Oncogenes and Cancer
Bioscience in the 21st Century
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People

Becoming Cancer

Genetic Defects
Our friends and family

![Incidence of cancer graph]

- Incidence of cancer
Other similar data

Weinberg, the Biology of Cancer

![Graph showing cumulative skin tumor risk and death rate among United States Caucasian population](image)
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.
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
Intestinal cells

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

Normal Epithelium → APC → Hyperplastic epithelium

Intermediate Adenoma → Smad 4

Late Adenoma → p53 → Carcinoma

Early Adenoma → KRas

Carcinoma → Invasion and Metastasis
Oxidative damage outcomes

mispairing of 8-oxo-dG with deoxyadenosine (dA)
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 removes nucleotides that are damaged.
- BRCA1 in breast cancer is gene where the product is involved in homology-directed repair of dsDNA breaks.
Growth factors and the cell cycle

Mitogens (Accelerators)

PI3K > PIP2 > PKD > Akt...
PLC > DAG (+IP3) > PKC (+Ca)
GRB > SOS > RAS > RAF...
Src > MAPK pathway

Others

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.
VEGF-A is over produced

In many neuroblastoma and some other cancer patients, lots of VEGF-A (vascular endothelial growth factor) is produced and the cancer 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

A  P-ERK  10 min  P-Elk  20 min  P-ERK  P-Elk

Control  A  B  I  J

PDGF  C  D  K  L

30 µm

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
Lots of defects
Massive changes in the nucleus

Translocations, duplications, deletions
Passengers

• **Driver mutations**
  – The ones we have discussed so far

• **Passenger mutations**
  – Lots of other mutations that accumulate
  – 90% or more of the mutations are passengers
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. Passengers come along for the ride.
- Cancer cell development progresses over time.