Viral carcinogenesis

About 15% of all cancers are of viral origin. Tumor-associated viruses in humans include:

- **DNA viruses** (from 4 different families): *herpesviruses, hepadnaviruses, papovaviruses, adenoviruses*
- **RNA viruses**: *retroviruses*

As intracellular parasites, viruses can interact either directly with the cell's genome or with certain cell regulatory proteins during their replication cycle. This interaction can cause malignant transformation of the infected cell.

Mechanism of action

1. Viral genetic information **integrates** into the cellular genome, disrupting the sequence of a cellular (proto) oncogene.
2. Viral gene products **interact with cellular** tumor suppressor gene products that are inactivated by this interaction, paving the way for a transformation process (e.g., inactivation of p53 and p105-Rb protein in infections caused by certain variants of human papillomavirus). Viral proteins can also interact with the basic regulatory proteins of the cell cycle (cyclins and CD-kinases); alternatively, they may directly affect the transcription and thus the expression of certain cellular genes (both in the sense of malignant transformation). In addition to promoting cell proliferation, we also encounter an anti-apoptotic effect.
3. Another mechanism by which some viruses contribute to the transformation process is an **increase in telomerase activity** in the cell. Telomeres are the nucleoprotein terminal parts of eukaryotic chromosomes that play an important role in the stability of the respective chromosomes, especially during the cell cycle. During each cell division, telomeres shorten (according to certain theories, there is a direct relationship between telomere length and cell age). Telomerase allows telomeres to lengthen and thus prolong the cell's further ability to divide. Telomerase activity is physiologically present in cells during prenatal development and in isolated groups of cells (eg cells of the hematopoietic lineage) as well as during an individual's life. In normal somatic cells, telomerase activity is almost undetectable. In recent years, an association between increased telomerase activity and infection with human papillomavirus (HPV 16), herpesvirus HHV8 or EB virus has been discovered.

RNA viruses - retroviruses - tumors in animals and humans

When infected with oncogenic retroviruses, viral RNA enters a eukaryotic cell and is copied to DNA (provirus) by viral reverse transcriptase (RNA-dependent DNA polymerase). The provirus integrates into the cellular genome and begins to behave like a cellular gene. The place of integration is non-specific. Cellular RNA polymerase II can transcribe the viral genome into RNA molecules identical to the original viral genome. Oncogenic viruses do not act as infectious agents, complete replication and release of viral particles, and cell-to-tumor transformation can occur.

Slowly transforming retroviruses

They do not **have an oncogene in their genome** and their genome contains only 3 genes:

1. encodes **capsid proteins**
2. carries information for **reverse transcriptase**
3. carries information for the synthesis of **specific glycoproteins** that form the components of the viral envelope

- Transformation of cells with these viruses occurs after a long period of latency.
- Malignant transformation is most often caused by an increase in the activity of one of the cellular proto-oncogenes caused by the influence of the enhancing region of the retrovirus genome.
- Most often cause leukemia in cats, mice, chickens.

Rapidly transforming retroviruses

In addition to the three basic genes, they have a gene classified as the viral oncogene v-onc, which encodes a protein responsible for oncogenesis.

- After their application, tumors develop within 2-3 weeks.
- **Rous chicken sarcoma virus**

The viral oncogene integrated into the cellular genome represents the redundant sequence of the cellular (proto)oncogene. This redundant copy could in itself have a transforming activity, which is, however, amplified by a strong viral promoter site and possibly a mutated sequence.

Transregulating retroviruses

HIV (human immunodeficiency virus)

- HIV is associated with Kaposi's sarcoma and B-lymphoma.

- HIV does not appear to have a direct oncogenic potential and other viruses (KSHV, EBV and HPV, respectively) are responsible for transformation, with HIV only "facilitating work" by inducing immunodeficiency.

HTLV I - adult T-cell leukemia

- HTLV 1 inactivates protein p16, activates D2 cyclin, increases expression of some cell genes supporting proliferation and decreases stability of cell genome.
- It does not contain an oncogene, but as with DNA viruses, the oncogenic activity of the virus is due to the action of the viral protein.

DNA viruses

- DNA viruses lead to **inactivation of oncosuppressor genes**.
- Oncogenic effect is due to the action of viral proteins on cell cycle regulators (they interact with some antioncogene products and prevent their oppressive effect).
- The target gene for mutagenesis is the tumor suppressor gene TP53, where point mutations in critical areas condition malignant transformation

1. **Papillomaviruses**: cervical cancer, laryngeal papillomatosis and squamous cell carcinoma of the mouth
2. **Adenoviruses**: tumors in rodents
3. **Human herpes viruses** (some):
    1. **Epstein-Barr virus** (EBV, HHV-4): associated with infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, T-cell lymphomas
    2. **Human herpesvirus 8** (HHV-8): Kaposi's sarcoma

4. Hepatitis B virus: liver cancer

EBV

EBV infects B-lymphocytes, does not replicate in them, but usually causes a so-called **latent infection**, during which new virions are not produced, but some viral genes are active. In healthy individuals, the number of EBV-infected B-cells decreases over several months due to EBV-specific cytotoxic T-lymphocytes. Within the host cell, EBV exists in the form of an extrachromosomal episome. During this latent period, latent genes are expressed in the infected cell to ensure EBV retention in the host cells. This expression stimulates the cells to proliferate and protects them from apoptosis (activation of cyclin D2, activation of the anti-apoptotic bcl-2 protein and activation of IL-6 and 10). However, malignant transformation of such infected cells can occur if other mechanisms controlling tissue homeostasis fail. Thus, latent EBV infection can be considered as precancerous. As with HPV infections, infection alone is not enough to complete the malignant transformation of an infected cell.

Burkitt's lymphoma

Burkitt's lymphoma is a **B-cell tumor** that is most common in Central Africa and New Guinea, where it is the most common childhood cancer.

- translocation between the eighth and fourteenth chromosomes **t(8; 14)**
- cellular proto-oncogene **c-myc** from chromosome 8 moved to chromosome 14, where it comes under the influence of the active promoter of the immunoglobulin heavy chain gene (75% of cases)

Papillomavirus

There are over 120 types of HPV, but most of them cause only **benign lesions** such as hyperplasia, warts and papillomas, especially in the genitals, upper respiratory tract, mammary glands and gastrointestinal tract. About 30-40 of them are transmitted through sexual intercourse. However, some subtypes of HPV (e.g., HPV8, HPV16, HPV18, HPV33, HPV36, etc.) are very potent carcinogens that cause the development of **squamous cell carcinomas** of the skin, vagina, rectum, and especially the cervix.

- **transformation activity** is probably associated with integration of the viral genome into the cell genome (while in benign hyperplasias we find viral genetic information in episomes outside the cell genome, in carcinomas the viral genome is integrated into the cell genome)
- two viral **proteins E6 and E7** (capable of binding and neutralizing functional products of tumor suppressor genes p53 and pRb) are involved in **carcinogenesis** induced by these viruses
- **transmission** by body contact of infected parts (sexual intercourse)
- Papillomavirus **infection** is only the beginning of the whole transformation process and there must be other factors necessary to complete the transformation process (eg: smoking, concurrent bacterial infections, poor nutrition or hormonal changes)
- vaccination against the most dangerous subtypes

Links

Related articles

- Physical carcinogenesis

- Chemical carcinogenesis

Bibliography

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