Cell Signaling

Slide 2 Cells do not exist in isolation. Whether they are the sole cell of a unicellular organism, or a small part of a multicellular organism, cells must constantly receive information from and react to their environment. Cells accomplish this by translating signals that they receive from their environment or adjacent cells into an appropriate reaction inside the cell, in a process called signal transduction.

The signals that a cell receives and reacts to can be virtually anything in the environment of a cell, including light, solute concentrations, temperature, humidity, tactile stimulation, chemical signals, sound, or other stimuli. Cells generally receive these signals using receptor molecules bound to the cell membrane, although some signals are received by receptor molecules present in the cytoplasm of cells. A cell's response to signals will vary, depending on what type of signal it receives. For example, cells may be signaled by a change in membrane potential to allow an influx of ions into the cell. Unicellular organisms may be signaled by changes in their surroundings to move to escape a predator or to take advantage of better environmental conditions. Alternatively, cells may be signaled to switch the transcription of specific genes on or off, in order to alter the production of enzymes or other cellular constituents. Before we tackle the specific types of signal receptors and transduction pathways, let's first take a look at the nature of chemical signals.

Slide 3 Signal molecules that bind receptor molecules are often called ligands. Ligands may be a variety of types of molecules. They may be large or small, and polar or non-polar. Signals may come directly from the external environment of single-celled organisms, from adjacent cells within multicellular organisms, from outside of a multicellular organism, or they may be transferred from one part of an organism to another, for example through the bloodstream of animals, or through the vascular system of plants.

Slide 4 Relatively large or polar signal molecules are not able to move through membranes, and so are generally bound by receptor molecules attached to the cell membrane. Small or non-polar ligands, on the other hand, are often able to diffuse through membranes and so may be received by receptor molecules in the cytoplasm. In either case, in order to receive and react to a specific ligand, a cell must have a receptor molecule specifically designed to bind that ligand. If the correct receptor is not there, the signal will go unheeded by the cell.

Receptor molecules are generally proteins or glycoproteins. Binding of a ligand causes a conformational, or shape change in the receptor molecule. This shape change generally alters the activity of the protein in some way. In the following slides, we will describe four common types of receptor molecules and the cellular effects that result when they bind a signal molecule. The four receptor types that we will discuss are ligand-gated ion channels, G protein-linked receptors, protein kinases and cytoplasmic receptors.

Slide 5 Ligand-gated ion channels are integral membrane proteins that act as receptors molecules. When open, they form a channel for the passage of specific types of ions, such as sodium, potassium, calcium, or chlorine ions. Ion channels may bind ligands directly, causing a conformational change that opens a channel through the membrane. Ions flow passively through this channel down a concentration or electrical gradient. The resulting flux of ions elicits a cellular response. For example, in the illustration here, sodium ions flow into a cell after a sodium ion channel binds the signal molecule acetylcholine. When this happens in a muscle tissue, the increased concentration of sodium causes the cells to contract, allowing the muscle to perform work for the organism.

Slide 6 G protein-linked receptors represent somewhat more complex signal reception pathways. G protein-linked receptors are integral membrane proteins with two binding sites. One site faces the outside of the cell, and binds specific signal molecules. The other site is on the cytoplasmic side of the cell membrane, and binds a particular type of protein called a G protein. When a G protein-linked receptor binds a signal molecule, the resulting conformational change exposes the second binding site, allowing the binding and activation of a G protein. The G protein is activated by exchanging a molecule of GDP, or guanosine diphosphate, for a molecule of GTP, or guanosine triphosphate. When this occurs, a part of the active G protein disassociates and moves along the membrane to bind to a third enzyme. By binding the disassociated G protein, the final enzyme is activated, and it can then take part in cellular reactions. Often, this final enzyme catalyzes many reactions, which effectively amplifies the original signal received by the cell.

Slide 7 Like ligand-gated ion channels and G protein-linked receptors, a third class of receptor molecules, called protein kinases, are also integral membrane proteins. Protein kinases are enzymes that take part directly in chemical reactions by phosphorylating other molecules. When no ligand is bound to the protein kinase, it is inactive. When a ligand is bound, the resulting conformational change exposes an active site on the molecule that is responsible for kinase activity. This active site is utilized to phosphorylate other molecules, usually other proteins. Phosphorylation, in turn, generally alters the activity of the other molecules. One key difference between protein kinases and other types of receptor molecules is that kinases may activate several to many other proteins, rather than just one. This allows the cell to activate several responses to the same signal.

Slide 8 Some protein kinase receptor molecules take part in a well-understood signal transduction pathway, called the protein kinase cascade. In the protein kinase cascade, a signal molecule, in this case a molecule called a growth factor, is received by a cell and initiates a cascade of phosphorylation events. Ultimately, the cell’s response to the growth factor will be to divide by mitosis. The receptor molecule, activated by binding of the signal, phosphorylates a second, cytoplasmic protein. This phosphorylation activates the second protein, which in turn phosphorylates and activates a third protein. This cascade continues until a final protein is phosphorylated and moves into the nucleus to act as a transcription factor. As a result, genes necessary for cell division are transcribed and the cell may divide by mitosis. This pathway is important in actively growing tissues within an organism.

You should note that the protein kinase cascade exhibits features important to many signal transduction pathways. On a fundamental level, a signal from outside the cell was translated into a response inside of the cell, in this case the transcription of specific genes and cell division. In addition, the original signal the cell received was amplified, as each activated enzyme in the pathway is capable of activating many molecules of the proteins that immediately follow it in the pathway. There are also other features which you may notice cropping up in other transduction pathways. For example, the enzymes in this pathway were activated by phosphorylation, which changed their conformation and exposed their active sites. Also, by carrying out the transduction of the signal through a set of several enzymatic reactions, the cell is able to produce a very specific response to a particular signal.

Slide 9 The final type of receptor molecules we will cover are cytoplasmic receptors. Cytoplasmic receptors are proteins found in the cytoplasm of cells. These receptors typically bind small, non-polar ligands that are able to diffuse through the cell membrane. Binding of a ligand results in the activation of the receptor, which in most cases, moves into the nucleus to act as a transcription factor.

Slide 10 Let’s take a brief moment to recap what we have covered so far. Cells must communicate with the environment around them. They do this by receiving signals at their cell membrane or in their cytoplasm, and translating those signals into an appropriate cellular response. We have covered four common types of receptors: ligand-gated ion channels, G protein-linked receptors, cytoplasmic receptors, and protein kinases. Further, we have seen several common responses to the binding of signal molecules, including the opening of membrane channels, the activation of enzymes, and the selective transcription of genes. Each of these receptors and responses allow a cell to respond in a different, yet signal-specific way.

Slide 11 To finish, it is worth noting that in some instances the action resulting from signal reception occurs directly at the membrane, as in many of the examples we have covered so far. In other instance, however, binding of a signal molecule results in the formation or influx of a messenger molecule, called a second messenger. Pathways that utilize second messenger molecules are referred to as indirect transduction pathways.

There are a number of types of molecules that act as second messengers in signal transduction pathways. Cyclic AMP, for example, is synthesized by an enzyme activated by G protein-linked receptors. cAMP plays many roles for the cell as a second messenger – it may diffuse through a cell and bind and open ion channels, it may influence gene transcription, or it may activate protein kinases. Calcium ions are also important second messengers. Calcium ions enter the cell when ligands bind calcium ion channels, causing them to open. Once inside the cell, calcium ions may directly or indirectly activate enzymes or open other ion channels.

There are also other types of second messengers. Some, such as the molecules IP_3 and DAG, are derived from lipids. Others, such as nitric oxide, are specialized for short distance signaling.