Genetics of Cancer

Chapter 18
What is cancer?

- Loss of cell cycle control
- When a cell becomes cancerous it either:
  - Divides too often – (Mitosis)
  - Divides at the wrong time/place
  - Fails to die off when it should – (Apoptosis)
- All of these steps are controlled by genes
- Misregulation of these genes causes a tumor to form
Cell Cycle

- **G₁ phase**: Inhibits cell cycle until DNA can be repaired.
- **S phase**: DNA damage checkpoint.
- **G₂ phase**: Apoptosis checkpoint.
- **Metaphase**: Spindle assembly checkpoint.
- **Anaphase**: Is spindle built? Do chromosomes attach to spindle? Are chromosomes aligned down the equator?
- **Telophase**: Cytokinesis.

**If survivin accumulates, mitosis ensues.**

**G₀**: Stop following cytokinesis.
Apoptosis

Death receptor on doomed cell binds signal molecule. Caspases are activated within.

Caspases destroy various proteins and other cell components. Cell undulates.

Phagocyte attacks and engulfs cell remnants. Cell components are degraded.
What is cancer?

- Tumor – growth or mass of cells
- Benign – tumor stays in place
- Malignant – tumor invades surrounding tissues
- Metastasis – cancerous cells spread through blood stream and form new tumors in “far away” places
- Carcinogen – cancer causing substance induces mutations
Cancer is a genetic disorder

• Not only because it may “run” in families
  – Some forms of cancer susceptibility are inherited
• Because it arises from alterations (mutations) in genes
• What sort of genes?
  – Growth Factors
  – Transcription Factors
  – Cell cycle “check point” genes
Cancer causing genes

• Oncogenes:
  – Genes that normally trigger cell division or growth

• Tumor Suppressors:
  – Genes that normally suppress cell division
  – Or cause cells to die off when appropriate

• DNA repair genes:
  – Genes that fix mutations in DNA sequence
Cancer: Many mutations

• Cancer is not normally caused by a single mutation in one gene
• Rather it is often the build up of mutations in many genes over time:
  – Inherited susceptibility to mutations
  – Exposure to carcinogens
  – Introduces somatic mutations
  – Cell with multiple mutations now grows faster
  – Cancerous cells take over the space for normal cells (have an advantage)
Sporadic Cancers

Causative mutation occurs in somatic tissue (any non-germline cell)

• Remember:
  – Mutations are spontaneously occurring
  – Normally corrected - if not may lead to cancer
  – Exposure to carcinogens increases mutations

• Some cancer cells metastasize to other organs – spreading the cancer

• Cancer cells always win because they don’t have to respond to cell cycle control
Inherited Cancers

Inherit susceptibility to mutations through gametes

- Every cell in body is susceptible
- However, cancer will only occur when a secondary mutation happens
- Exposure to carcinogens increases number of mutations
- This is why cancer risk is inherited, but not normally one specific type of cancer
Inherited vs. Sporadic

a. Germline (inherited) cancer

b. Sporadic cancer
Cancer is a complex genetic disorder

- May “run in families”
- Yet has no Mendelian inheritance pattern
- Often different types of cancer seen
- Some susceptibility mutation has been inherited
- Yet secondary mutation needs to occur
- Secondary mutation may occur in different body parts in different family members
Very rarely – Mendelian

• There are a few cases where cancer is inherited in a Mendelian fashion:
  • Retinoblastoma
    – Inherit mutation in RB (halts mitosis)
  • BRAC1/2
    – Inherit mutation in BRAC 1 or 2 (necessary for DNA repair)
  • Neurofibromatosis (NF 1 gene)
  • Others
Cancerous cells

• Cell cycle is incredibly tightly controlled
• Cancer cells escape that control and can grow forever as long as there is enough nutrients and space
• Cell Lines – are cells that are made “cancerous” so that they can become immortal
  – Then can be used forever
  – Grown in culture (in a dish in a lab)
Cancerous cells

Cancer cells have some specific attributes:

• Lost cell cycle control
• Rounder than normal cells
  – Because they have lost the need for contact
• Pile up on top of each other
  – Lost contact inhibition
  – Normal cells will die if they become “crowded”
• Invasive
  – Cells can squeeze into any space
Invasiveness

Healthy lung tissue

- Basal cells proliferate (1 year after smoking starts)
- Cilia and columnar cells destroyed. Squamous or "flattened" cells (5 years after smoking starts)
- Cancer cells with atypical nuclei (8 years after smoking starts)
- Cancer cells with atypical nuclei (20–22 years after smoking starts; first symptoms)
Cancerous cells

Cancer cells have some specific attributes:

• Undifferentiated
  – Cells are less specialized

• Heritable
  – Cancerous mutations are passed down to all daughter cells

• Transplantable
  – Cells will proliferate if moved to a different area (metastasis) or animal
Cancerous cells

Cancer cells have some specific attributes:

• **Angiogenesis** (when cells are starving)
  – Ability to induce growth of blood vessels

• **Increased mutation rate**
  – Once cell is cancerous – mutates more

• **Speed of Mitosis** – actually inconsistent
  – Most people think of cancer cells as dividing faster – this isn’t always true
  – They continue to divide when normal cells stop
Angiogenesis
Cancer causing genes

• Oncogenes:
  – Genes that normally trigger cell division or growth

• Tumor Suppressors:
  – Genes that normally suppress cell division
  – Or cause cells to die off when appropriate

• DNA repair genes:
  – Genes that fix mutations in DNA sequence
Oncogenes

Over-expression or miss-expression of a gene that normally triggers cell division

Caused by:

- Duplications – doubles expression
- Chromosomal Translocations
  - Now a gene controlling cell cycle is adjacent to a promoter that is constantly turned on
- Viruses
  - May activate expression of surrounding genes
Oncogenes

Over-expression or miss-expression of a gene that normally triggers cell division

Caused by:

• Gain of function
  – This gene normally promotes cell division in a controlled way
  – Some mutation causes this gene to be turned on without control/constantly
  – Expressed when/where it should be off
Oncogenes

• Gene for cell division (\textit{abl}) connected to ubiquitously expressed gene (\textit{bcr})
Tumor Suppressors

Loss of a gene that normally suppresses or controls cell division

Caused by:

• Deletion
  – Instantly lose entire gene’s function

• Point mutation
  – Especially a Nonsense mutation

• Lack of expression
Tumor Suppressors

Loss of a gene that normally suppresses or controls cell division

Caused by:

• Loss of function:
  – Normally these genes suppress cell division
  – A mutation causes them to lose their function
  – Often recessive because losing one allele doesn’t affect phenotype – only when both are lost that no protein product is made
RB gene

- Retinoblastoma (cancer of retina) caused by losing function of RB gene
- Rb's normal function:
  - Halt mitosis to give time for DNA repair before division
- Inherit a germline mutation in RB
- Second allele of RB still working normally
- Secondary mutation causes complete loss of function – get retinoblastoma
p53

- p53 – transcription factor that sends the cell into apoptosis
- Apoptosis is planned cell death
- Loss of p53 function – no apoptosis
- p53 may be initial cause of cancer
- Or mutations in p53 may be secondary mutations that occur in cancerous cells
- Never dying is ultimate advantage!
Defects in DNA repair or replication

All are associated with a high frequency of chromosome and gene (base pair) mutations; most are also associated with a predisposition to cancer, particularly leukemia

- Xeroderma pigmentosum (XP)
  - caused by mutations in genes involved in nucleotide excision repair
  - associated with a 2000-fold increase of sunlight-induced skin cancer and with other types of cancer such as melanoma
- Ataxia telangiectasia (AT)
  - caused by gene that detects DNA damage
  - increased risk of X-ray
  - associated with increased breast cancer in carriers
- Fanconi anemia
  - caused by deficient levels of excision repair
  - increased risk of X-ray
  - sensitivity to sunlight
- Bloom syndrome
  - caused by mutations in a DNA ligase gene
  - increased risk of X-ray
  - sensitivity to sunlight
- Cockayne syndrome
  - caused by a defect in transcription-linked DNA repair
  - sensitivity to sunlight
More than one mutation…

- In order to discover which mutations originated cancer check tumors at different stages
- Earlier tumors – show initial mutations
- Astrocytoma – brain tumor
More than one mutation…

FAP – familial colon cancer

• Family members inherit mutation in APC gene in Mendelian fashion
• Family members have small benign polyps in their colon even as young children
• APC gene normally regulates mitosis
• Lose second allele of APC – grow polyp
• Polyp selects for further mutations
• Further mutations become cancer
More than one mutation…

- FAP – colon cancer
- Inherit mutation in one copy of APC
- Further mutations form cancer
Cancer Prevention

• Can’t change the inherited susceptibility you may have been born with:
  – Inherited mutations
  – Fair skin, light eyes, many moles

• Can change your personal environment:
  – Avoid carcinogens
    (Smoking, alcohol, sun exposure, etc)
  – Eat antioxidants – Chemicals that fight off mutations
    (Broccoli, Brussels sprouts, red wine, etc)
Cancer Diagnosis

• Because cancer is caused by many different genes diagnosis is not genetic
• Usually diagnosed after finding a “lump”
  – Either feeling it
  – Or visualizing it on MRI, Mammogram, Colonoscopy
• Labeled by tissue where cancer began
• Epidemiology – looks at cancer risks population wide
Epidemiology

Epidemiology - The study of disease in human populations

- Use statistics to establish a link between environmental exposures and cancer
- 1775 – Chimney sweeps in London have high rates of scrotum cancer
- Population studies – look at current pop’s
- Case-Control – compare affecteds vs. un
- Prospective – follow population over time
Cancer Treatments

• Surgery
  – Removal of tumor
  – Preventative – removal susceptible tissue

• Radiation and Chemotherapy
  – Kill off cells that are rapidly dividing
  – Also kills off non-cancerous cells
  – Digestive tract, hair follicles, bone marrow

• Treat specific form of cancer present
Specific Treatments

• Inhibit telomerase:
  – In tumors with overactive telomerase

• Prevent angiogenesis:
  – Stop tumor from vascular growth
  – However, stops all vascular growth

• Promote cells to differentiate:
  – Treat with transcription factors to try to coax cells back to original cell type
Specific Treatments

• Use phenotype to determine drug:
  – Breast cancer with estrogen receptors – block estrogen

• Use genotype to determine drug:
  – BRCA1 and Her-2/neu genotypes determine next step

• Cancer cells can become resistant
  – MDR: Multi drug resistant
    – Cells pump out any drug before it can work
Her-2/neu protein is a receptor for a growth factor – a proto-oncogene

- Cancer cells genotyped
- If Her-2/neu positive
- Treat with Herceptin – an antibody that binds to Her-2/neu receptors
- Therefore blocks their signal to divide
- Cancer cells gain cell cycle control once again
Summary

• Cancer is a genetic disorder
• Know characteristics of cancerous cells and how they are different than normal cells
• Oncogenes vs. Tumor Suppressors
• Cancer is usually caused by mutations in many genes
• Ways to study, diagnose and treat cancer
Next Class:

- Homework – Chapter Eighteen Problems;
  - Review: 1, 2, 4, 5, 8, 10
  - Applied: 2, 3, 6, 9, 16
  - Also – write out at least 2 questions about material to review on Friday

- Review Chapters 14-18 and notes
Next Class:

Review Chapters 14-18

• Go through your review questions

• Exam 3 – November 20th