Cancer and Oncogenes
Bioscience in the 21st Century

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• Just a Few Numbers

• Becoming Cancer

• Genetic Defects

• Drugs
Our friends and family

- More mutations as you get older
- More DNA damage due to environment
- One mutation can lead to others
Required characteristics

- Original hypothesis – 2 mutations, one in signaling and one in the nucleus.
- Statistical analysis says more like 5 or 6 mutations probably contribute to cancer.
- Typically at least one mutation is in a proliferation pathway.
- Benign→cancer requires at least one additional mutation.
- And, almost certainly, there are other major chromosome changes.
Evolution of a cancer cell
Abilities acquired

- Grow without outside signals or cues
- Ignore neighboring cells (don’t stop)
- Don’t age, normal cells are limited
- Recruit new blood vessels for oxygen and nutrients
- Escape suicide signals (also the immune system)
- Invade and migrate (several steps here)
Epithelial cells from the digestive tract develop from a small number of stem cells.
Normal | Dysplasia

- Pre-malignant
- Appear abnormal
- Some excess growth
- Ideally when you would like to identify the problem
✓ Increased cell proliferation

✓ Additional possible changes here include decreased ability to catch mistakes
✓ Epithelial to mesenchymal transition.

✓ Cells are able to change characteristics and gain the ability to migrate across barriers or through membranes.
Extravasion

Blood vessels are recruited for nutrient delivery. Typically, these new vessels are much more leaky than regular blood vessels and are also disorganized.
One pathway

Normal Epithelium → APC → Hyperplastic epithelium

Smad 4 → Intermediate Adenoma → Kras → Early Adenoma

Late Adenoma → p53 → Carcinoma

Me of DNA → Invasion and Metastasis
Colon cancer genes (APC)

- APC > 70%
  - Binds β-catenin – Colon cell differentiation
- kRas ~ 50%
  - Activation of signals for growth
- DCC > 70%
  - Cell-cell adhesion
- p53 > 70%
  - Lots of changes allowed - carcinoma
- smad4 ~ 20%
  - Transcription factor – gene expression
Two ways to change

Figure 11-17 The Biology of Cancer (© Garland Science 2007)
Figure 11-18 The Biology of Cancer (© Garland Science 2007)
Cell Cycle

Restriction point

Cdk2/CycE

Cdk4,6/CycD

Cdk2/CycA

M

Cell cycle

G_1

G_2

S

Cdc2/CycB
Growth factors and the cell cycle

Together these pathways result in a complicated plan that results in a balance of proteins and other factors leading to cell growth and division.
In many Small Cell Lung Carcinoma patients, lots of SCF (stem cell factor) is produced and the cells also contain the growth factor receptor for this molecule. Therefore, continuous growth signaling occurs.
Ras signaling and cancer

Many mistakes in this pathway have been identified.
Ras (a G protein)

Mutant Ras doesn’t remove a Pi easily.

A protein that associates with Ras to help it remove a Pi is defective.
PI3K > PIP2 > PKD > Akt...
Types of genes that get mutated

- **Oncogenes** – gain of function
  - Hybrid proteins that change function
  - Over-production of a protein
  - Activity increases
  - **CANCER ONLY NEEDS ONE BAD COPY**

- **Suppressor** – loss of function
  - They can’t check growth
  - **USUALLY YOU LOSE BOTH GENES**
Massive changes in the nucleus

Absence of BUB

Missing Check point protein

SKY painting

Translocations, duplications, deletions
Early Chemotherapy

- Targets – rapidly growing cells.

Small molecules ≠ ATP, etc.
NTP ≠ dNTP
dNTPs ≠ DNA
Drug Antibodies

• Antibodies against growth factor receptors or modified forms of the receptors.

✓ Antibodies might recruit the immune system
✓ Antibodies might block ligand binding to remaining receptors
✓ Antibodies might block receptor function
Small molecule drugs

- Small molecule inhibitors.

- Some of these small molecule drugs are initially effective, but cancer cells can sometimes acquire mutations that make them less effective over time.
Long term goals

• Ultimately, targeting the stem cells that are cancerous rather than only the most rapidly growing cells will be important.

• Development of specific drugs based on specific cancer situations is also continuing.