HOW VIRUSES CAUSE CANCER
WHAT CAUSES CANCER?

- Some viruses or bacteria
- Some chemicals
- Radiation
- Heredity
- Diet
- Hormones
DAMAGED GENES ARE THE ROOT CAUSE OF MOST CANCERS
BASIC PRINCIPLES

- Cancer is a disease of damaged genes.
- Chemicals and radiation directly damage the genes (the DNA) of cells that result in the loss of control of cell division.
- Viruses damage/alter the genes of cells by bringing new genes into the cell that result in the loss of control of cell division.
WHAT IS CANCER?

- Cancer is **unregulated** growth of cells.
- Wound healing is **regulated** growth of cells.
- Why does unregulated growth occur?
TWO BASIC MECHANISMS

- What causes cells to lose control of cell division?
  1. **Mutations** in the genes that encode the proteins that regulate cell division. The altered proteins lose their ability to regulate cell division.
  2. Infection of a cell by a virus. The virus brings new genes into the cell that encode proteins that alter/inhibit the proteins that regulate cell division.
NORMAL CELL CYCLE ENDING IN CELL DIVISION (MITOSIS)
ONCOGENES AND TUMOR SUPPRESSOR GENES CONTROL THE CELL CYCLE

Normal Cell Growth: The Cell Cycle

- G1 (cell growth)
- M (mitosis)
- G2
- S (synthesis)

2 homologous pairs are shown

Oncogenes

DNA repair genes

Tumor suppressor genes

Repairs Ahead
PROTO-ONCOGENES AND NORMAL CELL GROWTH

Diagram showing the interaction between growth factors, receptors, signaling enzymes, transcription factors, and DNA in the cell nucleus, leading to cell proliferation.
CONCEPT OF ONCOGENES

- Normal cell: Normal genes regulate cell growth.
- Cancer cell: Oncogenes accelerate cell growth and division.
- Mutated/damaged oncogene.
ONCOGENES ARE MUTANT FORMS OF PROTO-ONCOGENES
## IMPORTANT PROTO-ONCOGENES INVOLVED IN HUMAN TUMORS

<table>
<thead>
<tr>
<th>Proto-Oncogene</th>
<th>Neoplasm(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abl</td>
<td>Chronic myelogenous leukemia</td>
</tr>
<tr>
<td>erbB-1</td>
<td>Squamous cell carcinoma; astrocytoma</td>
</tr>
<tr>
<td>erbB-2 (neu)</td>
<td>Adenocarcinoma of breast, ovary, and stomach</td>
</tr>
<tr>
<td>H-ras</td>
<td>Carcinoma of colon, lung, and pancreas; melanoma</td>
</tr>
<tr>
<td>N-ras</td>
<td>Carcinoma of genitourinary tract and thyroid; melanoma</td>
</tr>
<tr>
<td>myc</td>
<td>Burkitt’s lymphoma carcinoma of lung, breast, and cervix</td>
</tr>
<tr>
<td>jun</td>
<td>Several</td>
</tr>
<tr>
<td>fos</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>ras</td>
<td>Carcinoma of colon</td>
</tr>
<tr>
<td>src</td>
<td>Carcinoma of colon</td>
</tr>
</tbody>
</table>

WHAT IS NORMAL FUNCTION OF PROTO-ONCOGENES AND TUMOR SUPPRESSOR GENES?

- Most of the proto-oncogenes encode either growth factors such as epidermal growth factor (EGF) or are kinases such as tyrosine kinase. The latter are regulators of the cell cycle.

- One of the tumor suppressor genes (RB) encodes a protein that inhibits E2F, a transcription factor required for the cell cycle.
HOW DO VIRUSES CAUSE CANCER?

- Viruses bring new genes into the cell.
- Viral genes act in either of two ways:
  1. Viral genes encode proteins that activate the cell cycle to drive the cell into continuous cell division. ("Foot on the accelerator" model)
  2. Viral genes encode proteins that act as inhibitors of tumor suppressor proteins. ("Foot off the brake" model)
- End result is loss of control of the proteins that regulate the cell cycle
## Examples of Human Cancer Viruses

### Some Viruses Associated with Human Cancers

<table>
<thead>
<tr>
<th>Virus</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>Human T-cell lymphotrophic virus</td>
<td>Adult T-cell leukemia</td>
</tr>
<tr>
<td>Kaposi’s sarcoma-associated herpesvirus</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>
IMPORTANT HUMAN CANCER VIRUSES

- Human T-cell leukemia virus is a member of the **Retrovirus** family (RNA genome)
- Epstein-Barr virus and Kaposi’s sarcoma virus are members of the **Herpesvirus** family (DNA genome)
- Human papilloma virus is a member of the **Papillomavirus** family (DNA genome)
- Hepatitis B virus is a member of the **Hepadnavirus** family (DNA genome)
- Hepatitis C virus is a member of the **Flavivirus** family (RNA genome)
VIRAL DNA ENTERS HUMAN DNA

Viruses

Cancer-linked virus

Virus inserts and changes genes for cell growth
HOW RETROVIRUSES CAUSE CANCER: TRANSDUCTION OF CELLULAR ONCOGENE
SARCOMA FROM FILTRATE OF ORIGINAL TUMOR IN CHICKEN (1911)
SRC GENE OF ROUS SARCOMA VIRUS (A RETROVIRUS) IS REQUIRED FOR CANCER

The genome of non-defective RSV carries an extra gene, src

The genome of transformation-defective RSV has lost the src gene

Non-defective RSV transforms cells and replicates

Defective RSV replicates but does not transform cells
A kinase is an enzyme that phosphorylates a protein.
ABL ONCOGENE ON PHILADELPHIA CHROMOSOME NOT UNDER TRANSCRIPTIONAL CONTROL: CHRONIC MYELOGENOUS LEUKEMIA

Example: Translocation of Bcr-Abl Genes

![Diagram showing the translocation of Bcr-Abl genes with a fusion protein with tyrosine kinase activity.](attachment:image.png)
IMATINIB (GLEEVEC) IS AN INHIBITOR OF BCR-ABL KINASE
## CLASSES OF RETROVIRAL ONCOPROTEINS

### Table 1 | Functional classes of retroviral oncoproteins

<table>
<thead>
<tr>
<th>Functional class</th>
<th>Examples</th>
<th>Source virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factor</td>
<td>Sis (PDGFB)</td>
<td>Simian sarcoma virus</td>
</tr>
<tr>
<td>Receptor tyrosine kinase</td>
<td>ErbB (EGFR)</td>
<td>Avian erythroblastosis virus</td>
</tr>
<tr>
<td>Hormone receptor</td>
<td>ErbA (THRA)</td>
<td>Avian erythroblastosis virus</td>
</tr>
<tr>
<td>G protein</td>
<td>Ha-ras, a GTPase</td>
<td>Harvey sarcoma virus</td>
</tr>
<tr>
<td></td>
<td>Ki-ras, a GTPase</td>
<td>Kirsten sarcoma virus</td>
</tr>
<tr>
<td>Adaptor protein</td>
<td>Crk, a modular signalling link</td>
<td>CT10 avian sarcoma virus</td>
</tr>
<tr>
<td>Non-receptor tyrosine kinase</td>
<td>Src, a signalling protein kinase</td>
<td>Rous sarcoma virus</td>
</tr>
<tr>
<td></td>
<td>Abl, a signalling protein kinase</td>
<td>Abelson murine leukemia virus</td>
</tr>
<tr>
<td>Serine/threonine kinase</td>
<td>Akt, a signalling protein kinase</td>
<td>Akt8 murine thymoma virus</td>
</tr>
<tr>
<td></td>
<td>Mos, a signalling protein kinase</td>
<td>Moloney murine sarcoma virus</td>
</tr>
<tr>
<td>Transcriptional regulator</td>
<td>Jun, a component of the AP1 complex</td>
<td>Avian sarcoma virus 17</td>
</tr>
<tr>
<td></td>
<td>Fos, a component of the AP1 complex</td>
<td>Finkel–Biskis–Jenkins murine sarcoma virus</td>
</tr>
<tr>
<td></td>
<td>Myc, a transcription factor</td>
<td>Avian myelocytomatosis virus MC29</td>
</tr>
<tr>
<td>Lipid kinase</td>
<td>Pi3k</td>
<td>Avian sarcoma virus 16</td>
</tr>
</tbody>
</table>
ONCOGENES AND TUMOR SUPPRESSOR GENES CONTROL THE CELL CYCLE
CONCEPT OF TUMOR SUPPRESSOR GENES

Tumor Suppressor Genes

Normal cell

Normal genes prevent cancer

Remove or inactivate tumor suppressor genes

Cancer cell

Damage to both genes leads to cancer

Mutated/inactivated tumor suppressor genes
TUMOR SUPPRESSOR GENES ACT AS BRAKE PEDAL
FUNCTION OF RB TUMOR SUPPRESSOR GENE IN CONTROL OF CELL CYCLE

Regulation of E2F activity through pRb phosphorylation

Active repression E2F target genes off

Transactivation E2F target genes on
VIRAL PROTEINS INACTIVATE RB SO BRAKE ONCELL CYCLE IS REMOVED

Several DNA virus oncoproteins target the retinoblastoma protein

Normal cell

Virally transformed cell

pRb E2F

E2F activity regulated by pRb

E7
Papilloma virus

pRb E1A
Adenovirus

E2F
Polyoma viruses

E2F displaced by viral proteins: Deregulated E2F activity
HUMAN PAPILLOMA VIRUS
General Organization of a Papillomavirus Genome*,
E2 GENE INACTIVATED WHEN HPV INTEGRATES INTO CELL DNA
BINDING OF E7 TO RB RELEASES E2F

E7 → RB → RB

E2F

Cell Cycle
VACCINE AGAINST HPV

**HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis**

- L1 gene of HPV DNA
  - Inside HPV
- L1 gene inserted into a plasmid
- Eukaryotic Cell
- Transcription
  - mRNA
- Translation
- Capsid proteins
- Empty viral capsid (VLP)
- Elicits immune response in host
TWO SUCCESSFUL VACCINES AGAINST HUMAN CANCER

- HPV vaccine - protects against cervical, penile, and anal cancer
- HBV vaccine - protects against liver cancer, the most common cancer worldwide
CREDITS

- Slides used in this lecture are part of the National Cancer Institute “Understanding Cancer” series.
- Two titles in this series are: “Understanding Cancer” and “Understanding Cancer Genomics”