Cancer Genes & Cancer Genetics

No office hours this Friday (5-1). Please set up an appointment if you have any questions.
roelink@berkeley.edu

Reading: pp. 202-220
Somatic Cells/Germ line mutations

Mutations
- Usually little effect, cell death for damaged cell; however, all cancers arise from somatic cell mutation, one cell confined to one tissue
-passed on to progeny, all tissues, Mendelian

Mutations
- Passed on to progeny, all tissues, Mendelian

SOMATIC CELLS
- Embryo proper
- All tissues

GERM LINE
- Female: eggs (precursors)
- Male: sperm

This nothing to do with bugs
<table>
<thead>
<tr>
<th>Component</th>
<th>Acquired Capability</th>
<th>Example of Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>🟢</td>
<td>Self-sufficiency in growth signals</td>
<td>Activate H-Ras oncogene</td>
</tr>
<tr>
<td>🟦</td>
<td>Insensitivity to anti-growth signals</td>
<td>Lose retinoblastoma suppressor</td>
</tr>
<tr>
<td>⚽️</td>
<td>Evading apoptosis</td>
<td>Produce IGF survival factors</td>
</tr>
<tr>
<td>🌟</td>
<td>Limitless replicative potential</td>
<td>Turn on telomerase</td>
</tr>
<tr>
<td>🟣</td>
<td>Sustained angiogenesis</td>
<td>Produce VEGF inducer</td>
</tr>
<tr>
<td>🟤</td>
<td>Tissue invasion &amp; metastasis</td>
<td>Inactivate E-cadherin</td>
</tr>
</tbody>
</table>

B

[Diagram with arrows and Cancer circle]
Uncontrolled cell division comes from accumulation of genetic defects that lead to too much "go" signal, too little "stop" signal, and loss of cell suicide.

Proliferation and programmed cell death tightly regulated to ensure the integrity of organs and tissues.
The Cell Cycle

Mitosis (M-phase)

G1

S

G2

Checkpoint

proto-oncogenes (+)

tumor suppressors (-)

STOP

GO

STOP
Checkpoints ensure the cell cycle proceeds without errors.
Cancer Genes

Accumulation of multiple mutations

Potential cancer genes - about 100 (0.3% of total) genes

Inappropriate signals about need for cell division (hormonal signaling pathways: growth factors)

Malfunctions in (CDK-cyclin) complexes controlling cell cycle transitions

Checkpoint breakdowns leading to DNA instability

Loss of programmed cell death (cell suicide)

Invasion/Metastasis
**Part 1: Tumor Suppressor Genes**

**Function**

STOP signal at cell cycle checkpoint; DNA repair or apoptosis

**Loss-of-Function (LOF)**

no checkpoint stop; no DNA repair; cell cycle continuously cycles

---

**BRCA example**

Inherited BRCA1 mutation
breast cancer frequency
20% by age 40y
50% by age 50y
85% by age 60y

1 inherited germline mutation +
1 spontaneous somatic mutation

(inherited mutation all breast cells)

Inheritance:
- 2 copies: 1 good copy enough (somatic recessive)
- 1 inherited germline mutation + 1 spontaneous somatic mutation

Stop

----
Breast Cancer Genes

tumor suppressor genes

Breast cancer (inherited) 10%
BRCA1 or BRCA2 mutations 8%
US citizens 0.2%
Askenazi Jews 2.5%
All cases under 50 7%
Under 40 10%

BRCA 1
(location = D17S74)

BRCA 2
(q12-13)

Ch 17

Ch 13

NIH website
Function of BRCA proteins.
DNA damage, BRCA1 regulates repair:
a) gene transcription 
b) transcription-coupled DNA repair 
c) homologous recombination (double-strand break repair)
Defective BRCA1 (or BRCA2) - no repair
Activation of the p53-mediated cell cycle checkpoint(s):
a) Apoptosis (cell suicide) 
b) Cell cycle arrest 
c) Tumorigenesis
**p53**: The “guardian” of the genome

<table>
<thead>
<tr>
<th>Li-Fraumeni Syndrome (p53 heterozygote)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ several kinds of cancer are involved,</td>
</tr>
<tr>
<td>▪ cancer often strikes at a young age, and</td>
</tr>
<tr>
<td>▪ cancer often strikes several times throughout the life of an affected person.</td>
</tr>
</tbody>
</table>
>50% (!) of human tumors have abnormal p53 activity
pRb was the first ‘classic’ tumor suppressor

The disease; retinoblastoma

Retinoblastoma is a cancer which develops in the cells of the retina
-one of the less common cancers of childhood
-accounts for only about 3 out of every 100 cancers occurring in children under the age of 15 years

Children present with:
-an abnormal appearance of the pupil which reflects light as a white reflex, like a cat's eye.
-a squint.

An extreme example of leukocoria.
Tumor-Suppressor Gene: Rb (Retinoblastoma)
(eye tumor example)

CDK4/cyclinD complex phosphorylates Rb

Inactive Transcription Factor, E2F

Active Transcription Factor, E2F

Gene expression: cell progresses through cell cycle
Human Papiloma Virus (HPV)

AGE 14 to 19y (female)  25% HPV prevalence
AGE 20 to 24y (female)  45% HPV prevalence

Genital Warts
Cervical Cancer
Penile Cancer

14,000 U.S. women/year diagnosed cervical cancer
3,900 U.S. women/year die

National Cervical Cancer Coalition (NCCC) and Journal of the American Medical Association
HPV Types

HPV - Family of about 100 DNA-based viruses

A group of about 30-40 HPVs typically transmitted through sexual contact

Genital Warts
types 6 and 11 (90% of all cases)

Cervical Cancer
types 16, 18, 31 and 45

Some of the HPV "early" genes, such as E6 and E7, known to act as Oncogenes that promote tumor growth and malignant transformation.

HPV-induced cancers often have viral sequences integrated into the cellular DNA.
Your Choice
Part 2: Proto-Oncogenes (the GO signal)

Hormonal/Growth Factor Regulation

Proto Oncogene
(Normal gene product)

Mutation

self activated
(on only)

Oncogene
(Mutant gene product)
Dominant Oncogene
("Gain of Function" mutation)

mutant gene → excessive protein or abnormally active protein
(on only)

(normal gene)
(on/off)

GO
Dominant
Possible ways to activate proto-oncogenes

Three basic types

Protein Structure Changed

- a) increased enzyme activity
- b) loss of regulation

Protein Concentration Increased

- a) increased expression (through misregulation)
- b) increased protein stability, prolonging its existence
- c) gene duplication/amplification

Make a “new” gene often via chromosomal translocation

- a) expression in wrong cell type or at wrong times
- b) constitutively active hybrid protein
  (responsible for adult leukemia in hematopoietic stem cell)
Protein Structure Changed
Point Mutation, single bp change single aminoacid change

Oncogene: RAS
3 highly related genes in the genome
Chromosomal Translocation

BCR-Abl

Figure 1: The Philadelphia (Ph) Chromosome

Before translocation

ABL
#9

#22

BCR

After translocation

der(9)

Ph chromosome

ABL BCR

When chromosomes 9 and 22 exchange portions of their genetic material, this translocation results in the formation of der(9), an elongated chromosome 9, and the Ph chromosome, which contains the hybrid BCR-ABL gene.
Gleevec (amatinib), one of the first examples of “designer” anti cancer drugs
<table>
<thead>
<tr>
<th>Component</th>
<th>Acquired Capability</th>
<th>Example of Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Flag" /></td>
<td>Self-sufficiency in growth signals</td>
<td>Activate H-Ras oncogene</td>
</tr>
<tr>
<td><img src="image2" alt="Stop Sign" /></td>
<td>Insensitivity to anti-growth signals</td>
<td>Lose retinoblastoma suppressor</td>
</tr>
<tr>
<td><img src="image3" alt="Cross" /></td>
<td>Evading apoptosis</td>
<td>Produce IGF survival factors</td>
</tr>
<tr>
<td><img src="image4" alt="Infinity" /></td>
<td>Limitless replicative potential</td>
<td>Turn on telomerase</td>
</tr>
<tr>
<td><img src="image5" alt="Heart" /></td>
<td>Sustained angiogenesis</td>
<td>Produce VEGF inducer</td>
</tr>
<tr>
<td><img src="image6" alt="Tissue Invasion" /></td>
<td>Tissue invasion &amp; metastasis</td>
<td>Inactivate E-cadherin</td>
</tr>
</tbody>
</table>

B

![Diagram](Diagram)