PERSISTENT AND LATENT INFECTIONS

Relatively few viruses cause persistent or latent infections. HBV, HCV, rabies virus, measles virus, HIV, HTLV, HPV, HHVs, and MCV are notable exceptions. The mechanisms for persistent infection vary. HCV RNA polymerase and HIV reverse transcriptase are error-prone and generate variant genomes. Genome variation can be sufficient to permit evasion of host immune responses, thereby allowing persistent infection. HIV is also directly immunosuppressive, depleting CD4+ T lymphocytes and compromising CD8+ cytotoxic T cell immune responsiveness. Moreover, HIV encodes the Nef protein, which downmodulates MHC class I expression, rendering HIV-infected cells partially resistant to immune CD8+ T cell lysis.

DNA viruses have low mutation rates. Their persistence in human populations usually depends on their ability to establish latent infection in some cells, to reactivate from latency, and then to replicate at epithelial surfaces. *Latency* is defined as a state of infection in which virus is not replicating, viral genes associated with lytic infection are not expressed, and infectious virus is not made. The complete viral genome is present and may be replicated by cellular DNA polymerase in conjunction with replication of the cell's genome. HPVs establish latent infection in basal epithelial cells. The latently infected basal cell replicates, along with the HPV episome, by using cellular DNA polymerase. Some of the progeny cells provide new latently infected basal cells, whereas others go on to squamous differentiation. Infected cells that differentiate to squamous cells become permissive for lytic viral infection. Herpesviruses establish latent infection in nonreplicating neural cells (HSV and VZV) or in replicating cells of hematopoietic lineages (EBV, CMV, HHV-6, HHV-7, and Kaposi's sarcoma–associated herpesvirus [KSHV, also known as HHV-8]). In their latent stage, HPV and herpesvirus genomes are largely hidden from the normal immune response. Reactivated HPV and herpesvirus infections escape immediate and effective immune responses in highly immune hosts by inhibiting host innate immune and inflammatory responses. In addition, HPV, HSV, and VZV are somewhat protected because they replicate in the middle and upper layers of the squamous epithelium—sites not routinely visited by cells that mediate or amplify immune and inflammatory responses. HSV and CMV are also known to encode proteins that downregulate MHC class I expression and antigenic peptide presentation, enabling infected cells to escape recognition by and cytotoxic effects of CD8+ T lymphocytes.

Like other poxviruses, MCV cannot establish latent infection. This virus causes persistent infection in hypertrophic skin lesions that last for months or years. MCV encodes a chemokine homologue that probably blocks inflammatory responses, an MHC class I analogue that blocks cytotoxic T lymphocyte attack, and inhibitors of cell death that prolong infected-cell viability.

PERSISTENT VIRAL INFECTIONS AND CANCER

Persistent viral infection is estimated to be the root cause of as many as 20% of human malignancies. Cancer is an accidental and highly unusual or long-term effect of oncogenic human viral infection. With most "oncogenic viruses," infection is a critical and ultimately determinative early step in carcinogenesis. Latent HPV infection can block cell death and cause cervical cells to proliferate. A virus-infected cell with an integrated HPV genome overexpressing E6 and E7 undergoes subsequent cellular genetic changes that enhance autonomous malignant cell growth.

Most hepatocellular carcinoma is believed to be caused by chronic inflammatory, immune, and regenerative responses to HBV or HCV infection. Epidemiologic data firmly link HBV and HCV infections to hepatocellular carcinoma. These infections elicit repetitive cycles of virus-induced liver injury followed by tissue repair and regeneration. Over decades, chronic viral infection, repetitive tissue regeneration, and acquired chromosomal changes can result in proliferative nodules. Further chromosomal mutations can lead to the degeneration of cells in a proliferating nodule into hepatocellular carcinoma. In rare instances, HBV DNA integrates into cellular DNA, promoting overexpression of a cell gene that can also contribute to oncogenesis.

Most cervical carcinoma is caused by persistent infection with "high-risk" HPV type 16 or 18. In contrast to HBV and HCV infections, which stimulate cell growth as a consequence of virus-induced cell death, HPV type 16 or 18 proteins E6 and E7 destroy p53 and pRB, respectively. Elimination of these key tumor-suppressive cell proteins increases cell growth, cell survival, and cell genome instability. However, like HBV and HCV infections, HPV infection alone is not sufficient for carcinogenesis. Cervical carcinoma is inevitably associated with persistent HPV infection and integration of the HPV genome into chromosomal DNA. Integrations that result in overexpression of E6 and E7 from HPV type 16 or 18 cause more profound changes in cell growth and survival and permit subsequent chromosomal changes that result in cervical carcinoma.

EBV is the most unusual oncogenic virus in that normal B cell infection results in latency with expression of viral proteins that can cause endless B lymphocyte growth. In almost all humans, strong CD4+ and CD8+ T cell immune responses to the antigenic EBV latent-infection nuclear proteins prevent uncontrolled B cell lymphoproliferation. However, when humans are severely immunosuppressed by transplantation-associated medication, HIV infection, or genetic immune deficiencies, EBV-induced B cell malignancies can emerge.

EBV infection also has a role in the long-term development of B lymphocyte and epithelial cell malignancies. Persistent EBV infection with expression of an EBV latency-associated integral membrane protein (LMP1) in latently infected epithelial cells appears to be a critical early step in the evolution of anaplastic nasopharyngeal carcinoma, a common malignancy in populations in southern China and northern Africa. Genomic instability and chromosomal abnormalities also contribute to the development of EBV-associated nasopharyngeal carcinoma. EBV is an important cause of Hodgkin's lymphoma. High-level expression of LMP1 or LMP2 in Reed-Sternberg cells is a hallmark in up to 50% of Hodgkin's lymphoma cases. LMP1-induced nuclear factor-κB (NF-κB) activity may prolong the survival of defective B cells that are normally eliminated by apoptosis, thereby allowing other genetic changes leading to the development of malignant Reed-Sternberg cells.

The HTLV-1 Tax and Rex proteins are critical to the initiation of cutaneous adult T cell lymphoma/leukemias that occur long after primary HTLV-1 infection. Tax-induced NF-κB activation may contribute to cytokine production, infected-cell survival, and eventual outgrowth of malignant cells.

Molecular data confirm the presence of KSHV DNA in all Kaposi's tumors, including those associated with HIV infection, transplantation, and familial transmission. KSHV infection is also etiologically implicated in pleural-effusion lymphomas and multicentric Castleman's disease, which are more common among HIV-infected than among HIV-uninfected people. KSHV also has a virus-encoded cyclin, an IFN regulatory factor, and a latency-associated nuclear antigen that are implicated in increased-cell proliferation and survival.

Evidence supporting a causal role for viral infection in all of these malignancies includes (1) epidemiologic data, (2) the presence of viral DNA in all tumor cells, (3) the ability of the viruses to transform human cells in culture, (4) the results of in vitro cell culture–based assays that reveal transforming effects of specific viral genes on cell growth or survival, (5) pathologic data indicating the expression of transforming viral genes in premalignant or malignant cells in vivo, (6) the demonstration in animal models that these viral genes can cause malignant cell growth, and (7) the ability of virus-specific vaccines to reduce the incidence of virus-associated malignancy.

Virus-related malignancies provide an opportunity to expand our understanding of the biologic mechanisms important in the development of cancer. They also offer unique opportunities to develop diagnostics, vaccines, or therapeutics that could prevent or specifically treat cancers associated with viral infection. Widespread immunization against hepatitis B has resulted in a decreased prevalence of HBV-associated hepatitis and will probably prevent most HBV-related liver cancers. Current HPV vaccines can reduce rates of colonization with high-risk HPV strains and thereby decrease the risk of cervical cancer. The successful use of in vitro–expanded EBV-specific T cell populations to treat or prevent EBV-associated posttransplantation lymphoproliferative disease demonstrates the potential of immunoprevention or immunotherapy against virus-associated cancers.