

# ONCOGENIC VIRUSES WITH SKIN TROPISM AND THE INDUCED MUCO-CUTANEOUS PATHOLOGY

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**Abstract:** *The involvement of viruses, such as the ethiopathogenic factors, in the occurrence and the development of various malignancies, especially in skin cancers is a very current and constant issue. Also, highlighting the factors involved in malignant transformation of viral infected cells, makes the subject of many works in the field. This paper intends to be a summary of the role played by oncogenic viruses and those with cutaneous tropism for the muco-cutaneous pathology and the neoplasias induced by them.*

**Keywords:** *oncogenic viruses, muco-cutaneous lesions, neoplasias*

**Rezumat:** *Implicarea virusurilor ca factori etiopatogenici în apariția și dezvoltarea diferitelor neoplazii, în special a celor cutanate reprezintă o temă foarte actuală și în continuă extindere. De asemenea, evidențierea factorilor implicați în transformarea malignă a celulelor infectate viral constituie subiectul multor lucrări de specialitate. Lucrarea de față se dorește a fi o sinteză a rolului jucat de virusurile oncogene, respectiv a celor cu tropism cutanat în patologia cutaneo-mucoasă și a neoplaziilor induse de acestea.*

**Cuvinte cheie:** *virusuri oncogene, leziuni cutaneo-mucoase, neoplazii*

## INTRODUCTION

Even in the early XX-th century, the involvement of the viruses in the appearance and the development of neoplasias have been the subject of many studies (Borel in 1903 signaled the possibility of the virus origin of cancer). Today, perhaps more than ever the viral etiologies of malignancies is studied; this is one of the most controversial aspects of the experimental oncogenesis.

At present it is considered that from the total of 600 DNA and RNA viruses known to be able to infect humans, 150 have an oncogenic potential. After infecting the host cell with oncogenic viruses a series of changes in cellular physiology occurs, such as: Biological changes: lost contact inhibition, cell density increases with the formation of microfocuses; decreases of fixation; reduce the necessary nutrient materials

- Morphological changes: cells become rounded with a small protuberance on the surface
- Biochemical changes: increased the glycolytic

activity; lowers the concentration of cAMP, cGMP; fetal antigens appear; changing the glycoproteins composition

- Genetic changes: alterations of karyotype; aneuploidy; chromosomal translocations.
- Immunological changes: new antigens occur.

Viral carcinogenesis (the conversion of a normal cell into a malignant cell) is a multistadial process. In the achieving of this process three possible cancer mechanisms are incriminated:

- Viral genes can cause functional changes necessary for the malignant transformation of the infected host cells (tumour development occurs after a short period of latency). The expression of single oncogenic retroviruses may induce tumour development and the combinations of oncogenes are more aggressive. In vitro studies have shown that some oncogene prolong cell life, while others directly stimulate cell growth and division; both functions are needed for tumour development.
- For malignant transformation of infected cells beside the viral infection it is necessary to have some additional carcinogenic factors
- Viruses may induce malignancies through an indirect process.(6)

Oncogenic viruses present a number of common characteristics, such as:

- Containing modified genetic information that determine the transformation of normal host cells in to malignancy cells and the infection of a single cell with a single viral particle is sufficient.
- Viral genetic information (the entire viral genome or a fragment) is included in the nucleus cell, multiplied and transmitted successively to the later cell generations.
- The integration of oncogenic viruses in a cell genome causes irreversible alteration of the host cell.

Oncogenic viruses are DNA and RNA viruses.

**1. The Oncogenic RNA viruses** belonging to the retroviruses family (viruses that contain an enzyme called reverse transcriptase). Oncogenesis by retroviruses can be achieved through several mechanisms. Virus infections can cause the following changes:

- Synthesis in excess of a normal cellular protein that

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causes disturbance of the cellular function

- Reversing or blocking the path of normal cell differentiation
- Discontinuation of setting normal cellular function
- Modification of cellular proteins or enzymes by coupling them with viral proteins and thus produce competitive inhibition of their normal function
- Synthesis of hormone-like substances or growth factors that promote cell growth and proliferation.

The main RNA viruses that cause muco-cutaneous lesions are retroviridae, picornaviridae, paramyxoviridae and togaviridae (Table no. 1).(7)

**Table no. 1. The main virus RNA and the muco-cutaneous diseases produced (7)**

Family	Virus	Muco-cutaneous lesions
Retroviridae	HIV	SIDA
Picornaviridae	Coxsackie A16 Virus	Hand-foot-hand disease
	Coxsackie A Virus	Herpangina
	ECHO Virus	Maculo-papular rash
Paramyxoviridae	Measles Virus	Measles
Togaviridae	Rubella Virusul	Rubella

Parts of the oncogenic retroviruses category are:

- Rous sarcoma virus
- Moloney murine sarcoma virus
- Avian erythroblastosis virus
- Simian sarcoma virus
- HTLV1 human leukaemia virus and HTLV2 (incriminated in appearance of T-cell leukemia, adult T cell lymphoma and of some demyelination diseases – tropical spastic paraparesis).(13)
- Human immunodeficiency virus (HIV).

Based on their extracellular morphology retroviruses are divided into three classes: types B, C and D. The best known potentially oncogenic retroviruses are the type D or HTLV.(13)

**A) Human Immunodeficiency Virus (HIV)** is a lymphotrope retrovirus which has two types: HIV-1 (found in Europe and North America) and HIV-2 (met in Africa). Retrovirus has tropism for helper T lymphocytes, which bind to the CD4 receptor by gp120 glycoprotein. Clinical manifestations depended on the severity of the viral cytopathogenic effect and the number of CD4 receptors. Secondary to infection and destruction of lymphocytes appears the infectious events and/or neoplasias.

In HIV positive patients the cutaneous manifestations are:

- Neoplasias: Kaposi sarcoma, lymphomas (especially B cell lymphomas), carcinoma (often anogenital squamous cell carcinomas)
- Infectious: viral, bacterial, fungal, caused by protozoa

and arthropods

- Unclassified: papular and scaly lesions, vascular, autoimmune, postdrug treatment lesions.(7)

In HIV positive patient with Kaposi sarcoma the lesions have a particular location; there are many of them and they are associated with extracutaneous affections (gastrointestinal, pulmonary, lymph node, kidney, spleen, etc.).(2)

In general, oncogenic virus infections are more common than the incidence of malignancies. Studies to date have shown that malignant cell transformation required a simultaneous action of one/more carcinogenic cofactors from the external environment (physical, chemical) or internal (genetical, immunological, hormonal).(6)

**2. DNA viruses.** Unlike oncogenic retroviruses that possess oncogenic genes and that are correlated with the normal cell genes, oncogenic DNA viruses possess oncogene genes without correlation with the normal cellular genes.

The most common oncogenic DNA virus that causes muco-cutaneous lesions is papovaviridae and herpesviridae (Table 2).(7,9)

**A) Epstein-Barr virus (EBV)** or herpetic virus 4 (HHV4) is part of the Herpesviridae family, belonging to the Gamma herpesviridae subfamily. The life cycle is similar with the viral herpetic viruses, with periods of very long latency; latency favouring the malignant transformation of infected cells. Currently over 95% of the world's population is infected with EBV. The involvement of viruses in the appearance and development of malignancies was first certified by highlighting the oncogenic potential of EBV.

The etiological involvement of EBV in some lymphoproliferative diseases, especially in immunocompromised patients (Burkitt lymphoma, nasopharyngeal carcinoma) is well known.(11) Some researchers consider that EBV is a favorable factor in chronic fatigue syndrome, multiple sclerosis and some autoimmune diseases. The major nuclear proteins involved in malignant transformations are EBNA (Epstein-Barr Nuclear Activation) and LMP (Latent Membrane Protein) encoded by corresponding genes with the same names with the DNA genome of EBV.(3)

Burkitt lymphoma is a non-Hodgkin lymphoma that is more commonly seen in Africa where malaria commonly coexists with it. It was found that infection with Plasmodium falciparum stimulates polyclonal proliferation of EBV infected B lymphocytes, decreasing the cellular immunity response of T lymphocytes, thus contributing to tumor pathogenesis.(15)

Nasopharyngeal carcinoma is intimately associated with EBV; it is a highly metastatic malignant tumour, commonly encountered in China and Africa. In addition to the viral etiology of the nasopharyngeal carcinoma occurrence the genetic and environmental factors are involved (the increased effects of carcinogenic nitrosamines because of an increased consumption of smoked fish are recognized).

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**Table no. 2. The main DNA viruses, the diseases and the muco-cutaneous induced malignancies (7).**

Family	Virus	Muco-cutaneous lesions	Neoplasias
Papovaviridae	Human Papillomaviruses	- Verruca Vulgaris - Verruca Plana - Condyloma acuminata - Epydermodysplasia verruciformis - Recurrent respiratory papillomatosis - Papilloma - Bowenoid papulosis - Giant condylomatosis Buschke-Lowenstein	- Cervical cancer - Basal Cell carcinoma - Squamous Cell carcinoma - Malignant Melanoma - Bowen disease - Queyrat Erythroplasia - Other neoplasias (lungs, esophagus, larynx, sinuses, conjunctival, oral cavity, anal, genital, penis)
Herpesviridae	Herpes simples Virus	Herpes simples infection	
	Varicella-zoster Virus	Chicken pox Herpes Zoster	
	Cytomegalovirus	Macular lesions Muco-cutaneous ulcers	
	Epstein-Barr Virus	Infectious mononucleosis	Burkitt lymphoma Nasopharyngeal carcinoma Hodgkin disease (some time)
	Herpes virus type 6	Roseola infantum	
	Herpes virus type 8	Mononucleosis-like eruptions	Kaposi Sarcoma Castleman disease Hodgkin lymphoma
Poxviridae	Molluscum Contagiosum Virus	Molluscum contagiosum	
	Orthopoxviruses	Variola Vaccina	
	Parapoxviruses	Orf Milker`s nodules	
Hepadnaviridae	Hepatitis B virus	Urticaria Purpura Panarteritis nodosa Gianotti-Crosti syndrome	Liver carcinoma
Parvoviridae	Human B19 Parvovirus	Epidemia megaerythema Vasculare purpura Vesiculo-bullous lesions	

**B) The Herpetic virus type 8 (HHV8)** was discovered in 1994 and is part of the Gamma2 herpesviridae subfamily. Its presence is associated with Kaposi sarcoma, Castleman's disease and certain lymphomas.

The HHV8 overall prevalence is 2-5%, with increased values above the Mediterranean and Africa areas (up to 30%). Studies to date have identified HHV8 viral particles in all clinical forms of Kaposi sarcoma (Mediterranean, African, HIV-positive patients). Using molecular hybridization techniques to reveal the HHV8 in Kaposi sarcoma lesions was identified HHV8 in the vascular endothelial cells and perivascularly.(7)

HHV8 viral particles penetrate through the cell membrane and infect CD4 T lymphocytes found in mitosis. It was found that the HHV8 genome is a circular structure in periods of latency and a linear structure during viral replication. Based on gene analysis, 5 variants of HHV8 have been described, which in serological terms are not different but which differ in their geographic distribution (the B group is dominant in Africa, the D and E groups are present in the Pacific

Islands and the Amerindian population and the A and C groups predominate in Europe and North America). Current studies show the importance of some genes in Kaposi sarcoma pathogenesis, namely: K1, K2, vMIPS, K4, K4.1, K5, K9, K12, ORF6, ORF71, ORF 73, ORF 74 and K15.(1,18)

Identification of HHV8 infections is possible by molecular hybridization (the most accurate is the PCR technique that allows to identify the viral DNA), immunohistochemistry (using different monoclonal antibodies directed against different viral structures) and serological (identifying the lytic and latency antibodies and additional latent nuclear protein (LANA2) by immunofluorescence, ELISA and Western blots technique).

Castleman disease is an atypical lymphoproliferative disease which is characterized by multiple lymph nodes, autoimmune phenomena, cytopenia, intercurrent rash and skin infections. In evolution these patients may develop various malignancies, most frequently Kaposi sarcoma or non-

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Hodgkin lymphoma.(10)

**C) The Hepatitis B virus (HBV)** is part of the Hepadnaviridae family and is the main factor for liver cancer. Liver cancer is more common in men. In etiological terms HBV is incriminated in liver cancer in 75-90% of the cases.(21)

**D) Human Papillomaviruses (HPV)** are small DNA viruses with squamous epithelium tropism and are involved in the occurrence of benign (16) and malignant muco-cutaneous lesions. The malignant transformation of infected tissues with HPV is dependent on the virus subtype (over 150 subtypes of HPV) and the presence of carcinogen cofactors.

The HPV genome is a molecule of circular DNA double helix, consisting of 7900 pb (16). The HPV particles have diameters between 50 and 55 nm, with an icosahedral capsule consisting of major and minor proteins (L1 and L2) and E proteins (E1-E7). The L1 protein is a major capsule protein, while L2 is a minor component. The electronic exam of L1 particles reveal that this protein forms a particle approximately the size of a complete virion, which is why they are called virus-like particles (VLPs). L2 protein expression may be at the cell level where it will form a capsule structure similar to L1. The expression of the L1 and L2 causes increased levels of VLPs, suggesting that L2 help to stabilize the capsule. L2 can operate at the level of virion to link the genome. The VLP system is that there are differences between the serological types of HPV. The L1 protein of HPV16 and 31 viral subtypes have very low serological cross-reactivity and the HPV6 and 11 subtypes present four differences in reciprocal reactivity. Serological studies to detect the specific HPV infections can be distinguished only by using VLPs.

Proteins involved in viral HPV replication are HPV E1 and E2. Both proteins are synthesized early during infection, before viral replication can begin. E2 protein inhibits viral transcription from the viral promoter, binds the E1 protein and is required for HPV genome replication. The three proteins E6, E7 and E5 have the transformational properties, but their role in vivo is primarily to create a favourable environment for replication. They act together to stimulate the keratinocyte proliferation by interacting with regulatory proteins, including the tumour suppression gene products p53 and the retinoblastoma protein (pRb) and facilitate the replication of viral DNA.(20) The HPV E7 protein is involved in cell transformation. It is observed that both E2 and E7 proteins can induce cell apoptosis. In the case of E7, the binding and inactivation of pRb and pRb-like with CR2 of E7 are required for the induction of epidermal proliferation and carcinogenesis. It is frequently noted that the E7 HPV coded protein determines affecting the growth control of the host cells by binding them to pRb proteins. This and contributes to malignant phenotypic modulations by CMH-1 expression. This pRb-E7 complex can cause hyperexpression of c-myc.

Similar to E7 - pRb interaction, E6 protein interacts with p53 with its degradation and inactivation.

The coupling of E6 with p53 contributes to the development of ano-genital cancers HPV positive (19). The result of these changes is an anarchic cell proliferation and malignant transformation of the infected tissue.(14) The HPV16 subtype most commonly infects the genital tract and is generally known to be the causative agent of cervical cancer.(4)

90% of human cervical cancers and 25% of the penian and vulvar cancers seem to be due to HPV infection (in particular - HPV "high risk").(4) HPV subtypes "high risk" the most frequently involved in the appearance and development of various malignancies are HPV 16, 18, 31, 33, 35, 39, 45, 50, 51, 53, 55, 56, 58, 59, 64, 68.

Recent studies have found HPV particles in patients with carcinomas: cervical, gastrointestinal, esophagus, larynx, some lymphomas, skin tumours (basal cell carcinoma (8) squamous cell carcinoma (8) malignant melanoma (5) Bowen disease, erythroplasia of Queyrat) (17).

### CONCLUSIONS

- Far from being fully elucidated, oncogenic viral mechanisms are still a research theme and new data continue to appear.
- The oncogenic virus involvement in the skin cancers pathology is quite sure, but the exact role played by some viruses in the appearance and development of skin tumors remains an open research field (12).

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