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
Data from 2009

- More mutations as you get older
- More DNA damage due to environment
- One mutation can lead to others
Other similar data

Weinberg, the Biology of Cancer

Figure 11-3 The Biology of Cancer (© Garland Science 2007)
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.
Evolution of a cancer cell
Abilities acquired

- Grow rapidly
- Dissociate from neighboring cells
- Invade adjacent tissue
- Invade blood vessels or lymphatic system
- Escape immune system
- Arrest in a new location
- Get into target tissue
- Proliferate in new location
Normal Dysplasia

Pre-malignant, appear abnormal

Figure 12-2a The Biology of Cancer (© Garland Science 2007)
Carcinoma

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.
Blood vessels are recruited for nutrient delivery.
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
Many pathways
Two ways to change

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

Figure 11-18 The Biology of Cancer (© Garland Science 2007)
Reactive oxygen species damage DNA

deoxyguanosine (dG) → 8-oxo-deoxyguanosine (8-oxo-dG)

deoxy 5-methyl-cytosine (d 5’mC) → deoxythymidylde glycol (dTg)
Damage outcomes

mispairing of 8-oxo-dG with deoxyadenosine (dA)

Figure 12-12b The Biology of Cancer (© Garland Science 2007)
But repair enzymes fix most problems

- If you cannot fix the all of the DNA damage, mistakes accumulate more rapidly and cancer usually starts earlier.
- An example is individuals with Li-Fraumeni syndrome whose cells do not recognize damage (faulty p53).
- Another example is Xeroderma Pigmentosum, where patients cannot repair UV damage and get skin cancer more rapidly than most people – with much less exposure.
Growth factors and the cell cycle

Mitogens

PL3K > PIP2 > PKD > Akt...

PLC > DAG (+IP3) > PKC (+Ca)

Grb > Sos > Ras > Raf...

Src > MAPK pathway

Others

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.

Fos ← Ets ← MAPK ← MAPKK
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 if there is a defect leading to cancer
Early Chemotherapy

- Targets – rapidly growing cells.

Small molecules to ATP, etc.

NTP to dNTP

dNTPs to 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. Some cancer cells make pumps to dump the drugs back out.
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.