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

- Exposure to carcinogens
- Times that cells divide
- More than one mutation
Required characteristics

- Original hypothesis – 2 mutations, one in signaling and one in the nucleus.
- Statistical analysis says more like 5 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
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.
Extravasion

Blood vessels are recruited for nutrient delivery.
One pathway

Normal Epithelium → APC → Hyperplastic epithelium

Smad 4 → Intermediate Adenoma → K Ras → Early Adenoma

Late Adenoma → p53 → Carcinoma → 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
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.
SCF is over produced

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
  - YOU ONLY NEED ONE COPY

- Suppressor – loss of function
  - They can’t check growth
  - USUALLY YOU LOSE BOTH GENES
Early Chemotherapy

• Targets – rapidly growing cells.

Small molecules $\not\rightarrow$ ATP, etc.

NTP $\not\rightarrow$ dNTP

dNTPs $\not\rightarrow$ 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.