

Oncogenic viruses (Human cancer viruses)

Cell growth: is the cell proliferation (the increase in cell numbers that occurs through repeated cell division). Cell growth is regulated by **two groups of regulatory genes:**

A. Proto-oncogenes (cellular oncogene, c-onc): Are normal genes which control cell proliferation, but which have the potential to contribute to cancer development if their expression is altered (changed into oncogenes). So Oncogenes are genes that cause cancer.

B- Tumor Suppressor Genes include genes that inhibit cell growth, fixing broken DNA or causing a cell to die. Examples: P53, Rb (retinoblastoma).

An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the activation (**turning on**) of **protooncogenes**, but tumor suppressor genes cause cancer when they are inactivated (**turned off**). In normal cells, oncogenes are “switched off” or down-regulated by antioncogene proteins.

An **oncovirus** is a virus that can cause cancer. It refers to any virus with a DNA or RNA genome causing cancer and also called "**tumor virus**" or "**cancer virus**".

- Most viruses are non-transforming - however, they may play a role in reducing the host cell's ability to inhibit apoptosis. virus that is able to cause cancer is known as an **oncogenic virus**. Evidence that a virus is oncogenic includes the regular presence in the tumour cells of virus DNA, which might be all or a part of the virus is possible that the virus is just one of a number of carcinogenic factors that can give rise to these cancers.

At least **15-20%** of all human tumors worldwide have a viral cause. The viruses that have been strongly associated with human cancers. Viruses are etiologic factors in the development of several types of human tumors, including two of great significance worldwide cervical cancer and liver cancer. **They include human papillomaviruses (HPVs), Epstein-Barr virus (EBV), human herpesvirus 8, hepatitis B virus, hepatitis C virus,** and two **human retroviruses** plus several **candidate human cancer** viruses. Many viruses can cause tumors in animals, either as a consequence of natural infection or after experimental inoculation.

CLASSES OF ONCOGENIC VIRUSES: There are two classes of tumor viruses:

DNA tumor viruses

1- Papovaviridae include human papilloma virus causes uterine (cervical) cancer.

2-polyomaviridae include JK, BK causes solid tumor in rodents and Merkel Cell Polyomavirus cause Merkel Cell Carcinoma (rare skin cancer).

3-Herpesviridae include a) **EBV** infection increases the risk of Burkitt lymphoma, Nasopharyngeal carcinoma and some types of Hodgkin's and non-Hodgkin's lymphoma also stomach cancer. b) **Kaposi's sarcoma-associated herpesvirus** (KSHV or HHV-8) is associated with Kaposi's sarcoma, a type of skin cancer. c) **Human cytomegalovirus** (CMV or HHV-5) is associated with mucoepidermoid carcinoma and possibly other malignancies.

4-Hepadnaviridae include Hepatitis B virus causes hepatocellular carcinoma.

5-Adenoviridae include adenovirus causes various solid tumor in rodents.

6- Poxviridae include Smallpox; cowpox causes various solid tumor.

RNA tumor Viruses also being referred to as **Retroviruses**.

1-Retroviridae include Human T-cell leukemia virus (HTLV-1; HTLV-2) which causes Adult T-cell leukemia, Lymphoma.

2-Flaviviridae include Hepatitis C Virus causes Hepatocellular carcinoma.

General Features of Viral Carcinogenesis

- 1- Viruses can cause cancer in animals and humans.
- 2- Tumor viruses frequently establish persistent infections in natural host.
- 3- Viruses are seldom complete carcinogens.
- 4- Host factors are important determinants of virus-induced tumorigenesis
5. Virus infections are more common than virus-related tumor formation.
6. Long latent periods usually elapse between initial virus infection and tumor appearance.
- 7- Viral strains may differ in oncogenic potential.
- 8- Viruses may be either direct- or indirect-acting carcinogenic agents.
- 9- Oncogenic viruses modulate growth control pathways in cells.
- 10- Animal models may reveal mechanisms of viral carcinogenesis.

How do viruses cause cancer?

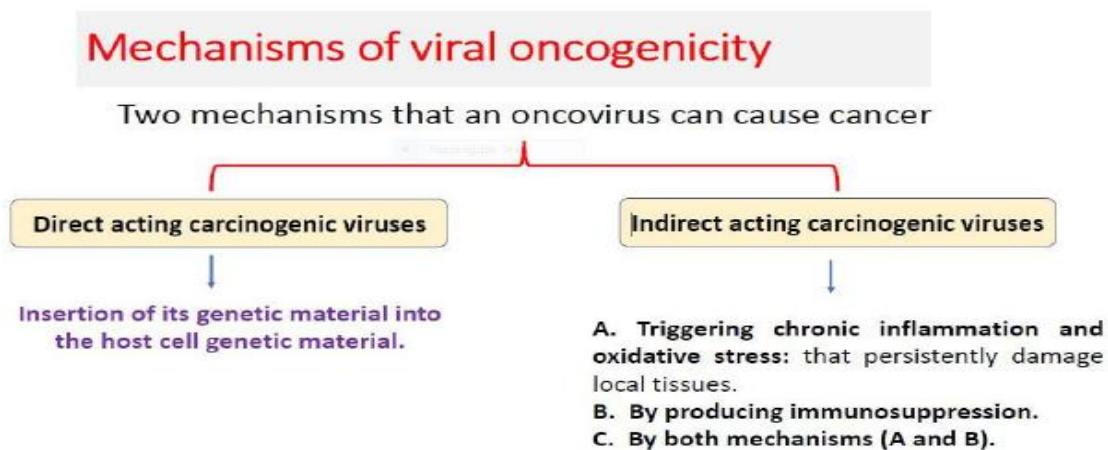
Viruses typically initiate cancer development by suppressing the host's immune system, causing inflammation over a long period of time or by altering host genes.

Most virus-induced cancers develop after a long period of persistent infection with an oncogenic virus; for adult T cell leukaemia this period is exceptionally long (around 60 years). The virus infections persist in their hosts in spite of immune responses, such as the production of virus-specific antibodies.

As cancer develops in only small percentages of virus-infected hosts it is clear that the several factors influence the progression. virus infections alone do not cause cancer from viral infection to cancer development. These factors include host's genetic makeup, mutation occurrence, exposure to cancer causing agents, and immune impairment.

Mechanisms of Action by Human Cancer Viruses

Tumor viruses mediate changes in cell behavior by means of a limited amount of genetic information. There are two general patterns by which this is accomplished: The tumor virus introduces a new "**transforming gene**" into the cell (**direct-acting**), or the virus alters the expression of a preexisting cellular gene or genes (**indirect-acting**). In either case, the cell loses control of normal regulation of growth processes. DNA repair pathways are frequently affected, leading to genetic instability and a mutagenic phenotype.



Papillomavirus-linked cancers

Cervical carcinoma is the third most common cancer in women, with approximately half a million new cases and 280 000 deaths in the world each year. Most, if not all, of these cancers result from infection with a papillomavirus.

The papillomaviruses are small DNA viruses of mammals and birds .

They enter the body through small abrasions and infect keratin-making cells (keratinocytes) in skin or a mucous membrane. Each HPV type infects a preferred site, such as the hands or the genitals, and infection may result in a benign wart (papilloma) or a carcinoma.

Most papillomavirus infections do not become persistent, but in a minority of hosts the infection is not cleared by the host's immune response. In individuals who harbour persistent infection there is a small risk of cancer developing. This risk is associated with about 15 of the HPV types; these '**high-risk**' types include **HPV-16 and 18**. Infection with other HPV types that infect the genitals (Warts) carries little or no risk of cancer; these '**low-risk**' HPV types include **HPV-6 and 11**.

Human Retroviruses

The human T-lymphotropic (HTLV) group of retroviruses has probably existed in humans for thousands of years. HTLV-1 has been established as the causative agent of **adult T cell leukemia-lymphomas (ATL)** as well as a nervous system degenerative disorder called tropical spastic paraparesis. It does not carry an oncogene. A related human virus, HTLV-2, has been isolated and associated with Some cases of **hairy cell leukemia**.

Transmission of HTLV-1 seems to involve cell-associated virus. Mother-to-child transmission via breast feeding is an important mode. Such early-life infections are associated with the greatest risk of ATL. Blood transfusion is an effective means of transmission, as are sharing blood-contaminated needles (drug abusers) and sexual intercourse.

Damage to immune defenses

Interactions between cell proteins and proteins produced by oncogenic viruses can lead to breakdown of immune defences that may allow the development of a cancer. Papillomavirus proteins interfere with apoptosis, and hence prevent the death of virus-infected cells.