Cancer

October is National Breast Cancer Awareness Month
Objectives 1: Gene regulation

Explain how cells in all the different parts of your body develop such **different characteristics and functions**.

Contrast the roles of the **promoter** and **protein encoding** (structural) portions of a gene.

Describe the interactions of the **promoter** region of a gene, **transcription** factors, and **RNA polymerase** in the expression of a gene.

Describe how water and fat soluble hormones and other extra-cellular signals regulate genes.

Example of a mutation of gene expression
Objectives 2: Cancer

Mechanisms by which cell division is controlled.

Characteristics of a cancer cell

How cells may be triggered to become cancerous.

Changes in genes and gene expression that lead to cancer.

The role of proto-oncogenes, oncogenes, and tumor suppressor genes in the development of cancer.

The "two hit" hypothesis.

How an understanding of the controls of the cell cycle might facilitate the development of cancer treatments.
Overview of the Control of Gene Expression

All of the living cells in our body have the same genetic information.

Cells develop very different structures and functions (skin, nerves, muscles, bone, fat, kidney, etc.).

Cells develop different structures and functions because different genes are "turned on" or "turned off" in different parts of your body.

Cells produce different types and quantities of proteins.

Organisms respond to the environmental changes by turning on (or off) specific genes or groups of genes.
Developmental Genes

Genes must be turned on or off in the correct sequence within a particular group of cells

**Homeotic genes** control proper embryo developmental sequence

"Master genes" whose products "turn on" a sequence of coordinated events.
Homeotic mutants

*Drosophila* homeotic mutant

The appendage on segment T3 of *Drosophila* is normally a haltere -- a small balancing organ.

Mutant deficient in *Ubx* expression grows a second wing instead of a haltere.
Controlling Gene Expression

A gene consists of two main parts:

**The Protein Encoding Region** - This is the section of DNA that is transcribed.

**The Promoter Region** - This is a section of DNA at the beginning of the gene that acts as an on/off switch for the protein encoding region.
a. 

b. 

c. DNA 

TATA binding protein 

Transcription factor 

RNA polymerase 

mRNA 

TRANSCRIPTION
Transcription factors

Proteins that bind to specific base sequences on the Promoter Region of a gene

Each gene locus has its own specific set of transcription factor proteins.
Role of Transcription Factors

General transcription factors are necessary for transcription to occur.

Activators are transcription factors that turn genes on or increase their rate.

Repressors are transcription factors that turn genes off or decrease their rate.

Activators and repressors interact with other cell signals (e.g. one gene can turn another on or off) and with external environmental signals.
Gene Expression

RNA Polymerase will not bind to the DNA and initiate transcription until all the required Transcription Factors are properly bound to the Promoter Region of the gene or the RNA Polymerase itself.

If a transcription factor gene is mutated the proper transcription factor protein will not be produced and the gene that the transcription factor helps turn on or off will not function properly.
Fat-Soluble Hormones

Easily pass through the phospho-lipid bilayer of the cell membrane of all cells.

Combines with Receptor Protein and turn on or turn off genes in that cell.

The Hormone-Receptor Protein Complex interacts with Transcription Factors.
Lipid-soluble hormones such as testosterone, estrogen, or thyroid hormone circulate in bloodstream

Hormone passes through cell membrane and binds to interior receptor

Certain genes activated, leading to production of new proteins

Altered cell activity
glucocorticoid receptor in absence of glucocorticoid hormone

- gene 1

- gene 2

- gene 3

genes expressed at low level

genes expressed at high level
Water-Soluble Hormones

Can't pass through the cell membrane.

Hormone Molecules interact with specific Receptor Proteins embedded in the surface of the cell membrane of only certain types of cells.

The chemical signal is passed through a series of Relay Proteins in the cytoplasm which eventually interact with Transcription Factors in the nucleus.
a. Water-soluble hormones such as epinephrine, insulin, or human growth hormone circulate in bloodstream.

- Hormone binds to receptor on target cell surface.
- Cascade of biochemical reactions ends by activating an enzyme.
- Altered cell activity.

Blood vessel (not to scale)

Target cell membrane

Adenyl cyclase

G protein

Receptor protein

ATP

cAMP

Effects on cell

Cytoplasm of target cell

Extra-cellular fluid
Light as an Environmental Signal

Fall colors
Triggered by day length

Environmental Estrogens (EEs)

Synthetic chemicals can disrupt hormones in humans and animals
Cancer Statistics

Third most common cause of death world wide (behind heart disease and infectious disease)

Second most common in the U.S (23%)

Overall lung cancer is most common form (15% of cases, 30% of deaths)

1 in 8 women will be diagnosed with breast cancer during their lifetime, most common among U.S. women

Prostrate cancer most common for U.S. men
Leading causes of death in the United States

Major cardiovascular diseases
- Malignant neoplasms
- Chronic lower respiratory disease
- Diabetes mellitus
- Influenza and pneumonia
- Alzheimers
- Motor vehicle accidents
- Renal failure
- Septicemia
- Firearms

Total number of deaths

Ages

Under 1 Yr, 1-4 yrs, 5-14 yrs, 15-24 yrs, 25-34 yrs, 35-44 yrs, 45-54 yrs, 55-64 yrs, 65-74 yrs, 75-84 yrs, 85 yrs and over
Characteristics of Cancer Cells

- Loss of cell cycle control
- Heritability
- Genetic mutability
- Dedifferentiation
- Loss of contact inhibition
- Angiogenesis (in growing tumours)
- Transplantability
- Ability to spread (metastasize)
**Cell Cycle**

- **Interphase**: 46 chromosomes
- **Prophase**: Chromosomes doubled to 92, nucleus dissolves, microtubules attach to centromeres
- **Prometaphase**: Chromosomes align at middle of cell
- **Metaphase**: Separated chromosomes pulled apart
- **Anaphase**: Micronuclei disappear, cell division begins
- **Telophase**: Two daughter cells formed, each with 46 chromosomes
- **Cytokinesis**: Cell division ends

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**Cells**

- **G0 phase**: Resting state
- **G1 phase**: Primary growth stage
- **S phase**: Genetic material replicates
- **G2 phase**: Secondary growth stage

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**Cell Division**

- **Prophase**
- **Prometaphase**
- **Metaphase**
- **Anaphase**
- **Telophase**

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**Cytokinesis**
Control of Cell Division

Cells normally have built in systems that check to be sure the cell is OK before initiating cell division. Proteins check for:

- complete DNA replication
- damaged DNA
- adequate nutrients

If the checks indicate the cell is not ready to divide it does not.

Cells normally divide when told to do so by some outside influence, like a hormone or growth factor.
Control of Cell Division

Cells also normally respond to signals that tell them to stop dividing.

Cellular Clock
Effect of Neighboring Cells - Contact Inhibition
Extra-cellular Influences
  - Hormones
  - Growth Factors
Intra-cellular Influences
  - Kinases and Cyclins
Cell Division in Cancer Cells

Cancer is often the result of some genetic loss of control of the cell cycle.

Genetic changes by mutation or chromosome abnormalities in a cell result in cells that divide when they should not be dividing.

Of the ~30,000 genes in the human genome, a small subset that seems to be particularly important in the prevention, development, and progression of cancer
Oncogenes

Proto-oncogenes are normal genes that we all have that control cell division or cell death.

Mutations in these genes can cause a cell to divide in an unregulated manner or prevent cell death. These genes are then referred to as oncogenes.

Cells no longer respond to signals that control mitosis.

A single altered copy leads to unregulated growth.
Tumor suppressor genes

Tumor suppressor genes produce products that inhibit the division of cells if conditions for growth are not met.

Cells would be kept from dividing if the DNA were damaged, a needed growth factor or hormone were missing, or if there were defects in the cell division machinery.

Loose their ability to control cell division when both copies of the gene are damaged by mutation.
Two-Hit hypothesis

If it takes mutations in both copies of a tumor suppressor gene on homologous chromosomes in a cell (to become homozygous recessive)

Chances for a germline mutation carrier to get a second somatic mutation at any of multiple sites in his/her body cells is much greater than the chances for a noncarrier to get two hits in the same cell
Two-Hit Hypothesis

- **Germline mutation**
- **Somatic mutation**

If first hit is a **germline mutation**, second somatic mutation more likely to enable cancer.
Cancer Treatment

Surgery
Chemotherapy
Radiation therapy
Angiogenesis inhibitors
Hormonal Therapy
Blocking Telomerase activity
Inducing cell differentiation or apoptosis

Diet
Chemotherapy

Stops or slows cell growth

Can also harm healthy cells that divide quickly

Anti-metabolites

masquerade as a purine (A,G) or a pyrimidine (C,T)
inhibition of thymidine synthesis (T)

Anti-mitotics

bind to tubulin and inhibit spindle dynamics and thus
block cell division

Topoisomerase inhibitors

prevent DNA from being unwound
Radiation

Injures or destroys cells in the area being treated (the “target tissue”) by damaging their genetic material, making it impossible for these cells to continue to grow and divide.

Effects of radiation therapy are localized and confined to the region being treated.

Damages both cancer cells and normal cells.
Angiogenesis inhibitors

1. Tumor releases factors that bind to endothelial cells of nearby capillaries and stimulate them.

2. Stimulated endothelial cells invade surrounding area (extracellular matrix) and proliferate (divide) toward tumor.

3. New blood vessel extension nourishes tumor.

Hormone Therapy

Used for reproductive cancers (prostate, breast)
Cell lines still dependent upon hormones
Respond to hormone deprivation
Block hormone receptors (e.g. Tamoxifen)
Reducing hormone levels (chem or surgery)
Blocking Telomerase activity

Sister chromatids

Telomeres

Heterochromatin (dark)

Centromere

Euchromatin (light)

Telomeres

One cell cycle

- Telomerase absent
  - Normal somatic cells
    b. (no telomerase produced)
  - Sperm-generating cells, blood cells, cancer cells
    c. (telomerase produced)

Telomerase present

- Telomerase absent
  - No more cell division. Cell remains functional or dies.

- Telomerase present
  - Cells continue dividing under influence of telomerase.

a. From L. Chong "A Human Telomeric Protein", Science, 270: 1663-1667, © American Association for the Advancement of Science. Photo courtesy Dr. Titas DeLange
Inducing cell differentiation or apoptosis

Differentiation therapy is based on the concept that cancer cells are normal cells that have been arrested at an immature or less differentiated state. Force the cancer cell to resume the process of maturation.

Retinoids can promote apoptosis in breast cancer and lung cancer cells.
Biomarkers and Early Detection and treatment of Cancer

Often cancer has already metastasized (spread) before a tumor is detected by physical exam or by imaging techniques.

Scientists are now attempting to find biomarkers that will help them detect cancer at an early stage.

Biomarkers are chemical variations found in certain types of cancer cells that are not found in healthy cells.
Biomarkers

Biomarkers may provide an avenue to disrupt the abnormal gene activity of cancer cells and put the cancer cells back on a track to normal activity.

Biomarkers can be proteins or other chemicals produced by cancer cells.

Cancer cells express genes that are not expressed in normal cells.

Mutations in cancer cells produce abnormal proteins.
Early Detection

Prostate-specific antigen (PSA) is a protein produced by cells of the prostate gland. The PSA test measures the level of PSA in the blood.

Use of Gene Chips or Micro Arrays to compare gene activation in tumor cells and normal cells

One way to find biomarkers is to find out which genes are active (or inactive) in cancer cells that are not active (or active) in normal cells of the same tissue
**Prepare cDNA Probe**

- "Normal"
- Tumor

- RT / PCR
- Label with Fluorescent Dyes

- Combine Equal Amounts

- Hybridize probe to microarray

**Prepare Microarray**

- SCAN

**Microarray Technology**
GUIDELINES FOR CANCER PREVENTION

Avoid carcinogens
Vaccination
Genetic testing
Screening

Choose mostly plant foods, limit red meat and avoid processed meat.

Be physically active every day in any way for 30 minutes or more.

Aim to be a healthy weight throughout life.

And always remember – do not smoke or chew tobacco.