Life Sciences 1a: Section 3A. Cancer: the enemy within

Objectives
Understand the distinction between the germ line and the soma
Understand how multicellular organisms enforce strict rules governing cell growth, proliferation, and death
Understand how accumulating multiple mutations allows cancer cells to overcome these rules
Understand the role of environmental and genetic factors in causing human cancer
Understand that cancer is a multitude of different diseases

Introducing cancer
Definitions: cell growth, proliferation, benign and malignant cancer
1971: Nixon declares war on cancer
2005: major decline in mortality from rare cancers, minor decline for common one (breast, lung, colon)

Germ line and soma
Our bodies evolutionary purpose: projecting our gametes as far into the future as possible
Germ line: eggs, sperm, and the cells that give rise to them
Soma: all other cells
Soma supports germ line because germ-line and somatic cells are genetically identical
All cells except egg and sperm are diploid
Germ-line mutation rate: 75 mutations per genome per human generation, roughly 4 in non-junk DNA
Most deleterious human mutations are recessive to the wild type form of the gene
Somatic mutations: most innocuous, a small fraction can give rise to cancer
Human body: a cooperative of more than 100 cell types

Regulating cell proliferation and defects in regulation in cancer cells
Proliferation and death of each cell type must be carefully regulated
Proliferation is regulated by matching supply and demand: small imbalances lead to long term problems
Most cells are neither growing nor proliferating
Cancer cells differ from normal cells in multiple ways:
1) Grow and proliferate when they should not
2) Ignore instructions to commit suicide (apoptosis)
3) Induce blood vessel growth
4) Metastasize: enter blood vessels, exit, and establish tumors at new sites
5) Genetic instability (increased point mutation, chromosome breakage or loss)

Epidemiology
Cancer has not been selected against because it occurs too late in human life
Number of mutations can be estimated from analyzing dependence of cancer incidence on age
Cancer rates show wide geographic variation & population migrations cause changes in cancer rates
Conclusion: important environmental factors play a major role in setting population cancer rates
SMOKING CAUSES LUNG CANCER CAUSES DEATH
Rare, strong mutations strongly predispose individuals to cancer
Examples: HNPCC (mismatch repair defective), adenomatous polyposis coli (APC)
Situation with common, weaker mutations much less clear
Different cancers have different mutations and destabilize genomes in different ways:
HNPCC (increased frequency of point mutations), APC (increased chromosome loss)

Reading: Alberts: pp. 293-294 (germ-line and soma) 726-736 (cancer)
3A. Cancer: the enemy within

1. An introduction to cancer Alberts, 726-730

2. The germ line and soma Alberts, 293-294
   a. Multicellularity and the division of labor
   b. Germ line mutations affect the next generation
   c. Somatic mutations affect this generation

3. Cell Proliferation and Cancer
   a. Balancing cell birth and death
   b. Multiple changes in cell behavior cause cancer

4. The epidemiology of cancer Alberts, 727-735
   a. Cancer results from multiple mutations
   b. Environmental contributions to cancer
   c. Genetic contributions to cancer

Cancer definitions

Cell growth: increase in cell mass

Cell proliferation: increase in cell number

Tumor: a group of cells that has grown and proliferated inappropriately

Benign tumor: confined to one part of the body, no migration

Malignant tumor: cells can escape, migrate, and settle at new locations, and establish secondary tumors (metastasis)

Cancer: malignant tumor
Committing to a man on the moon: May 25th, 1961

Apollo 11 landing: July 20th, 1969
Apollo program cost: $135 billion

Declaring war on cancer: Jan 22nd, 1971

Cost so far: > $200 billion
**Germ Line & Soma**

Multicellularity and the division of labor

Germ line mutations affect the next generation

Somatic mutations affect this generation
Germ-line and somatic mutations and cancer

Germ-line mutations can cause cancer in our children

Somatic mutations can cause cancer in us
All cells except eggs and sperm are diploid

3 x 10⁹ bp 
(23 chromosomes)

6 x 10⁹ bp
(46 chromosomes)

25 cell divisions

6 x 10⁹ bp

3 x 10⁹ bp

Mutation rates in HIV and woman

<table>
<thead>
<tr>
<th></th>
<th>Haploid Genome size</th>
<th>Mutations per bp per generation</th>
<th>Mutations per genome per generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>10000</td>
<td>3 x 10⁻⁵</td>
<td>0.3</td>
</tr>
<tr>
<td>Human cell</td>
<td>3 x 10⁹</td>
<td>10⁻⁹</td>
<td>3*</td>
</tr>
<tr>
<td>Human being</td>
<td>3 x 10⁹</td>
<td>2.5 x 10⁻⁸</td>
<td>75*</td>
</tr>
</tbody>
</table>

* Only 5% of these are in “useful” DNA
Dominant and recessive forms of a gene

*blue/blue*  *blue/BROWN*  *BROWN/BROWN*

*blue* is recessive, *BROWN* is DOMINANT

Different cells, different life styles

**Neutrophil**
- Life: 3 days
- Number: $2 \times 10^{10}$
- 80,000 born/sec

**Red blood cells**
- Life: 120 days
- Number: $2 \times 10^{13}$
- 2,000,000 born/sec

**Neuron (Purkinje cell)**
- Life: 100 years
- Number: $2 \times 10^{7}$

http://www.mcl.tulane.edu/lsavoie/pathology/Krause/Blood/Neutrophil.jpg

http://www.mcl.tulane.edu/lsavoie/pathology/Krause/Blood/Neutrophil2.jpg

Figure 11-8: Essential Cell Biology, 2nd, (c) 2004 Garland Science
Figure 1-1: Essential Cell Biology, 3rd. (c) 2004 Garland Science
Cancer: cell proliferation & behavior

Balancing cell birth and death

Multiple changes in cell behavior cause cancer

Balancing death and proliferation

Cell birth rate = 1.01 x Cell death rate

Start

1 month
(1.01^{31} = 1.36 x)

1 year
(1.01^{365} = 38 x)
Exponential proliferation is rare

1 month → 2 months → 3 months → 9 months

Some big scary numbers

Number of cells in your body ≈ 60,000,000,000

Number of cell divisions in a lifetime ≈ 10^{16}

Mutation rate ≈ 10^{-9}/base pair/cell division

Times any mutation occurs = 10^{-9} \times 10^{16} = 10,000,000
Problems with cell division: Cancer

Normal Cell
Obeys strict rules
Divides only when told to
Dies rather than misbehaving
Stays close to home
Careful with chromosomes

Cancer Cell
Disobeys rules
Divides at will
Bad behavior doesn’t kill
Wanders through body
Careless with chromosomes

At least 5 mutations

Cancer: Required genetic changes

1) Grow and proliferate under conditions where normal cells do neither
2) Ignore signals telling badly behaving cells to kill themselves (apoptosis)
3) Induce the growth of new blood vessels
4) Enter and exit blood vessels and form tumors at new sites (metastasis)
5) Become genetically unstable (increased mutation rate)
Cancer is an evolutionary disease

Evolution leads to imperfection: selecting for increased growth and proliferation is eventually suicidal

A few genetic changes can drastically alter cell behavior

Prolonged, strong selection selects for mutators

Cancer: Epidemiology

Cancer results from multiple mutations

Environmental contributions to cancer

Genetic contributions to cancer
Why natural selection hasn’t eliminated cancer

![Graph showing incidence of cancer](image)

UK life expectancy 1750

Multiple mutations: the dice analogy

Dice have one hundred sides and get thrown once a year

One dice: need to throw a hundred once to win

Two dice: need to throw a hundred on each dice, but not in the same year

<table>
<thead>
<tr>
<th>Probability of winning in</th>
<th>1st year</th>
<th>2nd year</th>
<th>3rd year</th>
</tr>
</thead>
<tbody>
<tr>
<td>One dice</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Two dice</td>
<td>0.01%</td>
<td>0.04%</td>
<td>0.09%</td>
</tr>
</tbody>
</table>
Cancer requires multiple mutations: the dice analogy

Linear scales

<table>
<thead>
<tr>
<th>Winning Probability</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
<td>0.04</td>
<td>4</td>
</tr>
<tr>
<td>0.06</td>
<td>6</td>
</tr>
<tr>
<td>0.08</td>
<td>8</td>
</tr>
<tr>
<td>0.1</td>
<td>10</td>
</tr>
</tbody>
</table>

Log scales

<table>
<thead>
<tr>
<th>Log(p(Success))</th>
<th>Log(Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9</td>
<td>0</td>
</tr>
<tr>
<td>-8</td>
<td>0.2</td>
</tr>
<tr>
<td>-7</td>
<td>0.4</td>
</tr>
<tr>
<td>-6</td>
<td>0.6</td>
</tr>
<tr>
<td>-5</td>
<td>0.8</td>
</tr>
<tr>
<td>-4</td>
<td>1</td>
</tr>
</tbody>
</table>

Cancer rates vary widely

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Region with highest rate (per 1000)</th>
<th>Region with lowest rate (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Queensland, Australia</td>
<td>Bombay, India</td>
</tr>
<tr>
<td></td>
<td>&gt;200</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan</td>
<td>Uganda</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>5</td>
</tr>
</tbody>
</table>

Indirect association: migrations alter cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Rate in Japan</th>
<th>Japanese immigrants to California</th>
<th>Sons of Japanese immigrants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>6.5</td>
<td>4.6</td>
<td>3</td>
</tr>
<tr>
<td>Colon</td>
<td>0.2</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.1</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

All rates relative to white Californian males.

*After Cairns, J., Cancer: Science and Society, W.H. Freeman, 1978*

Smoking causes lung cancer causes death
Rare mutations can cause cancer

<table>
<thead>
<tr>
<th>Subject</th>
<th>Chance of colorectal cancer</th>
<th>Average age of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.04</td>
<td>65</td>
</tr>
<tr>
<td>HNPCC mutant (0.2% of population)</td>
<td>0.8</td>
<td>44</td>
</tr>
<tr>
<td>APC mutant (0.01% of population)</td>
<td>1</td>
<td>39</td>
</tr>
</tbody>
</table>

Different cancers destabilize genomes in different ways

HNPCC: 46 chromosomes, no major rearrangements

Familial APC: 71 chromosomes