I. Introduction

A. Definition

The papillomaviruses are small DNA viruses that induce squamous epithelial tumors (warts and papillomas). The first papillomavirus described was the cottontail rabbit papillomavirus in the 1930s. Subsequently, papillomaviruses have been isolated and characterized from other vertebrate species, including man. Standard virology approaches to the study of these viruses have been limited, however, due to the lack of a tissue culture system for their propagation. This failure may, in part, be due to the fact that the productive functions of the papillomaviruses are expressed only in fully differentiated squamous epithelial cells.

B. Squamous Epithelial Cell Tropism

The productive functions of the papillomaviruses, including vegetative viral DNA synthesis and the expression of late viral genes, occur only in the fully differentiated squamous epithelial cells of the wart. Vegetative viral DNA synthesis occurs only in the more differentiated squamous epithelial cells and but not in the basal layer nor in the underlying dermal fibroblasts. Viral capsid protein production and virus assembly occur only in the super stratum spinosum and in the granular layer where the epithelial cells are terminally differentiated. As epithelial cells migrate upward through the epidermis, they undergo a program of differentiation. The control of papillomavirus viral capsid protein expression, therefore, is tightly linked to the state of differentiation of the squamous epithelial cells. The molecular basis for this transcriptional control is not yet known.

II. The Plurality of Human Papillomaviruses

There are no serologic reagents yet available to distinguish the various HPVs. Different HPV types are distinguished on the basis of their DNAs. To date, over 140 different HPVs have been described.

III. Molecular Biology

A. Sequence Analysis

Most of the papillomaviruses genomes have been completely or partially sequenced. The genomes are double-stranded closed circular molecules containing approximately 8000 base pairs. A circular map of the HPV-16 genome is shown in Figure 1.
Transcription occurs in a clockwise direction. All of the open reading frames (ORFs) greater than approximately 400 bases in size are located on one strand and are indicated as green arcs outside of the circular genome (Figure 1). These encode viral proteins. The LCR is the "long control region" which is a 1000 base pair region that contains no genes but does contain the origin for DNA replication and binding sites for transcription factors.
B. Papillomavirus Gene Functions

The known papillomavirus gene functions are listed in Table 1

**Table 1. Papillomavirus Gene Functions**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Functions</th>
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<tbody>
<tr>
<td>E1</td>
<td>DNA Replication, Helicase activity, ATP binding, ATPase.</td>
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<tr>
<td>E2</td>
<td>Viral transcription regulation and an auxiliary role in viral DNA replication. Required for genome maintenance in persistent infections.</td>
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<tr>
<td>E4</td>
<td>Abundant cytoplasmic protein; disrupts keratin filaments.</td>
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<tr>
<td>E5</td>
<td>Transformation. Prevents the down regulation of activated membrane receptors.</td>
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<tr>
<td>E6*</td>
<td>Transformation, binds p53 and promotes its ubiquitylation and degradation. Activates cellular telomerase.</td>
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<tr>
<td>E7*</td>
<td>Binds and inactivates pRB. Interferes with centrosome duplication leading to aneuploidy.</td>
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<tr>
<td>E8</td>
<td>Small open reading frame that is fused to C-terminus of E2 through mRNA splicing. Functions as a transcriptional repressor.</td>
</tr>
<tr>
<td>L1</td>
<td>Major capsid protein. Basis of VLP based preventive vaccines.</td>
</tr>
<tr>
<td>L2</td>
<td>Minor capsid protein.</td>
</tr>
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</table>

*E6 and E7 are expressed in HPV positive cancers.*
IV. Papillomaviruses and Carcinogenic Progression

A. Animal Models

The Shope papillomaviruses induces benign cutaneous papillomas in rabbits that can progress to invasive squamous cell carcinomas. First example of oncogenesis for a papillomavirus. Malignant progression is more frequent and more rapid in lesions painted with a co-carcinogen such as coal-tar or methylcholanthrene. The role of cofactors in malignant progression of papillomavirus induced lesions is a general one and may be important in those cancers associated with papillomaviruses in humans.

B. The beta genus HPVs and non-melanoma skin cancers

The first suggestion that HPV might be associated with human cancer came from the studies of Jablonska and Orth in the 1970s studying Epidermodysplasia Verruciformis (EV), a rare X-linked genetic disorder in which patients are covered with flat warts or pityriasis-like lesions that can progress to cancer. These lesions are caused by members of the beta genus of HPVs (such as types 5, 8, or 17). These lesions in about 20% of patients progress to skin cancers. These same HPV types are also often found in skin cancers of immunosuppressed patients. Whether these viruses have a role in the cancers or not has not yet been established.

C. Human Anogenital Carcinomas

Members of the alpha genus of human papillomaviruses are associated with anogenital lesions. In general, HPV-6 and HPV-11 have been associated with benign lesions and with lesions that are less likely to progress to carcinoma, and are referred to as “low risk” viruses. Approximately 14 different HPV types (most notably HPV 16 and 18) are found in the invasive carcinomas, as well as dysplasias and in situ carcinomas that may progress to malignancy. These HPV types are therefore referred to as “high risk” HPV types.

D. Head and Neck Cancers

Approximately 20% of head and neck cancers are associated with HPV. HPV-16 accounts for about 90% of the HPV-positive tumors. Most of these HPV-associated cancers are located in the oropharynx, which includes the tonsils, tonsillar fossa, base of the tongue, and soft palate. In the United States, the incidence of these cancers appears to be increasing.

E. Molecular Biology of HPV Expression in Anogenital Neoplasia

In general, HPV-16 and HPV-18 DNAs are found as extrachromosomal molecules in benign lesions. In contrast, the DNA is often integrated in malignant lesions. Integration generally occurs in a manner that disrupts the integrity of the E2 ORF of these viruses thus leading to the loss of expression of the E2 gene products. Since E2 functions as a repressor of the promoter that drives the expression of the viral E6 and E7 oncogenes, the loss of E2 leads to the deregulated expression of E6 and E7.
F. The HPV E7 Oncoprotein

The E7 protein encoded by the "high risk" HPVs is a small nuclear protein of about 100 amino acids and has functional similarities with the E1A and T-antigen transforming proteins encoded by the adenoviruses and SV40. E7 binds the product of the retinoblastoma tumor suppressor gene pRB, and RB related pocket proteins, p107 and p130. In doing so it inactivates the RB tumor suppressor activities and promotes cellular proliferation. E7 also contributes to causes genomic instability by causing abnormal centrosome duplication that can contribute to aneuploidy, one of the hallmarks of a cancer cell. E7 has many other cellular binding partners and activities that have been documented in the research literature.

G. The HPV E6 Oncoprotein

E6 also contributes to cellular transformation and does so by targeting the ubiquitylation and degradation of the cellular p53 tumor suppressor gene. E6 does so by binding to a cellular E3 ubiquitin protein ligase called the E6-associated protein (E6AP), forming a ternary complex with p53 and targeting the ubiquitin proteasome mediated proteolysis of p53. p53 functions as a sequence specific transcriptional transactivator and this functions to protect cells from genotoxic stresses by inhibiting cellular proliferation and causing apoptosis. In targeting the ubiquitylation of p53, E6 prevents apoptosis. The targeted proteolysis of p53 is a function of the high-risk HPV E6 proteins but not the low-risk HPV E6 proteins. E6 has other activities including the ability to contribute to cellular immortalization through the transcriptional activation of the catalytic subunit of telomerase.

Further Reading:
