Viruses causing Cancer (HPV)
Mechanisms of Human Disease
20190416 at 11:00 am
TM Gallagher

- Viruses are persistently infecting, lasting years in patients
- Viruses are geographically and culturally-restricted ("infectious" cancers)
- Viruses are more common than the tumors they cause (infection alone is not sufficient to cause cancer; infection is one "hit" in "multi-hit" carcinogenesis)
- Viruses operate "directly", in that the virus genomes, or parts of the genomes, are in the tumor cells (this does not apply, however, to HIV and HCV)
Virus-associated cancers:
- 10-20% of cancers are associated with virus infections.

Cervical cancers (blue) are the most common virus-associated cancers in females.

Liver cancers (purple) are the most common virus-associated cancers in males.

How do viruses cause cancers?

Papillomaviruses can be used as an example to (partially) answer this question.

Papillomaviruses cause warts (a form of epithelial dysplasia).
Some papillomavirus types can cause more severe epithelial carcinomas.

HPVs can be collected from warts:
From each type of wart (plantar warts, flat warts, anal or cervical warts, etc.), a distinct “type” of HPV is isolated.
There are nearly 100 HPV types
Type classification is based on relatedness of the HPV DNA genomes
HPV types are divided into cutaneous and mucosal groups

Note that each HPV type typically presents a distinct clinical picture, i.e., a cutaneous wart such as HPV1 will not cause a mucosal disease such as anogenital condyloma.

Cutaneous HPVs cause warts with distinct morphologies

HPVs in the mucosal group are divided into high- and low-risk categories
High-risk mucosal HPVs cause cervical intraepithelial neoplasias (CIN), which can advance to cervical carcinomas.

HPVs are nonenveloped DNA viruses (very stable viruses) that infect through breaks in epithelial layers.

The infection process that produces new HPV particles is tied to epithelial cell differentiation.
The E "early" genes are transcribed shortly after basal keratinocytes are infected.

The L "late" gene products are transcribed in the terminally-differentiated upper cell layers.

Several months elapse between inoculation and appearance of wart(s)

Cell transformation comes from abortive events that take place rarely and "stochastically" after infection of the basal cells
HPV integration into the host genome: An abortive event

E2 gene is “broken”
E6 and E7 genes are intact (note arrows)

Constitutive E6 and E7 production from integrated HPV DNA
p53 and Rb proteins can be viewed as part of an innate antiviral defense mechanism. p53 increases in response to some DNA virus infections, thereby causing cell (and thus virus) death. Viruses thwart this response to maintain themselves in nature. Some viruses interfere more effectively than others; some viruses are more tumorigenic than others.

Why are HPVs 16 and 18 "high-risk", while many others are "low-risk" for cancer?

**TABLE 46-2. Clinical Syndromes Associated with Papillomaviruses**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Common</th>
<th>Document</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skewed smear</td>
<td>1, 2</td>
<td>1, 2, 4</td>
</tr>
<tr>
<td>Cervix mass</td>
<td>2, 4</td>
<td>1, 7, 28, 29</td>
</tr>
<tr>
<td>Risk factors</td>
<td>3, 10</td>
<td>27, 38, 41</td>
</tr>
<tr>
<td>Benign squamous metaplasia</td>
<td>3, 8, 11, 26, 30</td>
<td>9, 12, 14, 15, 19, 21-25, 35, 40</td>
</tr>
<tr>
<td>Benign Verrucae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign Head and Neck tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condyloma planum</td>
<td>6, 14</td>
<td>—</td>
</tr>
<tr>
<td>Oral papillomas</td>
<td>6, 11</td>
<td>2, 16</td>
</tr>
<tr>
<td>Condyloma acuminata</td>
<td>81</td>
<td>—</td>
</tr>
<tr>
<td>Nevus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condyloma planum</td>
<td>6, 15</td>
<td>1, 2, 10, 14, 15, 44, 45</td>
</tr>
<tr>
<td>Benign squamous metaplasia</td>
<td>11, 36, 38, 42-46</td>
<td></td>
</tr>
</tbody>
</table>


**DIAGNOSIS:**

**IN HPV NEOPLASIA: LOOK FOR DYSPLASTIC CELLS**

Cervical carcinomas can be invasive (spread to regional lymph nodes) but metastasis beyond the pelvis is rare (only seen in very advanced disease)
**DIAGNOSIS:**
"Koilocytic" cells are hallmarks of HPV-induced dysplasia

- 5% of all Pap smears contain HPV-infected cells
- Development of koilocytic cells develops years after HPV infection

**Papinicolau stain:** Note vacuolated cells and haloes around nuclei

**DNA probe for HPV (*in situ* hybridization):** Note nuclei stain positive for HPV DNA. Nuclei are surrounded by vacuoles.

**THERAPY:**
Indications to remove warts: Pain, cosmetic reasons, or in the case of laryngeal papillomas, remove airway obstructions

- Surgical cryotherapy or electro cautery

- Podophyllotoxin cream [podophyllotoxin; aka PPT; is a plant-derived toxin that damages DNA to kill HPV-infected cells]

- Imiquimod cream [imiquimod is a synthetic TLR7 agonist that induces proinflammatory cytokines, notably interferons, which attract antiviral effector cells to destroy warts]

- Cidofovir [cidofovir is a nucleoside analog that blocks DNA polymerases; standard use is to reduce herpes infections but topical cidofovir has been shown to reduce some HPV-induced warts]

**In situ hybridization can identify HPV even when there is no evidence of dysplasia (i.e., neg. on pap smear)**
**VACCINATION:**

**GARDASIL**
Contains virus-like particles (VLPs) made in yeast cells
(vaccine is not recommended for patients with yeast allergies)

Vaccine contains four HPV VLPs
(types 6, 11, 16, 18). Vaccine can offer cross-protection to
some other HPV type, i.e., HPV58

Given in three injections

Protects against ~ 70% of cervical cancer (other HPV types
not present in the vaccine account for the remaining ~
30% of cancers)

Ineffective if patient already has CIN

---

**Note pharyngeal HPV-associated cancers in males**

HEAD AND NECK CANCERS are an under-appreciated justification for HPV vaccination for both girls and boys. HPV (typically HPV 16, which is included in the vaccine) can infect the squamous epithelia of the nasopharynx and oropharynx. HPV E6 and E7 contribute to development of squamous cell carcinomas of the head and neck (same MOA as for HPV-induced developments of cervical carcinomas).

Smoking, alcohol abuse and obesity are additional risk factors for developing head and neck cancers

---

A 35-year-old woman presents to her
gynecologist for a routine well-visit. She is
sexually active with multiple male partners and
uses an intrauterine device for contraception.
Her last menstrual period was two weeks ago.
She denies abnormal vaginal discharge or
sensations of burning or itching. Pelvic exam is
normal. Routine Pap smear shows the
following (see Image A). Which organism is
most likely responsible for her abnormal Pap
smear?

A. Treponema pallidum
B. Chlamydia trachomatis
C. Herpes simplex virus 1
D. Human papillomavirus
E. Trichomonas vaginalis