Cancer and Oncogenes
Bioscience in the 21st Century

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October 11, 2013
• Just a Few Numbers

• Becoming Cancer

• Genetic Defects

• Drugs
Our friends and family

Incidence of cancer
Other similar data

Weinberg, the Biology of Cancer
Mutations collected

- 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 cell growth pathway.
Evolution of a cancer cell
Abilities acquired

- Grow rapidly
- Dissociate from neighboring cells
- Invade adjacent tissue
- Recruit vasculature and 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.
One pathway

Normal Epithelium → APC → Hyperplastic epithelium

Intermediate Adenoma → Smad 4 → Early Adenoma

Late Adenoma → p53 → Carcinoma

Invasion and Metastasis
http://scienceblog.cancerresearchuk.org/2012/08/03/the-queen-in-the-hive-scientists-find-more-evidence-for-cancer-stem-cells/
Oxidative damage outcomes

mispairing of 8-oxo-dG with deoxyadenosine (dA)
But repair enzymes fix most problems

- If you cannot fix all of the DNA damage, mistakes accumulate more rapidly and cancer usually starts earlier.

- An example when repair is not complete 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

Together these pathways control a complicated set of events that result 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.
Grb > Sos > Ras > Raf > MAPKK > MAPK > ETS

Control

A P-ERK 10 min P-Elk
B

PDGF

C P-ERK 20 min P-Elk
D
E
F
G
H
I
J
K
L

30 μm
PI3K > PIP2 > PKD > Akt...

PI3K (Adds phosphate)

PIP2

PIP3

PTEN (Removes phosphate)

PKD
Types of genes that get mutated

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

- Suppressor – loss of function (brakes)
  - They can’t stop growth
  - USUALLY YOU LOSE BOTH GENES if there is a defect leading to cancer
Massive changes in the nucleus

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 mutated overactive 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 (personalized medicine).

• http://www.cancer.gov/