Cancer and Oncogenes
Bioscience in the 21st Century
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People

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 are probably important for most cancer in humans.
- Typically at least one mutation is in a cell growth pathway.
More numbers

- The 5 year survival rate is now about 66% for all cancer.
- Overall death rates from cancer are continuing to decline at somewhere between 1% and 2% per year.
- The most progress has been made in the most common forms of cancer.
- But, overall deaths from cancer will likely not continue to drop – why?
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
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.
Vascular differences
Cancer Evolution

http://scienceblog.cancerresearchuk.org/2012/08/03/the-queen-in-the-hive-scientists-find-more-evidence-for-cancer-stem-cells/
Not like classic evolution

simple linear clonal succession

dynamic clonal diversification

Figure 11.20b The Biology of Cancer (© Garland Science 2014)

Figure 11.20c The Biology of Cancer (© Garland Science 2014)
Intestinal cells

From stem cell to death in a very short time span.
One example pathway

Normal Epithelium → APC → Hyperplastic epithelium

Hyperplastic epithelium → Less Me of DNA

Intermediate Adenoma → Smad 4

Intermediate Adenoma → KRas → Early Adenoma

Late Adenoma → p53 → Carcinoma

Carcinoma → Invasion and Metastasis
Oxidative 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 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

PDGF

A  P-ERK  B  P-Elk  C  D
A  B  C  D

10 min

P-ERK  P-Elk

20 min

P-ERK  P-Elk

30 µm
PI3K > PIP2 > PKD > Akt...

PI3K (Adds phosphate)

PIP2

PTEN (Removes phosphate)

PIP3

Akt
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

Figure 10-38 The Biology of Cancer (© Garland Science 2007)

Translocations, duplications, deletions
Early Chemotherapy

- Targets – rapidly growing cells.
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).

What we discussed.

- It takes multiple mutations to get cancer.
- The collection of mutations is more rapid and complex than in typical evolution.
- Mutations in oncogenes and suppressors both play roles.
- Cancer cell development progresses over time, and cancer stem cells may remain.
- Treatments are becoming more specialized.