Genetics of Cancer

1. Properties of Cancer
2. Regulation of normal proliferation
3. Genes involved with cancer
4. Causes of Cancer
5. Cancer Therapies

Cancer

1. Increased Proliferation
   Increase cell division/decrease cell death
2. Cell migration - metastasis
Incidence

Lifetime Risk
Men ~1 in 2 (~50%)
Women ~1 in 3 (~33%)

Clonal, progressive, genetic
Regulation of normal cell proliferation

- Cell Cycle Checkpoints
  - “cell brake”
- Hormonal Regulation of Cell Growth
  - “accelerator”
- Apoptosis
  - “emergency brake”
- Genomic stability
  - “maintenance”
Checkpoint Machinery

Conc of Cdk and Cyclin D

Different cyclins for different checkpoints
Cyclin/cdk targets
Rb example

G2 Cell
- E2F activation domain masked
  - No production of DNA polymerase

Late G1 Cell
- Rb phosphorylated by Cdk
- Phosphorylated RB releases E2F
- E2F recruits CBP
- DNA polymerase gene transcribed

Hormonal Regulation

1. Growth factor binds to cell surface receptor
2. Ras transiently exchanges GTP for GDP
3. Ras sends signal to cascade of activated proteins
4. Signal transduction proteins activate transcription factors
5. Activation or repression of gene transcription
Apoptosis

 Regulation of Apoptosis

Unregulated
Cell division

DNA Damage

Activate p53

Inhibits Bcl-2

Release Cytochrome c

Excess Mutagens

Defective DNA Repair

http://plaza.ufl.edu/cleeuwen/LECTURE-6.PDF
Genomic Instability

• DNA Repair mechanisms
  – BER
  – NER
  – Others

Xeroderma – genetic defect in NER

Two types of Cancer Genes

Oncogenes
  – dominant effectors of cancer

Tumor suppressor genes
  – normally suppress cancer
  – loss of both alleles triggers cancer. (null allele acts like a recessive effector of cancer)
Oncogenes

- Viral Oncogenes
  - Oncoviruses
    - Rous Sarcoma Virus - chickens
    - Harvey and Kirsten rat sarcoma viruses
  - Viral Oncogenes
  - Source – host genome

![Diagram of Oncogene Structure with LTR, gag, pol, env, and Ras]

Proto-oncogenes → Cellular Oncogenes

Classes of cellular oncogenes

1. Growth Factors
2. Growth Factors receptors
3. Signal Transduction proteins
4. Transcription Factors

![Diagram of Growth Factor Pathway]

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Mutations in proto-oncogenes

Alberts, Mol Biol of the Cell, 4th ed
Classes of Tumor Suppressor Genes

- Genes involved in checkpoints
- Genes that stimulate apoptosis
- Genes important to genomic stability

Genes involved in checkpoints
Example Rb

2 copies Rb gene

<table>
<thead>
<tr>
<th>Rb</th>
<th>NuCoR</th>
<th>DNA Pol Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2F</td>
<td></td>
<td></td>
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</tbody>
</table>

Cell cycle inhibited

1 copies Rb gene

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Cell cycle inhibited
Genetic Predisposition Retinoblastoma

0 copies Rb gene

<table>
<thead>
<tr>
<th>CBP</th>
<th>E2F</th>
<th>DNA Pol Gene</th>
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</thead>
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Cell cycle inhibited
Retinoblastoma
Genes that stimulate apoptosis
example p53

DNA Damage → Activate p53 → Inhibits Bcl-2 → Release Cytochrome c

DNA Damage → Activate p53 → Induces p21 expression → P21 inhibits Cyclin/cdk → Rb not phosphorylated

Genes important to genomic stability

• Example
  – BRCA2 – repair of double strand breaks

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>Cumulative Risk(%)</th>
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</thead>
<tbody>
<tr>
<td>30 yrs</td>
<td>3.2%</td>
</tr>
<tr>
<td>40 yrs</td>
<td>19.1%</td>
</tr>
<tr>
<td>50 yrs</td>
<td>50.8%</td>
</tr>
<tr>
<td>60 yrs</td>
<td>54.2%</td>
</tr>
<tr>
<td>70 yrs</td>
<td>85%</td>
</tr>
</tbody>
</table>
Order progression of tumor suppressor and oncogene mutations

Cooper, The cell, a molecular approach, 2nd ed.

Epidemiology

Cancer	Cancer Epidemiology
Breast Cancer	High Incidence
Stomach	Hawaiians 1/1000
Lip	Japan .8/1000

Low Incidence
Palestinians .05/1000
Palestinians .03/1000
Japanese .001/1000

{New cases/year}
Causes of Cancer

• Carcinogens
  – Chemical mutagens
    • Tumor initiator
  – Non-mutagenic carcinogens (Tumor Promoter)
    • Phorbol esters (TPA)
• Tissue irritation
• Viruses
  – Papovavirus – uterine cancer
  – Epstein-Barr virus – Lymphoma
  – HIV – Kaposi sarcoma
• Genetic Predispositions

Other Causes
Treatments for Cancer

• DNA damaging treatments
  – Radiation
• Targeted Therapy
  – Tamoxifen (estrogen agonist)
  – Viruses that target p53 lacking cells
  – Target angiogenesis
  – Target oncogenes like BCR-ABL fusion
• Note cancers evolve in response to selective pressures of treatments.