UNIT 3A -ONCOVIRUS

human cancer, malignancy is defined as the ability of cells to grow progressively and kill their host. For this to happen, it is necessary for a solid tumor to acquire several hallmark biological capabilities during the process of multistep development of the tumor. These include a sustained proliferative capacity, the ability to induce new angiogenesis, invasion, and metastasis.

The notion that viruses have a role in the etiology of malignancy originated from the studies published in 1911 by Peyton Rous, who reported a filterable agent (Rous sarcoma virus [RSV]) in cell extracts of a chicken tumor that could transmit the tumor into healthy chickens . The discovery of this retrovirus opened up the field of tumor virology, demonstrating that some cancers could have an infectious etiology and eventually leading to the discovery of oncogenes. In the 1930s, two tumor viruses were described in mammals, suggesting the possibility that viruses may play a similar causal role in human cancers.

In humans, the first tumor viruses were discovered in the 1960s and 1970s. Epstein-Barr virus (EBV) (also called human herpesvirus 4 [HHV-4]) was first observed in cells cultured from Burkitt's lymphoma by electron microscopy, marking the starting point of human tumor virology.

Oncogenic viruses are significant pathogens for humans, farm animals, and pets. These pathogens are classified into different virus families such as Hepadnaviridae, Flaviviridae, and Retroviridae.

Members of six distinct families of animal viruses, called **tumor viruses**, are capable of directly causing cancer in either experimental animals or humans.

viruses belonging to five of these families have DNA genomes and are referred to as DNA tumor viruses. Members of the sixth family of tumor viruses, the retroviruses, have RNA genomes in virus particles but replicate via synthesis of a DNA provirus in infected cells. The viruses that cause human cancer include hepatitis B virus (liver cancer), papillomaviruses (cervical and other anogenital cancers), Epstein-Barr virus (Burkitt's lymphoma and nasopharyngeal carcinoma), Kaposi's sarcoma-associated herpesvirus (Kaposi's sarcoma), and human T-cell lymphotropic virus (adult T-cell leukemia). In addition, HIV is indirectly responsible for the cancers that develop in AIDS patients as a result of immunodeficiency, and hepatitis C virus (an RNA virus) is an indirect cause of liver cancers resulting from chronic tissue damage.

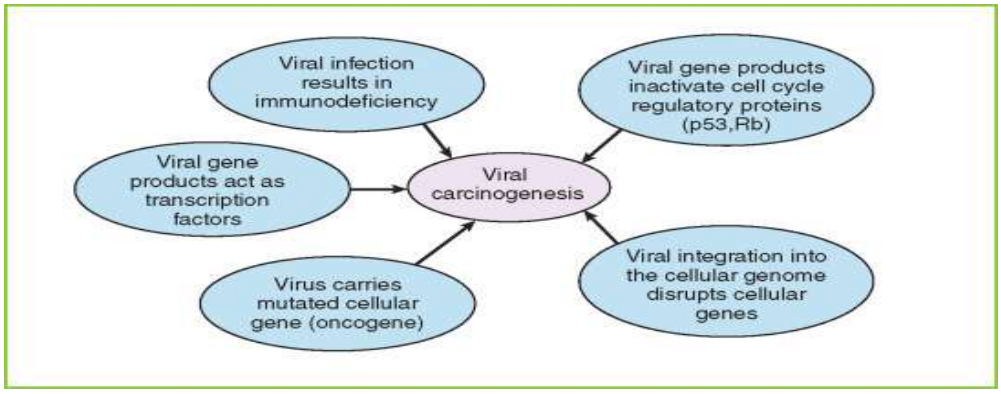
Virus family	Human tumors	Genome size (kb)
DNA tumor viruses		
Hepatitis B viruses	Liver cancer	3
SV40 and polyomavirus	None	5
Papillomaviruses	Cervical carcinoma	8
Adenoviruses	None	35
Herpesviruses	Burkitt's lymphoma, nasopharyngeal carcinoma, Kaposi's sarcoma	100–200
RNA tumor viruses		
Retroviruses	Adult T-cell leukemia	9

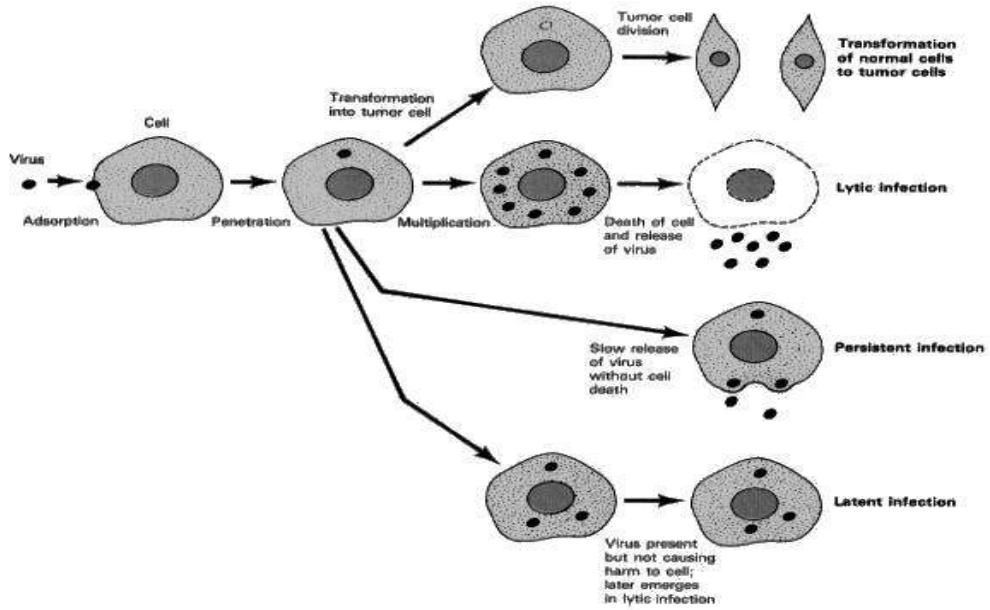
General mechanism of oncovirus

Oncogenic viruses (tumor viruses) consist of both DNA and RNA viruses. Unlike RNA tumor viruses, DNA tumor virus oncogenes encode viral proteins necessary for viral replication. RNA tumor viruses carry changed variants of normal host cell genes, which are not necessary for viral replication. Oncogenic viruses promote cell transformation, prompt uncontrollable cell generation, and lead to the development of malignant tumors . All malignant tumors are called cancer. Oncogenic abnormalities are seen in pediatric leukemias, lymphomas, and various solid tumors.

Virus-promoted malignant transformations in cells are the first step in the complex oncogenesis process . The genes in the viral genome that change host cell proliferation control, lead to the synthesis of new proteins, and are responsible for transformation characteristics are called viral oncogenes (v-onc genes).

Oncogenic viruses Oncogenic viruses can be divided into 2 groups, based on their genetic material, as DNA and RNA tumor viruses. DNA tumor viruses DNA tumor viruses have 2 life forms. In permissive cells, viral replication causes cell lysis and cell death. In nonpermissive cells, viral DNA is mostly integrated into the different sites of cell chromosomes. It encodes binding proteins and inactivates cell growth, regulating proteins like p53 and retinoblastoma. The cell is transformed as a result of the expression of proteins that control viral and cellular DNA synthesis. RNA tumor viruses All oncogenic RNA viruses are retroviruses. In 1961, it was found that Rous sarcoma virus (RSV) particles contain RNA; thus, oncogenic retroviruses were called RNA tumor viruses). In retroviruses, more than 30 oncogenes were defined. Retroviruses have 3 basic genes (gag, pol, and env), which are used for the synthesis of structural proteins, virion-associated enzymes, and envelope glycoproteins. Complex retroviruses such as lentiviruses have an extra nonstructural gene (v-onc) that allows them to transform the cell . For example, this fourth gene in the RSV is the v-scr (sarcoma) gene. RSV gains this cellular origin gene aft er infecting cells. In tumor development, RNA tumor viruses use diff erent oncogenic mechanisms. Some encode oncogenic proteins, which are similar to the cellular proteins in cellular growth control. Overproduction of these oncogenic materials or modifi cation in their functions stimulates cellular proliferation. These RNA viruses can cause rapid tumor development. The second group of retroviruses integrates their promoter sequences and viral enhancers near the cellular growth-stimulating gene and initiates cell transformation. The third group of RNA tumor viruses encodes a protein tax that transactivates the expression of cellular genes The infection of permissive cells with RNA tumor viruses causes the release of progeny virus from the cell surface through budding, and permanent genetic mutations transform the infected cell into cancer (3). When the virus is integrated into the cell chromosome, it falls under the control of the cell's regulator genes and can remain in the cell without causing any harmful effects. Such retroviruses are called endogenous retroviruses. If cells that carry such a virus are exposed to various mutagenic or cancerogenic factors (irradiation, mutagenic, or cancerogenic chemicals; hormonal or immunological stimulations; etc.), the virus is activated and starts to proliferate.





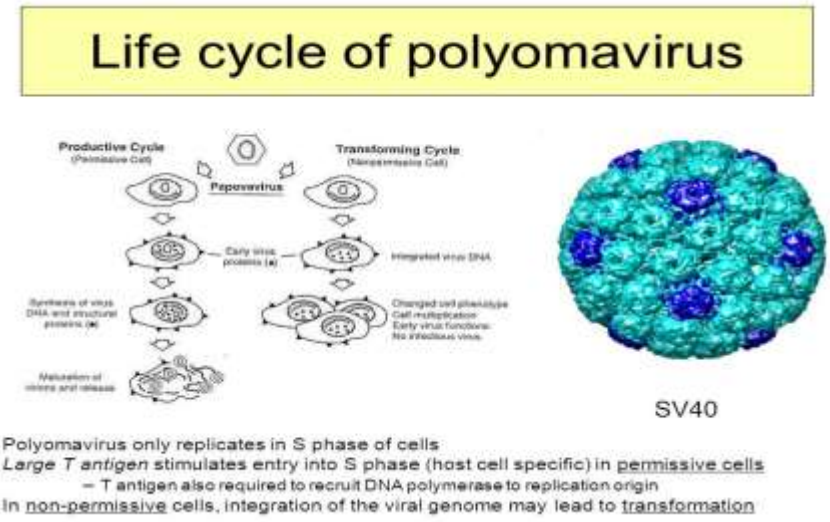
Hepatitis B Viruses

The **hepatitis B viruses**, which have the smallest genomes (approximately 3 kb) of all animal DNA viruses, specifically infect liver cells of several species, including ducks, woodchucks, squirrels, and humans. Infection with hepatitis B virus usually results in acute liver damage. In 5 to 10% of cases, however, the acute infection is not resolved and a chronic infection of the liver develops. Such chronic infection is associated with more than a hundredfold increased risk of liver cancer. Hepatitis B virus infection is particularly common in parts of Asia and Africa, where it is associated with up to a million cases of liver cancer annually (approximately 10% of worldwide cancer incidence).

Cell transformation by hepatitis B virus is mediated by a viral gene (called the *X* gene) that affects expression of a variety of cellular genes that drive abnormal cell proliferation and survival. In addition, the development of cancers induced by hepatitis B virus is driven by the continual proliferation of liver cells that results from chronic tissue damage.

SV40 and Polyomavirus

The best studied DNA tumor viruses, from the standpoint of molecular biology, are probably **simian virus 40** (**SV40**) and **polyomavirus**. Although neither of these viruses is associated with human cancer, they have been critically important as models for understanding the molecular basis of cell transformation. The utility of these viruses in cancer research has stemmed from the availability of good cell culture assays for both virus replication and transformation, as well as from the small size of their genomes (approximately 5 kb).SV40 and polyomavirus do not induce tumors or transform cells of their natural host species—monkeys and mice, respectively. In cells of their natural hosts (permissive cells), infection leads to virus replication, cell lysis, and release of progeny virus particles (Figure 15.13). Since a permissive cell is killed as a consequence of virus replication, it cannot become transformed. The transforming potential of these viruses is revealed, however, by infection of nonpermissive cells, in which virus replication is blocked. In this case, the viral genome sometimes integrates into cellular DNA, and expression of specific viral genes results in transformation of the infected cell.The SV40 and polyomavirus genes that lead to cell transformation have been identified by detailed molecular analyses. The viral genomes and mRNAs have been completely sequenced, viral mutants that are unable to induce transformation have been isolated, and the transforming potentials of individual viral genes have been determined by gene transfer assays. Transformation by these viruses has thus been found to result from expression of the same viral genes that function in early stages of lytic infection. The genomes of SV40 and polyomavirus are divided into early and late regions. The early region is expressed immediately after infection and is required for synthesis of viral DNA. The late region is not expressed until after viral DNA replication has begun, and includes genes encoding structural components of the virus particle. The early region of SV40 encodes two proteins, called small and large T antigens, of about 17 kd and 94 kd, respectively (Figure 15.14). Their mRNAs are generated by alternative splicing of a single early-region primary transcript. Polyomavirus likewise encodes small and large T antigens, as well as a third early-region protein of about 55 kd, designated middle T. Transfection of cells with cDNAs for individual early-region proteins has shown that SV40 large T is sufficient to induce transformation, whereas middle T is primarily responsible for transformation by polyomavirus.



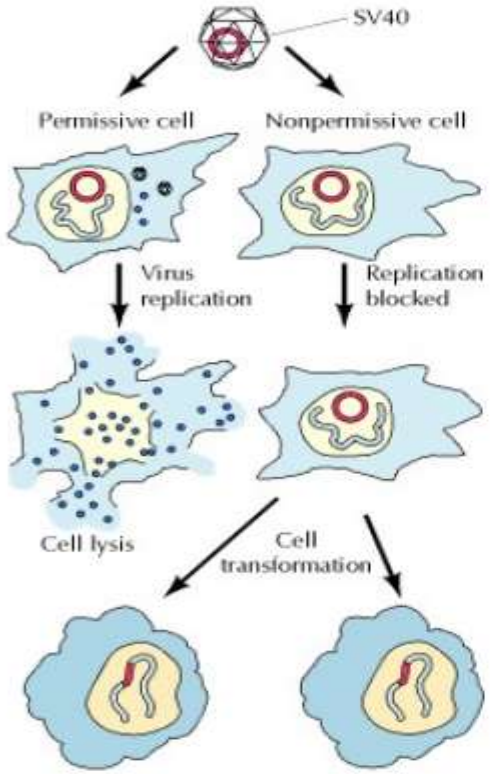


Figure 15.13 SV40 replication and transformation

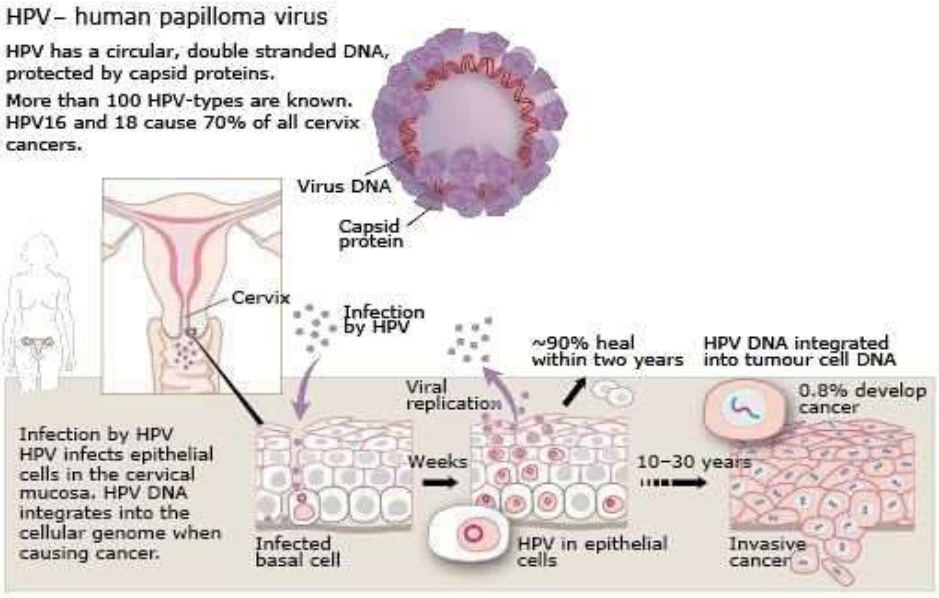
During lytic infection, these early-region proteins fulfill multiple functions required for virus replication. SV40 T antigen, for example, binds to the SV40 origin and initiates viral DNA replication (see Chapter 5). In addition, the early-region proteins of SV40 and polyomavirus stimulate host cell gene expression and DNA synthesis. Since virus replication is dependent on host cell enzymes (e.g., DNA polymerase), such stimulation of the host cell is a critical event in the viral life cycle. Most cells in an animal are nonproliferating, and therefore must be stimulated to divide in order to induce the enzymes needed for viral DNA replication. This stimulation of cell proliferation by the early gene products can lead to transformation if the viral DNA becomes stably integrated and expressed in a nonpermissive cell.

As discussed later in this chapter, both SV40 and polyomavirus early-region proteins induce transformation by interacting with host proteins that regulate cell proliferation. For example, SV40 T antigen binds to and inactivates the host cell tumor suppressor proteins Rb and p53, which are key regulators of cell proliferation and cell cycle progression

Papillomaviruses

The **papillomaviruses** are small DNA viruses (genomes of approximately 8 kb) that induce both benign and malignant tumors in humans and a variety of other animal species. Approximately 60 different types of human papillomaviruses, which infect epithelial cells of several tissues, have been identified. Some of these viruses cause only benign tumors (such as warts), whereas others are causative agents of malignant carcinomas, particularly cervical and other anogenital cancers. The mortality from cervical cancer is relatively low in the United States, in large part as a result of early detection and curative treatment made possible by the Pap smear. In other parts of the world, however, cervical cancer remains common; it is responsible for 5 to 10% of worldwide cancer incidence.

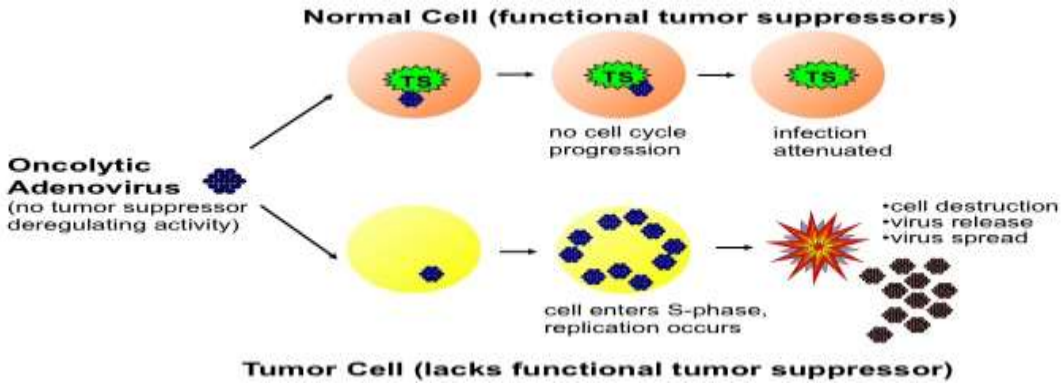
Cell transformation by human papillomaviruses results from expression of two early-region genes, *E6* and *E7* (Figure 15.15). The E6 and E7 proteins act analogously to SV40 T antigen by interfering with the function of the cellular Rb and p53 proteins. In particular, E7 binds to Rb, and E6 stimulates the degradation of p53 by ubiquitin-mediated proteolysis.



Adenoviruses

The **adenoviruses** are a large family of DNA viruses with genomes of about 35 kb. In contrast to the papillomaviruses, the adenoviruses are not associated with naturally occurring cancers in either humans or other animals. However, they are widely studied and important models in experimental cancer biology.

Like SV40 and polyomaviruses, the adenoviruses are lytic in cells of their natural host species, but can induce transformation in nonpermissive hosts. Transformation by the adenoviruses results from expression of two early genes, *E1A* and *E1B*, which are required for virus replication in permissive cells. These transforming proteins inactivate the Rb and p53tumor suppressor proteins, with E1A binding to Rb and E1B binding to p53. It thus appears that SV40, papillomaviruses, and adenoviruses all induce transformation by a common pathway, in which altering regulation of the cell cycle by interfering with the activities of Rb and p53 plays a central role.



Herpesviruses

The **herpesviruses** are among the most complex animal viruses, with genomes of 100 to 200 kb. Several herpesviruses induce tumors in animal species, including frogs, chickens, and monkeys. In addition, two members of the herpesvirus family, **Kaposi's sarcoma-associated herpesvirus** and **Epstein-Barr virus**, are associated with human cancers. Kaposi's sarcoma-associated herpesvirus plays a critical role in the development of Kaposi's sarcomas, and Epstein-Barr virus has been

implicated in several human malignancies, including Burkitt's lymphoma in some regions of Africa, B-cell lymphomas in AIDS patients and other immunosuppressed individuals, and nasopharyngeal carcinoma in China.

In addition to its association with these human malignancies, Epstein-Barr virus is able to transform human B lymphocytes in culture. Partly because of the complexity of the genome, however, the molecular biology of Epstein-Barr virus replication and transformation remains to be fully understood. Several viral genes required to induce transformation of lymphocytes have been identified, but their functions have not been established.

Go to:

Retroviruses

Members of one family of RNA viruses, the **retroviruses**, cause cancer in a variety of animal species, including humans. One human retrovirus, human T-cell lymphotropic virus type I (HTLV-I), is the causative agent of adult T-cell leukemia, which is common in parts of Japan, the Caribbean, and Africa. Transformation of T lymphocytes by HTLV-I results from expression of the viral gene *tax*, which encodes a regulatory protein affecting expression of several cellular growth control genes. AIDS is caused by another retrovirus, HIV. In contrast to HTLV-I, HIV does not cause cancer by directly converting a normal cell into a tumor cell. However, AIDS patients suffer a high incidence of some malignancies, particularly lymphomas and Kaposi's sarcoma. These cancers, which are also common among other immunosuppressed individuals, apparently develop as a secondary consequence of immunosuppression in AIDS patients.

Different retroviruses differ substantially in their oncogenic potential. Most retroviruses contain only three genes (*gag*, *pol*, and *env*) that are required for virus replication but play no role in cell transformation (Figure 15.17). Retroviruses of this type induce tumors only rarely, if at all, as a consequence of mutations resulting from the integration of proviral DNA within or adjacent to cellular genes.

Other retroviruses, however, contain specific genes responsible for induction of cell transformation and are potent carcinogens. The prototype of these highly oncogenic retroviruses is **Rous sarcoma virus (RSV)**, first isolated from a chicken sarcoma by Peyton Rous in 1911. More than 50 years later, studies of RSV led to identification of the first viral oncogene, which has provided a model for understanding many aspects of tumor development at the molecular level.

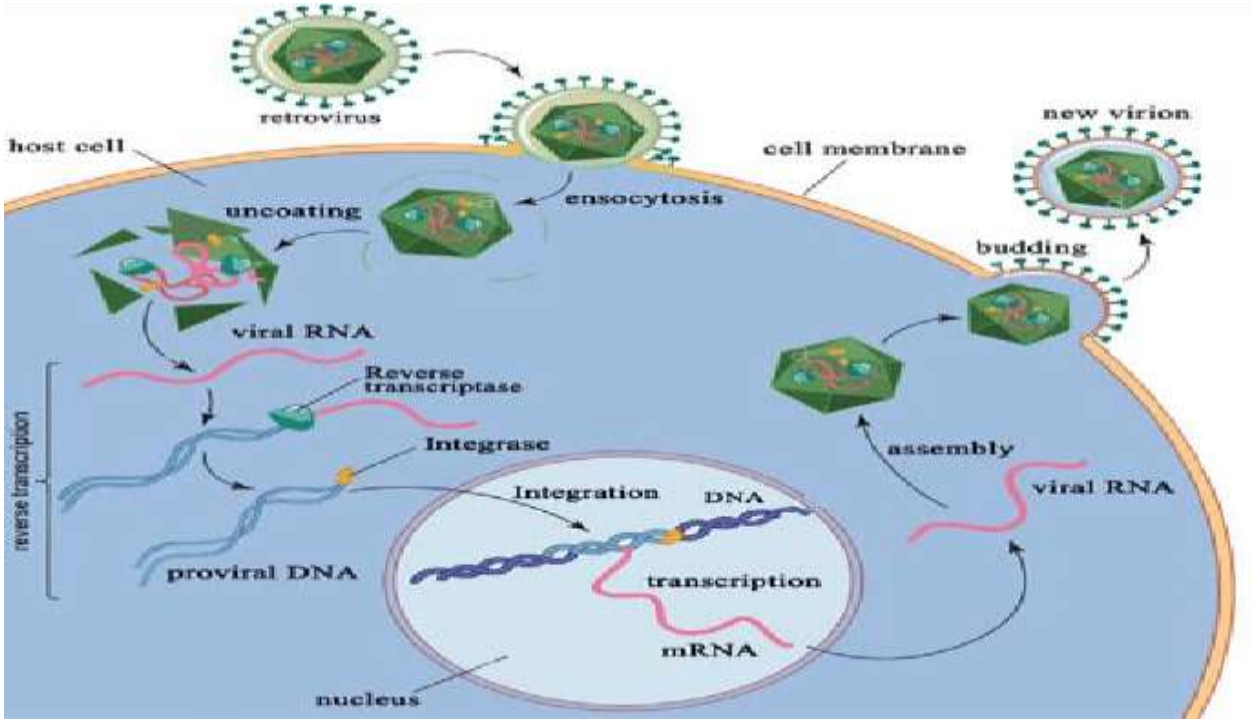


Table 1. Animal oncogenic DNA viruses.

Taxonomic grouping	Examples	Tumor types
Adenoviridae	BAV type 3	Various solid tumors
Hepadnaviridae	GSHV, WHV	Hepatocellular carcinoma
Herpesviridae	MDV, HVS	Lymphoma, carcinoma
Papillomaviridae	BPV types 1, 2, 4 CRPV	Papilloma, carcinoma, sarcoma, lymphoma
Polyomaviridae	MPYV, SV40	Various solid tumors
Poxviridae	FIBV, MYXV, RFV, SQFV	Myxoma, fibroma

BAV: Bovine adenovirus, GSHV: Ground squirrel hepatitis virus, WHV: Woodchuck hepatitis virus, MDV: Marek disease virus, HVS: Herpesvirus saimiri, BPV: Bovine papilloma virus, CRPV: Cottontail rabbit papillomavirus, MPYV: Murine polyomavirus, SV40: Simian virus 40, FIBV: Hare fibroma virus, MYXV: Myxoma virus, RFV: Rabbit fibroma virus, SQFV: Squirrel fibroma virus.

Table 2. Human oncogenic DNA viruses.

Taxonomic grouping	Examples	Tumor types
Adenoviridae	Adenovirus types 9, 12, 18, 31	Various solid tumors in rodents
Hepadnaviridae	HBV	Hepatocellular carcinoma
Herpesviridae	EBV	Burkitt's lymphoma
		Nasopharyngeal carcinoma
		B-cell lymphoma
		Hodgkin's lymphoma
	KSHV (HHV-8)	Kaposi's sarcoma
		Primary effusion lymphoma
		Multicentric Castleman's disease
Papillomaviridae	HPV types 6, 11, 16, 18, 31, 45	Oral, cervical, and anal cancer
Polyomaviridae	Merkel cell polyomavirus	Merkel cell carcinoma
	BK virus, JC virus	Solid tumors in rodents
Poxviridae	MCV	Various solid tumors

Table 4. Human oncogenic RNA viruses.

Taxonomic grouping	Examples	Tumor types
Retroviridae	HTLV type 1	Adult T-cell leukemia
Flaviviridae	Hepatitis C virus	Hepatocellular carcinoma

HTLV: Human T-cell leukemia virus.