Cancer and Oncogenes
Bioscience in the 21st Century

Linda Lowe-Krentz

September 4, 2015
People

Becoming Cancer

Genetic Defects
Our friends and family

Incidence of cancer

- 0 to 5
- 5 to 15
- 15 to 30
- 30 to 45
- 45 to 60
- 60 to 75
- 75 to 90

[Bar chart showing the incidence of cancer across different age groups.]
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.
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.
Vascular differences
initiating mutation

second mutation

- FIRST CLONAL EXPANSION
- SECOND CLONAL EXPANSION

increased mutation rate

multiple independent mutations

- MULTIPLE PARALLEL CLONAL EXPANSIONS

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 vs. dynamic clonal diversification.
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 → Early Adenoma

Late Adenoma → p53 → Carcinoma

Me of DNA → 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.
In many neuroblastoma and some other patients, lots of VEGF-A (vascular endothelial growth 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**
- 10 min: A (P-ERK), B (P-Elk)
- 20 min: I (P-ERK), J (P-Elk)

**PDGF**
- 10 min: C, D
- 20 min: K, L
PI3K > PIP2 > PKD > Akt...

PI3K (Adds phosphate)

PI2P2

PTEN (Removes phosphate)

PI3P3

Akt
EMT

carcinoma in situ

PROGRESSION

basement membrane

normal stroma

invasive carcinoma

EMT

INVASION

reactive stroma

EMT

INTRAVASATION

epithelial
mesenchymal

TRANSPORT through circulation

micrometastasis

COLONIZATION

macrometastasis

normal stroma

basement membrane

MET

EXTRAVASATION

Figure 14.18b The Biology of Cancer (© Garland Science 2014)
Migration

control culture

+ MMP-3 for 3 days

Figure 13.13c The Biology of Cancer (© Garland Science 2014)
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 loose BOTH GENES if there is a defect leading to cancer
Figure 7.18 The Biology of Cancer (© Garland Science 2014)
Lots of defects

Figure 12.35b The Biology of Cancer (© Garland Science 2014)
Massive changes in the nucleus

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

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.