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SOME MECHANISMS OF ONCOGENIC ACTION OF HUMAN PAPILLOMAVIRUS

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Introduction. Human papillomavirus (HPV) is a large group of common viruses (over 200 types) that can pose a serious health risk. Some HPV types are oncogenic, and at least 25 of these are considered high-risk viruses, as they possess carcinogenic activity and can cause cancer, including cervical, laryngeal, and anal cancers, as well as intraepithelial neoplasia of the vagina and vulva. Anogenital condylomas are very common. However, not all HPV types are dangerous: some cause only benign growths, such as warts. According to the World Health Organization, 40,000 HPV-associated cases of vulvar and vaginal cancer, 100,000 cases of anal cancer, and 400,000 cases of oral and pharyngeal cancer are registered annually.

Aim. To analyze the neoplastic properties of human papillomaviruses and identify possible mechanisms of carcinogenesis inherent to this group of viruses.

Materials and methods. Analysis of modern scientific research and literary sources in the field of pathophysiology, virology, immunology, genetics, oncology.

Results. All papillomaviruses have a similar genetic structure. The viral genome is a circular DNA molecule consisting of 72 capsomeres, approximately 8,000 nucleotide pairs, containing three functional regions: the first, the "noncoding upper regulatory region," responsible for regulating DNA replication; the second, the "early region" (E), encoding proteins E1, E2, E4, E5, E6, and E7, which are involved in viral replication and neoplastic transformation of the host cell; and the third, the "late region" (L), encoding proteins of the viral capsid. L proteins are characterized by the highest immunogenicity, which is why the L2 protein is used as an antigenic structure in the development of a prophylactic vaccine. The target cell for HPV is the basal epithelial cell. When infected, the viral genome replicates in the cell nucleus, and the lengthy process of viral particle formation occurs only during the final stages of epithelial cell differentiation. The reactogenic basis of the immune response is the HPV surface proteins L1 and L2, which act as specific antigens, enabling B lymphocytes to produce antibodies complementary to the viral proteins. HPV has significant oncogenic potential. There are HPV types with a low oncogenic risk, such as 6, 11, 42, 43 and 44, as well as HPV types with a high risk - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. However, cervical cancer can also be caused by other subtypes of HPV group 1, and these cases are known.

There are two stages of human papillomavirus infection: transient, when the virus is in a "free state", and integrative, when the viral DNA genome integrates into the genome of infected cells. In mucosal epithelial cells, HPV can exist in both an integrated form and a free episomal form. Integration of viral DNA into the genome of basal epithelial cells leads to malignancy, while the nonintegrated form leads to productive persistence, followed by the development of genital warts, which have a low risk of developing into precancerous lesions and cancer. The intermediate result of

the integrative process is nonproductive flat warts, which carry a significant oncogenic risk for the development of cervical intraepithelial neoplasia (CIN) and cervical cancer.

According to research, HPV types 16 and 18 account for 70% of cases and 10 types of cervical cancer of viral etiology. HPV types 31, 33, 45, 52, and 58, along with types 16 and 18, account for up to 90% of neoplasms. Low-oncogenic types of viruses can also have an adverse effect on human health; types 6 and 11 cause up to 90% of genital warts in men and women worldwide. When the virus persists in its integrative form, the synthesis of the cell's own proteins is suppressed, which causes a disruption in the differentiation and maturation of epithelial cells, with the formation of viral proteins E6 and E7. In this case, the E6 protein acts as a suppressor and transactivator; its activity is determined by the position, nature, and number of transcription factor binding sites.

The p97 promoter of HPV type 16 plays a role in maintaining latent viral infection. The interaction of the E6 oncoprotein of HPV types 16 and 18 with the p53, pRb, E6-AP, and E6-BP proteins of the host cell leads to a disruption of their function. The p53 and pRb proteins regulate cell cycle progression to prevent neoplastic transformation of the host cell. The mechanism of p53 binding to the E6 oncoprotein of HPV types 16 and 18 causes a loss of control over basal epithelial cell proliferation. E6-AP (E6-associated protein), in complex with the E6 oncoprotein, is involved in the degradation of p53 and reduces its production in HPV-contaminated cells. The interaction of the E6-BP protein (E6-binding protein) and the E6 gene of HPV types 16 and 18 inhibits cell differentiation and creates favorable conditions for viral DNA replication. The viral protein E7, also binding to regulatory proteins to form a stable, inactive complex, dysregulates cell cycle control. The resulting complex disrupts cell cycle arrest in the G phase, exerting a mitogenic effect, which stimulates uncontrolled DNA synthesis. Furthermore, E7 stimulates events in the S phase of the cell cycle by initiating the replication of viral genes and stimulating the proliferation of transformed cells.

One of the risk factors for malignancy is the immunological pathway, whereby immunodeficiency develops due to the combined suppression of the cellular immune response, viral particle-mediated mechanisms, and external factors. This is associated with mononuclear cells and Langerhans cells, whose effectiveness is determined by the expression of adhesion molecules and the type of antigen structures associated with the major histocompatibility complex. These factors are involved in the activation of T-lymphocytes and the presentation of viral antigens by these cells, resulting in cytotoxic aggression of T-lymphocytes against CIN 3 cells and the E6 and E7 proteins presenting HPV-16. Th1 cells produce a number of humoral factors, such as proinflammatory cytokines, interleukins (IL-1, IL-2), interferon (IFN), and tumor necrosis factor, which has pronounced antitumor, antiviral, and antibacterial activity. These factors include IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13.

As a rule, persistent HPV infection alone is not sufficient for tumor development; a number of associated risk factors, both controllable and uncontrollable, are also necessary. The primary route of transmission is sexual. According to C. Critchlow, the incidence of HPV infection is directly proportional to the number of sexual partners: with one partner, HPV is detected in 17–21% of women, while with five or more

partners, the rate is 69–83%. Risk factors for HPV infection include early age at first sexual intercourse, three or more sexual partners, and concomitant genital infections (*Chlamydia trachomatis*, genital herpes, bacterial vaginosis). HPV is eliminated in 70% of cases within the first year of infection, and in 91% of cases within two years. The presence of the same HPV type in a woman's body for two or more years is considered persistent.

HPV is believed to cause 5% of all cancers in men and 10% in women. Chronic human papillomavirus infection accounts for approximately 100% of cervical cancers (CC), 70% of vaginal cancers, 40% of vulvar cancers, 29% of penile cancers, 87% of anal cancers, and 20% of oropharyngeal cancers in Europe. Of the aforementioned HPV-associated cancers, types 2 (HPV 16 and 18) are the etiologic factor in the majority of cases (73–94%), while HPV 16 and 18, along with 5 other types (HPV 31, 33, 45, 52, and 58), are responsible for the development of neoplastic processes in up to 98% of cases. In cervical cancer, HPV 16 accounts for two-thirds of cases, HPV genotypes 16 and 18 account for more than 70% of cases, and HPV 31, 33, 45, 52, and 58 account for the remaining 20%. HPV infection is also common among men. In a study conducted in the Netherlands, 62% of men who have sex with men were seropositive for at least one high-risk HPV type, and 41% had DNA detected by polymerase chain reaction (PCR) in the anus, penis, or oral cavity. In most cases, the host immune system eventually reactivates and clears the infection: within 24 months in 80% of cases and within 48 months in 90% of cases. The median clearance time is longer for high-risk HPV types (hrHPV) than for low-risk HPV types (lrHPV): 8 months for lrHPV and 11–17 months for hrHPV. Viral clearance is largely explained by a cell-mediated immune response after antigen-presenting cells present HPV proteins (primarily E2 and E6) to T helper cells, which subsequently activate cytotoxic T cells. The humoral immune response to the L1 protein is quite weak: in fact, during natural HPV infection, antibody production is slow, antibody titers are low, and some women never seroconvert, especially if the infection is transient. Only 50–70% of women infected with HPV seroconvert, providing limited protection against new infections with the same subtype.

Conclusions. Thus, the oncogenic effect of HPV is achieved through HPV integration into the host cell genome and is caused by overexpression of the E6/E7 tumor suppressor proteins, which suppress the actions of p53 and retinoblastoma (pRb) proteins. This subsequently leads to disruption of apoptosis, neoangiogenesis, and tumor transformation of cells. A specific (antiviral) treatment for HPV has not yet been developed due to the complex processes of viral carcinogenesis and the specific features of the immune response. Therefore, the only effective method for preventing cervical cancer and other HPV-associated diseases, according to the overwhelming majority of researchers, is primary prevention of HPV infection, which includes vaccination.

Keywords: human papillomavirus, cervical cancer, oncogenic potential, cervical intraepithelial neoplasia.