Cell Communication

Chen, J. H., 020806

- Cell-to-cell communication is essential for multi-cellular organisms and is also important for many unicellular organisms.

An overview of cell signaling

<u>Cell signaling evolved early in the history of life</u>

- One topic of cell "conversation" is sex - mating
  - Baking yeast (*Saccharomyces cerevisiae*) has two mating types, a and α: Each cell secretes its mating factor, a-factor or α-factor, which binds to the receptor on other cell. Without entering the cells, the receptor-bound mating factors cause the cells to grow toward each other and to form mating.

- **Signal-transduction pathway**: The process by which a signal on a cell's surface is converted into a series specific cellular response. Amazingly, the molecular details of signal transduction in yeast and mammals are similar.

<u>Communicating cells maybe close together or far apart</u>

- Cells can communicate by **direct contact**
  - **Cell junction**s: cytoplasmic continuity between the adjacent cells
  - Animal cells may communicate directly via the **cell adhesion molecule**s (**CAM**s) on their surfaces: embryonic development and immune system.

- **Paracrine** signaling: travel only short distances - **local regulator**
  - **Growth factor**s stimulate nearby target cells to grow and multiply.
  - Pre-synaptic nerve cells secret **neurotransmitter**s, which diffuse through synapse and bind to the receptors on the post-synaptic cells.
- **Endocrine** signaling: longer distance - **Hormone**

- Insulin secreted from pancreas is transported to other parts of body by blood.
- Ethylene (C_2H_4): fruit ripening and growth regulation.

The three stages of cell signaling are reception, transduction, and response

- Earl W. Sutherland, Nobel Prize owner in 1971.
  - Epinephrine - glycogen phosphorylase – glycogen de-polymerization

1. Reception: a chemical signal is detected when it binds to a cellular protein, receptor, usually at the cell's surface.
2. Transduction: the signal is converted to a form that activates a series of different relay molecules.
3. Response: the transduced signal triggers a specific cellular response.

Signal reception and the initiation of transduction

- The signal receptor is the identity tag on the target cell.

A signal molecule binds to a receptor protein, causing the protein to change shape

- A cell targeted by a particular chemical signal has specific receptor proteins to recognize the signal molecule-**ligand**.
  - Most ligands are water-soluble and too large to pass freely through the plasma membrane.

Most signal receptors are plasma-membrane proteins

- Ligand binding generally causes a receptor protein to undergo a change in conformation (shape change), which directly activates the receptor or aggregates two or more receptor molecules. Those activated receptors then interact with another cellular molecule(s).

1. **G-protein-linked receptor**s

- **G protein**s (**G**uanosine binding protein), loosely attached to the cytoplasmic side of the membrane, function as switch: G protein-GDP is inactive (off) and G protein-GTP is active (on).
- These receptors vary for recognizing signal molecules and for recognizing different G proteins inside the cell.
- G-protein-linked receptor proteins are all remarkably similar in structure, **seven α-helices** spanning the membrane**.**

- G protein activation:
  A. The receptor binds a specific, inactive G protein to cause its GDP replaced by GTP.
  B. The activated G protein then binds to another protein, usually an enzyme, and temporarily alters its activity.
  C. G protein also functions as a **GTPase** and soon hydrolyzes its bound GTP to GDP

- G protein systems are involved in many human diseases, including bacterial infections: the producing toxins interfere with host's G protein function.
- Pharmacologists now realize that up to 60% of all medicines used today exert their effects by influencing G protein pathways.

2. **Tyrosine-kinase receptor**s

- One of a major class of plasma-membrane receptors characterize by having **tyrosine kinase** (TK) activity that catalyzes the transfer of phosphate groups from ATP to the amino acid tyrosine on a substrate protein.
- Each has an extracellular signal-binding site, an intracellular tail containing a number of tyrosines, and a single α helix spanning the membrane.

- TK receptor activation:
  A. The ligand binding causes two receptor polypeptides to aggregate and form a dimer.
  B. This aggregation activates the tyrosine-kinase parts of both polypeptides.
  C. Each phosphorylates the tyrosines on the tail of the each other polypeptide.
     - A single ligand-bound receptor does not cause enough of conformation change.
- The activated receptor protein is now recognized by specific relay proteins inside the cell. The relay protein may or may not be phosphorylated by the tyrosine kinase.

- The receptor for a growth factor is often a tyrosine-kinase receptor.
  - Abnormal tyrosine-kinase receptors aggregate even without ligand or malfunctioning of growth-factor pathways can cause cancer.

3. **Ion-channel receptor**s
  - Ligand-gated ion channels: When a ligand binds at a specific site on the extracellular side of channel proteins, the shape change in the channel protein immediately leads to a change in the concentration of a particular ion inside the cell.

  - **Voltage-gated ion channel**s: voltage change

4. **Intracellular receptor**s: in the cytoplasm or nucleus.
  - Not all receptors are membrane proteins.
  - Some signal molecules like NO are small enough to pass the membrane phospholipids or like steroid hormones are soluble in the membrane.

Signal-transduction pathways

Pathways relay signals from receptors to cellular responses

- The original signal molecule is not physically passed along a signaling pathway: In most cases, it never even enters the cell. The information is passed on. At each step the signal is transduced into a different form.

- The relay molecules are mostly proteins. The interaction of proteins is a major theme of cell signaling

- Conformational change commonly in a protein causes by **phosphorylation**.

Protein phosphorylation, a common mode of regulation in cells, is a major mechanism of signal transduction

- **Protein kinase**s: Those enzymes can transfer phosphate groups from ATP to amino acid tyrosine (tyrosine kinase) or either serine or threonine (serine/threonine kinases) on a substrate protein.

- Many of the relay molecules in signal-transduction pathways are protein kinases- the signal is transmitted by a cascade of protein phosphorylations.

- Fully 1% of our own genes are thought to code for protein kinase. A single cell may have hundreds of different kinds, each with specificity for a different substrate protein.

- The effects of protein kinases are rapidly reversed in the cell by **protein phosphatases**.

Certain small molecules and ions are key components of signaling pathways

- Not all components of signal-transduction pathways are proteins.

- S**econd messengers**: small non-protein, water-soluble molecules or ions.

- A large variety of relay proteins are sensitive to the cytosolic concentration of one or the other of these second messengers.

1. **Cyclic AMP (cAMP)**
   - Adenylyl cyclase, built into the plasma membrane, converts ATP to cAMP in response to an extracellular signal.
   - **Protein kinase A (PKA)**, a serine/threonine kinase, can be activated when binds with cAMP.
   - A different signal molecule activates a different receptor, which activates an inhibitory G protein.
   - **Phosphodiesterase** converts the cAMP to an inactive product, AMP.
   - Cholera bacteria, *Vibrio cholerae,* colonize the lining of the small intestine and produce cholera toxins, which modified the G proteins of regulating salt and water secretion to stop the ability of GTP hydrolysis - patients die from the loss of water and salts.

2. **Inositol trisphosphate**
   - Certain kinds of phospholipids like **phosphatidylinositol bisphosphate** (**PIP_2**) in the plasma membrane are cleaved into **diacylglycerol (DAG)** and **inositol trisphosphate** (**IP_3**) by **phospholipase C**.
   - DAG can activate some types of **protein kinase C** (**PKC**).
   - IP_3 binds with **IP_3-gated calcium channel** to release calcium ions.

- **Inactivation** or **reversibility** mechanisms are essential for cell signaling:

3. **Calcium ion**s

- In both G-protein pathways and tyrosine kinase receptor pathways.
- The level of Ca^{2+} in extracellular fluid of an animal can exceeds 10^5 times than in cytosol. Calcium ions are actively transported out of the cell and are actively imported from the cytosol into ER, mitochondria or chloroplasts.
- **Calmodulin**, a Ca^{2+}-binding protein presents at high levels in eukaryotic cells, usually regulates protein kinases and phosphatases

Cellular responses to signals

<u>In response to a signal, a cell may regulate activities in the cytoplasm or transcription in the nucleus</u>

- Active (phosphorylated) transcription factors can bind with specific DNA sequence to turn the specific genes on or off.

<u>Elaborate pathways amplify and specify the cell's response to signals</u>

- Signal **amplification** depends on that these proteins persist in active form long enough to process numerous substrate before they become inactive.

- The **specificity** of cell signaling: short circuit or eavesdropping?

A. A signal molecule leads to a single response.

B. A signal molecule leads to branch pathways in one cell:
  - WAS (Wiskott-Aldrich syndrome) protein:
  - **Scaffolding protein**, which binds several relay proteins simultaneously, can facilitate a specific phosphorylation cascade.

C. Two pathways triggered by separate signals converge to modulate a single response: **cross-talk** between pathways.

D. A signal molecule leads to different responses in different types of cells.