Non-Enveloped **DNA Viruses**:

Adenoviruses, Papillomaviruses Parvoviruses and Polyomaviruses

Papillomaviruses

Diseases

Human papillomavirus (HPV) causes papillomas, which are benign tumors of squamous cells, e.g., warts on the skin. Some HPV types, especially types 16 and 18, cause **carcinoma of the cervix and penis.**

Important Properties: Papillomaviruses are nonenveloped viruses with double-stranded circular DNA and an icosahedral nucleocapsid. Two of the early genes, **E6** and **E7,** are implicated in carcinogenesis. They encode proteins that inactivate proteins encoded by tumor suppressor genes in human cells, e.g., the p53 gene and the retinoblastoma (RB) gene, respectively. Inactivation of the p53 and RB proteins is an important step in the process by which a normal cell becomes a cancer cell.

There are at least 100 types of papillomaviruses, classified primarily on the basis of DNA restriction fragment analysis. There is a pronounced **predilection of certain types to infect certain tissues.** For example, skin warts are caused primarily by HPV-1 through HPV-4, whereas genital warts are usually caused by HPV-6 and HPV-11. Approximately 30 types of HPV infect the genital tract.

Summary of Replicative Cycle: Little is known of the specifics of viral replication, because the virus grows poorly, if at all, in cell culture. In human tissue, infectious virus particles are found in the terminally differentiated squamous cells rather than in the basal cells. Note that HPV initially infects the cells of the basal layer in the skin but no virus is produced by those cells. Rather, infectious virions are produced by squamous cells on the surface, which enhances the likelihood that efficient transmission will occur.

In malignant cells, viral DNA is integrated into host cell DNA in the vicinity of cellular proto-oncogenes, and E6 and E7 are overexpressed. However, in latently infected, nonmalignant cells, the viral DNA is episomal and E6 and E7 are not overexpressed. This difference occurs because another early gene, E2, controls E6 and E7 expression. The E2 gene is functional when the viral DNA is episomal but is inactivated when it is integrated.

Transmission & Epidemiology: Papillomaviruses are transmitted primarily by skin-to-skin contact and by genital contact. Genital warts are among the **most common sexually transmitted diseases.** Skin warts are more common in children and young adults and tend to regress in older adults. HPV transmitted from an infected mother to the neonate during childbirth causes warts in the mouth and in the respiratory tract, especially on the larynx, of

the infant. Many species of animals are infected with their own types of papillomaviruses, but these viruses are not an important source of human infection.

Pathogenesis & Immunity: Papillomaviruses infect squamous epithelial cells and induce within those cells a characteristic cytoplasmic vacuole. These vacuolated cells, called **koilocytes,** are the hallmark of infection by these viruses. Most warts are benign and do not progress to malignancy. However, HPV infection is associated with carcinoma of the uterine cervix and penis. The proteins encoded by viral genes E6 and E7 interfere with the growth-inhibitory activity of the proteins encoded by the p53 and RB tumor suppressor genes and thereby contribute to oncogenesis by these viruses. The E6 and E7 proteins of HPV type 16 bind more strongly to p53 and RB proteins than the E6 and E7 proteins of HPV types not implicated in carcinomas—a finding that explains why type 16 causes carcinomas more frequently than the other types.

Both cell-mediated immunity and antibody are induced by viral infection and are involved in the spontaneous regression of warts. Immunosuppressed patients, e.g., AIDS patients, have more extensive warts, and women infected with HIV have a very high rate of carcinoma of the cervix.

Clinical Findings

Papillomas of various organs are the predominant finding. These papillomas are caused by specific HPV types. For example, skin and plantar warts are caused primarily by HPV-1 through HPV-4, whereas genital warts (**condylomata acuminata**) are caused primarily by HPV-6 and HPV-11. HPV-6 and HPV-11 also cause respiratory tract papillomas, especially laryngeal papillomas, in young children.

Carcinomas of the uterine cervix, the penis, and the anus, as well as premalignant lesions called intraepithelial neoplasia, are associated with infection by HPV-16 and HPV-18. Occult premalignant lesions of the cervix and penis can be revealed by applying acetic acid to the tissue. HPV-16 is also implicated as the cause of oral cancers.

Laboratory Diagnosis

Infections are usually diagnosed clinically. The presence of koilocytes in the lesions indicates HPV infection. DNA hybridization tests to detect the presence of viral DNA are commercially available. Diagnostic tests based on detection of antibodies in a patient's serum or on isolation of the virus from a patient's tissue are not used.

Treatment & Prevention: The usual treatment for genital warts is podophyllin; alpha interferon is also effective and is better at preventing recurrences than are non-antiviral treatments. Liquid nitrogen is commonly used for skin warts. Plantar warts can be removed surgically or treated with salicylic acid topically. Cidofovir may be useful in the treatment of severe HPV infections.

A recombinant vaccine against four types of HPV was approved by the FDA in 2006. The vaccine, called Gardasil, contains the capsid proteins of types 6 and 11, which cause genital warts, and types 16 and 18, which are the two most common causes of cervical carcinoma. It

is approved for use in female's patients between the ages of 9 and 26 years. The role of cesarean section in preventing transmission of HPV from a mother with genital warts to her newborn is uncertain. Circumcision reduces the risk of infection by HPV.

Polyomaviruses

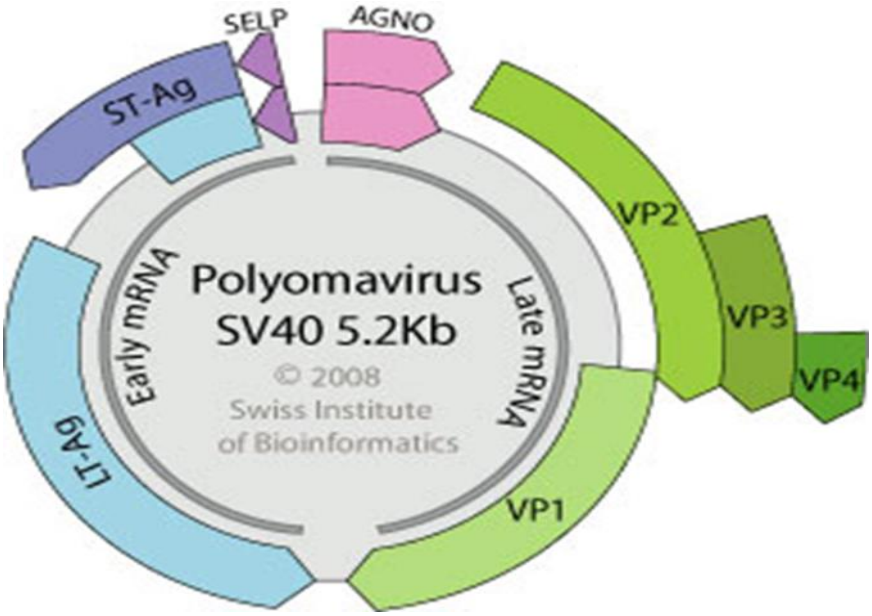
Polyomaviruses are small viruses (diameter 45 nm) that possess a circular genome of double-stranded DNA (5 kbp; molecular weight 3 × 106) enclosed within a non-enveloped capsid exhibiting icosahedral symmetry .Cellular histones are used to condense viral DNA inside virus particles.

Multiple species have been identified, including the tumor virus SV40 and others known to infect humans (BK, JC, KI, WU, MCV, HPyV6, HPyV7, HPyV10, and TSV). Many species of mammals and some birds have been found to carry their own species of polyomavirus.

Polyomavirus Replication

The polyomavirus genome contains “early” and “late” regions .The early region is expressed soon after infection of cells; it contains genes that code for early proteins—for example, the SV40 large tumor (T) antigen, which is necessary for the replication of viral DNA in permissive cells, and the small tumor (t) antigen. The late region consists of genes that code for the synthesis of coat protein.

SV40 T antigen interacts with the cellular tumor suppressor gene products, p53 and pRb family members. Interactions of T antigen with the cellular proteins are important in the replicative cycle of the virus. This complex formation functionally inactivates the growth-inhibitory properties of pRb and p53, allowing cells to enter S phase so that viral DNA may be replicated.



Pathogenesis and Pathology

There are two members of the polyomavirus family that infect humans, JC virus and BK virus, and one member, **SV40 virus**, that is primarily a monkey virus but can infected humans.

The human polyomaviruses BK and JC are widely distributed in human populations, as evidenced by the presence of specific antibody in 70–80% of adult sera. Infection usually occurs during early childhood. Both viruses may persist in the kidneys and lymphoid tissues of healthy individual's after primary infection and may reactivate when the host's immune response is impaired, for example, by renal transplantation, during pregnancy, or with increasing age.

BK virus acquire infection during childhood and remain latent in kidney, lymphocytes and brain. It cause hemorrhagic cystitis in bone marrow transplant recipients. It is the cause of polyomavirus-associated nephropathy in renal transplant recipients, a serious disease that occurs in up to 5% of recipients and that results in graft failure in up to 50% of those affected patients.

JC virus is the cause of progressive multifocal leukoencephalopathy, a fatal brain disease that occurs in some immunocompromised persons, especially those with depressed cell-mediated immunity .

SV40 DNA has been detected in selected types of human tumors, including brain tumors, mesotheliomas, bone tumors, and lymphomas. The role SV40 may be playing in formation of human cancers is unknown.

Merkel virus: The Merkel virus was newly discovered in 2008 from several cases of a rare and aggressive type of skin cancer called *Merkel cell cancer*.