Cancer is genetic

- **Hereditary cancers**
  - Predisposition genes
  - Ex. some forms of colon cancer

- **Sporadic cancers**
  ~90% of cancers

- **Descendants of cancerous cells all cancerous (clonal)**

- **Mutagens increase cancer risk**

- **Certain mutations cause certain cancers**
Terms

• Tumor (neoplasm) = mass of cells
  – Benign = cells in a single, contained, mass
  – Malignant = invades surrounding tissue
• cells may break off and move = metastasis
• Transformed cell – has lost normal growth controls
  – Loses contact inhibition
  – Immortal
metastasis
• Oncogenesis = initiation of cancer
The cell cycle

- Time from one cell division to the next
- G1 (Gap 1)
  - Prepare
- S
  - Synthesize DNA
- G2 (Gap 2)
  - Prepare
Checkpoints are tightly controlled

Arrest cell cycle
→ repair damage or
→ send cell to apoptosis

1. $G_1$-S checkpoint
   – Should cell continue to S?
• **G\textsubscript{2}-M**
  – Is the DNA replicated
  – Is the cell large enough?

• **M**
  – Are chromosomes attached to the spindle?
• **Proteins** that control the cell cycle
  1. Cyclins
2. CDKs (cyclin-dependent kinases) complex with cyclins

<table>
<thead>
<tr>
<th>Checkpoint</th>
<th>Cyclins/CDK</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 to S</td>
<td>D/Cdk4, E/Cdk2</td>
</tr>
<tr>
<td>S</td>
<td>A/Cdk2</td>
</tr>
<tr>
<td>G2 to M</td>
<td>B/Cdk 1</td>
</tr>
</tbody>
</table>
**Table 1:** Known CDKs, their cyclin partners, and their functions in the human and consequences of deletion in mice.

<table>
<thead>
<tr>
<th>CDK</th>
<th>Cyclin partner</th>
<th>Function</th>
<th>Deletion Phenotype in Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cdk1</td>
<td>Cyclin B</td>
<td>M phase</td>
<td>None. ~E2.5.</td>
</tr>
<tr>
<td>Cdk2</td>
<td>Cyclin E</td>
<td>G1/S transition</td>
<td>Reduced size, Viable, but both males &amp; females sterile.</td>
</tr>
<tr>
<td>Cdk2</td>
<td>Cyclin A</td>
<td>S phase, G2 phase</td>
<td>Viable, fertile.</td>
</tr>
<tr>
<td>Cdk3</td>
<td>Cyclin C</td>
<td>G1 phase ?</td>
<td>Viable, fertile.</td>
</tr>
<tr>
<td>Cdk4</td>
<td>Cyclin D</td>
<td>G1 phase</td>
<td>Reduced size, diabetes. Viable, but infertile.</td>
</tr>
<tr>
<td>Cdk5</td>
<td>p35</td>
<td>Transcription</td>
<td>Severe neurological defects. Died immediately.</td>
</tr>
<tr>
<td>Cdk6</td>
<td>Cyclin D</td>
<td>G1 phase</td>
<td>Viable, fertile.</td>
</tr>
<tr>
<td>Cdk7</td>
<td>Cyclin H</td>
<td>CDK-activating kinase, transcription</td>
<td></td>
</tr>
<tr>
<td>Cdk8</td>
<td>Cyclin C</td>
<td>Transcription</td>
<td></td>
</tr>
<tr>
<td>Cdk9</td>
<td>Cyclin T</td>
<td>Transcription</td>
<td>Embryonic lethal</td>
</tr>
<tr>
<td>Cdk11</td>
<td>Cyclin L</td>
<td>?</td>
<td>Mitotic defects. E3.5.</td>
</tr>
<tr>
<td>?</td>
<td>Cyclin G</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
CDK1; cyclin A, cyclin B
CDK2; cyclin A, cyclin E
\textit{CDK3}
CDK4; cyclin D1, cyclin D2, cyclin D3
CDK5; CDK5R1, CDK5R2.
CDK6; cyclin D1, cyclin D2, cyclin D3
CDK7; cyclin H
\textit{CDK8}; cyclin C
CDK9; cyclin T1, cyclin T2a, cyclin T2b, cyclin K
\textit{CDK10}
CDK11 (\textit{CDC2L2}); cyclin L
CDK12 (\textit{CRKRS}); cyclin L
CDK13 (\textit{CDC2L5}); cyclin L
Figure 20.2

Complex forms between $G_1$ cyclin and Cdk; the Cdk phosphorylates proteins needed for progression into S

Detailed overview  WH Freeman
3. Signal transducers

Growth factor receptor complex cascade Plattsburgh
Genes

Proto-oncogenes (Harold Varmus and Michael Bishop Nobel Prize 1989)

– Genes involved in cell cycle
– All people have them

100 identified → Table 20.2
<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Factors</td>
<td>c-sis, Int-2, PDGF B chain, FGF-related growth factor</td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinases</td>
<td>c-erbB, c-fms, neu (c-erbB-2), c-src, C-abl</td>
<td>EGF receptor, CSF-1 receptor, EGF receptor-like</td>
</tr>
<tr>
<td>Serine/threonine kinases</td>
<td>c-raf-1</td>
<td></td>
</tr>
<tr>
<td>G-protein-like</td>
<td>c-Ha-ras, c-Ki-ras, c-N-ras</td>
<td></td>
</tr>
<tr>
<td>Nuclear proteins</td>
<td>c-erbA, snoA and B, c-myb</td>
<td>Thyroid hormone receptor</td>
</tr>
<tr>
<td>Leucine zipper protein</td>
<td>c-fos, fra-1 and -2</td>
<td>AP-1 complexes</td>
</tr>
<tr>
<td>Helix-loop-helix</td>
<td>c-myc</td>
<td></td>
</tr>
</tbody>
</table>
• If mutated $\rightarrow$ **oncogene**
• Leads to uncontrolled growth $\rightarrow$ tumor
• Dominant mutation
• Skip viral oncogenes pages 582 - 584
Proto-Oncogenes and Proteins

Growth Factors

GF receptors

Signal transducers

- Bone morphogenetic proteins (BMPs)
- Brain-derived neurotrophic factor (BDNF)
- Epidermal growth factor (EGF)
- Erythropoietin (EPO)
- Fibroblast growth factor (FGF)
- Glial cell line-derived neurotrophic factor (GDNF)
- Granulocyte macrophage colony-stimulating factor (GM-CSF)
- Hepatocyte growth factor (HGF)
- Insulin-like growth factor (IGF)
- Nerve growth factor (NGF)
- Platelet-derived growth factor (PDGF)
- Thrombopoietin (TPO)
- Transforming growth factor beta (TGF-β)
- Tumor_necrosis_factor-alpha (TNF-α)
- Vascular endothelial growth factor (VEGF)
- Placental growth factor (PIGF)

Stimulate cell division in target cells
Oncogene examples:

**HER2** (Human Epidermal Growth Factor Receptor 2) is encoded by the *ERBB2* gene. Overexpression of the gene has been shown to play a role in the progression of 30% of breast cancers. Overexpression of this gene has also been observed in ovarian, stomach, and uterine cancer.

**Ras** proteins transduce signals from growth factor receptors. These signals are then passed protein-to-protein along several different pathways, ultimately effecting mitogenic functions such as lipid metabolism, DNA synthesis, and cytoskeletal organization. Disruption of these signals through mutation of the *ras* gene is involved in many tumor types, including roughly half of all colon cancers and 90% of pancreatic carcinomas.

**Myc** is a nuclear transcription factor involved in the expression of ~15% of all genes. Found mutated in bladder, breast, colon, stomach, melanoma, brain, ovarian, prostate…… cancers
The EGFR story

• A growth factor receptor $egfr$ (epidermal growth factor receptor).
• The proto-oncogenic needs EGF to bind to to enable its kinase activity
• Phosphorylation ultimately leads to translation of proteins involved in mitosis.
• The oncogenic form of $egfr$ produces a receptor that does not require binding of growth factor, but instead is constitutively active
• Why is this a dominant mutation?

iGenetics Regulation of cell division in normal cells
Try iactivity in chapter 10 online – tracking down the cause of cancer
KNOW THE FLOW

cancer quest