Intracellular signaling.

Intracellular signaling pathways. Membrane receptors. Secondary intermediaries. Cytoplasmic and nuclear receptors.

1. Give the definition of intracellular signaling (signal transduction).
2. Classify and characterize membrane cell receptors, give specific examples.
3. Describe and provide examples of secondary intermediaries.
4. Predict the signaling pathways when the cell is exposed to insulin and thyroid hormone, steroid hormones.
5. Characterize the cytoplasmic and nuclear receptors.
6. Give examples of signaling pathways when a cell is exposed to steroid hormones

The environment in which higher organisms live is changing all the time, and the coordination of the functions of the organism requires a perfect mechanism for mutual recognition, response and interaction between cells. The mechanism is called cell communication. In this system, cells recognize cells in contact with them, or recognize various signals present in the surrounding environment (from surrounding or distant cells) and transform them into functional changes in various molecules within the cell, thereby changing certain metabolic processes within the cell, affecting the growth rate of the cells, and even inducing cell death. The ultimate goal of signal transduction is to permit the body to respond appropriately to the changes in the environment at an overall level

The essence is that a part of the cell in the body emits signals, and another part of the cells receive signals and transforms them into changes in cell function. Therefore, signal transduction will directly affect the regulation of cell proliferation, differentiation, metabolism and death.

Signal transduction (also known as cell signaling) is the transmission of molecular signals from a cell's exterior to its interior. Signals received by cells must be transmitted effectively into the cell to ensure an appropriate response.

Cell signal transduction refers to the binding of extracellular factors to a receptor (membrane receptor or nuclear receptor), triggering a series of biochemical reactions and protein interactions in the cell, until the genes which required for cellular physiological reactions begin to express and the process of forming biological effects. It is now known that there is a variety of signal transduction methods and pathways in cells, and there are multiple levels of cross-regulation between various methods and pathways, which are a very complicated network system.

Signals are most often chemicals that can be found in the extracellular fluid around cells. Some cells also respond to mechanical stimuli. For example, sensory cells in the skin respond to the pressure of touch, whereas similar cells in the ear react to the movement of sound waves. In addition, specialized cells in the human vascular system detect changes in blood pressure — information that the body uses to maintain a consistent cardiac load.

Summarizing our words we can say that there 2 processes occur during signal transduction, the original **intercellular** (between-cells) signal is converted into an **intracellular** (within-cell) signal that triggers a response

Cell signaling process can be divided into 3 stages.

1. Reception: A cell detects a signaling molecule from the outside of the cell. A signal is detected when the chemical signal (also known as a ligand) binds to a receptor protein on the surface of the cell or inside the cell.

2. Transduction: When the signaling molecule binds the receptor it changes the receptor protein in some way. This change initiates the process of transduction. Signal transduction is usually a pathway of several steps. Each relay molecule in the signal transduction pathway changes the next molecule in the pathway.

3. Response: Finally, the signal triggers a specific cellular response.

Types of signaling

Cell-cell signaling involves the transmission of a signal from a sending cell to a receiving cell. However, not all sending and receiving cells are next-door neighbors, nor do all cell pairs exchange signals in the same way.

There are four basic categories of chemical signaling found in multicellular organisms: paracrine signaling, autocrine signaling, endocrine signaling, and signaling by direct contact. The main difference between the different categories of signaling is the distance that the signal travels through the organism to reach the target cell.

Paracrine signaling

Often, cells that are near one another communicate through the release of chemical messengers (ligands that can diffuse through the space between the cells). This type of signaling, in which cells communicate over relatively short distances, is known as **paracrine signaling**.

Paracrine signaling allows cells to locally coordinate activities with their neighbors. Although they're used in many different tissues and contexts, paracrine signals are especially important during development, when they allow one group of cells to tell a neighboring group of cells what cellular identity to take on. [Example: spinal cord development]

Synaptic signaling

One unique example of paracrine signaling is **synaptic signaling**, in which nerve cells transmit signals. This process is named for the **synapse**, the junction between two nerve cells where signal transmission occurs.

When the sending neuron fires, an electrical impulse moves rapidly through the cell, traveling down a long, fiber-like extension called an axon. When the impulse reaches the synapse, it triggers the release of ligands called **neurotransmitters**, which quickly cross the small gap between the nerve cells. When the neurotransmitters arrive at the receiving cell, they bind to receptors and cause a chemical change inside of the cell (often, opening ion channels and changing the electrical potential across the membrane).

Synaptic signaling. Neurotransmitter is released from vesicles at the end of the axon of the sending cell. It diffuses across the small gap between sending and target neurons and binds to receptors on the target neuron.

The neurotransmitters that are released into the chemical synapse are quickly degraded or taken back up by the sending cell. This "resets" the system so they synapse is prepared to respond quickly to the next signal.

Autocrine signaling

In **autocrine signaling**, a cell signals to itself, releasing a ligand that binds to receptors on its own surface (or, depending on the type of signal, to receptors inside of the cell). This may seem like an odd thing for a cell to do, but autocrine signaling plays an important role in many processes.

When cells need to transmit signals over long distances, they often use the circulatory system as a distribution network for the messages they send. In long-distance **endocrine signaling**, signals are produced by specialized cells and released into the bloodstream, which carries them to target cells in distant parts of the body. Signals that are produced in one part of the body and travel through the circulation to reach far-away targets are known as **hormones**.

Cells usually communicate with each other through extracellular messenger molecules. Extracellular messengers can travel a short distance and stimulate cells that are in close proximity to the origin of the message, or they can travel throughout the body, potentially stimulating cells that are far away from the source. Cell signaling is initiated with the release of a messenger molecule by a cell that is engaged in sending messages to other cells in the body.

The extracellular environments of cells contain hundreds of different informational molecules, ranging from small compounds (e.g., steroids and neurotransmitters) to small, soluble protein hormones (e.g., glucagon and insulin) to huge glycoproteins bound to the surfaces of other cells.

Cells can only respond to a particular extracellular message if they express receptors that specifically recognize and bind that messenger molecule. The molecule that binds to the receptor is called a **ligand**. Different types of cells possess different complements of receptors, which allow them to respond to different extracellular messengers. Even cells that share a specific receptor may respond very differently to the same extracellular messenger

Receptors are protein molecules inside the target cell or on its surface that receive a chemical signal.

Internal receptors, also known as intracellular or cytoplasmic receptors, are found in the cytoplasm of the cell and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane. Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis. Recall that mRNA carries genetic information from the DNA in a cell's nucleus out to the ribosome, where the protein is assembled. When the ligand binds to the internal receptor, a change in shape is triggered that exposes a DNA-binding site on the receptor protein. The ligand-receptor complex moves into the nucleus, then binds to specific regions of the DNA and promotes the production of mRNA from specific genes Internal receptors can directly influence gene expression (how much of a specific protein is produced from a gene) without having to pass the signal on to other receptors or messengers.

Cell-surface receptors, also known as **transmembrane receptors**, are proteins that are found attached to the cell membrane. These receptors bind to external ligand molecules (ligands that do not travel across the cell membrane). This type of receptor spans the plasma membrane and performs **signal transduction**, in which an extracellular signal is converted into an intercellular signal. Ligands that interact with cell-surface receptors do not have to enter the cell that they affect. Cell-surface receptors are also called cell-specific proteins or markers because they are specific to individual cell types.

Structure of Cell Surface Receptors

Cell surface receptors are integral membrane proteins and, as such, have regions that contribute to three basic domains:

- **Extracellular domains:** Some of the residues exposed to the outside of the cell interact with and bind the hormone - another term for these regions is the *ligand-binding domain*.
- **Transmembrane domains:** Hydrophobic stretches of amino acids are "comfortable" in the lipid bilayer and serve to anchor the receptor in the membrane.
- **Cytoplasmic or intracellular domains:** Tails or loops of the receptor that are within the cytoplasm react to hormone binding by interacting in some way with other molecules, leading to generation of second messengers. Cytoplasmic residues of the receptor are thus the *effector region* of the molecule.
- Signals received by receptors at the cell surface or, in some cases, within the cell are often relayed throughout the cell via generation of small, rapidly diffusing molecules referred to as **second messengers.** These second messengers broadcast the initial signal (the "first message") that occurs when a ligand binds to a specific cellular receptor; ligand binding alters the protein conformation of the receptor such that it stimulates nearby effector proteins that catalyze the production or, in the case of ions, release or influx of the second messenger. The second messenger then diffuses rapidly to protein targets elsewhere within the cell, altering the activities as a response to the new information received by the receptor.
- There are 3 second messenger pathways
- (1) activation of adenylyl cyclase by G-protein-coupled receptors (GPCRs) to generate the cyclic nucleotide second messenger 3′-5′-cyclic adenosine monophosphate (cAMP);
- (2) stimulation of phosphoinositide 3-kinase (PI3K) by growth factor receptors to generate the lipid second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP_3);
- and (3) activation of phospholipase C by GPCRs to generate the two second messengers membrane-bound messenger diacylglycerol (DAG) and soluble messenger inositol 1,4,5-

trisphosphate (IP_3), which binds to receptors on subcellular organelles to release calcium into the cytosol.

The activation of multiple effector pathways by a single plasma membrane receptor and the production of multiple second messengers by each effector can generate a high degree of amplification in signal transduction, and stimulate diverse, pleiotropic, responses depending on the cell type.

Second messengers fall into four major classes:

- cyclic nucleotides, such as cAMP and other soluble molecules that signal within the cytosol;
- lipid messengers that signal within cell membranes;
- ions that signal within and between cellular compartments;
- and gases and free radicals that can signal throughout the cell and even to neighboring cells.

Second messengers from each of these classes bind to specific protein targets, altering their activity to relay downstream signals. In many cases, these targets are enzymes whose catalytic activity is modified by direct binding of the second messengers. The activation of multiple target enzymes by a single second messenger molecule further amplifies the signal.Second messengers are not only produced in response to extracellular stimuli, but also in response to stimuli from within the cell. Moreover, their levels are exquisitely controlled by various homeostatic mechanisms to ensure precision in cell signaling.

Literature:

1. Alberts et al., pp. 813-887;

2. Lodish et al., pp. 673-774.