Tumor Viruses

Dr. Mushtak T. S. Al-Ouqaili
<table>
<thead>
<tr>
<th>Virus</th>
<th>Human cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>Genital tumors; benign or malignant</td>
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<tr>
<td></td>
<td>Oropharyngeal carcinoma</td>
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<tr>
<td>EBV</td>
<td>Nasopharyngeal carcinoma</td>
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<tr>
<td></td>
<td>African Burkitt’s lymphoma</td>
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<tr>
<td></td>
<td>B-cell lymphoma</td>
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<tr>
<td>HBV, HCV</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HTLV</td>
<td>Adult T-cell leukemia</td>
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</tbody>
</table>
Growth parameters and behavior of transformed cells

- Immortal (can grow indefinitely)
- Reduced requirement for serum growth factors
- Loss of capacity for growth arrest upon nutrient deprivation
- Loss of contact inhibition (can grow over other cells)
- Increased ability to grow in suspension
- Anchorage independence (can grow in soft agar)
- Altered morphology (appear rounded and refractile)
- Tumorigenicity
- Induction of DNA synthesis
- Chromosomal changes
Multistep Carcinogenesis

- Multistep genetic changes must occur to convert a normal cell into a malignant one. Tumors usually develop slowly over a long period of time. 3 – 8 mutations are thought to underlie this process; resulting in activation of multiple cellular oncogenes and inactivation of tumor suppressor genes.

- Tumor virus acts as a cofactor in the carcinogenesis process. Viruses are necessary but not sufficient for development of tumors with a viral etiology.
The clinical stages in the development of human colon cancer, which is the fourth most common cancer in the United States, are particularly well defined. Furthermore, as shown, several genes that are frequently mutated to allow progression from one stage to the next have been identified. The early adenomas or polyps that initially form are benign lesions. Their conversion to malignant metastatic carcinomas correlates with the acquisition of additional mutations in the \textit{p53} and \textit{dcc} (deleted in colon carcinoma) genes. Inherited mutations in the genes listed can greatly increase the risk that an individual will develop colon carcinoma. For example, patients with familial adenomatous polyposis can inherit defects in the \textit{apc} (adenomatous polyposis coli) gene that result in the development of hundreds of adenomatous polyps. The large increase in the number of these benign lesions increases the chance that some will progress to malignant carcinomas. In contrast, patients with hereditary nonpolyposis colorectal cancer develop polyps at the same rate as the general population. However, polyps develop to carcinomas more frequently because defects in genes encoding proteins that correct mismatched bases in DNA lead to a higher mutation rate. Consequently, the likelihood that an individual polyp will develop into a malignant lesion increases from 5% to 70%.
Model of progression in cervical carcinogenesis

HPV infection → Clearance

HPV infection → CIN I/II → Regression

CIN III → Invasive Cancer

Cofactors:
- Viral integration
- Smoking
- Hormones
- Immune status
- Other infections
- 2nd genetic changes

Modified from Southern and Herrington, 1998
Oncogenes

- Oncogene is a gene that causes cancer.

- Normal versions of these transforming genes are present in normal cells and have been designated proto-oncogenes.

- Cellular oncogenes represent individual components of complicated pathways responsible for regulating cell proliferation, division and differentiation.
Tumor suppressor genes

- These are negative regulators of cell growth. They form complexes with oncoproteins of certain DNA tumor viruses. The inactivation or functional loss of both alleles of such a gene is required for tumor formation.

- The prototype of these genes is retinoblastoma (Rb) gene. The function of normal Rb protein is regulated by phosphorylation.

- Another crucial tumor suppressor gene is p53 gene. p53 acts as transcription factor and blocks cell cycle progression. p53 causes cells with DNA damage to undergo apoptosis. p53 gene is mutated in over half of all human cancers.
Molecular mechanisms of viral transformation

I. Activation of cellular signal transduction pathways

- viral mimics of cellular signaling molecules
- virus-specific signal transduction molecules (EBV LMP1)
- alteration of the expression or activity of cellular signal transduction proteins
  - Bovine Papillomavirus type 1 E5 protein
  - HBV x protein
II. Cell cycle control pathways

- Abrogation of restriction point control exerted by pRb
- Inhibition of negative regulation by Rb-related proteins
- Production of virus-specific cyclins
- Inhibition of p53 functions

III. Cellular DNA repair impairment

- HBV X protein
- HCV core protein
- HPV E6 protein
Mutations in a proto-oncogenes are dominant mutations (gain of function) e.g. c-myc

However, mutations in tumor suppressor genes are recessive mutations (loss of function) e.g. p53 and retinoblastoma (pRb)
<table>
<thead>
<tr>
<th>Human cancers that involve p53</th>
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<tbody>
<tr>
<td>cervix</td>
</tr>
<tr>
<td>breast</td>
</tr>
<tr>
<td>bladder</td>
</tr>
<tr>
<td>prostate</td>
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</tbody>
</table>

In total, 60% of human cancers involve p53
80% of colon cancers involve p53 gene
p53
Guardian of the genome
- Cell cycle control
- DNA replication control
- DNA repair control
Viral Oncogenes
<table>
<thead>
<tr>
<th>Virus</th>
<th>Viral Oncoproteins</th>
<th>Cellular Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyomavirus SV40</td>
<td>Large T antigen</td>
<td>p53, pRb</td>
</tr>
<tr>
<td></td>
<td>Small t antigen</td>
<td>PP2A</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>E6</td>
<td>p53, DLG, MAGI-1, MUPP1</td>
</tr>
<tr>
<td></td>
<td>E7</td>
<td>pRb</td>
</tr>
<tr>
<td>Bovine papillomavirus</td>
<td>E5</td>
<td>PDGFβ receptor</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>E1A</td>
<td>pRb</td>
</tr>
<tr>
<td></td>
<td>E1B-55K</td>
<td>p53</td>
</tr>
<tr>
<td>Adenovirus 9</td>
<td>E4ORF1</td>
<td>DLG, MAGI-1, MUPP1</td>
</tr>
<tr>
<td>Herpesvirus EBV</td>
<td>LMP1</td>
<td>TRAFs</td>
</tr>
</tbody>
</table>

1 Abbreviations used: p53, product of \( p53 \) gene; pRb, retinoblastoma gene product; PP2A, protein phosphatase 2A; PDGF, platelet-derived growth factor; EBV, Epstein-Barr virus; TRAF, tumor necrosis factor receptor-associated factor. DLG, MAGI-1, and MUPP1 are members of a family of cellular proteins that contain PDZ domains.
Human Papillomaviruses

- Virus: 55 nm diameter
- Genome: ds DNA, circular, 8 kbp

- Highly tropic for epithelial cells of the skin and mucous membrane.
- Viral replication is strictly associated with the differentiated keratinocytes.

- Papillomaviruses causes warts, including skin warts, plantar warts, flat warts, genital condylomas and laryngeal papillomas.
HPVs are accepted as the cause of anogenital cancers including cervical cancer.

Cervical cancer is caused most commonly by HPV-16 and -18 (high risk types) and less commonly by types 31, 33, 35 and 45. Types 6 and 11 are considered low risk types causing benign tumors.

Integrated copies of viral DNA are present in cancer cells. HPV DNA is episomal in non cancerous cells or pre-malignant lesions.
<table>
<thead>
<tr>
<th>HPV types</th>
<th>Clinical lesion</th>
<th>Oncogenic potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 4</td>
<td>Plantar warts</td>
<td>Benign</td>
</tr>
<tr>
<td>2, 4, 26, 27</td>
<td>Common warts</td>
<td>Benign</td>
</tr>
<tr>
<td>6, 11</td>
<td>Anogenital condylomas, Laryngeal papillomas, Cervical intraepithelial neoplasia (CIN)</td>
<td>Low</td>
</tr>
<tr>
<td>16, 18, 30, 31, 33, 35, 45, 51</td>
<td>Genital carcinoma, Laryngeal and esophageal carcinoma</td>
<td>High</td>
</tr>
</tbody>
</table>
Model of progression in cervical carcinogenesis

HPV infection → Clearance

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CIN III

CIN III → Invasive Cancer

Cofactors
- Viral integration
- Smoking
- Hormones
- Immune status
- Other infections
- Potential genetic changes

Modified from Southern and Herrington, 1998
Herpesviruses

- Large viruses (100 – 200 nm diameter), enveloped.
- Linear ds DNA genome (124 – 235 kpb).
- Causes acute infections followed by latency.
- EBV causes acute infectious mononucleosis when it infects B lymphocytes of susceptible humans. EBV can immortalize such lymphocytes.
- EBV is linked to
  - Burkitt’s lymphoma
  - Nasopharyngeal carcinoma
  - Post-transplant lymphoma
  - Hodgkin’s disease
EPSTEIN-BARR VIRUS

EBV has a very limited host range and tissue tropism defined by the limited cellular expression of its receptor (CD21).

This receptor is expressed on

- B lymphocytes
- Epithelial cells of the oro – and nasopharynx
Diseases

- Infectious Mononucleosis
- African Burkitt’s Lymphoma
- Nasopharyngeal Carcinoma
- EBV-induced lymphoproliferative disease
EBV in saliva → Epithelial cells of oropharynx → B cells proliferation → T cells activation → Liver
   Shedding in saliva → Heterophile antibodies → Atypical lymphocytes → Lymph node
   → Spleen → swelling
   Pharyngitis
THE LATENT CYCLE

EB nuclear antigen 1 (EBNA-1)
(Viral promoter ori P)) → EBNA-2
Monoclonal antibodies (Heterophile antibodies) → B cell immortalization

Antibodies to EBNA persist for life.
Antibodies to viral capsid antigen (VCA) appear during active disease.
CD8+ T cells are activated against EBNA proteins
- Destroy infected B cells
- Atypical lymphocytes

T cell immunodeficiencies → B cell lymphoma
African (endemic) Burkitt’s lymphoma

- Poorly differentiated monoclonal B-cell lymphoma
- jaw and face
- endemic to children of malarial regions of Africa.
- The tumor cells contain chromosomal translocations that moves the C-myc oncogene to a very active promoter. (Immunoglobulin gene promoter)
LABORATORY DIAGNOSIS

- Atypical lymphocytes, lymphocytosis
- **Heterophile Antibody**
  - *(Paul-Bunnell or Monospot Test)*
  - IgM antibody that recognizes the Paul-Bunnell antigen on sheep and bovine erythrocytes but not guinea pig kidney cells. It is an excellent indication of EBV infection in adults, not children.

- **Other Serological Tests**
  - IgM antibody to VCA, most specific test.

- **Treatment**
  - No vaccine available.
  - Acyclovir is used in treating oral hairy leukoplakia.
<table>
<thead>
<tr>
<th>Disease</th>
<th>C-onc</th>
<th>translocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt's lymphoma *</td>
<td>myc</td>
<td>8 to 14</td>
</tr>
<tr>
<td>Acute myeloblastic leukemia</td>
<td>mos</td>
<td>8 to 21</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>abl</td>
<td>9 to 22</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia</td>
<td>fes</td>
<td>15 to 17</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>myb</td>
<td>6 deletion</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>myb</td>
<td>6 to 14</td>
</tr>
</tbody>
</table>

* In Burkitt's lymphoma, the c-myc on chromosome 8 is brought to a site on chromosome 14 close to the gene for immunoglobulin heavy chains. It seems that the proto-oncogene may thus be brought under the control of the Ig promotor, which is presumably very active in B lymphocytes.
Human T cell Leukemia Virus (HTLV)

- Two human isolates, HTLV-I and HTLV-II, both of which are associated with leukemias and lymphomas.
- Transmission: sexual contact and contaminated blood.
- Target cells: CD4-positive T cells.
- HTLV-I has no viral oncogene.
- It has two special genes (in addition to retroviral genes *gag*, *pol* and *env*), called *tax* and *rex* that play a role in oncogenesis by regulation of mRNA transcription and translation.
Conclusions

- Carcinogenesis is a multi-step process
- The process involves mutations of cellular proto-oncogenes and tumor suppressor genes
- Molecular mechanisms of viral transformation includes
  - Activation of cellular signal transduction pathways
  - Cell cycle control pathways
  - Cellular DNA repair impairment
- p53 role as tumor suppressor includes
  - Cell cycle control
  - DNA replication control
  - DNA repair and apoptosis