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I. Chapter Overview

The first documented cases of acquired immunodeficiency syndrome (AIDS) were characterized by the presence of rare Kaposi's sarcoma (KS) skin lesions. More than 10 years later, it was discovered that the causative agent of KS was a γ-herpesvirus, human herpesvirus-8 (HHV-8) (KS-associated herpesvirus, KSHV). It is now abundantly clear that cancers induced by viral agents [such as, Epstein-Barr virus (EBV) and human papillomavirus (HPV)] are exacerbated by human immunodeficiency virus (HIV) infection and subsequent immune suppression. For example, the incidence of and primary central nervous system (CNS) lymphoma (PCNSL) and Hodgkin's and high grade B-cell non-Hodgkin's lymphomas (NHL), nasopharyngeal carcinoma (NPC), anal, penile, oral, and invasive cervical carcinomas are much higher in AIDS patients. Also common in the AIDS-afflicted, are hematopoietic cancers, B- and T-cell lymphomas, myelosarcomas, lung cancers, and gastrointestinal tract cancers. The development of highly active antiretroviral therapy (HAART) has proved effective in inducing regression of PCNSL, NHL, KS, and other cancers caused by viruses, extending the life span and quality of life of AIDS patients. However, the general availability of HAART and other antiretrovirals in developing countries, where most HIV infections are reported, is still poor. Furthermore, several reports indicate that HAART is not effective in reversing HPV-induced cervical cancers, for unknown reasons. The development of the prophylactic HPV vaccine offers some hope that future generations can be protected against cervical and penile cancers. However, in countries with high rates of cervical cancers, such as in sub-Saharan Africa, the rate of HIV-positivity approaches 30%, antiretrovirals are scarce, and the HPV vaccine is not available, nor would it be effective for those already infected with HPVs. Thus, better methods of surveillance and management of these malignancies in HIV-positive individuals continues to be a need.

II. Introduction

Since the first report of AIDS over 25 years ago, it was noted that there is a close association between HIV infection and the development of a number of cancers (Levine, 2006; Noy, 2006; Pantanowitz *et al.*, 2006; Wood and Harrington, 2005). They include KS, Hodgkin's and high-grade B-cell NHL, anal, and invasive cervical carcinomas. In fact, AIDS was recognized in 1981 through an unusual increase in the number of cases of KS found among the young adult male having sex with male (MSM) population (Durack, 1981). Since then, increasing numbers of KS as well as other cancers were found in this population. Subsequently in 1982, the US Center for Disease Control and Prevention (CDC) included two malignancies, KS and PCNSL, as definitions for AIDS (1982). A third AIDS-associated malignancy, NHL, was also included as one of the AIDS-defining illnesses in 1987, and a fourth, the invasive cervical carcinoma was added in 1992. In addition to these four malignancies commonly found in AIDS patients, a number of other cancers have also increased substantially in the HIV-1infected immunosuppressed population. These cancers include multiple myelomas, leukemia, and leiomyosarcomas in children, oral cavity cancers, lung cancers, and Hodgkin's disease (Goedert *et al.*, 1998; Grulich *et al.*, 2002). Prior to the era of HAART, it has been estimated that up to 25% of all cancers in males under 45 years of age in the United States were associated with HIV and up to 30%

of all HIV-infected individuals will develop cancer. Especially with NHL, it has been estimated that individuals with immune deficiency have between 10- and 150-fold higher risk in developing NHL (Biggar and Rabkin, 1996; Grulich and Vajdic, 2005). Moreover, the management and prognosis of these patients were poor, mainly due to the aggressiveness of the tumors on immunosuppression, an increase in hematological toxicity due to treatment, and complications due to opportunistic infections (Kaplan *et al.*, 1997). Treatment outcomes were shown to be poor, regardless of the types of treatment, with the response rate for AIDS-related lymphomas (ARL) of about 50% and the medium survival rate time of between 5 and 8 months (Kaplan *et al.*, 1991; Navarro and Kaplan, 2006).

With the introduction of antiretroviral treatment in the mid-1990s, the spectrum of AIDS-associated malignancies and the epidemiology of the disease has been completely changed. There was a substantial decline in incidence of KS. It has been shown in a Swiss cohort that the standardized incidence rates for KS was 25 for those on HAART versus 239 for those that were not on treatment (Clifford *et al.*, 2005). Similarly, changes in the incidences of ARL were observed for individuals that were on HAART. A number of studies have shown a decrease in incidence and mortality in patients with ARL (Besson *et al.*, 2001; Kirk *et al.*, 2001; Lee and Hurwitz, 2000; Navarro and Kaplan, 2006). The same Swiss cohort study has shown an overall decrease of HNL incidence of about 76% on HAART treatment. Similarly, for PCNSL, the impact of HAART is even more dramatic than other systemic ARL; a combination of radiotherapy with HAART had led to improvement of survival rate (Hoffmann *et al.*, 2001; Newell *et al.*, 2004). HAART alone has also been shown to lead to a regression of PCNSL (McGowan and Shah, 1998). In spite of the effects of HAART on ARL, similar dramatic effects have not been observed with cervical and anal cancers, and the results have been controversial. A study by the Women's Interagency HIV study group has shown an association between HAART and regression of cervical lesions (Minkoff *et al.*, 2001), while other studies did not show such a correlation (Lillo *et al.*, 2001; Schuman *et al.*, 2003). Even with the successes of HAART on a number of AIDS-associated cancers, with the increase of the longevity of treated individuals and the prolonged effects of immunosuppression, it is likely that AIDS-associated malignancies will continue to be a major clinical manifestation of HIV-infected individuals. There is still a lack of widespread antiretroviral therapy in many developing countries where AIDS is epidemic and HIV continues to spread. Better tools for detection and better regimens for management of these malignancies are necessary. Moreover, a better understanding of the biology and the pathogenesis of these cancers is needed.

The mechanisms by which malignancies are induced in HIV-1 infected individuals are not exactly known. It is likely to vary with different types, but a common underlying course is a lack of immunological controls due to immunodeficiencies. In addition, several types of cancers have been linked to viral etiological agents. In fact, the three major types of cancers included as part of the AIDS-defining illnesses, such as KS, NHL, and cervical cancers, have been linked to infectious viral agents. KS primary effusion lymphomas (PEL) and Castleman's disease have been linked to HHV-8 or KSHV. NHL, PCNSL, Hodgkin's disease, and leiomyosarcoma were found to be associated with EBV. Cervical carcinoma and squamous cell neoplasm were linked to HPV. Substantial information is known about these tumors and their potential etiological agents. A number of mechanisms and viral genes were found to have transforming activities, and they may play a direct and indirect role in tumorigenesis. A better understanding on how infections by these viral agents can lead to tumors will lead to the development of methods to enhance the immune response to control these agents as well as development of therapeutic agents to treat these malignancies. The major focus of this chapter is to examine KSHV-, EBV-, and HPV-associated tumors and what is known about their potential mechanisms in cellular transformation and tumorigenesis.

III. Kaposi's Sarcoma

KS was originally described by Moritz Kaposi in 1872 as an idiopathic, multiply pigmented sarcoma of the skin (Kaposi, 1872). The initiation of a KS lesion is called the patch stage of KS, and this stage is characterized by bluish red, well-demarcated, painless maculae, most often unilateral on the lower extremities. The lesion is composed of irregularly shaped vascular spaces present around preexisting vasculature. The lesion progresses into the plaque stage as these irregular spaces become lined with endothelial cells and proliferating spindle-shaped cells, presumed to be of endothelial origin. At this stage the lesion appears to be slightly elevated on the skin. The nodular stage can then develop and is characterized by a hard and solid appearance, brownish in color, and can be hyperkeratotic and ulcerative in nature. In advanced stages of KS, lesions are often bilateral and may involve the entire extremity as well as mucosal tissues and present with edema in the surrounding tissue. The nodular lesion is composed of bundles of proliferating spindle-shaped cells, extravasated lymphocytes and erythrocytes in an abundance of slit-like spaces. These lesions become raised on the skin and sometimes coalesce to form large nodular masses (Friedman-Kien and Saltzman, 1990; Iscovich *et al.*, 2000)

There are four epidemiological types of KS recognized: classic, endemic, iatrogenic, and HIV/ AIDS-associated KS. Classic KS is the disease originally described by Kaposi (Kaposi, 1872). It predominantly occurs in elderly persons, aged 50-80 years, in the Mediterranean and Eastern European regions or in persons of Jewish ancestry. It is seen primarily in men, with a male:female ratio of 10-15: 1. It is infrequently detected in children and young adults (Friedman-Kien and Saltzman, 1990). Endemic KS was first characterized in African populations from Southern and Central Africa in the early 1960s (Cook, 1962; Lothe and Murray, 1962; Oettle, 1962). Endemic KS was predominantly seen in men, with male:female ratio of 10-17: 1, a mean age of 40 years, and presented with multiple, nodular, and sometimes ulcerative lesions in a centrifugal distribution. Health was well maintained while the disease was indolent for several years and rapidly deteriorated as more aggressive lesion growth and dissemination occurred. Iatrogenic- or transplant-associated KS was first recognized in the 1960s and 1970s (Gange and Jones, 1978; Harwood *et al.*, 1979; Kapadia and Krause, 1977; Klepp *et al.*, 1978; Penn, 1979). It was associated with patients receiving immunosuppressive therapy, most often from organ transplant. KS lesions appeared from 2 months to 8 years after therapy. Iatrogenic KS had a male:female ratio of 2-3: 1. The lesions were mostly localized to the skin and infrequently involved the visceral organs and often regressed when therapy was discontinued.

The fourth type of KS is the AIDS-KS. In contrast to the slow development of classic KS, lesions developed rapidly and often disseminated to several locations in the body. AIDS-KS not only involves the lower extremities and skin, but also the upper body, the head regions, and the lymph nodes. It can also disseminate to other organs, such as the spleen, the lungs, the liver, and gastrointestinal track (Hengge *et al.*, 2002). AIDS-KS, due to its rapid dissemination, multiple organ involvement, and difficulty with treatment, can be a painful and debilitating disease (Friedman-Kien and Saltzman, 1990). Since the HIV-1/AIDS epidemic, the patterns and clinical manifestations of KS have dramatically changed, especially in Africa. Prior to the early 1980s, Kaposi sarcoma was a rare and indolent tumor of elderly adults, primarily men (Beral, 1991; Friedman-Kien and Saltzman, 1990; Kaposi, 1872). It was extremely rare in children; but with the AIDS epidemic, KS are often seen in young children, and when present, caused a rapidly disseminated disease that failed to respond to chemotherapy and led to death within 1-3 years (Bayley, 1991; Friedman-Kien and Saltzman, 1990).

A. Viral Etiology in KS

With the association of KS to AIDS, an infectious agent has been suspected in the development of KS, including HIV and cytomegalovirus (CMV). A report has shown that herpesvirus-like particles were found in short-term KS tissue culture, and were subsequently identified as CMV (Giraldo *et al.*, 1980). However, the involvement of CMV in KS has never been confirmed. In 1994, herpesvirus-like sequences were isolated from biopsy material from an AIDS-KS patient using a subtractive PCR technique called representational difference analysis (Chang *et al.*, 1994). This technique allows the preferential amplification of DNA sequences representative of affected tissue, which is absent in normal tissue from the same individual. The sequence was found to be homologous but not identical to any known herpesviruses. Thus, the virus was named KSHV or HHV-8 since it is the eighth known HHV. KSHV DNA sequences were found only in the KS tissue but not in normal skin tissues. Soon after KSHV DNA sequences were identified, the viral DNA was detected in biopsies from all clinical forms of KS, but was absent in normal tissue (Chang and Moore, 1996; Memar *et al.*, 1995). KSHV is found in all KS lesions, and is mainly located in the vascular endothelial cells and perivascular spindle-shaped cells (Li *et al.*, 1996).

To confirm the etiological role of KSHV in KS, the presence of the virus must be detected in patients prior to the appearance of the disease. Several studies have examined this by detecting viral DNA and seroconversion prior to KS development. In HIV-1-positive patients followed before and after onset of KS, it was observed that patients with KSHV viral DNA at study entry or any time prior to KS were significantly more likely to develop KS than those who were negative for viral DNA prior to KS (Moore *et al.*, 1996c; Whitby *et al.*, 1995). Similarly, in HIV-1-infected patients, those that developed KS were significantly more likely to be KSHV seropositive prior to the onset of KS than those that never developed KS (Gao *et al.*, 1996a; Melbye *et al.*, 1998). However, it is clear that not all KSHV-infected individuals will develop KS, thus KSHV infection plays a major role, but not sufficient, for the development of KS. It is likely that other cofactors, such as immunosuppression, are required for KS development.

In addition to KS, KSHV was found to be associated with two other lymphoproliferative disorders, PEL and multicentric Castleman's disease (MCD) (Cesarman *et al.*, 1995; Soulier *et al.*, 1995). PEL is a very rare subtype of NHL, predominantly associated with HIV-infected individuals. PEL was first identified as a subset of body cavity-based lymphomas (BCBL), which were subsequently called PELs (Cesarman *et al.*, 1995). This type of lymphoma is distinguished from others as having a distinctive morphology, bridging large cell immunoblastic lymphoma and anaplastic large cell lymphoma. PELs are extremely rare tumors, and estimated to be about 0.13% of all AIDS-related malignancies in AIDS patients in the United States (Mbulaiteye *et al.*, 2002). PELs are unique as they were found to contain KSHV DNA and are most frequently found in male AIDS patients. Most PELs are coinfected with EBV and KSHV and lack c-myc gene rearrangements, and the role of EBV in this type of tumors will be described in a section. MCD, also known as multicentric angiofollicular lymphoid hyperplasia, is a very rare polyclonal B-cell lymphoproliferative disorder with vascular hyperplasia involving multiple lymphoid organs. This disease is both clinically and morphologically heterogeneous, and is defined using clinical and pathological characteristics (Soulier *et al.*, 1995). Unlike KS, where KSHV sequences can be detected in almost all KS samples, the B cells in MCD are usually not infected. *In situ* hybridization studies showed that the KSHV-infected cells are mainly located in the mantel zone of the follicle and high levels of the viral homologue of the cellular cytokine vIL-6 can be detected, suggesting that uninfected cells are recruited and stimulated to grow in the affected areas (Katano *et al.*, 2000). It is likely that KSHV may be playing an indirect role in the disease.

B. KSHV Epidemiology

KSHV belongs to the γ-herpesvirus subfamily, which can be further subdivided into two subgroups, gamma-1 or lymphocrytovirus, and gamma-2 or rhadinovirus. EBV is the prototype gamma-1 virus and the simian herpesvirus saimiri is the prototype gamma-2 herpesvirus (Roizmann *et al.*, 1992). KSHV is classified as a gamma-2 rhadinovirus and is the first human virus of this subfamily identified (Moore *et al.*, 1996b). The genome of KSHV is about 165 kb in length, with ~140 kb of long unique DNA surrounded by two terminal repeat regions, 25-35 kb each (Russo *et al.*, 1996). It encodes over 80-open reading frames and has significant homology to the *Rhadinovirus* genus of the γ-herpesvirus subfamily, all of which are known to infect lymphocytes (Moore *et al.*, 1996c). KSHV is the only member of the rhadinovirus genus known to infect humans, but is closely related to another human γ-herpesvirus, EBV, which belongs to the lymphocryptovirus genus. A feature of γ-herpesviruses like KSHV is its ability to incorporate or pirate host genes such as cyclin D and growth factor IL-6 into their genome (Moore *et al.*, 1996a), and these genes can then play a role in the replication, survival, and transformation function of the virus. Deciphering the functions of these viral genes will lead to a better understanding of viral pathogenesis and oncogenesis.

Unlike most other herpesviruses, KSHV infection does not seem to be widely distributed in most populations. The detection of KSHV infection relies on the presence of antibodies against either lytic and/or latent antigens and varies among the different tests that were used in different seroprevalence studies. There are several different methodologies for the detection of antibodies to KSHV. Most of these assays are based on immunofluorescence antigen (IFA), utilizing B-cell lymphoma cell lines known to be infected with KSHV as the antigen source or based on ELISA with recombinant immunogenic proteins or peptides of KSHV. The performance of these assays can be quite variable, and could account for the differences in seroprevalence reported in different studies (Pellett *et al.*, 2003; Rabkin *et al.*, 1998; Tedeschi *et al.*, 2002). In North America and Northern and Western Europe, KSHV seroprevalence in adult general population or blood donors ranges from 0% to 8% (Challine *et al.*, 2001; de Sanjose *et al.*, 2002; Gambus *et al.*, 2001; Gao *et al.*, 1996b; Goedert *et al.*, 1998; Lennette *et al.*, 1996; Simpson *et al.*, 1996). In these countries, the seroprevalence of KSHV in different risk groups mirrors the incidence of AIDS-KS, with a seroprevalence rate of between 25% and 50% among homosexual men. On the contrary, the reported seroprevalence of KSHV is high in the adult general population in regions of Brazil, French Guiana, the Mediterranean basin, and Central and Southern Africa, where it ranges from 10% to over 80%; these regions are considered endemic for KSHV (Cunha *et al.*, 2005; Freitas *et al.*, 2002; Kazanji *et al.*, 2005; Klaskala *et al.*, 2005; Mayama *et al.*, 1998; Mbulaiteye *et al.*, 2003; Olsen *et al.*, 1998; Plancoulaine *et al.*, 2000, 2004; Wilkinson *et al.*, 1999). Central African countries, like the Republic of Congo, Uganda, and Zambia, also have the highest KSHV infection rates in the world (Gao *et al.*, 1996b). Therefore, KSHV seroprevalence tracks very closely with KS, with the highest infection rate in geographic areas where classic or endemic forms of KS are more common.

C. Viral Oncogenesis

A common property shared between KSHV and several other members of the γ-herpesviruses, such as EBV, is their ability to cause proliferation of infected host cells and lead to neoplasm in the infected host. Infection of primary endothelial cells by KSHV has been shown to lead to morphologic and phenotypic changes of these cells that resemble the characteristics of KS spindle cells, suggesting that KSHV can lead to malignant transformation and plays a role in the pathogenesis of KS (Flore *et al.*, 1998; Foglieni *et al.*, 2005; Moses *et al.*, 1999). KSHV has been shown to encode for a number of viral genes that may contribute to tumorigenesis. These genes include both unique viral genes and gene homologues of cellular genes. Some of these viral genes have transformation potential, such as

the viral K1 gene kaposin and viral G protein-coupled receptor (vGPCR). Others are viral proteins that have homology to their cellular counterparts. These proteins may deregulate cell growth and lead to transformation. These genes include the viral IL-6, viral IL-10, viral cc-class chemokines, and viral FLICE-inhibitory protein (vFLIP). Yet there are other viral genes that are involved in maintaining viral latency such as the latency-associated nuclear antigen (LANA) and K15. These genes are involved in a number of strategies that the virus uses in sustaining viral infection in pathogenesis and in the development of malignancies. These mechanisms involved the stimulation of cell proliferation, activation of cellular gene expression, immune suppression, and modulation of immune surveillance. These viral genes may also participate indirectly via upregulation of other viral genes. A summary of the viral genes involved is shown in Table I.

The KSHV K1 gene is the first open reading frame of the viral genome. It encodes a transmembrane protein with a cytoplasmic domain containing a functional immunoreceptor tyrosine-based activation motif (ITAM) (Lagunoff and Ganem, 1997; Lee *et al.*, 2003). ITAM motifs are known to be involved in signal transduction on ligand-receptor interaction. However, K1 signaling appears to be constitutive and may be responsible for the activation and proliferation of infected B lymphocytes by inducing phosphorylation of several cellular signal transduction proteins (Lagunoff *et al.*, 1999; Lee *et al.*, 1998a,b). The K1 gene was shown to have transforming activities; it transformed mouse cells *in vitro* and caused tumors in nude mice (Lee *et al.*, 1998b). K1 was also found to be able to replace the transforming gene (STP) of the herpesvirus saimiri and caused immortalization of marmoset T lymphocytes (Lee *et al.*, 1998b). Transgenic mice expressing K1 gene developed malignant plasmacytomas and these cells have elevated levels of NF-κB and other cellular transcription factors, further suggesting that deregulation of normal cellular functions by K1 may lead to the development of B-cell lymphomas (Prakash *et al.*, 2002).

The viral kaposin or open reading frame K-12 has also been found to play a role in transformation. The kaposin gene is expressed during latency but can also be induced on lytic replication (Muralidhar *et al.*, 1998,2000;Sadler *et al.*, 1999;Wang and Boshoff, 2005). This gene is most abundantly expressed during latency and has a complex translational pattern resulting in three different forms of the kaposin proteins, known as A, B, and C (Sadler *et al.*, 1999). Kaposin A is a type II membrane protein, and it was shown to have transforming activities and can transform cells *in vitro*; the transformed cells caused tumors in nude mice (Kliche *et al.*, 2001; Muralidhar *et al.*, 1998,2000). Its transforming activities were linked to its interaction with a guanine nucleotide exchange factor for ARF GTP ase known as cytokesin-1 and a domain known as the LXXLL motif on the protein seems to be important for transformation (Tomkowicz *et al.*, 2005). Kaposin B appears to play a role in cytokine release; it binds to host cell protein kinase, such as mitogen-activated protein kinase (MAPK)-associated protein kinase 2, which plays an important role in the proinflammatory p28 MAPK signaling pathway, resulting in an enhancement of inflammatory cytokine secretions to enhance the development of KS (McCormick and Ganem, 2006). Currently, nothing is known about the function of Kaposin C.

The viral GPCR is a lytic viral gene and is a homologue of the cellular IL-8 receptor except that it is constitutively expressed. It binds to the CXC and CC families of chemokines (Arvanitakis *et al.*, 1997; Cesarman *et al.*, 1996; Gershengorn *et al.*, 1998). KSHV GPCR has been shown to transform cell *in vitro* and promote immortalization of endothelial cells and tumor formation in the presence of KSHV latent genes, suggesting that both lytic and latent genes are important during the development of KS (Arvanitakis *et al.*, 1997; Bais *et al.*, 2003). The signal transduction property of GPCR is important for its transforming activities. It is known to stimulate the MAPK and PI3K pathways, leading to the stimulation of a large number of cellular genes that could enhance the proliferation of KSHV-infected

cells. Activation of vGPCR has been associated with an increase in the secretion of vascular endothelial cell growth factors (VEGF) and VEGF receptors, which leads to an induction of the angiogenic response, to enhance the growth of immortalized KSHV-infected cells both *in vitro* and *in vivo* through a paracrine pathway mediated by vGPCR (Montaner *et al.*, 2003; Sodhi *et al.*, 2000; Yang *et al.*, 2000).

In addition of vGPCR, there are other viral genes that have homology to cellular homologue genes, such as the viral IL-6, viral cc-chemokines (vCCLs), and vFLIP. KSHV vIL-6 has both sequence and functional homology to the cellular IL-6, but they differ in their ability to bind to cellular receptors. Cellular IL-6 requires both the a and the pg130 subunits for binding and signaling, whereas vIL-6 requires only the pg130 subunit (Molden *et al.*, 1997). KSHV-infected PEL MCDD cells secrete vIL-6 to support the growth of the infected cells and also protect the cells from the antiviral effects mediated by the interferon pathway (Moore *et al.*, 1996a; Nicholas *et al.*, 1997). Thus, vIL-6 appears not only to have the ability to support the growth of infected cells, but also can protect infected cells from the effects of interferon. In addition to vIL-6, several viral genes, K4, K4.1, and K6, encode viral homologues of the cellular CC chemokines, such as RANTES and MIP-1a (Boshoff *et al.*, 1997). These chemokines can induce signaling transduction, enhance angiogenesis, and contribute to the tumorigenesis process (Nakano *et al.*, 2003). The KSHV FLIP gene ORF71 is a latent viral gene which encodes the FLIP protein and is structurally most homologous to the cellular FLIP. It facilitates lymphoma cell growth by activating NF-κB expression and its signaling pathway, and by conferring the infected cells resistance to apoptosis (Djerbi *et al.*, 1999; Guasparri *et al.*, 2004; Thome *et al.*, 1997). In addition, vFLIP was shown to induce morphological changes in primary endothelial cells to become spindle-like in shape, similar to KS tumor cells (Grossmann *et al.*, 2006). These together with the antiapoptotic functions of vFLIP reflect two features that are known to be the hallmark of KS.

Another KSHV latently expressed protein that may contribute to neoplasm is LANA. The KSHV LANA is a nuclear phosphoprotein that is important for the maintenance of viral latency (Dittmer *et al.*, 1998). It has been shown to bind to the terminal repeat region of the viral genome and tethered the viral episome to the host chromosome so that it can be maintained during cellular mitotic replication and segregation (Ballestas *et al.*, 1999; Cotter *et al.*, 2001). LANA is a multifunctional viral protein and can bind to a number of cellular proteins. It can bind to tumor suppressors p53 and Rb and protect infected cells from apoptosis (Friborg *et al.*, 1999; Radkov *et al.*, 2000). This together with its ability to upregulate ß-catenin expression promotes S-phase entry, modulates cell cycle pathways, and contributes to the development of neoplasm (Fujimuro *et al.*, 2003).

IV. AIDS-Associated Lymphomas

As persons with HIV infection survive longer despite significant immunosuppression, more cases of malignancy are likely to appear. Although HIV infects T lymphocytes, AIDS-associated lymphomas are of B lymphoid origin in at least 95% of all cases described. As with other lymphomas, AIDS-associated lymphomas also fall into two broad categories: AIDS-associated Hodgkin's disease and NHL. AIDS-associated NHLs are primarily encountered in patients with more advanced HIV infection, with a low CD4 count. Although Hodgkin's disease is included in the HIV-associated lymphomas in the WHO classification, it will not be discussed in this chapter because the relation between HIV infection, AIDS, and Hodgkin's disease is unclear (Carbone and Gloghini, 2005). Whether HIV infection promotes the development of Hodgkin's disease or merely modifies its clinical progression is not yet known

Mechanistic studies have revealed that potential factors contributing to lymphoma development. Three major factors promoting the development of lymphoma are HIV-induced immunosuppres-

sion, chronic antigenic stimulation, and cytokine overproduction. These alterations are associated with the development of oligoclonal B-cell expansions. The appearance of lymphomas is characterized by the presence of a monoclonal B-cell population displaying a variety of genetic lesions, including EBV infection, c-myc gene rearrangement, bcl-6 gene rearrangement, ras gene mutations, and p53 mutations/deletions. The number and type of genetic lesions varies according to the anatomic site and histopathology. Thus, it is apparent that more than one pathogenic mechanism is operational in the development and progression of AIDS-associated lymphomas (Carbone and Gloghini, 2005; Epeldegui *et al.*, 2006). This chapter attempts to summarize the potential role of viral etiological factors, especially EBV, on the development of the malignancies.

A. EBV, Its Latency, and Its Role in AIDS-Associated Lymphomas

EBV is a ubiquitous human-herpesvirus that infects about 95% of the adult population worldwide. The majority of primary infections occur in early childhood and are generally asymptomatic. However, when primary infection is delayed until adolescence or adulthood, as often occurs in developed countries, it may cause infectious mononucleosis (IM), which is a self-limiting lymphoproliferative disorder characterized by increased numbers of EBV-infected B cells in peripheral blood and massive oligoclonal expansion of EBV-specific CD8 + T cells. The biologic hallmark of the EBV-cell interaction is latency. EBV establishes several latencies on infection of target cells. Three types of latency have been described, each having its own distinct pattern of EBV gene expression. Type I latency is exemplified by Burkitt's lymphoma (BL) tumors *in vivo* and earlier passages of cultured cell lines derived from BL biopsies. Epstein-Barr Nuclear Antigen 1 (EBNA-1) and small EBV-encoded, nonpolyadenylated nuclear RNAs (EBER-1 and -2) are expressed in this form of latency. Type II latency is exemplified by NPC and Hodgkin's disease. EBNA-1, latent membrane protein 1 (LMP-1), LMP2A, and LMP2B proteins, as well as EBERs, are expressed in type II latency. EBV transforms adult primary B cells into continually growing lymphoblastoid cell lines (LCLs) and concomitantly establishes type III latency *in vitro*. Nine viral proteins are expressed, including six nuclear proteins (EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-LP) and three integral membrane proteins (LMP-1, LMP-2A, and LMP-2B) plus EBERs (Kieff, 1996; Rickinson and Kieff, 1996). Extensive mechanistic studies on EBV transformation have identified several key viral genes that contribute to the viral transformation processes. They are LMP-1, LMP-2, EBNA-1, and EBNA-2.

B. Latent Membrane Protein 1 (LMP-1)

The role of LMP-1 in EBV transformation of primary B lymphocytes is well established. LMP-1 was initially identified as a viral oncoprotein on the basis of its ability to transform rodent cells. Fibroblasts constitutively expressing LMP-1 demonstrate reduced serum requirements, increased growth in soft agar, loss of contact inhibition, and tumorigenic potential in nude mice (Dawson *et al.*, 1990; Fahraeus *et al.*, 1990; Wang *et al.*, 1985). Moreover, expression of LMP-1 as a transgene in mice under the control of the immunoglobulin promoter/enhancer results in increased frequency of B-cell lymphomas, indicating that this viral protein has oncogenic properties *in vivo* (Kulwichit Raab-Traub). In viral transformation assays with primary B cells, deletion of LMP-1 prevents the transformation of primary B cells (Izumi *et al.*, 1997; Kaye *et al.*, 1993), and inhibition of LMP-1 expression in EBV-transformed cells reverts the transformed phenotypes (Kilger *et al.*, 1998). Thus, LMP-1 is required for EBV transformation of primary B cells *in vitro* in tissue culture system.

LMP-1 expression alone modulates cellular gene expression that is responsible for phenotypic and functional changes associated with EBV latency. These changes include the upregulation of adhe-

sion molecules (LFA-1, ICAM-1, LFA-3), B-cell activation markers (CD23, CD30, CD40, CD71), transcriptional factors [signal transducer and activator of transcription 1 (STAT-1), -2, IRF-7], and anti-apoptotic genes (Bcl-2, BclxL, Mcl1, A20). Thus, LMP-1 appears to be a central effector of altered cell growth, survival, adhesive, invasive, and even antiviral potential in EBV-infected cells (Fries *et al.*, 1996; Miller *et al.*, 1995; Wang *et al.*, 1985, 1990; Yoshizaki *et al.*, 1998).

Extensive studies have led to some insight into the molecular mechanisms underlying the function of LMP-1. LMP-1 is an integral membrane protein with six transmembrane-spanning domains and a long C-terminal domain located in the cytoplasm (Kieff, 1996; Liebowitz *et al.*, 1986). LMP-1 acts as a constitutively active, receptor-like molecule that does not need the binding of a ligand (Gires *et al.*, 1997). The six transmembrane domains mediate oligomerization of LMP-1 molecules in the plasma membrane, a prerequisite for LMP-1 function (Floettmann and Rowe, 1997; Gires *et al.*, 1997). Two regions in the C-terminus of LMP-1 have been shown to initiate signaling processes, the C-terminal activator regions 1 (CTAR-1, amino acids 194-231) and 2 (CTAR-2, amino acids 332-386) (Huen *et al.*, 1995; Mitchell and Sugden, 1995). In a more refined analysis, several kinds of functional domains have been identified. The PXQXT domain is located within the CTAR-1 and is involved in the interaction with tumor necrosis factor receptor (TNFR)-associated factors (TRAFs), and the binding of TRAFs to LMP-1 results in the induction of the NF-κB and AP-1 transcription factors. It is thus apparent that LMP-1 shares functional properties with members of the TNF-receptor superfamily, particularly CD40. Moreover, LMP-1 can partially restore the wildtype phenotype of mice deficient in CD40 (Devergne *et al.*, 1996, 1998; Miller *et al.*, 1997, 1998; Sandberg *et al.*, 1997). LMP-1 also interacts with TNFR-associated death domain protein (TRADD) and receptor-interacting protein (RIP) at the C terminal (Devergne *et al.*, 1998; Floettmann and Rowe, 1997; Izumi *et al.*, 1997, 1999; Izumi and Kieff, 1997; Kaye *et al.*, 1996). Interaction with these two molecules contributes the majority of the NF-κB activity induced by LMP-1. Also, c-Jun N-terminal kinase (JNK) is activated by CTAR-2. The domain for activation is mapped to most C-terminal amino acids and apparently overlaps the TRADD interaction domain. However, whether TRADD and TRAF2 are involved in the activation of JNK is disputed (Eliopoulos and Young, 1998; Eliopoulos *et al.*, 1999; Kilger *et al.*, 1998). In addition, two janus kinase 3 (JAK3) binding sites have been identified between CTAR-1 and CTAR-2. JAK3 binding to the sites is responsible for the activation of STAT-1(Gires *et al.*, 1999). However, some other experimental evidence suggests an alternative mechanism (Brennan *et al.*, 2001; Higuchi *et al.*, 2002; Zhang *et al.*, 2004b). In summary, the hijacking of these cellular signaling pathways by LMP-1 is likely to contribute to the pathogenesis of most EBV-associated disorders through the simultaneous or sequential activation of signals involved in the promotion of cell activation, growth, and survival.

C. Latent Membrane Protein 2

The LMP-2 protein contains multiple membrane spanning domains and cytoplasmic N- and C-terminal domains and forms aggregates in the membrane of EBV-infected B cells. The N-terminal domain can bind to the tyrosine kinases Lyn and Syk through their SH2 domains (Longnecker *et al.*, 2000). These kinases are recruited to the BCR following antigen cross-linking, and their subsequent activation stimulates downstream events resulting in B-cell differentiation and proliferation. LMP-2A may work as a decoy protein sequestering Lyn and Syk to inhibit BCR signaling, which make LMP-2 an inhibitor of EBV lytic replication induced by BCR ligation (Longnecker, 2000; Longnecker *et al.*, 2000). The property of LMP-2 may play a major role in mediating EBV persistence *in vivo.*

Unlike LMP-1 and EBNA-2, the LMP-2 protein is not essential for B-cell transformation *in vitro*. Nevertheless, the constant expression of LMP-2 in EBV-carrying memory B cells from healthy individu-

als suggests that LMP-2 probably plays an important role in viral persistence. LMP-2 in transgenic mice model has shown that LMP-2 provides survival signals that allow immature B cells to progress through developmental checkpoints and prevent cell death. This property may be related to the ability of LMP-2A to activate the serine-threonine kinase Akt. Akt is a multifunctional mediator of phosphatidylinositol 3-kinase (PI3-K) activity. Activation of the pathway results in the constitutive delivery of an antiapoptotic signal. Akt is also involved in the control of B-cell proliferation because chemical inhibition of PI3-K induced growth arrest of EBV-transformed B cells (Brennan *et al.*, 2002).

D. Epstein-Barr Nuclear Antigen

The EBNA-1 protein is expressed in all EBV latency states and all EBV-associated tumors. The only exception is that EBNA-1 is hardly detectable in the circulating EBV-infected memory B cells. This alone suggests that the biologic properties of this protein are critical for EBV-mediated transformation (Kieff, 1996). EBV establishes itself efficiently in infected B lymphocytes, where it exists as 165 kb, circular episome which is duplicated once per cell cycle. Remarkably only EBNA-1 protein is required for the synthesis and partitioning of the viral episomes. EBNA-1 binds to two regions of the viral origin of replication (OriP), referred to as the family of repeats (FR) and the dyad symmetry (DS) element. FR is essential for episome maintenance, while DS is required for initiation of OriP-dependent DNA replication. EBNA-1 is also a transcriptional regulator that modulates the activity of the viral promoters: Wp and Cp and its own latent promoter Qp. Moreover, EBNA-1 is essential to drive transcription of EBV's transforming genes after infection of primary B lymphocytes (Altmann *et al.*, 2006). In addition, EBNA-1 can inhibit apoptosis in B cells that likely contributes to the persistence of EBV-infected cells and survival of EBV-transformed cells *in vivo.*

E. EBNA-2

The EBNA-2 protein is localized in the nucleus and is one of the first viral proteins expressed during EBV infection of primary B lymphocytes. In cooperation with EBNA-LP (also known as EBNA-5), EBNA-2 induces the transition of resting B cells from G0 to G1. EBNA-2 is a key regulator of viral gene expression, being able to stimulate transcription from the major latency BamHI-C promoter, which directs expression of all the EBNA genes, and the promoters of LMP-1 and LMP-2. In addition, EBNA-2 modulates the transcriptional activity of some cellular genes. Cellular C-fgr, c-myc, CD21, CD23, and EBI1/BLR2 are upregulated whereas the immunoglobulin heavy chain genes are repressed in lymphocytes. There is no evidence that EBNA-2 binds to DNA directly. Rather, its transcriptional activity is mainly mediated by its interaction with the DNA-binding cellular protein RBP-Jk (also called RBP-J, CBF1, KBF2, or CSL). EBNA-2 is essential for EBV-induced immortalization of B lymphocytes and complex formation with RBP-Jk is crucial for such activity. RBP-Jk is expressed ubiquitously and is an important component of the Notch signaling pathway that is involved in the regulation of lymphoid development. Notch proteins are a family of transmembrane receptors that on ligand binding undergo proteolytic cleavage of their intracellular domain (Notch1 IC). The cleaved and released Notch1 IC fragment is transported to the nucleus where it interacts with RBP-Jk and modulates the activity of target promoters. Although Notch1 IC and ENBA-2 share the ability to transactivate genes by interacting with RBP-Jk, the set of promoters regulated by Notch1 IC and EBNA-2 is overlapping but not identical.

Generally, transformation of a cell requires multiple molecular events (Cole and McMahon, 1999; Kelekar and Cole, 1986; Kohl and Ruley, 1987; Ralston, 1991; Shalloway *et al.*, 1987; Weinberg, 1985, 1989). Several viral genes, such as LMP-1 and EBNA-2, are required for the transformation of primary B cells *in vitro* and are believed to drive EBV transformation process *in vivo*. EBV contributes to the cellular transformation processes through the activity of viral proteins that act cooperatively to

modify cellular gene expression that involved in cell proliferation, apoptosis, angiogenesis, immune regulation, and signal transduction (Cahir-McFarland *et al.*, 2000; Chen *et al.*, 2003; Fries *et al.*, 1996; Henderson *et al.*, 1991; Miller *et al.*, 1995; Wang *et al.*, 1985, 1990; Yoshizaki *et al.*, 1998; Zhang and Pagano, 1999; Zhang *et al.*, 2004a,c).

V. AIDS-Associated NHL

AIDS-associated NHL is generally divided into three subtypes: PCNSL, PEL ("body cavity"), and systemic NHL (Knowles, 2003). The vast majority of AIDS-associated NHL is clinically aggressive B-cell-derived neoplasms. Approximately 80% arise systemically (nodal and/or extranodal), and the remaining 15-20% arise as PCNSL. A small proportion is BCBLs (Knowles, 2003). EBV apparently contributes to the development of these tumors in various fashions.

A. Primary Central Nervous System Lymphoma

PCNSL is a form of NHL arising within and confined to the CNS. It was first described by Bailey in 1929 as a perithelial sarcoma (Bailey, 1929). Subsequent classifications have included reticulum cell sarcoma and microglioma. Improvements in histopathology and immunohistochemical techniques definitively established the lymphoid nature of PCNSL. PCNSL accounts for up to 15% of NHLs in HIV-infected patients compared to only 1% of NHLs in the general population. The reported incidence of PCNSL in HIV-infected patients is 2-6% (at least 1000 times higher than in the general population) and has been as high as 10% in autopsy series. Although CNS involvement also occurs in AIDS-associated systemic lymphoma in the form of secondary spread of the tumor to the meninges, the disease is limited to the CNS in PCNSL (Cheung, 2004; Cingolani *et al.*, 2005; Eichler and Batchelor, 2006; Gates and Kaplan, 2002; Sparano, 2003). Prior to the introduction of HAART, the incidence of PCNSL in the HIV-infected population was continuing to rise. However, the impact of these new drug regimens on the CD4 count may result in a decline in PCNSL, as the susceptibility to PCNSL is inversely proportional to the CD4 count (Sparano *et al.*, 1999). In normal individuals, a small number of circulating B cells enter the CNS, and may do so in increased numbers as HIV infection advances (Cingolani *et al.*, 2005; Ivers *et al.*, 2004). EBV establishes latent, life-long infection in over 90% of adults. During the course of HIV infection, EBV-specific T cells progressively lose the capacity to produce interferon-gamma in response to EBV peptides. In addition, EBV-positive B lymphocytes occur more frequently in the CNS of HIV-infected individuals than in normal brains, which may set up a stage for EBV transformation of these infected cells.

EBV appears to play a major pathogenetic role in AIDS-associated PCNSL: (1) EBV genome within tumors is present in more than 95% of AIDS patients, but in only 0-20% (probably <5%) of immunocompetent patients. (2) More than half of AIDS PCNSL examined so far expressed at least EBNA-2, LMPs, and EBERs, a pattern referred to as type III latency and closely resembling that seen in transformation of primary B lymphocytes *in vitro* EBV (Cingolani *et al.*, 2005; Ivers *et al.*, 2004). Expression of type III latency genes leads to a variety of cellular effects, including upregulation of the genes that are involved in transformation, such Bcl-2 and IRF-7, and inactivation of the p53 and Rb tumor suppressor gene products. It is believed that the EBV triggers certain PCNSL *in vivo* in a process similar to transformation processes of primary B cells *in vitro* (Pagano, 1999).

B. Primary Effusion Lymphoma

PELs, also known as BCBL, are B-cell NHLs and most frequently occur in AIDS patients as lym-

phomatous effusions in the serous cavities without a detectable solid tumor mass. In the setting of AIDS, the clinical course for most of these lymphomas is extremely aggressive, with a mean survival from diagnosis of 5-7 months (Nador *et al.*, 1996). While PELs are almost universally KSHV positive, the majority of PELs have concomitant EBV infection (reviewed in Dourmishev *et al.*, 2003; Drexler *et al.*, 1998; Moore and Chang, 2001). EBV apparently establishes levels type II latency in PELs with low of LMP-1 expression (Callahan *et al.*, 1999; Fassone *et al.*, 2000; Horenstein *et al.*, 1997; Lacoste *et al.*, 2000).

Both KSHV and EBV are oncogenic herpesviruses. It is thus interesting to examine if there are any interactions between the two viruses in PELs. Comparing to KSHV-only PELs, coinfection with EBV enhances the tumorigenecity of the dually infected PELs in severe combined immunodeficiency (SCID) mice model (Trivedi *et al.*, 2004). The mechanism of the enhancement is currently unknown. However, LMP-1 might be involved in the enhancement because LMP-1 is expressed and its expression may be enhanced by both KSHV latent gene (LANA) and lytic gene (K-RTA). Although expression of LMP-1 at least in some of the PEL specimens strongly suggests the contribution of EBV to the development of the tumor, this enhancement was not apparent in clinical settings, possibly due to the fact that patients with PEL are usually at advanced HIV-infection stage.

At molecular levels, unique sets of cellular genes are expressed in dually infected, but not singly KSHV-infected PELs (Fan *et al.*, 2005). KSHV reduces the expression of EBV EBNA-1 and represses EBV EBNA-2 activation (Krithivas *et al.*, 2000). EBV inhibits KSHV lytic replication, in part, because of a regulatory loop in which KSHV lytic gene induces EBV LMP-1, and LMP-1, in turn, inhibits the lytic gene expression programs of KSHV (Xu *et al.*, 2007). Like EBV EBNA-2, KSHV replication and transcriptional activator (K-RTA) bind to RBP-Jk (Liang *et al.*, 2002), a key cellular target of the EBV latent transforming program (Zimber-Strobl and Strobl, 2001). Also, KSHV induces the expression of CD21, the cellular receptor for EBV, and thus facilitates EBV infection (Chang *et al.*, 2005). All this data suggests that coordinated cellular transformation by the two viruses is a possibility. However, how these two viruses interact and affect each other and the pathobiology of PELs remains to be determined.

C. Systemic AIDS-Associated NHL

Systemic AIDS-associated NHLs are aggressive B-cell lymphomas of high or intermediate grade and heterogeneous in nature. Approximately one-third can be classified as small noncleaved cell lymphomas, which are Burkitt or Burkitt-like lymphomas. The remaining two-thirds of the lymphomas are diffuse large cell lymphomas, which are immunoblastic lymphomas or large noncleaved cell lymphomas (Brockmeyer and Barthel, 1998). EBV infection and c-myc oncogene rearrangements are the two well-established factors in the pathogenesis of the systemic NHL. The diffuse large cell lymphomas frequently express EBV latency type III antigens including EBNA-2 and LMP-1 and -2, which have transforming activity *in vitro* are well established. EBV establishes type I latency expressing only EBNA-1 in BLs. However, the EBV genome can be detected in only 60% of the diffuse large cell lymphomas, and in around 30% of the AIDS-associated BLs. Because EBV is less frequently detected in systemic and lymphomas, and the increasing incidence type of this of cancer in HIV-infected patients, some additional common latent or chronic viral infections may be involved in the development of these tumors (Mueller, 1999; Shibata *et al.*, 1993). In the setting of underlying HIV infection, systemic NHL truly behaves as an opportunistic neoplasm, overwhelming those immune mechanisms that may normally attempt to keep the cancer in check.

VI. HPV-Associated Cancers

A. Types of HPV-Induced Cancers

HPVs infect the stratified epithelia of skin or mucosa, where they cause benign warts. Of the 200 different types of HPVs (Cates and Dallabetta, 1999), the most common HPVs (types 2 and 4) are those that cause warts on the hands and feet of affected individuals (Howley, 1996). Anogenital tract HPVs, of which ~40 have been identified, are divided into those which confer a "low risk" (types 6, 11, 42) or a "high risk" (types 16, 18, 31) for cervical cancer (Howley, 1996; Sakai *et al.*, 1996; zur Hausen, 1999, 2000). Studies performed by Harold Zur Hausen's laboratory provided the first definitive evidence that HPVs were present in genital cancers (Bosch *et al.*, 1991; Durst *et al.*, 1983; Gissmann *et al.*, 1984; Schwarz *et al.*, 1985; zur Hausen, 1999, 2000; zur Hausen *et al.*, 1975, 1981). After more than 20 years of work, HPVs are now recognized as a necessary cause in 95% of invasive cervical cancers worldwide (Walboomers *et al.*, 1999). Approximately 20 million US adults are infected with genital HPVs and there are 5.5 million new infections each year, representing a major public health concern (Cates and Dallabetta, 1999). In human cervical cancer cells, high-risk papillomavirus DNA is most often found integrated into the host chromosomes (Londesborough *et al.*, 1996; Schwarz *et al.*, 1985; Yee *et al.*, 1985b).

HPVs are most commonly associated with cervical cancer, although, it is now known that many cancers are induced by HPV, including penile, anal, oral, and conjunctival cancers (Durst *et al.*, 1983; Koutsky, 1997; Newton *et al.*, 2002; Syrjanen, 2003; Waddell *et al.*, 1996). High-risk HPVs have also been implicated recently in ~30% of oral cancers (Gillison *et al.*, 2000). In fact, HPVs are responsible for cancers in the tonsils, the palate, gums, tongue, and the larynx (Aaltonen *et al.*, 2005; de Villiers *et al.*, 1986; El-Mofty and Lu, 2003; Lopez Amado *et al.*, 1996; Milde-Langosch *et al.*, 1989; Mineta *et al.*, 1998; Sinclair *et al.*, 2005; Syrjanen, 2005; Yoshpe, 1995). High-risk HPVs have been further implicated in upper respiratory tract and lung cancers (Cheah and Looi, 1998; Clarke *et al.*, 1991; de Villiers *et al.*, 1986). Furthermore, evidence suggests that some digestive cancers are also HPV positive (Milde-Langosch *et al.*, 1989; Nakano, 1994). HPVs are some of the most ubiquitous and stable viruses in nature, thus, it is not surprising that multiple tissues are targets of HPV-induced tumorigenesis.

Penile cancers are much less common than cancers of the cervix, for reasons that are not entirely clear (Gloeckler Ries *et al.*, 2003). Despite the fact that men seldom show clinical signs, it is likely that many could be persistently infected and that the progression to penile cancer occurs under immunosuppressive conditions. Cancers of the vulva and vagina are also relatively rare compared to cervical cancers. The reason for these differences in incidence of cancers in different tissues is related to the cell-type infected. The cells of the cervical transformation zone at the squamous and columnar cell junction are the most susceptible to HPV-induced cell transformation (Jastreboff and Cymet, 2002; Jordan and Monaghan, 2004; Ponten and Guo, 1998). An analogous cell type apparently does not exist in men. However, despite lack of studies on the subject, it would be assumed that men are transmitters of HPVs (Baldwin *et al.*, 2003; Dunne *et al.*, 2006; Giuliano *et al.*, 1999). Predictably, the incidence of penile cancers increases dramatically in individuals who are HIV positive (Aboulafia and Gibbons, 2001; Arany and Tyring, 1998; Laurence, 2003; Palefsky and Barrasso, 1996; Sirera *et al.*, 2006; von Krogh *et al.*, 1995), which likely reflects the overall increase incidence of HPV infections detected in women.

Anal cancer is a relatively rare disease, ~80% of which are HPV positive (Gloeckler Ries *et al.*, 2003; Hankey *et al.*, 1999; Zippin and Lum, 1993). Anal cancer amounts to about 4% of all digestive tract cancers. The incidence of anal cancers in women is slightly higher than in men (Gloeckler Ries *et al.*, 2003; Hankey *et al.*, 1999; Zippin and Lum, 1993), which could be indicative of the overall higher

rate of HPV infection among women. It appears that the incidence of anal cancers are rising in the past 10 years, reflecting changes in sexual behavior (http://seer.cancer.gov/) (Gloeckler Ries *et al.*, 2003). The highest level of risk for anal cancer caused by HPV is associated with MSM (Piketty *et al.*, 2004). The rate of anal cancer among HIV-negative heterosexual men is ~1.3/100,000, while the rate of anal cancers in HIV-negative MSM is 35/100,000. Among MSM who are HIV positive, the rate of anal cancer is twofold higher than HIV-negative MSM (Fakhry and Gillison, 2006).

HPV infections of the conjunctiva of the eye are more common than previously appreciated, although resulting HPV-induced tumors of the conjunctiva are very rare (Mincione *et al.*, 1992, 2006; Reszec and Sulkowski, 2005;Tabrizi *et al.*, 1997;Waddell *et al.*, 2003). Though the incidence of eye or eye-orbit tumors in the United States is extremely low (<1/100,000) (Gloeckler Ries *et al.*, 2003), in African countries, conjunctival tumors are more common and are undoubtedly influenced by nutrition, additional disease burdens, but most obviously by the relatively high impact of HIV in Africa (Ateenyi-Agaba *et al.*, 2006; Frisch *et al.*, 2000; Goedert, 2000; Newton *et al.*, 2002; Waddell *et al.*, 1996, 2003).

Given the wide range of cancers caused by HPV, the recent development of an HPV vaccine provides some hope for providing protection against many of the cancers described earlier. However, vaccine efforts have concentrated on only two high-risk strains (HPV16 and HPV18) (Mao *et al.*, 2006; Villa *et al.*, 2005), while there are at least 15 known high-risk strains. We also have evidence that multiple regional HPV variants exist, particularly in Africa, for which, the extent of protection by the current vaccine is unknown (Calleja-Macias *et al.*, 2004; Chan *et al.*, 1992; Ong *et al.*, 1993; Touze *et al.*, 1998; Williamson *et al.*, 1994; Xi *et al.*, 1998). Furthermore, the distribution of high-risk HPVs varies from country to country (Calleja-Macias *et al.*, 2004; Chan *et al.*, 1992; De Vuyst *et al.*, 2003; Munoz *et al.*, 2004; Ong *et al.*, 1993; Williamson *et al.*, 1994; Xi *et al.*, 1998). Therefore, it is important to take a long-range view of prevention of HPV-induced cancers by use of vaccination strategies that take into account variants.

VII. HPV—The Causative Agent

A. Papillomavirus Genome Structure

HPVs are a family of small, nonenveloped, double-strand DNA viruses that establish a persistent infection, which may remain subclinical in the skin or genital tract for up to 10-20 years, but can often cause acute warts. Papillomavirus genomes are small circular DNA of 8 kb, which encodes eight major proteins. As is typical for DNA viruses, the immediate early genes (E6 and E7) are involved with taking over the cell cycle (Fig. 1) (Howley, 1996;Howley *et al.*, 1989; zur Hausen, 1999,2000). Unlike more complex viruses like herpesviruses, HPVs use the strategy of replicating at low copy, and thus, do not carry their own polymerase gene. Instead, gene products encoded by E1 and E2 recruit cellular polymerase a to the viral origin (Frattini and Laimins, 1994;Howley, 1996;Howley *et al.*, 1989;Sedman and Stenlund, 1995). The genome is simply organized into early and late genes, with only two capsid genes, L1 and L2.

The functions of the viral proteins are well established and are summarized below (Table II).

B. The HPV Life Cycle

HPVs initiate their life cycle by gaining access to basal keratinocytes of the stratified epithelium; either skin or mucosa through a site of wounding (Fig. 2). Papillomavirus DNA replication is closely coupled to the process of keratinocyte differentiation in infected squamous epithelium (reviewed in Chow and Broker, 1994). In the basal and parabasal epithelial cells, HPV is maintained as a low-copy number episome (5-50 copies per cell) that under-goes regulated DNA replication under the con-

trol of viral and host proteins. As infected keratinocytes differentiate and enter the stratum spinosum layer of the epithelium, there is a coincident increase in concentration of E1 and E2 proteins (for review, see Shaw and Howley, 2001). Induction of vegetative replication is consistent with a mode switch from theta to rolling-circle replication mechanisms (Flores and Lambert, 1997). As a consequence of this rolling-circle DNA replication mechanism, multiple rounds of viral DNA synthesis occurs in a given S-phase of the host keratinocyte (Hoffmann *et al.*, 2006), and an increase in copy number up to between 100 and 1,000 copies per cell. Vegetative HPV DNA replication requires the virus-encoded E1 (a DNA helicase per ATPase) and E2 (a transcriptional trans-modulator) proteins, and initiates at the E1 binding site palindrome near the 5' end of the viral long control region (Kuo *et al.*, 1994).

C. The HPV Capsid and the Vaccine

Capsid assembly of HPVs occurs in the more terminally differentiated layers of the stratified epithelium (Fig. 2). HPVs have icosahedral capsids arranged in a T = 7d lattice (Baker *et al.*, 1991). The capsids are made up of 360 L1 molecules organized into 72 pentamers. Disulfide bond interactions between L1 molecules are important in particle assembly and disassembly (Li *et al.*, 1998). There are 12 L2 minor capsid proteins that are associated with the inner surface of the L1 pentamers (Belnap *et al.*, 1996). High resolution cryoelectron microscopic structures of bovine papillomavirus (BPV) have been achieved (Baker *et al.*, 1991); less is known about HPV structure, assembly, and uncoating. L1 expression is sufficient to allow self-assembly of virus-like particles (VLPs) in the absence of other viral components (Casini *et al.*, 2004). However, L2, when coexpressed with L1, intercalates into L1 VLPs and appears to be required for virion infectivity (Kawana *et al.*, 2001;Stauffer *et al.*, 1998). Though the precise role of L2 during infection is not clear, it may nucleate L1-pentamer formation. The simple, nonenveloped icosahedral HPV virions lend themselves to vaccine development. The recently developed quadrivalent vaccine targets two high-risk HPVs (16 and 18) and two low-risk HPVs (6 and 11). However, there is little evidence of significant cross-protection against the other 14 oncogenic HPVs. Furthermore, there are at least 40 genital HPVs. Thus, the development of vaccines that have a wider cross-protection or tailoring HPV vaccines for different regions of the world will become necessary.

D. Epidemiology of HPV and HIV/AIDS

Epidemiological evidence gathered over several years has determined that 15-20 of the 40 of the mucosal HPV types are associated with a higher risk of progression to cervical cancer (24, 29). The frequency of individual high-risk HPV types worldwide has been shown to vary in respect to major global regions such as Asia, Europe, North America, South America, and sub-Saharan Africa (5, 14, 23). The rate of genital HPVs in the United States, as detected by PCR of the L1 region, is ~39.2% (Peyton *et al.*, 2001). Estimates of the rates of HPV in Africa vary from 14% to 60% depending on the country, the coincident STDs, and the methods of detection (Czegledy *et al.*, 1992; Gravitt *et al.*, 2002; Hassen *et al.*, 2003; Langley *et al.*, 1996; Mayaud *et al.*, 2001; Motti *et al.*, 1996; Nzila *et al.*, 1991; O'Farrell *et al.*, 1989; Ong *et al.*, 1993; Serwadda *et al.*, 1999; St. Louis *et al.*, 1993; Thomas *et al.*, 2004; Waddell *et al.*, 1996; Williamson *et al.*, 2002). The rate of HPV infections in HIV-positive patients in Zambia are very high, though rather little data is available (Mosunjac *et al.*, 2003; Patil *et al.*, 1995). As a whole, sub-Saharan Africa has the among the highest rates of cervical cancer in the world (Bailie *et al.*, 1996; Clarke and Chetty, 2002; Langley *et al.*, 1996; ter Meulen *et al.*, 1992; Williamson *et al.*, 2002). The distribution of oncogenic HPVs in Africa differs from the United States and Europe. For example, studies done by Nubia Munoz have pointed out that in Nigeria, the most prevalent oncogenic HPV is HPV35,

not HPV16, which is the most common in the United States and Europe (Thomas *et al.*, 2004). Several studies have described HPV variants unique to Africa (Calleja-Macias *et al.*, 2004; Chan *et al.*, 1992; Ong *et al.*, 1993; Williamson *et al.*, 1994). This points to a need to further investigate HPV variants in terms of HPV pathogenesis and a potential need to expand the selection of vaccine targets.

The rates of HIV infection in urban area along a contiguous stretch from Uganda to Botswana and South Africa have continued to climb in recent years (Morison, 2001). Several studies have addressed HIV-related malignancies associated with HHV-8 (KSHV) and EBV, which are associated with increased morbidity (Ablashi *et al.*, 1999; Contreras *et al.*, 1997; Lazzi *et al.*, 1998; Parkin *et al.*, 2000; Sapp *et al.*, 2001). Despite frequency variation, HPV16 infection has been shown to be more prevalent than any other high-risk HPV type in most regions of the world. However, HIV-positive populations have a much higher rate of HPV16 positive tumors than most HIV-negative populations (1, 2, 9, 18, 28). Thus, the incidence of high-risk HPV-malignancies is amplified by HIV immune suppression.

It is clear that impaired cell-mediated and humoral immunity influences the advancement of high-risk HPVs in HIV-positive individuals. Since the pool of memory and effector T cells can be dramatically shifted in HIV-positive individuals (even those who do not have AIDS), it would be expected that a certain degree of derepression of HPV replication would occur as well as a lack of adequate surveillance preneoplastic lesions. Several studies have shown a strong and consistent association between HIV and HPV coinfection and the development of cervical intraepithelial neoplasia (CIN) and genital cancer (7, 11, 13, 15). There is evidence to show that HIV-positive women have a significantly higher rate of CIN than their counterparts and are more likely to progress to invasive carcinoma than HIV-negative women (4, 12, 20). A recent study in Brazil has shown that a very high proportion of HIV-infected women is infected with HPV and often carries multiple HPV genotypes (15).

A relationship between the HIV and HPV pathogenesis has been investigated by several studies (Durante *et al.*, 2003; Heard *et al.*, 2004; Klencke and Palefsky, 2003; Massad *et al.*, 2004; Palefsky, 1991, 2003; Piketty *et al.*, 2003, 2004; Silverberg *et al.*, 2002; Strickler *et al.*, 2003; Williams *et al.*, 1994). For example, a study by Silverberg *et al.* (2002) found that HIV-seropositive women were 3.2-fold more likely to present with genital warts than HIV-seronegative women. Malignancies as complications are an increasing cause of morbidity of HIV-infected individuals (Patil *et al.*, 1995; Thomas, 2001). The EBV-induced malignancy, NHL, occurs at a rate of 2.9% in AIDS patients, ~60 times the average in non-AIDS patients (Beral *et al.*, 1991). Occurrences of AIDS-related KS still occur at elevated levels, but recent advances in detection and stage analysis has improved the prognosis for HIV-positive patients (Quinlivan *et al.*, 2002). Likewise, an improved understanding of the HPV disease process, as it relates to HIV, is essential, since antiretroviral therapy in HIV-positive individuals has not been shown to effectively reverse HPV-related disease.

The association of malignancies, such as NHL and KS, has been recognized since the beginning of the HIV epidemic, and KS is the neoplasm most commonly found in people infected with HIV. These neoplasms are responsible for extensive morbidity and mortality. In Zambia and other sub-Saharan nations, cervical cancer is the most common cancer (Baay *et al.*, 2004; Hawes *et al.*, 2003; Xi *et al.*, 1998, 2003). Although in Africa, public education campaigns about STDs and condoms have been instituted in urban areas, there has been little success in poorer rural areas (Agha and Kusanthan, 2003). Thus, combined with endemic HIV, a high prevalence of high-risk HPVs presents a great risk for progression of dysplasias to cancer.

Infection by high-risk HPVs, especially HPV16, can induce warts; low-grade dysplasias, CIN, CIN 1 and CIN 2 designations are reversible forms of precancerous lesions (Fig. 3). Integration of the HPV

genome can lead to an increase of expression of E6 and E7 resulting in progression to CIN 3, which is irreversible. Accumulation of mutations in cellular genes results in permanent changes in cell character leading to invasive carcinoma *in situ*. Progression from a benign cervical lesion to invasive cervical cancer usually occurs years after infection.

Cervical cancer and precancerous lesions (CIN) are now the most common cancer-related affliction affecting women in sub-Saharan Africa and other developing countries in the world. The rates of cervical cancer in Africa are fourfold higher in than in North America and Europe.

E. The Mechanism of HPV-Induced Transformation and Cancer Progression

High-risk HPVs (types 16, 18, and 31 for example) are often found integrated into the host genome (Yee *et al.*, 1985a). The integrated state of the viral genome is not supportive of the viral life cycle, but can confer a growth advantage to cells due to increased expression of E6 and E7 (Jeon *et al.*, 1995). The common feature in cancers is the expression of E6 and E7 genes which functionally inactivate p53 and Rb, respectively (Durst *et al.*, 1987; Howley *et al.*, 1989; Munger *et al.*, 1989) (Fig. 4). In oncogenic HPV strains, E6 and E7 oncoproteins can block the negative growth signaling pathways of the cell via interactions with p53 and pRB tumor suppressor proteins. As a result, high-risk HPV-infected cells proliferation become disregulated and then, transformation develops. The full-length HPV E6 genes encode a 160amino acids protein, which contains two domains including zinc binding Cys-X-X-Cys motifs. High-risk HPV E6 proteins both have antiapoptotic activities and can interfere with the antiproliferative functions of p53, the cellular tumor suppressor. For this to occur, E6 first forms a complex with a cellular ubiquitin-protein ligase E6AP, the E6/E6AP complex then acts as a p53-specific ubiquitin-protein ligase to accelerate degradation of p53. E6 is also known to induce expression of human telomerase (htert), leading to the functional outcome of increased life span of infected keratinocytes. Upregulation of htert is also hallmark of a number of human cancers. Although the mechanism by which E6 suppresses cell death is established, relatively little is known about the localization of E6 proteins and its related splice products and how this relates to these functional interactions. Furthermore, the localization of E6AP in normal and E6-expressing cells is essentially unknown. Also, unknown is whether interactions and localization changes between E6 and htert alter E6 function.

E7 binds Rb family member proteins resulting in their displacement from E2F and eventual degradation. Release of E2F allows it to freely activate S-phase related genes responsible for the G1 to S transition. Just as E6 causes inactivation of p53, allowing unchecked DNA synthesis, E7, by releasing E2F, activates the expression of genes required for cellular DNA synthesis. Even if the cellular DNA is damaged, the lack of p53 allows the cell to survive through an E7-induced S-phase and replicate the viral genome.

The rate of advancement of HPV lesions, from benign hyperplasia to carcinoma *in situ*, is affected by additional factors, which includes immunocompetence. HIV status, directly affects immune status which determines susceptibility to secondary infections, including HPV. In addition, progression of HPV tumors are affected by HIV status since surveillance of cancer cells is impaired. It is well established that cofactors in addition to immune status, such as alcohol, drugs, smoking, oral contraceptives, and hormone levels influence HPV infection and progression of HPV-induced cancers (Fig. 5). The ability of E6 and E7 of high-risk HPVs to inactivate p53 and pRb directly correlates with the probability to develop tumors. HPV coinfection, variants, genome integration, as well as other STDs affect the propensity for HPV-induced cancer to occur and progress.

HPV-related diseases are common causes of morbidity and mortality, both in the United States and worldwide. During the year of 2006, the American Cancer Society (ACS) estimated that there were 9,710 new cases of cervical carcinoma and 3,700 cervical cancer deaths in the United States. The ACS

estimates that there were 4,660 new anal cancers with 660 deaths and 1,470 new penile cancers with 280 deaths (ACS, 2006). There were ~6,000 new cases of oral and pharyngeal cancers with 1,400 deaths are attributable to HPV infection. In developing countries, the second greatest cancer cause of death among women is cervical cancer. Still, there are few effective antiviral therapies for prevention or treatment of HPV-related diseases. Furthermore, while the quadrivalent VLP HPV vaccine has the longterm potential to reduce HPV-induced cancers by 70%, population-based studies indicate that, until all girls are immunized prior to the onset of sexual activity, the vaccine will prevent only 30-50% of cervical malignancies. More of a concern is the lack of availability of the prophylactic vaccine in countries which are afflicted with high rates of cervical cancer. Thus, we will continue to face a great deal of cervical cancer morbidity and mortality in the years to come. We are far from eliminating the need for treatments for HPV infection and HPV-induced anogenital dysplasias and cancers. Hence, the continuing need for research into papillomavirus pathogenesis especially in the context of the ongoing HIV crisis.

VIII. Conclusions

AIDS malignancies have been a major complication of the HIV disease course, and this is likely to continue in HIV-infected individuals. In the era of HAART therapy, the survival rate of the HIV-infected individuals has increased dramatically mainly because of the suppression of HIV viral load and the restoration of the immune response. However, even though HAART appears to be effective, still only leads to partial immune reconstitution. Prolonged immunosuppression will likely lead to a resurgence of AIDS-associated cancers. This coupled with the fact that there are still over 40 million individuals living with HIV today, many of whom are located in regions of the world where HAART is still not widely available, such as the African continent. It is expected that AIDS-associated cancers will continue to pose a major challenge globally for many years to come. As described earlier in this chapter, many of the cancers associated with immunosuppressed individuals are those that were found to have viral etiology. Other than the development and refinement of effective vaccines against these viruses, as in the case of HPV, there is a need for a better understanding on the role of oncogenic viral cofactor in the disease, the potential mechanisms, the viral genes and the host immune response that are involved. This knowledge will lead to the development of better strategies that could prevent infection and the malignant transformation by these potentially oncogenic viruses.

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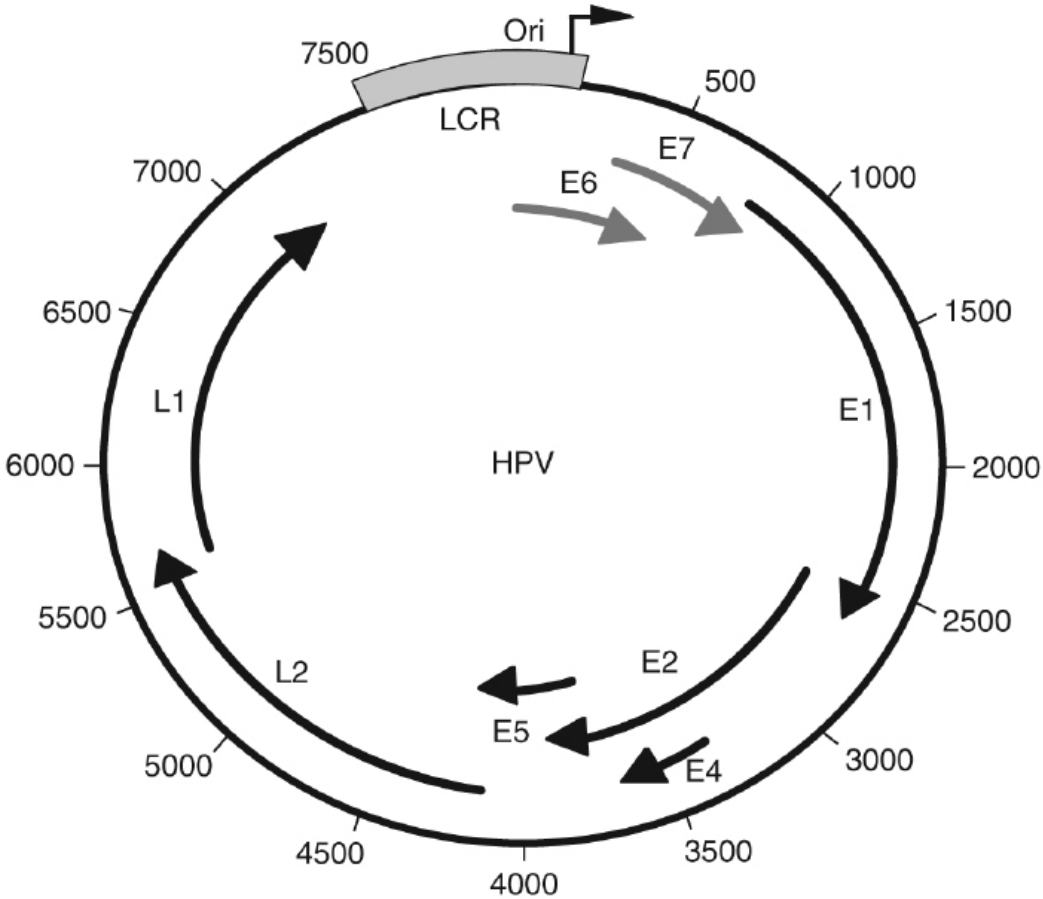

Figure 1.
The HPV genome is a 7.9 kb double-stranded circular genome. The genome is controlled by a single keratin-dependent promoter element; the long control region (LCR; *in blue*). At the 3'end of the LCR is the origin of replication (*nucleotide position 1*). E6, E7 (*red*), and E5 are viral oncogenes; E1 and E2 early genes encode replication proteins. The E4 ORF is actually expressed early and late in the viral life cycle. The late genes, L1 and L2, are the major and minor capsid genes, respectively. The viral protein functions are detailed in Table I.

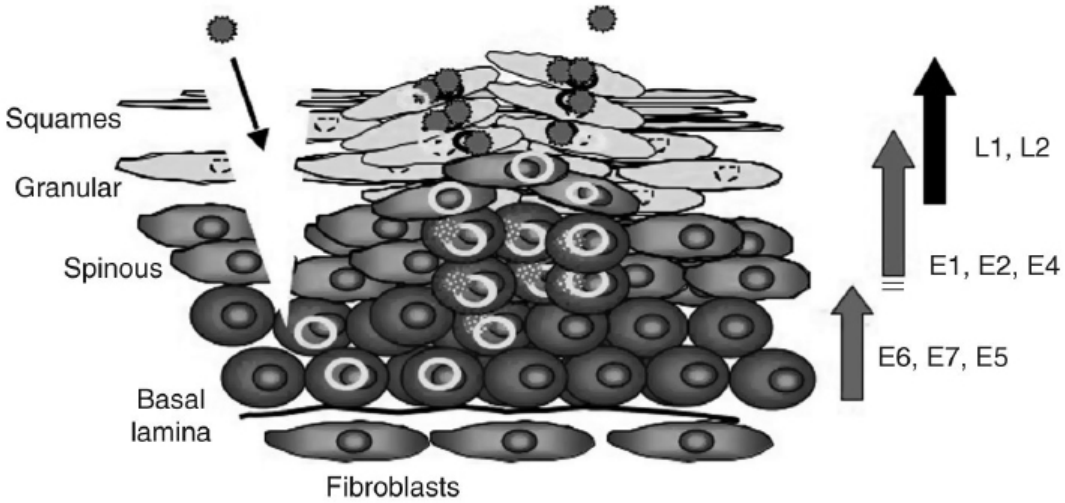

Figure 2.
The HPV life cycle. Virions enter the stratified epithelium through a site of wounding, where they gain access to the mitotically active basal-layer keratinocytes. During the maintenance phase, expression of E6, E7, and E5 induces cell proliferation, and the viral genome is replicated extrachromosomally at low-copy number (5-50 copies per cell). As the cells differentiate, the expression level of E1, E2, and E4 increases in the spinous layer. A transition from theta to rolling-circle replication results in an increase in copy number up to 100-1000 copies per cell. Postamplification, high levels of L1 and L2 capsid genes are expressed and capsid assembly occurs in the granular and squamous layers of the stratified epithelium. Progeny virus is released by desquamation.

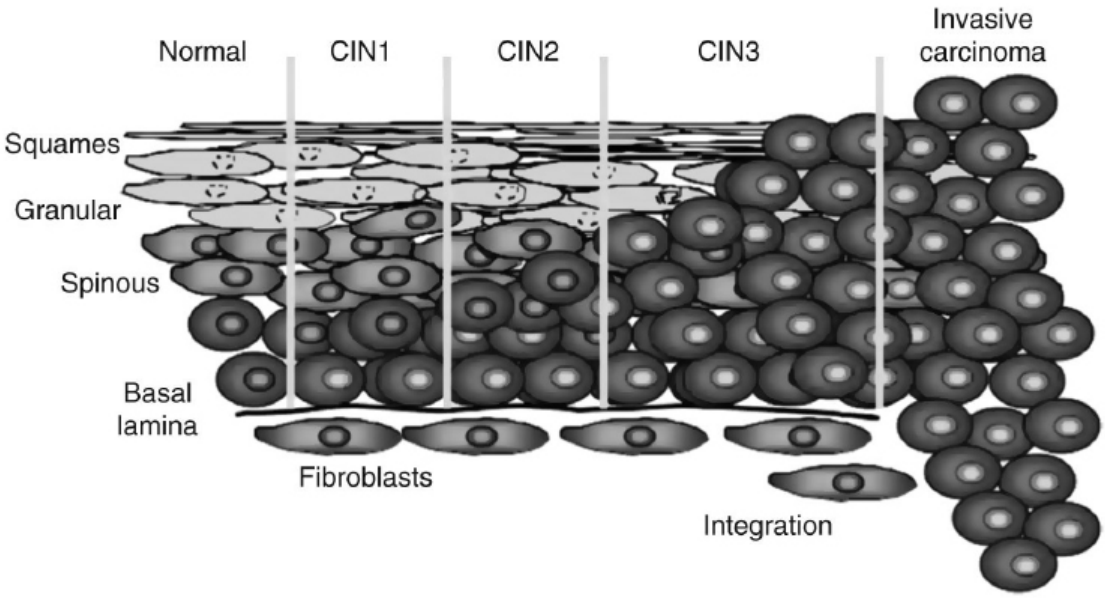

Figure 3.
Progression from a benign cervical lesion to invasive cervical cancer. In the diagram, HPV-positive cells are depicted by yellow nuclei. Infection by oncogenic HPV types, especially HPV16, can cause formation of a benign wart, low or high-grade dysplasia- r. CIN 1 and CIN 2 designations are reversible forms of precancerous lesions and CIN 3 is irreversible. Carcinoma *in situ* occurs many years after an infection. This results from the effects of HPV genes, particularly those encoding E6 and E7, which are the two viral oncoproteins that are preferentially retained and expressed in cervical cancers by integration of the viral DNA into the host genome.

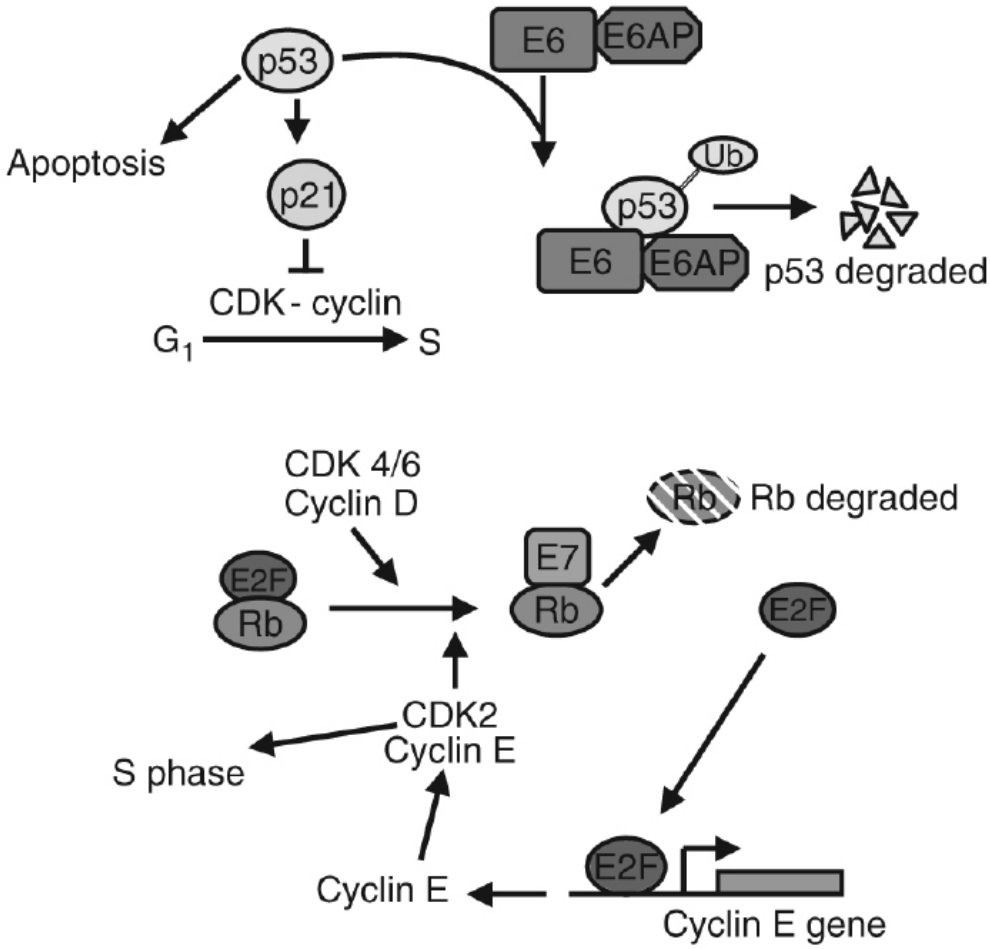

Figure 4.
Diagram of the role of E6 and E7 in disregulation of the cell cycle. Expression of E6 leads to recruitment of E6AP (a ubiquitin ligase). This complex causes degradation of p53, which then inhibits the p21-dependent block of the G1 to S transition. Similarly, E7 binding to Rb displaces E2F, resulting in Rb's degradation. E2F can then activate expression of cyclin E and other S-phase related gene products.

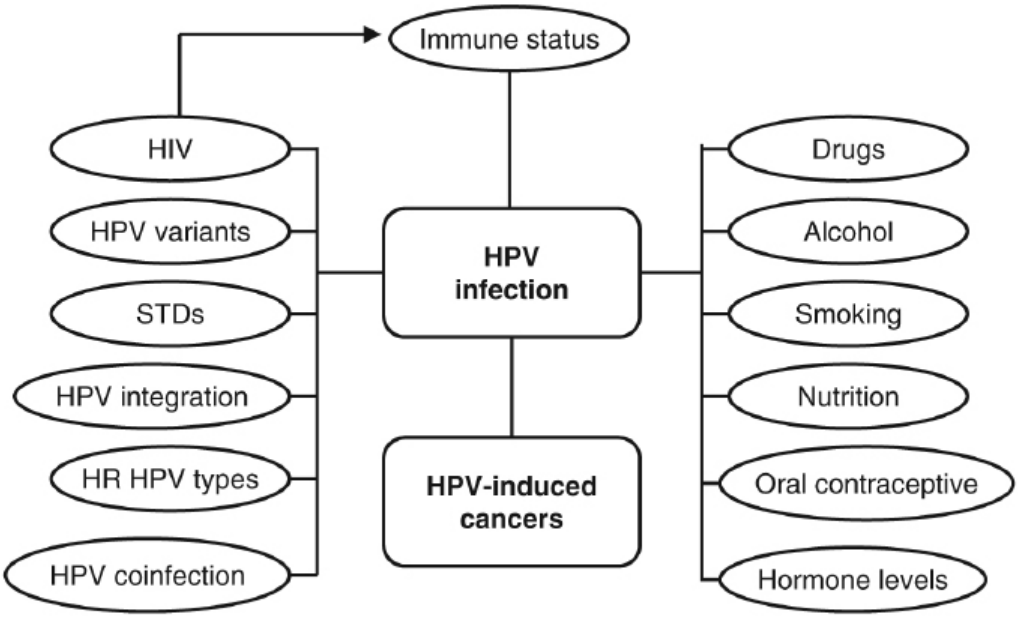

Figure 5.
The rate of advancement of HPV lesions, from benign hyperplasia to carcinoma *in situ*, is affected by additional factors, which includes immunocompetence. HIV status, alcohol, drugs, smoking, oral contraceptives, and hormone levels influence HPV infection and progression of HPV-induced cancers. High-risk HPVs, HPV coinfection, variants, genome integration, and infection of other STDs affect the propensity for HPV-induced cancer to occur and progress.

TABLE I

Potential KSHV Genes Involved in Tumorigenesis

Viral gene	*Function*
K1 (KSHV open reading frame 1)	Signal transduction on receptor binding. Homologue of the herpesvirus saimiri STP transforming gene and is involved in the deregulation of NF-κB
K12 (Kaposin)	Two forms, Kaposin A and B. Kaposin A is a type II membrane protein; Kaposin B is involved in the MAPK signaling pathway
vGPCR (Viral G protein-coupled receptor)	Homologue of cellular IL-8 receptor and binds to CXC and CC chemokines. It stimulates MAPK pathway and leads to secretion of VEGF
vIL-6 (viral IL-6)	Homologue of cellular IL-6, it supports cell growth and protects the cells from undergoing apoptosis
K4, K4.1, and K6 (KSHV open reading frame 4, 4.1, and 6)	Viral homologues of cellular CC chemokines such as RANTES and MIP-1α. They induce signal transduction and enhance angiogenesis
vFLIP (viral FLICE-inhibitory protein or ORF71)	Homologue of cellular FLIP, it activates NF-κB pathway and protects cells from apoptosis
LANA (viral latency associated nuclear antigen)	Important in the maintenance of viral latency and binds to viral genome and a number of cellular factors, such as p53

TABLE II

Designation	*Function*
E6	Viral oncoprotein; functions by binding and degrading p53 tumor suppressor via activity of E6AP, ubiquitin ligase, resulting ubiquitin pathway-mediated degradation of p53, preventing apoptosis
E7	Nuclear oncoprotein; functions by binding and degrading of pRb family tumor suppressor products. This causes release of E2F that induces expression of S-phase-related genes
E1	An ATP-dependent DNA helicase; has double and single strand DNA-binding activities. Required for viral DNA replication; interacts with E2 protein and with DNA polymerase α. Significant structural homology to SV40 large Tantigen (Clertant and Seif, 1984; Mansky *et al.*, 1997; Seif, 1984). Sequence-specific DNA binding by E1 is mediated by the papillomavirus E2 protein; association of E1 with E2 enhances the affinity of E1 for DNA (Frattini and Laimins, 1994; Sedman and Stenlund, 1995)
E2	Binds a 12 base pair palindromic sequence: $ACCG(A)_4CGGT$ in the Ori and functions as a transcriptional activator; binds and recruits the E1 protein that stimulates initiation of DNA replication; E2 also functions in HPV genome maintenance by tethering newly synthesized DNAs to chromosomes during mitosis, which allows equal partitioning to daughter cells
E4	Expressed as a late protein; blocks cell cycle at G2/M; induces collapse of cytokeratin network; possibly promoting virus release; poorly conserved across HPV types
E5	A viral oncoprotein; binds EGF receptor; able to transform rodent cells in culture; membrane associated; functions include binding to β receptor for platelet-derived growth factor
L1	Major capsid protein
L2	Minor capsid protein