Bio11

- TODAY
  - Mutations
  - Genetic causes of cancer and other diseases
  - How genes switch on and off
  - Stem cell therapy
- Lab Test 2 – next week
  - Take-home genetics problems (20 pts)
  - Multiple choice questions based on lab worksheets (50 pts)
  - Biotech lab – 10 pts on Final exam

Recap:
Structure and Function of DNA

What are genes?
- Genes are “recipes” for proteins
- Sequence of bases (e.g. ACGTCGAT…) that programs the amino acid sequence of a protein

Mutations

What is a mutation?
- Any change in the nucleotide sequence of DNA.

Mutations:
2 general ways to alter DNA
- A change in a single DNA base
  - Result from errors in DNA replication, UV radiation, or chemical mutagens
- Or entire sections of DNA can move from one place to another
  - Crossing-over
Changes in a single DNA base

**Base substitution**

- Insertions and deletions
  - Can have disastrous effects.
  - Change the reading frame of the genetic message.

**Insertions or deletions**

- Insertions and deletions
- Can have disastrous effects.
- Change the reading frame of the genetic message.

**Types of Mutations**

- Normal gene
- Point mutation
- Deletion
- Insertion
- Frame shift

**Mutations are rare**

- The dance of the chromosomes in a dividing cell is so precise that only one error occurs in 100,000 cell divisions.

**Mistakes happen—DNA repair**

- The cell has many mechanisms to correct these mistakes
  - DNA proofreading mechanisms
  - The proofreading process involves comparing the daughter strand to the parent DNA to check for mistakes
  - Proofreading is not perfect—mutations are still possible, although rare

**Mutations—key features**

- Mutations are rare changes in DNA
- Can affect genes and the proteins they encode
- Mutations are inherited only if they occur in germ-line cells
- Mutations are important for genetic variation and evolutionary change
Mutations are important for evolution

- Mutations are the source of the rich diversity of genes in the living world.

The Genetic Basis of Cancer

Cancers are caused by mutations in genes

Genes that cause cancer

- Cancer cells divide uncontrollably
- Often result from mutations in genes whose products regulate the cell cycle
  - Many "oncogenes" code for proteins that regulate cell division

Genes and cancer

- Oncogenes
  - Cancer-causing genes
- Proto-oncogenes
  - Normal genes that sometimes become oncogenes.
  - Code for growth factors that stimulate cell division.
- Tumor suppressor genes
  - Help prevent uncontrolled cell growth.

DNA mutations cause proto-oncogenes to become oncogenes

- Help prevent uncontrolled cell growth.
- If mutated, they can contribute to cancer

Tumor-suppressor genes

- Help prevent uncontrolled cell growth.
- If mutated, they can contribute to cancer
Mutations in DNA repair genes cause cancer

- DNA repair or proofreading genes make enzymes that help the cell fix mutations in its DNA.
- When a DNA repair gene is mutated, the cell can’t repair mistakes in its DNA.
- These mistakes build up until an oncogene is hit. Then the cell becomes cancerous.

Accumulation of mutations in cancer cells

The Progression of a Cancer

- Cancer develops after a series of mutations

Is Cancer Inherited?

- Cancer results from mutations in DNA.
- Most occur in the organ where the cancer starts e.g. the colon or lung
- Usually germ-line cells aren’t affected
  - the mutations are not passed from parent to child
- But cancer-causing mutations can occur in gametes

BRCA1, an inherited cancer gene

- In the vast majority of cases, breast cancer is not caused by inherited mutations
- The normal allele for BRCA1 codes for a tumor suppressor protein
- Some mutations in the BRCA1 gene put a woman at high risk for breast and ovarian cancers.

Viruses: “Genes in a box”

- Viruses sit on the fence between life and nonlife.
- Have some characteristics of living organisms
  - genetic material – DNA or RNA
- But cannot reproduce on their own

Mammograms of healthy (left) and cancerous (right) breasts
Viruses require host cells to reproduce

Herpes virus
- DNA virus that reproduces in the cell’s nucleus
- Causes cold sores and genital herpes
- Why is infection by herpes permanent?
  - Because the virus leaves behind DNA as mini-chromosomes in the nuclei of nerve cells

HIV, the AIDS Virus
- HIV is a retrovirus
  - Genetic material is RNA
  - It copies its RNA to DNA using reverse transcriptase
  - RNA → DNA
  - The envelope proteins help HIV bind to and enter white blood cells called helper T cells

Treating AIDS
Two types of anti-HIV drugs:
- Reverse transcriptase inhibitors
  - Inhibit conversion of RNA to DNA
  - AZT – shaped like thymine but the enzyme can’t add more nucleotides to the growing DNA chain
- Protease inhibitors
  - Inhibit enzymes called proteases that are needed for making viral proteins
  - Taken in combination
    - “drug cocktail”

How do new viruses arise?
- Mutation of existing viruses
- Spread to new host species
  - HIV - originally infected monkeys
  - “Avian flu” jumped from birds to humans
  - So far, no human-to-human transmission

How Genes Are Controlled
Gene activity is regulated
- When cells differentiate
  - Certain genes are turned on and off.
  - Cells become specialized
    - Muscle cells make contractile proteins (actin and myosin)
    - Blood cells make hemoglobin

Different types of cells express different combinations of genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>(c) Three muscle cells (part)</th>
<th>(d) Bone not part</th>
<th>(e) Liver cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Myosin</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Insulin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

How do cells regulate gene expression?
- Cells have sophisticated mechanisms of turning genes on and off
- Main switch point occurs at transcription

Turning on a gene
- Transcription involves many proteins called transcription factors.
- These proteins interact with DNA to switch transcription on

Example of transcriptional control: Lactose intolerance
- Lactose is a disaccharide found in milk.
- Most adults in the world have trouble digesting lactose
  - they lack the digestive enzyme that breaks down lactose.

Genetic basis of lactose intolerance
- A genetic mutation in the promoter of the lactase gene (C is replaced with T) allows some groups to digest milk
- Transcription of the lactase gene is not turned off in adults
Other ways cells control gene expression

- RNA processing
  - The removal of introns.
  - The splicing together of the remaining exons.
- Different cells start with the same RNA transcript but cut out different introns
  - Different proteins

Turning on a gene

- A cell can secrete chemicals, such as hormones, that affect gene regulation in other cells.
- Hormones can turn on genes in other cells.
- Important for coordinating cell activities.

What are Stem Cells?

- Unspecialized cells
- Have the potential to form any cell type in the body, or pluripotent
- Can keep dividing and make unlimited copies of themselves

Stem cell therapy

Medicine of the future?

Types of stem cells

- Embryonic stem cells
  - Can become all tissues of the body
- “Adult” or tissue-specific stem cells
  - More restricted; give rise to cells within a tissue family
- Induced pluripotent stem cells or iPS cells
  - Created in a laboratory by reprogramming a previously specialized cell like a skin cell
- Cancer stem cells
  - Fuel a growing tumor

Adult stem cells

- Replenish cells that turnover rapidly
  - Found in bone marrow and skin
- Tissue-specific
  - Have the potential to develop into most of the cells in their specific tissue
- Stem cells in the bone marrow give rise to the many types of blood cells:
  - red blood cells, white blood cells, platelets
- Not pluripotent – they are part way along the road to differentiation
Embryonic stem cells

- Originate as inner mass cells in an embryo
- Pluripotent – the stem cells can develop into any of the 220 cell types of the adult
- Need chemical signals to differentiate
- Ethical concerns

Differentiation of stem cells in culture

- Scientists are discovering growth conditions that stimulate stem cells to differentiate into specialized cells

Using embryonic stem cells to combat paralysis

- In Oct 2010 a paralyzed patient with spinal cord injury was given embryonic stem cells
- 1st ever FDA-approved clinical trial of stem cell therapy

iPS cells (reprogrammed cells)

- iPS cells = induced pluripotent stem cells
- Mature body cells that are reprogrammed
- Important step toward treating diseases with a patient’s own ‘repaired’ cells
- Advantage: iPS cells will not be attacked as foreign by the patient’s immune system

Creating iPS cells

- De-differentiate using transcription factors
- Reprogram to form another cell type

Stem cell breakthrough

- Specialized cells can be induced to assume new ID without passing thru a stem cell state
Custom-tailored cells to cure disease

Applications
- Disease modeling
  - Convert iPSCs to the diseased cell type
  - Study disease progression
  - Treat disease in culture, response to drugs
- Cell therapy
  - Convert iPSCs derived from a sick patient into healthy cells, then transplant them back into that patient

Disease-in-a-dish
- Research team created iPSC cells from skin cells donated by patients who have a severe genetic heart defect.
- They reprogrammed the cells into heart-muscle cells, which can be used to study the disease.
- Then tested the effects of many compounds

The promise of stem cell therapy
- Currently we use donated organs to replace ailing or destroyed tissue
  - Problem with rejection of the ‘foreign’ organ
  - With stem cells it may be possible to:
    - Generate nerve cells and transplant them into patients with spinal cord injuries (in clinical trials)
    - Generate healthy heart muscle cells in the lab and transplant them into patients with chronic heart disease
    - Generate insulin-producing cells and transplant them into diabetics.
      - In type 1 diabetes, the pancreatic cells that produce insulin have been destroyed.

Transforming stem cell science into stem cell medicine

Unanswered questions:
- Need safer and more effective techniques for creating iPSCs
- Will iPSCs work in humans?
- Will iPSC cells created in the lab find their way to a diseased organ?
- Will they hook up with the healthy cells in that organ to work in harmony with them?