15.1: Cell communication

Cell communication is a fundamental homeostatic process.

Figure 15.1: Summary of types of cell signaling.

Generically speaking, it uses various communication modalities to sense and respond to neighboring cells and environmental cues, which can be categorized into the following types of communication (figure 15.1):

- **Autocrine**: These signals act on the cell from which it is secreted or on nearby cells that are the same type of cell as the secreting cell. Most autocrine cells are also paracrine cells.

- **Juxtocrine or signaling through gap junctions**: These types of signals require physical contact between cells in order for a signal to be transduced. These are two different types of signaling that both involve cell contact.

- **Paracrine**: The paracrine substance is secreted from cells that are not normally thought of as endocrine cells. Actions are performed on nearby cells and very low amounts are too dilute to affect distance cells. The location of the cell plays a role in the specificity of the response.

- **Endocrine**: Endocrine cells secrete the hormone into the blood and exerts its action on specific target cells that can be very far away (for example: insulin, glucagon, and cortisol).

General characteristics:

- Cellular signaling begins with the release of a chemical messenger, which will either diffuse or is transported in the blood/extracellular fluids to its location of action.

Once at the intended location it will bind to its receptor, which can be intracellular or extracellular, to elicit a response.
This could be in the form of:

- A conformational change
- Activation of a second messenger
- Protein recruitment
- Cleavage of a receptor

Finally, the signal can be terminated by:

- Degradation of the receptor or ligand.

The outcome of a signaling cascade is diverse. For example, elevated insulin may signal for increased uptake and storage of glucose (see section 3) or a signal may initiate apoptosis (see section 15.2).

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**Types of ligands**

- **Steroid hormones**: These are often cholesterol-derived and can diffuse through membranes to bind intracellular receptors (figure 15.2).
- **Amino acid metabolites**: These types of hormones are often neurotransmitters and contain nitrogenous groups.
- **Gases**: Both \( \text{NO} \) and \( \text{CO} \) are common gases that elicit unique signaling cascades.
- **Proteins**: These can be small polypeptides (e.g., insulin) or larger membrane-bound proteins that elicit a cellular response.
- **Lipids**: Eicosanoids and other phospholipids can function as cell signals either in a membrane bound or free form.
General G-protein-coupled receptor cascade

G-protein-coupled receptors (GPCR) can come in several different classes: \( \Gamma(\alpha_s) \), \( \Gamma(\alpha_i) \), and \( \Gamma(\alpha_q) \). Activation of a \( \Gamma(\alpha_s) \) (activated by glucagon) will increase the second messenger cAMP, while both \( \Gamma(\alpha_i) \) or \( \Gamma(\alpha_q) \) cascades function to reduce cAMP, either through inhibition of adenylyl cyclase (also known as adenylate cyclase) or through activation of phosphodiesterase, respectively.

The classic cascade starts with hormone binding, to an extracellular domain of a seven-helix receptor (GPCR), which causes a conformational change in the receptor that is transmitted to a G protein on the cytosolic side of the membrane (figure 15.3).

Figure 15.3: Common G-protein-coupled receptor signaling cascade.

- The nucleotide-binding site on \( \Gamma(\alpha) \) becomes more accessible to the cytosol, where [GTP] is usually higher than [GDP]. \( \Gamma(\alpha) \) releases GDP and binds GTP (GDP–GTP exchange). Substitution of GTP for GDP causes another conformational change in \( \Gamma(\alpha) \).
- \( \Gamma(\alpha) \)-GTP dissociates from the inhibitory subunit complex and activates adenylyl cyclase.
- Adenylyl cyclase catalyzes synthesis of cAMP (second messenger), and in turn cAMP activates protein kinase A (cAMP-dependent protein kinase).
- The cascade can be terminated by the action of phosphodiesterase, which can degrade cAMP and terminate signal.

Phosphatidylinositol-derived second messengers

Phosphatidylinositols are membrane-bound compounds that can be phosphorylated or cleaved to function as second messengers in a signaling cascade (figure 15.4).
The common membrane component, phosphatidylinositol (PI), can be phosphorylated (by any number of kinases) to form PI 4,5-bisphosphate. This molecule can undergo two different fates.

1. First it could be phosphorylated by a kinase, such as P-I3 kinase, downstream of insulin; this produces phosphatidylinositol 3',4',5'-trisphosphate (PI-3,4,5-trisP), which can serve as a plasma-membrane docking site for signal transduction proteins with pleckstrin homology domains (PH).

2. Alternatively, PI 4,5-bisphosphate can be cleaved into two second messengers: inositol-1,4,5-trisphosphate (IP$_3$) and diacylglycerol (DAG) by activation of phospholipase C (PLC). Phospholipase C is downstream of a $G_\text{oq}$ cascade.

This cascade will become important for calcium signaling, which is modulated through interactions of IP$_3$ with the mitochondria.

1. DAG recruits protein kinase C.
2. IP$_3$ initiates release of $\ce{Ca^{2+}}$ from the smooth ER.

Changes in intracellular calcium can alter membrane permeability through calcium-induced calcium release.

**Receptor Tyrosine Kinase (RTK)**

RTKs are in the cell membrane and typically function as a dimer.

- Upon binding of the hormone to the receptor, autophosphorylation occurs on the inner side of the membrane. This forms a phosphorylated tyrosyl residue that will act as a docking site for proteins with SH2 domains. In the case of insulin signaling, the insulin receptor substrate (IRS) will bind this activated receptor (figure 15.5).

- The IRS protein will also become phosphorylated at subsequent tyrosine residues, and in this manner insulin signaling can be amplified. Other proteins such as PI 3-kinase, PLC, and Grb2 all have SH2 domains and all bind to different tyrosyl residues on the IRS.
Two major cascades are activated downstream of insulin and other growth hormones:

- **Ras-dependent signaling:** The activated Grb2 binds a SOS-Ras complex leading to a conformational change exchanging GDP for GTP. Ras-GTP binds Raf, and activated Raf is the first step in a MAP-kinase cascade that can lead to a change in gene transcription.
- **Ras-independent signaling:** This involves activation of phosphoinositol 3-kinase and is discussed under phosphatidylinositol-derived second messengers.

**Jak-STAT and serine threonine kinases**

Jak-STATs are also types of tyrosine kinases. The difference here is that these receptors lack autocatalytic abilities and require an intracellular kinase (Jak) to phosphorylate the transcription factor STAT. Jak-STAT signaling is most commonly associated with immune cell signaling.
Serine threonine kinase

This receptor family encompasses many of the growth factors for the body (EGF, VEGF, and TGF-β). These receptors usually form heterodimers, and the Type II receptor will autophosphorylate the Type I receptor upon ligand binding. These receptors have an autocatalytic domain that will phosphorylate and typically activate a transcription factor.

Intracellular receptors

Intracellular receptors bind hydrophobic chemical messengers such as steroid hormones. Binding of the intracellular receptor (which could be cytosolic or nuclear) usually elicits a transcriptional response. Cortisol is an example of a hormone that binds an intracellular receptor. It is released from the adrenal cortex and diffuses into the bloodstream attached to serum albumin and steroid hormone-binding globulin. After diffusing through the plasma membrane, it binds to the cortisol receptor (intracellular receptor) in the cytosol and forms a homodimer exposing a nuclear localization signal (NLS). Exposure of the NLS targets the complex to the nucleus.

Intracellular receptors commonly have three domains:

- Transactivation domain,
- DNA-binding domain, and
- Ligand-binding domain.

Intracellular receptors will function as a transcriptional activator by binding specific DNA elements, altering transcription of downstream genes. The signal is terminated by the lowering of the concentration of the hormone.

\((\text{NO})\) as a messenger

Nitric oxide \((\text{NO})\) is a gas that also acts as a ligand. It is able to diffuse directly across the plasma membrane, and one of its roles is to interact with receptors in smooth muscle and induce relaxation of the tissue.

\((\text{NO})\) has a very short half-life and, therefore, only functions over short distances. It activates guanylyl cyclase to synthesize cGMP. This in turn results in smooth muscle relaxation.

Nitroglycerin, a treatment for heart disease, acts by triggering the release of \((\text{NO})\), which causes blood vessels to dilate (expand), thus restoring blood flow to the heart. \((\text{NO})\) has become better known recently because the pathway that it affects is targeted by prescription medications for erectile dysfunction, such as Viagra (erection involves dilated blood vessels).

References and resources

Text

Clark, M. A. *Biology*, 2nd ed. Houston, TX: OpenStax College, Rice University, 2018, Chapter 9: Cell Communication, Chapter 10: Cell Reproduction.


**Figures**

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