Review paper

THE ROLE OF HERPES SIMPLEX VIRUS AND HUMAN PAPILLOMAVIRUSES IN TRIGGERING MALIGNANCY

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ABSTRACT

Certain DNA viruses are important as known causes of cancers in humans. Oncogenesis by DNA viruses is best understood for polyoma-, papilloma- and adenoviruses. All of them contain genes that behave as oncogenes. As for herpesviruses there is suggestion that a cellular oncogene might be involved. A number of HSV-specific proteins are produced and expressed by the transformed cells. Herpes simplex virus type 2 was seriously implicated in the etiology of cancer of the cervix. During the past years the theory of herpes simplex virus oncogenesis has lost favour in the face of mounting evidence to incriminate human papillomaviruses in the same disease.

KEY WORDS

herpes simplex virus, human papillomaviruses, tumor induction

When discussing tumor induction by DNA viruses we must have in mind that DNA tumor viruses interact with cells in one of the two ways:

- productive infection - virus completes its replication cycle resulting in cell lyses;
- nonproductive infection - virus transforms the cell without completing its replication cycle; the viral genome is integrated into the cellular DNA or the complete genome persists as an autonomously replicating episome. The genome continues to express early gene functions (1).

The molecular basis of oncogenesis by DNA viruses is best understood for polyomaviruses, papillomaviruses and adenoviruses; all of them contain genes which behave as oncogenes. These oncogenes act primarily in the nucleus, where they alter patterns of gene expression and regulation of cell growth. In every case the relevant genes encode early proteins having dual role: in viral replication and in cell transformation (2).

As for human herpesviruses no specific herpesvirus-transforming gene has been identified. It is possible that herpesvirus-induced oncogenesis might be fundamentally different from transformation mediated by viruses that encode transforming proteins (3). Human herpesvirus type 2 (HHV-2) has been associated with cervical squamous cell carcinoma. These observations have been predicted upon the site of cancer and the known natural tendency of HHV-2 to infect this site and upon the excess of specific antibodies determined. In support of this

later point several large seroepidemiologic studies have demonstrated seroprevalence among patients with the selected cancer to be as high as 100%. These studies have often failed to consider other sexually transmitted diseases (4,5). Even the use of molecular diagnostic techniques failed to satisfy the criteria necessary to demonstrate a casual relationship. The situation became clearer with the association between human papillomavirus (HPV) infection and cervical carcinoma; for this reason during the past few years the relationship of HHV-2 oncogenesis and carcinoma of the cervix is no more as strong as for HPV (6).

If we review the recent experimental data on HHV-2 related malignancies we can have some important pieces of information: Knight et al. mention a tumor-specific polypeptide (designated U 90); it is specific for the transformed cell and is precipitated by the sera of tumor-bearing animals. It is precipitated also by antibodies against HHV-2. U 90 polypeptide is indistinguishable from that of U 90 present in mouse cells transformed by HPV 16 (7).

Macnab et al. report about the production of HHV-2 induced tumor specific cell polypeptide (m.w. 40 000). Sera from patients with cancer of the cervix contain antibodies to this cell coded polypeptide (8). Smith et al. found the large subunit of HHV-2 ribonucleotide reductase which (to their opinion) is required for virus growth and neoplastic transformation (9). It seems possible that HHV-2 initiates an overexpression of a cellular oncogene; such abnormal oncogen transcription (which can be monitored in different ways) consequently results in tumor production. Very similar mechanisms are well recognized in Epstein-Barr virus related tumors (10).

HPV are one of the few types of DNA viruses known to cause natural tumors in their hosts of origin. HPV are highly tropic for epithelial cells of the skin and mucous membranes. All the studies concerning their molecular and biological properties progressed slowly because in general HPV can not be propagated in cell culture. Over 70 types of

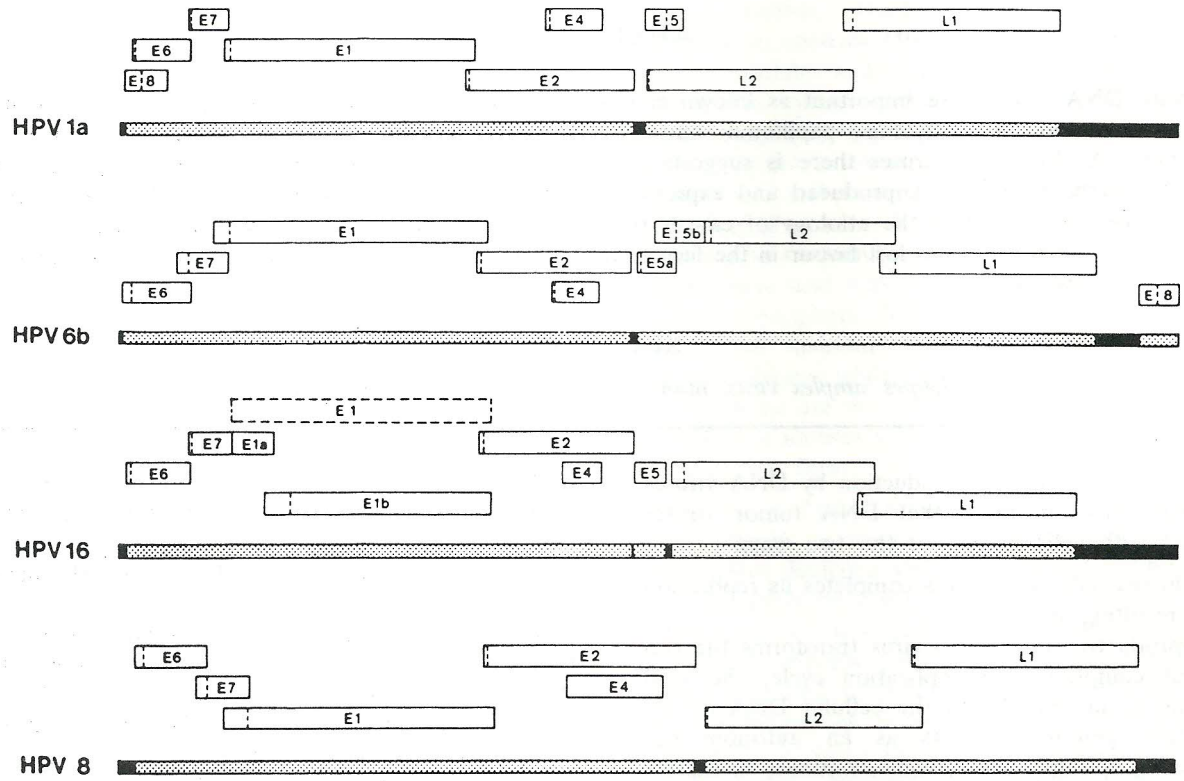

Figure 1. Genome organization of some human papillomaviruses. Open reading frames are indicated by open bars. Dotted lines within the frames represent the first methionine codon, which could serve as a start point of translation. In HPV 16 the E1 frame appears to be split. Stippled areas of the genome represent coding sequences, black regions stand for noncoding regions (14).

HPV are recognized and the number is rising rapidly. These types have been classified into about a dozen groups reflecting the degree of homology of their nucleotide sequences. HPV types 16 and 18 have been especially associated with lesions that have a tendency to undergo malignant conversion (11). These types are associated with genital, anal and laryngeal carcinoma of humans. The majority of cervical, penile and vulvar cancers carry HPV DNA copies. Epidemiologically cervical cancer associated with HPV types 16 and 18 is strongly correlated with several genetic and environmental factors (the age of infected person, number of sexual partners, frequency of intercourses per week, smoking, warts in partner and concomitant other STD infections) (12).

The HPV genome (Figure 1) in the form of an unintegrated, autonomously replicating episome is regularly found in the nuclei of the premalignant cells in cervical dysplasia. In contrast, invasive cervical cancers reveal cromosomally integrated HPV 16 or HPV 18. Each cell carries at least one, and sometimes up to hundreds copies of the HPV genome (13, 14). Integration disrupts one of the early viral genes, E2 and other genes may be deleted, but the viral oncogenes E6 and E7 remain intact and are expressed efficiently. Transfection of cultured cells with just the HPV-16 E6 and E7 genes immortalizes them. Further, the protein encoded by E6 and E7 genes from the highly oncogenic HPV types, but not from nononcogenic, have been demonstrated to bind to the protein products of the human tumor suppressor genes p 53 and Rb.

Interestingly, it has been reported recently that HPV-negative cervical cancers reveal a genetic mutation in the p 53 gene. Thus it appears that E6 and E7-mediated inactivation of a tumor suppressor gene product may represent an important event, but probably not the only one required for the full expression of malignancy in HPV-induced genital cancer (15). Other factors have already been mentioned above.

Most cutaneous types of HPV cause benign skin warts which do not turn malignant. However there is a rare condition known as epidermodysplasia verruciformis in which the child becomes infected with one or more unusual HPV types which produce red patches on the skin; later, some of the lesions tend to undergo malignant change. HPV types 5 or 8 were found in these squamous cell carcinoma; E6 gene of the two HPV types displays greater transforming activity than that of other dermotropic types (16).

The development of full malignancy requires multiple steps. A potentially neoplastic clone of cells must bypass apoptosis (programmed death), circumvent the need for growth signals from other cells, escape from immunologic surveillance, organize its own blood supply, and possibly progress in metastases (17). Tumors associated possibly with HHV-2 and probably with HPV arise as a result of a series of steps leading to progressive loss of regulation of cell division. To achieve full malignancy it should be emphasized that mutations in tumor suppressor genes may also be needed (18).

Some theories on cancer origin viewed viruses as analogous to other mutagenic carcinogens - both being capable of initiating a chain of two or more events leading eventually to malignancy. If viruses or oncogenes are considered as cocarcinogens in a sequence of genetic events culminating in a tumor, it may be important to determine whether their role is that of initiator or promoter, or both. The most probable hypothesis may be that:

- oncogenes represent targets for carcinogens (chemicals, radiation, tumor viruses)
- the full expression of malignancy may generally require enhanced expression of more than one class of oncogenes, and perhaps also mutation in both copies of critical tumor suppressor genes (1).

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