GENERAL ANALYSIS ON THE INVOLVEMENT OF HUMAN PAPILLOMAVIRUSES IN THE ETIOPATHOGENESIS OF CUTANEOUS TUMOURS

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Abstract: *The worldwide incidence of skin cancer has dramatically increased. The genetic, hormonal and environmental factors are involved in the development of skin cancer. Recently, human papillomaviruses are considered to play an important part in skin cancer etiopathogeny. Human papillomaviruses produce epithelial tumours of skin and mucous membranes. The number of patients identified with human papillomaviruses (HPV) has increased dramatically in the last 20 years due to the high awareness of the various clinical manifestations caused by HPV and due to the increased use of HPV DNA testing. The purpose of this work is to present the recent HPV data and the possible relationship between HPV and skin cancer.*

Keywords*: human papillomaviruses, skin cancers, malignant melanoma.*

Rezumat: *Pe plan mondial este recunoscută incidenţa în continuă creşterea a neoplaziilor, inclusiv a celor cutanate. În apariţia şi dezvoltarea tumorilor cutanate sunt incriminaţi o serie de factori (genetici, hormonali şi de mediu), însă în ultimul timp, studiile de specialitate acordă o atenţie specială rolului posibil jucat de papilomavirusuri în etiopatogenia cancerelor de piele. Este cunoscut faptul că Papilomavirusurile umane produc numeroase infecţii cutaneo-mucoase benigne şi maligne cu diferite manifestări clinice. În ultimii 20 de ani s-a constatat o creştere importantă a incidenţei infecţiilor cu papilomavirusuri atât prin diversitatea manifestărilor clinice cât şi prin îmbunătăţirea tehnicilor de evidenţiere a virusului prin teste ADN. Lucrarea de faţă îşi propune o reactualizare a informaţiilor legate de implicarea papilomavirusurilor în etiopatogenia tumorilor cutanate, prin prisma ultimelor studii de specialitate pe această temă.*

Cuvinte cheie*: papilomavirusuri, tumori cutanate, melanom malign.*

GENERAL CONSIDERATIONS

Malignant melanoma is the most aggressive cutaneous tumour, representing almost 4-5% of the total number of cutaneous tumours and being responsible for about 77% of the deaths due to cutaneous cancers.

The most frequent cutaneous neoplasms (nonmelanocitary tumours) are keratinocyte carcinoma: basocellular and spinocellular carcinoma.

Basocellular carcinoma is the most frequent cutaneous tumour; it has a very slow evolution, it rarely reaches the metastasis stage and has a very good prognostic when treated. Spinocellular carcinoma is the second most frequent cutaneous tumour; it occurs mainly in photo-exposed areas, either de novo or at the level of precancerous lesions (frequently actinic keratoses); it shows the risk of metastasis. (2). Less encountered forms of nonmelanocitary tumours are Kaposi's sarcoma, cutaneous lymphomas, tumours of cutaneous annexes, sarcomas, Merkel cell carcinoma. International studies prove that the incidence of cutaneous tumours is increasing yearly with 5% all around the world. The early detection of cutaneous cancer would enormously contribute to the treatment of cutaneous neoplasias.

We could notice an increased incidence of melanoma in the last years, both of the classic forms and of those atypical, what could impose the early recognition of tumour, especially of the atypical forms.

The sequence of events that bring about the transformation of melanocytes in atypical cells (melanogenesis) is not entirely known. The following factors are considered to be involved:

- Processes of genetic progressive mutation that cause alterations in cells proliferation and differentiation;
- Carcinogenetic effects of ultraviolet radiations;
- A series of genetic, hormonal and environmental factors are involved in the occurrence and development of melanoma:
- Cutaneous phenotype,
- Aggressive sun exposure with sunburns in childhood;
- Presence of a large number of dysplasic nevi;
- Melanoma personal or family history;
- Presence of nonmelanocitary cancers antecedents;
- Alteration of certain pre-existing nevus lesions;
- Presence of giant congenital nevi (more than 20 cm),
- Male gender;
- Age (more than 50 years old);
- Presence of xeroderma pigmentosum, but the melanoma's etiology remains unknown. (3)

It is known the fact that ultraviolet radiation is one of the main factors that contribute to the development of melanoma. From molecular and cellular point of view, UV radiations, especially UVB radiations are associated

to the occurrence of certain genetic mutations in vitro that are inconstant.

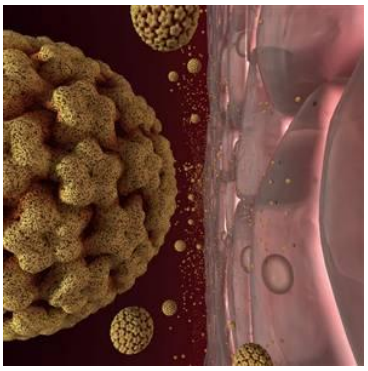
The molecular genetics emphasized the part played by the suppressor CDKN2A gene (p16) in melanoma development. A large number of melanomas and nevi and the presence of mutations in other genes, respectively the BRAF gene were also correlated to the beginning of the melanocitary neoplasic process. These mutations were emphasised only in the patients with melanoma familial antecedents, especially in the families with many members affected. These data suggest that genetic mutations are present both in the process of carcinogenesis but are insufficient for explaining the development and progression of melanoma. These observations suggest the possibility that other agents might also be involved directly or indirectly in the development and progression of melanoma.

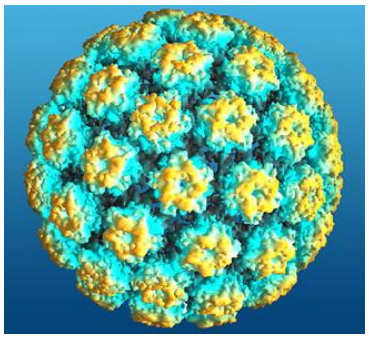
The intensification of the education efforts and the use of new techniques of diagnosis and investigation in the developed countries ended with an earlier diagnosis and treatment of melanoma and with a possible cure of the small tumours.

Lately, it has been observed that viruses may play an important part in the occurrence and development of certain carcinomas, such as the cervical one, gastrointestinal carcinoma, oesophageal, laryngeal carcinoma and certain lymphomas. Certain recent papers of the specialized literature report the presence of papillomaviruses at the level of certain cutaneous biopsies drawn from nonmelanocitary tumors and even from melanocitary ones.

It is well known the fact that human papillomaviruses (HPV) produce numerous cutaneous and mucous infections, benign or malign with different clinical manifestations (7). The number of patients identified with human papillomaviruses (HPV) has increased dramatically in the last 20 years due to the high awareness of the various clinic manifestations caused by HPV and due to the increased use of HPV DNA testing.

Picture 1 a, b. Molecular aspects of HPV





Human papillomaviruses (picture 1a,b) are DNA viruses with tropism for squamous epithelia. The existence of certain solutions of epithelial discontinuity allows the contact of the basal cells with the viral structures. Viral replication takes place either at the level of the basal layer or in different cellular structures. All infected cells contain the viral genome, but the genetic expression is closely related to the status of the cellular differentiation. The majority of the viral genes are inactive until the infected keratinocytes leave the basal layer.

The malign transformation of the tissues infected with HPV depends both on the virus subtype and on the presence of certain co-factors:

- smoking
- UV radiations;
- pregnancy;
- folic acid deficiency;
- immunosuppression;
- oral contraceptives;
- early sexual activity, multiple sexual partners;
- Chlamydia infections.

Today, more than 150 subtypes of HPV are known, out of which the genome of more than 90 subtypes has been decoded.

The identification of the HPV subtype is of major importance, allowing the accomplishment of a clinical prognostic of lesions and of a therapeutic plan. HPV cannot be detected through serological tests or through cultures and the immunohistochemical methods used for the detection of the viral capsid antigens have a reduced sensitivity. The molecular techniques based on the hybridisation of the nucleic acids are the most specific and sensitive for the identification of HPV. These are:

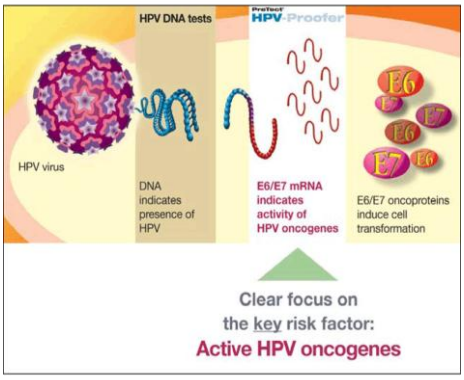
- hybridisation in situ;
- southern blot – the most sensitive and specific hybridisation technique, being considered "the golden method";
- dot blot – the only method that may identify the integration of the virus in the genome of the host cell;
- FISH method (fluorescent hybridisation in situ) – is a more simple and rapid method;
- PCR – allows the amplification of the certain viral DNA specific sequences into a large number of copies, allowing even the detection of subclinical, asymptomatic infections.

The molecular studies identified that within the HPV subtypes with oncogenic risk, the viral DNA is extracellularly exposed and regarding the HPV 16,18 oncogenic subtypes, the viral DNA is intracellularly disposed, being integrated in the structure of the host cell. ***The integration of the viral genome in the genome of the host cell is considered to be the marker of the malign transformation.***

Low oncogenic-risk HPV subtypes determine benign genital lesions (HPV 6,11,53,54), while the HPV subtypes with high oncogenic risk (HPV 16,18,31,33,35,39,45,50,51,53,55,56,58,59,64,68) are associated to the development of dysplasic states and anogenital carcinomas (6). The subtype 16 is considered to have the highest risk in the development of the anogenital cancers.

The present genetic studies proved that certain proteins (E6 and E7 proteins) of the HPV subtypes with high oncogenic risk (HPV 16, 18, 35) interfere with p53 and pRb proteins, both being key regulatory proteins of the cellular cycle. E6 protein influences the actions of p53 protein, a suppressing tumoral protein involved in the recovery of cellular DNA destructions by UV radiations. E6 initiates the degradation of p53 protein determining the alteration of the cellular response to the DNA changes. (6)

Picture 2. Role of E6 and E7 viral proteins in oncogenesis



E7 protein affects the cellular cycle through the alteration of the retinoblastoma protein (pRb) function and through the alteration of E cyclin regulation. ***HPV E6 and E7 proteins, through the inactivation of the tumoral suppressing proteins, p53 and Rb, of the host determine the anarchic cellular proliferation and the malign transformation of the infected tissues. (6)*** (picture 2). All these cellular and molecular alterations arising from the cells infection with HPV with high oncogenic risk are considered by some of researchers as being responsible for the development and progression of certain neoplasias, such as the melanocitary and nonmelanocitary cutaneous tumours (spinocellular and basocellular carcinoma) (4).

Associating HPV infections with cervical cancer, with different risk degrees is a well known fact. Today, it is possible to prevent the infection with HPV associated to dysplasic/neoplasic states due to the discovery of a specific vaccine. It is a quadrivalent vaccine indicated in the prevention of HPV infections produced by the subtypes of HPV6,11,16,18, more frequently involved in the cervical cancer, acuminate condylomas and precancerous genital lesions. Vaccination provides a protection of 70%, and the use of this vaccine in noninfected populational groups will allow the decrease of the number of infections produced by HPV oncogenic subtypes.

Certain HPV subtypes (HPV16, 18) were emphasised in some cases of spinocellular and basal carcinomas, Bowen's disease, Bowenoid papulosis, Queyrat's erythroplasia, but their part remains uncertain (1). More, different subtypes of HPV were associated with the malign melanoma (more frequently HPV16, 18, 33). Whether HPV is or is not a cofactor in the development of melanoma still remains a big question.

From the point of view of the studies published until now, we cannot exclude the fact that HPV subtypes with high oncogenic risk might serve as cofactors in the development of a more aggressive form of melanoma. Until now, it has been proved that HPV 16 and 18 oncogenic subtypes are involved in the etiology of spinocellular and basocellular carcinomas (5).

The controversial data of the specialized literature about HPV involvement in carcinogenesis and evolution of melanocitary tumours still makes the object of further speciality studies. Today, further research is necessary in order to confirm the involvement of HPV oncogenic subtypes in the occurrence and development of the melanocitary tumours.

The increasing incidence of cutaneous neoplasias and their evolutive aggression makes necessary a more profound investigation of the etiological factors involved in the occurrence and development of the cutaneous tumours, inclusive of HPV, what would allow the discovery of certain antitumoral ethyopatogenic therapies.

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