## Essential Knowledge:

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Learning Objectives:

Section 11.1
2.12- The student is able to use representations and models to analyze situations or solve problems qualitatively and quantitatively to investigate whether the dynamic homeostasis is maintained by the active movement of molecules across membranes

Sections 11.1, 11.4
3.22- The student is able to explain how signal pathways mediate gene expression, including how this process can affect protein production
3.23- The student can use representations to describe mechanisms of the regulation of gene expression

Section 11.1, 11.2
3.31- The student is able to describe basic chemical processes for cell communication shared across evolutionary lines of descent
3.32- The student is able to generate scientific questions involving cell communication as it relates to the process of evolution
3.33- The student is able to use representation(s) and appropriate models to describe features of a cell signaling pathway.
3.34- The student is able to construct explanations of cell communication through cell to cell direct contact or through chemical signaling
3.35- The student is able to create representation(s) that depict how cell to cell communication occurs by direct contact or from a distance through chemical signaling

Section 11.2, 11.3
3.36- The student is able to describe a model that expresses the key elements of signal transduction pathways by which a signal is converted to a cellular response

Section 11.4
3.37- The student is able to justify claims based on scientific evidence that changes in signal transduction pathways can alter cellular response
3.38- The student is able to describe a model that expresses key elements to show how change in signal transduction can alter cellular response
3.39- The student is able to construct an explanation of how certain drugs affect signal reception and, consequently, signal transduction pathways

I. Chapter 11.1: External signals are converted into responses within the cell.
   a. Evolution of cell signaling: *Saccharomyces cerevisiae*- yeast cells identify mates by chemical signaling.
i. Two mating types: (a) and (α): has to do with two mating types which is related to separate alleles on the gene designated for that locus
   1. Mating type (a) – haploid- secretes a (a) factor chemical signal, which will bind to specific receptors on type (α) cells
   2. Mating type (α)- haploid - secretes a (α) factor chemical signal, which will bind to specific receptors on type (a)
      a. The two mating factors do not actually enter the cell
      b. Cause the two cells to grow towards one another
      c. Result is the fusion of the two cells to form a type (a/α) cell (diploid cell)
         i. This cell contains the genes of both original cells
         ii. Sterile organism
         iii. Subsequent cells arise by cell division with the combined genetics providing genetic advantages (meiosis).
   1. Forms two (a) types and two (α) types.

b. **Signal Transduction Pathways:** process by which a signal on a cell's surface is converted into a specific cellular response in a series of steps.

i. signal molecule can be: cell, bacteria, proteins, steroids or other chemicals

ii. Examples:
   a. tyrosine- kinase pathway- activates transcription factors in the nucleus
   b. G Protein linked reception- plasma membrane receptors that works with a specific protein (G protein)
   c. Ion channel receptors: gated channels

iii. Effector specificity: same receptor on different cells may have different functions
   a. acetylcholine (neurotransmitter) will slow contraction in cardiac muscles, activate contractions in striated muscle and cause exocytosis of granules from pancreatic cells

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c. **Local and Long-Distance Signaling:**

i. cells communicate via chemical messengers
   a. can be by direct contact via junctions which transmit chemical signals dissolved in the cytosol.
   b. also by membrane bound cell surface molecules- cell to cell recognition (immune response)

ii. paracrine signaling vs. synaptic signaling and other types of signaling.
   a. paracrine signaling involves a secreting cell releasing a regulator that will be picked up by a target cell causing a response- example: growth factors- which are cells that stimulate nearby target cells to grow
   b. synaptic signaling: nerve cell releases a neurotransmitter into the synapse stimulating a target cell
   c. **Intracrine** signals are produced by the target cell that stay within the target cell.

   d. **Autocrine** signals are produced by the target cell, are secreted, and effect the target cell itself via receptors. Sometimes autocrine cells can target cells close by if they are the same type of cell as the emitting cell. An example of this are **immune cells**.

   e. **Juxtacrine:** signals target adjacent (touching) cells. These signals are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.
f. Paracrine: signals target cells in the vicinity of the emitting cell. 

Neurotransmitters represent an example.

g. endocrine: signals target distant cells. Endocrine cells produce hormones that travel through the blood to reach all parts of the body.

   iii. hormones are used for long distance signaling: hormones released by the endocrine system travel via the blood to the target cells in other parts of the body

      a. examples: growth regulators in plants such as ethylene and insulin in animals

d. Three Stages of Cell Signaling:

   i. Reception: detection of a signal molecule by the target cell.

      a. involves binding of signal molecule to a receptor on the cells surface

   ii. Transduction: binding of signal molecule causes a conformational change of the receptor protein.

      a. converts signal to a specific cellular response

      b. can be single step but often requires a multistep pathway involving a sequence of changes in a series of molecules (signal transduction pathway)

   iii. Response: a multitude of cellular activity including: enzyme catalysis, rearrangement of the cytoplasm, activation of specific genes

   iv. Ensure the right cells and cell processes are activated at the right time

II. Chapter 11.2: Reception- A signal molecule binds to a protein causing it to change shape.

   a. receptor proteins on the cell surface (or inside the cell) allows the cell to detect and respond to signals.

      i. Have a specific shape which is complementary to the signal molecule providing a level of specificity (lock and key)

      ii. example: epinephrine will encounter many different cells as it circulates through the blood but will only be detected by specific target cell.

   b. the signal molecule behaves as a ligand

      i. specifically binds to a target molecule

      ii. causes conformational change

         1. for receptors this change in shape activates it and enables it to interact with other inner-cellular molecules

      iii. could also result into the aggregation of many molecules which leads to further molecular activity within the cell.

      iv. most are plasma membrane proteins

         1. water soluble

         2. transmits information from outside the cell to the inside of the cell

         3. causes either change in shape or aggregation of proteins

   c. there are some intracellular receptors

      i. can be found in the cytoplasm or the nucleus

      ii. have the ability to pass through the plasma membrane directly into the cell

         1. hydrophobic enough

            a. steroid and thyroid hormones

         2. small enough

            a. nitric oxide (NO)

               i. small enough to pass through the phospholipids in the plasma membrane.

      iii. Example:
1. Testosterone passes through the plasma membrane
   a. Steroid hormone- very hydrophobic
2. Binds to a receptor in the cytoplasm activating it and forming a hormone-receptor complex.
3. Hormone- receptor complex enters the nucleus to bind with specific genes
4. Stimulates the transcription of the gene into mRNA
5. The mRNA is translated into a specific protein

d. G-Protein Linked Receptors: plasma membrane receptor that works with a G protein
   a. Examples:
      i. Yeast mating
      ii. Epinephrine
      iii. Hormones
      iv. Neurotransmitters
      v. Phospholipase C- m enzyme that breaks down phosphatidylinositol 4, bisphosphate (PIP2- membrane phospholipid) into diacylglycerol (DAG- remains in the cell membrane) and inositol triphosphate (IP3- which acts as a signal molecule for calcium channels along the endoplasmic reticulum.
   b. Structure:
      i. Seven α- helices that span the membrane with loops in between the structures that act as binding sites for the signal molecule and the G- protein.
   c. G-Protein
      i. Attached loosely to the cytoplasmic side of the membrane
      ii. Functions as a molecular switch
      iii. Attaches to GDP and/or GTP (guanosine triphosphate)
         1. If GDP is bound the protein is inactive
         2. Becomes activated when GDP becomes phosphorylated to GTP, this happens only when the appropriate signal molecule is bound to the G- protein linked receptor
         3. Once phosphorylated, the G-protein releases from the receptor, diffuses along the membrane to a specific enzyme altering its activity which can lead to a cellular response
         4. G- protein then becomes dephosphorylated
      iv. Acts as its own enzyme- GTPase, which hydrolyses the terminal phosphate group shutting down the pathway.

  e. Receptor Tyrosine Kinases: helps the cell coordinate aspects of cell growth and cell reproduction
     i. Kinase- enzyme that catalyzes the transfer of phosphate groups
     ii. Tyrosine kinase- enzyme that extend from the cell surface to the cytoplasm that catalyzes the transfer a phosphate group from ATP to an amino acid tyrosine found on the substrate protein
     iii. Can activate several transduction pathways
        1. This is what separates it from G- protein pathways
        2. Problems along the signaling pathways may lead to cancer
     iv. Receptor tyrosine kinase proteins exist as two monomers in there inactive state
        1. When two signaling molecules are detected, the two monomers bind to form a dimer
2. Dimerization activates the tyrosine kinase region
3. Each tyrosine kinase adds a phosphate from ATP to the tyrosine,
4. Once fully activated, several cellular responses are possible.

f. **Ion Channel Receptors:** ligand gated membrane receptor act as a gate when the receptor changes shape, blocking or allowing the flow of specific ions. (Na+, Ca++)

### III. Chapter 11.3: Transduction: Cascades of molecular interactions relay signals form receptors to target molecules in the cell.

a. **Protein kinases** - general name for an enzyme that transfers phosphate groups from ATP to a protein
   - i. Can act on proteins that are the same or different from themselves.
      1. Tyrosine kinase act on proteins that are the same
      2. Serine and threonine kinases phosphorylate the amino acids serine or threonine rather than tyrosine
      3. Protein kinases can act on other protein kinases to create a phosphorylation cascade where each molecule in the pathway adds a phosphate group to the next molecule in line.

b. **Phosphorylation Cascade:**
   - i. Relay molecule activates a protein kinase
   - ii. That protein kinase transfers a phosphate from ATP to an inactive protein kinase
   - iii. The second protein kinase phosphorylates the next protein kinase
   - iv. The third protein kinase activates a fourth protein kinase through phosphorylation
   - v. Brings about a cellular response to the signal
   - vi. Protein phosphatase is an enzyme that dephosphorylates the protein kinases inactivating them.

c. **Secondary Messengers:** small, non protein, water soluble molecules or ions
   - i. Readily diffuse through out the cell
   - ii. Participate in the pathway by carrying the signal to the cells interior.
   - iii. **Cyclic AMP (cAMP):** cyclic adenosine monophosphate
      1. Converted by an enzyme in the cell membrane from ATP in response to an extracellular signal
      2. Cholera: bacterial disease that comes from contaminated drinking water
         - a. Bacteria produce an exotoxin that modifies the G-protein that regulates salt and water secretion
         - b. The G-protein can no longer hydrolyze GTP to GDP leaving it stuck in the active conformation
         - c. cAMP is continuously being made from ATP causing intestinal cells to secrete large amounts of salts and water into the intestines causing massive dehydration
   - iv. Ca++ as a secondary messenger: many signal molecules induce responses in their target cells to increase Ca++ concentrations in the cytosol.
      1. Used more widely as a secondary messenger than cAMP
         - a. Used in muscle contraction
         - b. Secretion
         - c. Cell division
         - d. Used in plants response to light
         - e. Also used in G-protein and tyrosine kinase pathways
   - 2. Example:
      - a. Signal molecule binds to a receptor and activates phospholipase C
b. Phospholipase C converts PIP2 into DAG and IP3

c. DAG acts as a secondary messenger for other pathways

d. IP3 diffuses through the cytosol and binds to an IP3 calcium gated channel in the ER

e. The channel opens and Ca++ flows out of the ER into the cytosol

f. Ca++ acts as a secondary messenger to stimulate other cellular responses

IV. Chapter 11.4: Response:

a. Cytoplasmic and Nuclear Response

i. Cytoplasmic response-
   1. opening or closing of an ion channel
   2. change in cell metabolism
   3. activate enzymes that catalyzes the break down of glycogen
   4. regulate the synthesis of enzymes and other proteins
      a. turning on or off specific genes

ii. Nuclear response- the final activated molecule of the signal transduction pathway may enter the nucleus and act as a transcription factor turning on a gene
   1. Could be synthesis of mRNA- if growth factor signal is received
   2. Example: glut- 4 gene that codes for the glut-4 protein which acts as a glucose channel
   3. Transcription factor may turn off a gene

b. Fine Tuning of the Response:

i. Signal transduction processes have a multitude of steps for two reasons:
   1. Signal amplification- with each step of the signal cascade, the signal becomes amplified and is greater than the preceding step
      a. Epinephrine signal pathway
   2. The Specificity of the Cell Signal: different collection of proteins allows specific cells to recognize and responds to different signaling molecules
      a. Dependent upon the different protein receptors.

c. Signaling Efficiency:

i. Signaling efficiency is increased by scaffolding proteins
   1. Large relay proteins to which several other relay proteins are simultaneously attached.

ii. Example: Wiskott- Aldrich syndrome (WAS)
   1. Absence of a single relay protein leads to such diverse effects as abnormal bleeding, eczema, and a predisposition to infection and leukemia.
   2. Absence of relay protein in immune cells

d. Termination of the Signal:

i. The process of signal transduction is reversible
   1. Signal molecule releases from receptor, inactivating the protein and the signal transduction process all together
   2. Phosphatases catalyze the de-phosphorylation of the proteins of the cascade inactivating them