Cancer is a diverse disease with common cellular themes

Phenotypes that distinguish cancer cells from normal cells

- Autocrine stimulation – tumor cells make their own signals to divide
- Loss of contact inhibition – normal cells stop dividing when contacted by another cell
- Loss of cell death – apoptosis normally eliminates cells with potentially serious problems
- Loss of gap junctions – normal cells have channels for communicating with neighbor cells

Cancer cells have typically lost multiple regulatory pathways that enable normal cells to respond appropriately to their environment.

Cancer cells are characterized by “genome instability” - they do not replicate and segregate their genetic information as faithfully as normal cells.

- Cancer cells often have mutations in genes required for DNA replication, repair, or segregation.

Chromosome painting or spectral karyotyping (SKY), reveals extensive chromosome rearrangements and aneuploidy.
Phenotypes that distinguish cancer cells from normal cells

Tumor cells also gain the capacity to invade through barriers that would block the growth or movement of normal cells.

...and they acquire the ability to feed themselves by secreting growth factors to promote blood vessel development.

Two classes of cancer-causing mutations

<table>
<thead>
<tr>
<th>Oncogenes</th>
<th>Mutant tumor-suppressor genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>gain-of-function, dominant mutations</td>
<td>loss-of-function, recessive mutations</td>
</tr>
</tbody>
</table>

- **Oncogenes**
  - cell heterozygous for oncogene mutation
    - Abnormal or excessive protein
    - Excessive cell proliferation
- **Mutant tumor-suppressor genes**
  - cell heterozygous for tumor suppressor mutation
    - No protein or inactive protein
    - Normal cell proliferation
  - cell homozygous for tumor suppressor mutation
    - Normal protein
    - Excessive cell proliferation

How do cancer-causing mutations arise?

Evidence indicates that most tumors are the descendants of a single normal cell.

Development of a malignant phenotype requires the acquisition of multiple mutations. These mutations often synergize with each other (remember enhancers?)

Evidence indicates that most tumors are the descendants of a single normal cell.
How do cancer-causing mutations arise?

It takes time for cells to acquire the multiple mutations that result in malignancy.

The incidence of human cancer rises sharply with age.

**Tumor Suppressors** are genes whose NORMAL function protects a cell from genomic instability.

For example: DNA replication, DNA repair, chromosome segregation, cell cycle checkpoint, and apoptosis-promoting genes.

**TABLE 19.5 Mutant Alleles of These Tumor-Suppressor Genes Decrease the Accuracy of Cell Reproduction**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Normal Function of Gene (if known), or Disease Syndrome Resulting from Mutation</th>
<th>Function of Normal Protein Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>Controls G1 to S checkpoint</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>RB</td>
<td>Controls S to G2 transition</td>
<td>Inhibits a transcription factor</td>
</tr>
<tr>
<td>ATM</td>
<td>Controls G1 to S phase, and G2 to M checkpoint</td>
<td>DNA-dependent protein kinase</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Recombinational repair of DNA damage</td>
<td>DNA/RNA ligase</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Excision of DNA damage</td>
<td>Several enzymes</td>
</tr>
<tr>
<td>FANCC</td>
<td>Correction of base-pair matches</td>
<td>Several enzymes</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Fanconi anemia</td>
<td>Unknown</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Repair of DNA breaks</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Many tumor-suppressor genes have been associated with a specific function in the cell cycle necessary for accuracy of cell division.

For example: DNA replication, DNA repair, chromosome segregation, cell cycle checkpoint, and apoptosis-promoting genes.
**Tumor Suppressors** are genes whose NORMAL function protects a cell from genomic instability.

For example: DNA replication, DNA repair, chromosome segregation, cell cycle checkpoint, and apoptosis-promoting genes.

**Tumor Suppressors** are genes whose NORMAL function protects a cell from genomic instability.

Because mutations in tumor suppressors usually act recessively to promote cancer, both copies of the gene must be mutated. How does this happen?

- Usually, a mutation in one of the two copies is followed by loss-of-heterozygosity (LOH).
- The “good” copy gets lost due to...
  - a spontaneous mutation,
  - a chromosome segregation error,
  - mitotic recombination,
  - or some other rare event.

Inherited mutations in tumor suppressor genes can cause a dominant predisposition to cancer, even though they behave recessively on a cell-by-cell basis. This is an important concept!

Retinoblastoma is inherited as a dominant trait, even though both alleles must be mutated for the tumor to develop.

A heterozygote for a mutation in the RB gene (RB+/RB−) is 36,000 times more likely to develop the disease than a RB+/RB+ individual.

**“Cancer Free at 33, but Weighing a Mastectomy”**


Deborah Lindner, 33, did intensive research as she considered having a preventive mastectomy after a DNA test.

Heterozygous mutations in the BRCA1 or BRCA2 tumor suppressor genes lead to a 36-85% chance of developing breast cancer (compared to 12.7% for all women).
ONCOGENES are normal genes (protooncogenes) in which a gain-of-function mutation leads to unregulated cell proliferation. Many oncogenes encode components of signal transduction systems.

We've talked about how gain-of-function mutations can make one protein no longer dependent on another for its function, or can simply hyperactivate a particular function.

<table>
<thead>
<tr>
<th>Name of Oncogene</th>
<th>Tumor Associations</th>
<th>Mechanism of Activation</th>
<th>Properties of Gene Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>ret</td>
<td>Stomach carcinoma</td>
<td>Rearrangement</td>
<td>Growth factor</td>
</tr>
<tr>
<td>erb-B</td>
<td>Mammary carcinoma, glioblastoma</td>
<td>Amplification</td>
<td>Growth factor receptor</td>
</tr>
<tr>
<td>trk</td>
<td>Papillary thyroid carcinomas</td>
<td>Rearrangement</td>
<td>Growth factor receptor</td>
</tr>
<tr>
<td>Ha-ras</td>
<td>Bladder carcinoma</td>
<td>Point mutation</td>
<td>GDP/GTP binding signaling protein</td>
</tr>
<tr>
<td>raf</td>
<td>Stomach carcinoma</td>
<td>Rearrangement</td>
<td>Cytoplasmic serine/threonine kinase</td>
</tr>
<tr>
<td>myc</td>
<td>Lymphomas, carcinomas</td>
<td>Amplification, chromosomal translocation</td>
<td>Nuclear transcription factor</td>
</tr>
</tbody>
</table>

*The roles of several oncogene products that are members of the signal transduction pathway and the ways in which they get activated in human cells are shown.

We've talked about how gain-of-function mutations can make one protein no longer dependent on another, or can simply hyperactivate a particular function.

ONCOGENES are normal genes (protooncogenes) in which a gain-of-function mutation leads to unregulated cell proliferation. Oncogenes can arise in several ways:

- A protooncogene (the normal version of the gene) can mutate, usually by translocation, amplification, or other rearrangement.
- A virus can carry an oncogene into a cell. Viruses often harness oncogenes as a way to promote the proliferation of the cells they infect. The replication mechanism of retroviruses makes them particularly prone to picking up genetic material from their host during an infection cycle.
- A viral infection can insert a strong promoter next to a cellular gene.

A combination of unregulated growth and genome instability creates enormous potential for new mutations to arise...in other words, oncogenes enhance tumor suppressor mutations, and vice versa.

Some cancers are caused by viruses that carry oncogenes. Cervical cancer is caused by HPV (human papilloma virus). Because HPV is a DNA virus, not a retrovirus, it took a while to convince people that this was true.

The HPV genes E6 and E7 are oncogenes. They inactivate p53 and Rb, respectively, in infected cells.

Harald zur Hausen won 1/2 of the 2008 Nobel Prize in Physiology or Medicine.