oncogenic viruses establish persistent infections, which usually occur decades before malignancy. Table 8.5.26.1 lists the viruses implicated in human cancer. In most, but not all cases, the viral genome is present in the malignant cells; the exceptions appear to be those that promote cancer indirectly, such as HIV and hepatitis C virus (HCV). Several of these viruses and the nonmalignant dis- eases they cause are discussed in detail in the chapters devoted to individual viruses. Cancer is usually a rare outcome of virus infection, and other cofactors play a part in viral carcinogenesis. For example, Epstein– Barr virus (EBV) is a ubiquitous infection, yet childhood Burkitt’s lymphoma occurs only in areas of holoendemic malarial infection, whereas undifferentiated nasopharyngeal carcinoma occurs mainly in southern Chinese populations. Aflatoxin in the diet acts syner- gistically with hepatitis B virus (HBV) to induce liver cancer, and in hereditary epidermodysplasia verruciformis, ultraviolet radiation acts with human papilloma virus strains (usually HPV-5) to cause skin cancer. The underlying cause of all forms of Kaposi’s sarcoma is Kaposi’s sarcoma herpes virus (KSHV), also known as human herpes virus 8 (HHV-8), which also causes primary effusion lymphoma and plasmablastic multicentric Castleman’s disease. Kaposi’s sarcoma occurs much more frequently in immunodeficient patients. Its rela- tive risk in recipients of organ transplants is about 400, and in people with AIDS about 20 000. Oncogenic viruses belong to many virus families with different routes of transmission. HBV is frequently acquired perinatally or through subsequent exposure to blood. Human T-cell lymphotropic virus type 1 (HTLV-1) is transmitted vertically through infected cells in breast milk. Sexual transmission is common to HIV, HBV, HPV, and HTLV-1 (with a male to female bias). Oncogenic vir- uses do not appear to be transmitted by the respiratory route or via arthropod vectors, except for some veterinary cases (e.g. bovine leucosis virus). Whereas EBV (transmitted through saliva) occurs throughout the global population, HBV, HTLV-1, and HHV-8 have a higher prevalence in those population groups in which the associ- ated cancers occur. Certain common human viruses are highly oncogenic in ex- perimental animals but are not linked epidemiologically to human cancer, namely the polyomaviruses BK and JC, and the adenoviruses types 2 and 12. There are claims that a simian relative of BK virus, simian vacuolating virus 40 (SV40), is linked with mesothelioma, osteosarcoma, and ependymoma in humans, but these findings re- main controversial. However, in 2008, a novel virus, MCPyV, was linked to Merkel skin cell cancer as a genuinely oncogenic human polyoma virus. Mechanisms of viral carcinogenesis Physical and chemical carcinogens are usually mutagens. They cause DNA mutations in specific genes that contribute to the eventual ma- lignant phenotype of the cancer. Oncogenes were first discovered in animal retroviruses, such as the Rous sarcoma virus of chickens, and originate from cellular genes. Most retroviruses do not carry onco- genes, but the DNA provirus integrates into chromosomal DNA and can activate adjacent cellular oncogenes. Oncogene activation by retro- viruses is comparable to activation by chromosomal translocation. The mechanism of cell transformation by HTLV-1 is different from that of most animal retroviruses. HTLV-1 encodes viral proteins, Tax, and HBZ, which are essential to promote full viral gene transcription Table 8.5.26.1 Viruses implicated in human cancer Virus Malignancy Human papilloma virus (HPV): types 16, 18 HPV types 5, 8 Cervical cancer c.40% head and neck squamous cancer Skin cancer in epidermodysplasia veruciformis Polyomavirus (MCPyV) Merkel cell skin cancer Hepatitis B virus (HBV) Primary liver cancer Hepatitis C virus (HCV) Primary liver cancer Epstein–Barr virus (EBV) Burkitt's lymphoma, immunoblastic lymphoma, c.25% Hodgkin's disease, undifferentiated nasopharangeal carcinoma, leiomyosarcoma, c.10% breast cancer Kaposi's sarcoma herpesvirus (KSHV or HHV-8) Kaposi's sarcoma, primary effusion, lymphoma, multicentric Castleman's disease Human T-lymphotropic virus type 1 (HTLV-1) Adult T-cell leukaemia

 and cell transformation. Tax acts as a transcriptional activator, by as- sociating with host nuclear proteins which activate expression of the viral genome. However, Tax also up-regulates certain cellular genes, such as the interleukin-2 receptor. HTLV-1 'immortalizes' CD4+ T lymphocytes in culture, rather as EBV 'immortalizes' B lymphocytes, but this is only one step in the pathway to malignancy. Cell transformation by DNA viruses is best understood for polyomaviruses and adenoviruses. The transforming genes of these viruses are expressed early in the infection cycle and prevent tumour suppressor protein function. Adenovirus proteins E1A and E1B and polyomavirus large T antigen bind to p53 and retinoblastoma (Rb) proteins and block their normal interaction in the cell cycle. Thus, instead of mutating these cellular tumour suppressor genes, DNA tumour viruses block the normal function of their proteins, which similarly results in unregulated cell proliferation. The Kaposi's sar- coma herpes virus genome carries several oncogenes, including a homologue of cyclin D2 (CCND2), which inactivates Rb by a dif- ferent mechanism, phosphorylation. Most oncogenic viruses persist in the tumour cells, often by integrating into chromosomal DNA. Oncogenic herpesviruses do not integrate but are maintained episomally. Epstein–Barr virus- associated nuclear antigen 1 (EBNA-1) is required for episomal replication of EBV, and latency-associated nuclear antigen for main- tenance of Kaposi's sarcoma herpes virus, while other nuclear and latent membrane proteins are responsible for the transformed cell phenotype. With HBV, integrated copies are found in many liver carcinoma lines, but a requirement for integration has not been un- equivocally shown. HBV expresses transactivating functions from the X gene, so its transformation may resemble that of HTLV-1. Indirect carcinogenic effects are those in which damage to tis- sues by viruses may allow clones of premalignant cells to prolif- erate that would not otherwise do so. HCV and possibly HBV do this by destroying normal liver cells, resulting in a much greater rate of liver cell regeneration. HIV promotes tumour development by destroying helper T-cell immunity to other oncogenic viruses. The cancers which occur more frequently in AIDS are also seen in im- munosuppressed transplant patients (e.g. non-Hodgkin’s lymphoma and Kaposi’s sarcoma), and usually have a viral aetiology. Treatment and prevention Oncogenesis is multifactorial, requiring several sequential events before a patient presents with a fully malignant tumour. Yet, if a virus plays a crucial role in oncogenesis, its elimination should prevent that type of cancer. Currently, there is no special approach to the treatment of cancers that have a viral aetiology. Among the lymphoid malignancies, some respond well to radiotherapy or chemotherapy, such as Hodgkin’s disease, whereas others seldom show remission, such as adult T-cell leukaemia. Cancers that express viral antigens should be responsive to immunotherapy. For tumours in which viral proteins are required for the maintenance of the malignant state, those proteins are potential molecular targets, as drugs that block them might spare normal cellular functions. Prevention offers the greatest promise of reducing cancer mor- tality due to viruses. Prevention can be accomplished by three strat- egies: (1) early screening for tumours, (2) screening for the virus with prevention of transmission, and (3) immunization. Early screening is exemplified by cervical smears. Screening to prevent iatrogenic transmission via blood and blood products is routinely employed for potentially oncogenic viruses such as HBV, HCV, HIV, and HTLV-1. In Kyushu, Japan, where infection was endemic, HTLV-1 is being steadily eradicated through a policy of antenatal screening to pre- vent transmission via milk. Prevention of cancer by immunization against infection by onco- genic viruses is likely to have a major impact on world cancer mor- tality. The HBV vaccine is based on surface antigen and two HPV vaccines protective against cervical cancer were licensed in 2006. Intensive research is also being undertaken on vaccines for HIV and HCV, but there are immense obstacles to successful immunization against HIV as the virus is extraordinarily variable. Nevertheless, immunization against oncogenic viruses is becoming a most ef- fective cancer prevention strategy. Viruses as therapeutic agents Viruses may be put to use in the fight against cancer. First, some cytopathic viruses preferentially replicate in proliferating cells and destroy them, such as parvoviruses and mutant adenoviruses. Second, viruses as foreign antigens may aid the recognition of cancer cells by the host’s immune system. Although the mechanism is ill understood, ‘xenogenization’ of tumour cells by virus infection can, in some cases, enhance immune attack against noninfected cells in the same tumour. Third, viruses are used as vectors for immuniza- tion and for gene therapy, by restoring tumour suppressor functions, by enhancing immune responses through the expression of antigens or cytokines, and by locally delivering genes for enzymes that con- vert inert prodrugs into active, chemotherapeutic agents.

FURTHER READING

Ajila V, et al. (2015). Human papilloma virus associated squamous cell carcinoma of the head and neck. J Sex Transm Dis, 2015, 791024. Astbury K, Turner MJ (2009). Human papillomavirus vaccination in the prevention of cervical neoplasia. Int J Gynecol Cancer, 19, 1610–13. Chang Y, Moore PS, Weiss RA (2017). Human oncogenic viruses: na- ture and discovery. Proc Trans R Soc London B, 372, 20160264. Desjardins A, et al. (2018). Recurrent glioblastoma treated with re- combinant poliovirus. N Engl J Med, 379, 150–61. De Martel C, et al. (2012). Global burden of cancers attributable to in- fections in 2008: a review and synthetic analysis. Lancet Oncol, 13, 607–15. Goossens N, Hoshida Y (2015). Hepatitis C virus-induced hepato cellular carcinoma. Clin Mol Hepatol, 21, 105–14. Gutierrez-Xicotencatl L, et al. (2016). Humoral immune response against human papillomavirus as source of biomarkers for the pre- diction and detection of cervical cancer. Viral Immunol, 29, 1–12. Matsuoka M, Jeang KT

(2011). Human T-cell leukemia virus type 1 (HTLV-1) and leukemic transformation: viral infectivity, Tax, HBZ and therapy. Oncogene, 30, 1379–89. Morrison BJ, et al. (2015). Serodiagnosis for tumor viruses. Semin Oncol, 42, 191–206. Pierangeli A, Antonelli G, Gentile G (2015). Immune deficiency asso- ciated viral oncogenesis. Clin Microbiol Infect, 21, 975–83.

Revision #1
Created 2026-01-22 16:45:25 UTC by Omar Ayman
Updated 2026-01-22 16:45:25 UTC by Omar Ayman