Signal Transduction

Chapter 11 - Pg. 207 – 227

Cell Signaling

- Autocrine signals diffuse from one part of a cell to another part of the same cell.
- Synaptic signaling (ligand: neurotransmitters) is local; occurs in the animal nervous system.
- Paracrine signals are local; send a message to nearby cells by diffusion.
- Endocrine signals (hormones) are long-distance; travel anywhere in the blood to reach their target cells.

Signal Transduction Pathway

- Coordinates activities within, between, and among individual cells.
- It is a sequence of molecular interactions that transforms an extracellular signal into a specific cellular response.
- Incorrect signaling can lead to diseases and cancer.
- Drugs, poisons, and pesticides often target signaling pathways.
- It can be summarized as:
  - Signal (1st messenger) → receptor → proteins or other 2nd messengers → cellular responses

Ligands

- Signaling molecules that are first (1st) messengers.
  - Small molecules that bind to larger receptor proteins of specific target cells.
- Binding of a ligand to a receptor induces a 3D shape change of the receptor.
  - This initiates some kind of activity in the receptor.
- Ligands may be
  - Hydrophilic: cannot cross membrane, but bind to membrane receptors.
  - Hydrophobic: cross membrane easily; bind to intracellular receptors in the cytoplasm or nucleus.
Receptor Proteins

• Molecules that have binding sites for signaling molecules.
• When activated by a ligand, they initiate reactions that activate a cellular process.
• Two types:
  – Membrane receptors: span the entire membrane; ligand binding site on the outside, inside initiates a chemical reaction.
  – Intracellular receptors: in the cytoplasm/nucleus.

Cell Surface Receptors

• Cell surface/membrane receptors all span the entire membrane and contact the extra- and intracellular environment.
  – Make up about 30% of all human proteins (VERY COMMON)
• Hydrophilic signaling molecules cannot diffuse through the membrane, but bind to cell surface receptors. A signal is then transmitted to the cytoplasm. Once inside the cell, the signal is carried by a second messenger.
  – The most common is cyclic AMP (cAMP).
• Three examples: ion channel receptors, G-protein-coupled receptors, and protein kinase receptors.

(Gated) Ion Channel Receptors

• Transmembrane protein with a gated channel that opens and closes in response to a specific signal
• When OPEN, the channel allows a specific ion to pass through
• Other variations:
  – Ligand-gated ion receptor: responds to a specific ligand – a molecular signal
  – Voltage-gated-ion receptors: open or close in response to voltage differences across the membrane

Typical Ligand-Gated Ion Sequence

1. Signal is received.
2. Messenger ligand binds to outward-facing surface of the receptor.
3. Receptor changes shape, channel opens, and ions pass through.
4. Once inside the cytoplasm, ions initiate chemical response.
5. Ligand detaches from receptor and deactivates channel.
   – Detachment can happen when the ligand is broken down by an enzyme, the binding site is blocked by an allosteric ligand, or the ion passage is obstructed by a channel blocker.

Ligand-Gated Ion Channel Example

• Acetylcholine (Ach) – neurotransmitter that signals the transmission of nerve impulses between nerves
  – An active neuron releases Ach into the synapse
  – Ach binds to the ligand-gated receptor molecules of the receiving neuron
  – Receptor molecules open a gated channel that allows Na+ to enter the cell
  – As Na+ enters the cell, the inside of the cell becomes more positive
  – This change in membrane voltage (action potential) initiates a nerve impulse
• Neurons stimulate muscle contraction similarly
Voltage-Gated Ion Channel Example

- Occurs during the transmission of a nerve impulse along a neuron (rather than between them)
- When the ligand-gated-ion receptor responds to Ach and Na+ enters the cytoplasm, voltage inside the neuron becomes more positive
- This voltage change, if strong enough, stimulates a voltage-gated Na+ channel and, subsequently, a voltage-gated K+ channel to open
- The opening and closing of these voltage-gated ion channels transmits the nerve impulse along the neuron

G-Protein-Coupled Receptors

- A transmembrane protein that activates a G protein, which in turn activates another membrane protein, which triggers a cellular response or activates a second messenger
  - Largest family of signal receptors (vision, taste, airborne signals, hormones, neurotransmitters, immune system)
  - Diabetes, blindness, allergies, depression, and some cancers are believed to originate from faulty G proteins
  - Up to 60% of medicine used actually influences GPCR
- It is named because it has a GTP or GDP attached to it
  - GTP is just like ATP, except with a guanine instead of an adenine nitrogen base
  - In its inactive (“off”) state, a GDP is attached to the G protein
  - It is activated (turned “on”) when the GDP is replaced with GTP

Typical Sequence for G Protein-Coupled Receptor

1. Ligand binds to receptor and it changes shape.
2. Receptor uses GTP to activate the G protein.
3. G protein binds to effector protein, activating the effector (usually an enzyme).
4. Effector initiates a response (enzymatic activity, production of second messengers, kinase cascade).
5. GTP is hydrolyzed into GDP, deactivating the GPCR. The released GDP may reassociate with another G protein.

Protein Kinase Receptors

- A transmembrane protein (enzyme) that is a kinase (enzymes that add phosphate group to a protein)
  - Best understood is the receptor tyrosine kinase (RTK)
  - Most important in cell reproduction and regulation
- Two major differences between an RTK receptor pathway and the GPCR pathway:
  - RTK receptor is usually directly responsible for initiating a transduction pathway, in contrast, the GPCR indirectly activates a transduction pathway via a G protein and an effector molecule.
  - RTK receptor may trigger multiple transduction pathways, directing a host of coordinated cellular responses. In contrast, a typical GPCR triggers a single transduction pathway, ultimately activating a single final product that leads to a specific cellular response.
Typical RTK Sequence

- Ligand binds to RTK.
- RTK forms dimer (two associated RTKs).
- In the inner surface of the membrane, the RTKs phosphorylate each other using phosphates from ATP.
  - Autophosphorylation – it activates the protein complex
- Relay protein attaches to RTK and is phosphorylated.
- Relay proteins are released.
  - They will activate a cellular response or initiate a protein kinase transduction pathway leading to a cellular response.
  - Each relay protein participates in a different response.
- RTK pathway is deactivated by dephosphorylation of kinases or when the membrane folds and encircles the receptor protein in a vesicle (endocytosis).

RTK Pathway Example

- Insulin signal transduction is an example of an RTK pathway.
  - Insulin from the pancreas enters blood in response to increased blood glucose.
  - Insulin binds to insulin receptor on target cells.
  - Receptor is activated via conformational change.
  - RTK dimer forms and autophosphorylates.
  - RTK complex binds to insulin response protein and phosphorylates it.
    - Insulin response protein initiates several signaling cascades.
    - Muscle: glycogen synthesis for short-term energy storage, glucose transport
    - Liver: glycogen synthesis, glucose synthesis inhibited
    - Fat cells: triglyceride formation (rather than glycogen formation)
- Mitogen-activated protein (MAP) kinases are another example, initiated by a G protein.
  - Mitogens stimulate cell division.
  - Protein kinase receptor is activated by ligand.
  - Dimerization of receptor, autophosphorylation.
  - GDP → GTP; activation of Ras (G protein), which activates a mitogen-kinase (MK) cascade
  - The final MK activates nuclear regulatory proteins (transcription factors), that turn genes on or off.

Cytoplasmic (Intracellular) Receptors

- Small, nonpolar (lipid-soluble) ligands enter the plasma membrane and bind to cytoplasmic receptors.
- This ligand-receptor complex will activate a pathway in the cytoplasm immediately or migrates to the nucleus where it switches genes on or off.
- Such hydrophobic chemical messengers include steroid hormones (testosterone, estrogen), thyroid hormones, the gas NO (nitric oxide), and second messengers like IP3 that come from signal transduction pathways from membrane receptors.
11/13/2014

Typical Intracellular Receptor Pathway

• Lipid-soluble or small ligand enters cytoplasm.
  – May also be a second messenger introduced as part of a membrane receptor pathway.
• Ligand binds to and activates intracellular receptor in the cytoplasm or nucleus.
• Receptor-signaling molecule complex acts as a transcription factor, binding to DNA and promoting or suppressing gene transcription.
• The pathway is deactivated when the ligand or receptor proteins are enzymatically degraded.
  – May also occur by phosphorylation of the receptor protein.
  – Hormonal systems are shut down using negative feedback.

Example of Intracellular Signaling

• Steroid hormones (testosterone or estrogen) diffuse across the plasma membrane and bind to a cytoplasmic receptor.
• The activated complex (hormone + receptor protein) moves to the nucleus, where it binds to DNA and promotes transcription of genes that direct cellular activities.
• Gene expression varies on cell type and gender.
  – Males – testosterone activates genes in testes that direct sperm development and in muscles, stimulates the production of muscle fibers.
  – Females – estrogen activates genes that direct the uterus to prepare for pregnancy, but in mammary cells inactivates those same genes.

Summary of Receptors and Their Functions

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Receptor Description</th>
<th>Ligand Examples</th>
<th>Supporting Mechanisms</th>
<th>Cellular Response Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gated ion receptor</td>
<td>Ligand-gated ion channel</td>
<td>Acetylcholine</td>
<td>Na+ gate opens; nerve impulse or muscle contraction</td>
<td></td>
</tr>
<tr>
<td>Voltage-gated ion channel</td>
<td>Change in membrane voltage</td>
<td>Na+, K+ gates open; nerve transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G protein-coupled receptor (GPCR)</td>
<td>GPCR + G protein + effector protein</td>
<td>Various</td>
<td>Enzymatic effector proteins</td>
<td>Enzyme activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cAMP (2nd messenger)</td>
<td>Glycogen → glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IP3/DAG (2nd messengers)</td>
<td>IP3 releases Ca2+ as 2nd messenger</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca2+ (2nd messenger)</td>
<td>Muscle contraction</td>
</tr>
<tr>
<td>Protein kinase receptor</td>
<td>Receptor tyrosine kinase (RTK)</td>
<td>Insulin</td>
<td>Multiple kinase cascades</td>
<td>Glucose → glycogen; glucose metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ras (G protein); mitogen-kinase cascade)</td>
<td>Activation of transcription factors that promote growth and cell differentiation</td>
</tr>
<tr>
<td>Intracellular receptor</td>
<td>Cytoplasmic or nuclear receptor</td>
<td>Steroid hormones (testosterone, estrogen)</td>
<td>Development of primary and secondary sex characteristics</td>
<td></td>
</tr>
</tbody>
</table>

Second Messengers

• Molecules that relay a signal from the inside face of a receptor protein to other molecules that may initiate a cellular response or may act as additional second messengers. They have the following characteristics:
  – Small, nonprotein molecules
  – Hydrophilic, hydrophobic, or gaseous molecules
  – Examples include Ca2+, IP3 (inositol trisphosphate), cAMP (cyclic adenosine monophosphate), and DAG (diacylglycerol).
Cascade Effect

- Signal transduction pathways utilize a small number of extracellular signal molecules to produce a major cellular response.
- Advantage: this effect amplifies the signal and provides multiple opportunities for coordination and regulation.
- Many signal transduction pathways have been identified and studied extensively across several kingdoms – bacteria, yeast, animals, plants.
- The amazing similarity in all of these pathways and in all these diverse organisms suggests that signal transduction pathways evolved hundreds of millions years ago in a common ancestor.

Signaling Cascade

- Series of enzymatic reactions.
- The first enzyme activates a second enzyme, the second activates a third, and so forth.
  - Adenylyl cyclase converts ATP to cAMP after binding of ligand to receptor. cAMP activates protein kinase A, which phosphorylates proteins.
  - Because each enzyme can be used repeatedly, the products of each reaction magnify as the sequence progresses, like a chain reaction.
  - Ultimately, a signal that may have begun with a single signaling molecule may be amplified to produce a huge number of molecules that elicit a strong cellular response.

Kinase Cascade

- Also known as a phosphorylation cascade.
- It is a signaling cascade consisting of a number of different kinase enzymes.
  - A kinase is an enzyme that phosphorylates its substrate – it adds a phosphate group to it.
- In a kinase cascade, each kinase phosphorylates, and thus activates, the next kinase in the sequence, ultimately phosphorylating and activating a protein that initiates a cellular response.
- The kinase cascade amplifies the signaling response.

Scaffold Proteins

- Improve the efficiency of a signaling cascade.
- Hold all participating enzymes in close proximity.
- Keeps the members of one signaling cascade isolated from others.
Protein Phosphatase

• A protein phosphatase is an enzyme that dephosphorylates its substrate
  — Removes a phosphate group from it
• When these enzymes dephosphorylate the kinases in a kinase cascade, they terminate the signaling response.

Response

• Ultimately, signal transduction pathways lead to a multitude of cytoplasmic or nuclear responses
• Regardless of the outcome, you need to remember four things about these pathways:
  — They are characterized by a signal, a transduction, and a response.
  — They are highly specific and regulated.
  — One signal molecule can cause a cascade effect, releasing thousands of molecules inside a cell.
  — These pathways evolved millions of years ago in a common ancestor.

Advantages

• Some advantages of the complexity of signal transduction pathways include
  — Amplification: it provides a mechanism for amplifying the effect of a signaling molecule.
  — Control: it gives the cell more control over the accuracy of the signaling pathway. Because all components of the pathway must be functioning properly, there is a smaller chance that the transduction might occur in error.
  — Multiplicity: a single signaling molecule can activate multiple cytoplasmic proteins, each generating a different biochemical response. As a result, multiple processes can be coordinated to produce a single cellular response.

Role of Disease and Cancer

• External signals strongly influence how genes actually express genetic information.
• Signals are sometimes inaccurately acted upon because the signal transduction pathway is distorted and does not operate properly.
• Two examples include cholera and cancer.
  — Cholera: discussed yesterday
  — Cancer: result of faulty signal transduction pathways that don’t respond to regulating molecules