

Present in small concentrations in the plasma membrane, **inositol phospholipids** are lipids that can also be converted into second messengers. Because these molecules are membrane components, they are located near membrane-bound receptors and can easily interact with them. Phosphatidylinositol (PI) is the main phospholipid that plays a role in cellular signaling. Enzymes known as kinases phosphorylate PI to form PI-phosphate (PIP) and PI-bisphosphate (PIP₂).

The enzyme phospholipase C cleaves PIP₂ to form **diacylglycerol (DAG)** and **inositol triphosphate (IP₃)** (Figure 9.13). These products of the cleavage of PIP₂ serve as second messengers. Diacylglycerol (DAG) remains in the plasma membrane and activates protein kinase C (PKC), which then phosphorylates serine and threonine residues in its target proteins. IP₃ diffuses into the cytoplasm and binds to ligand-gated calcium channels in the endoplasmic reticulum to release Ca²⁺ that continues the signal cascade.

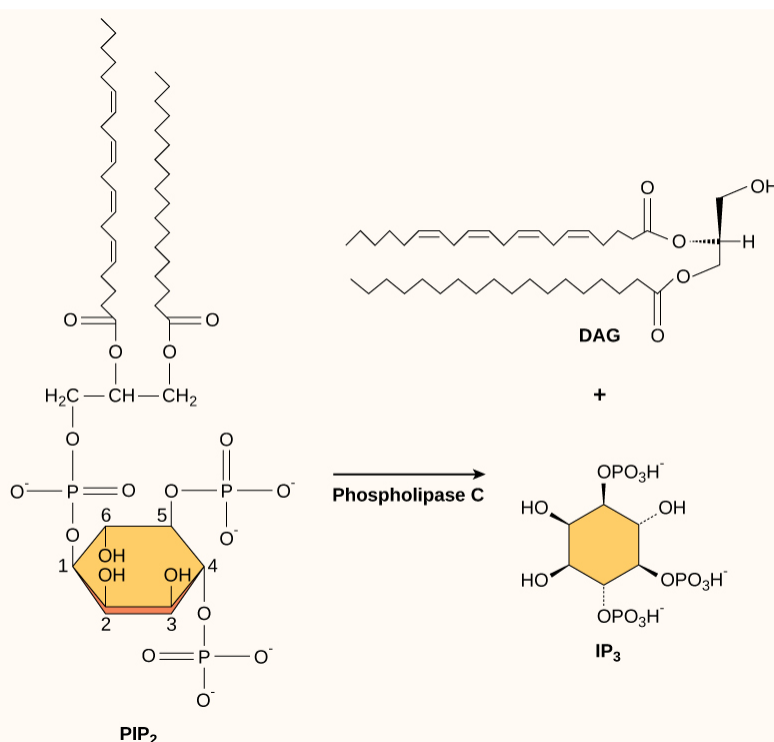


Figure 9.13 The enzyme phospholipase C breaks down PIP₂ into IP₃ and DAG, both of which serve as second messengers.

9.3 Response to the Signal

By the end of this section, you will be able to do the following:

- Describe how signaling pathways direct protein expression, cellular metabolism, and cell growth
- Identify the function of PKC in signal transduction pathways
- Recognize the role of apoptosis in the development and maintenance of a healthy organism

Inside the cell, ligands bind to their internal receptors, allowing them to directly affect the cell's DNA and protein-producing machinery. Using signal transduction pathways, receptors in the plasma membrane produce a variety of effects on the cell. The results of signaling pathways are extremely varied and depend on the type of cell involved as well as the external and internal conditions. A small sampling of responses is described below.

Gene Expression

Some signal transduction pathways regulate the transcription of RNA. Others regulate the translation of proteins from mRNA. An example of a protein that regulates translation in the nucleus is the MAP kinase ERK. The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the nuclear DNA. ERK is activated in a phosphorylation cascade when epidermal growth factor (EGF) binds the EGF receptor (see Figure 9.10). Upon phosphorylation, ERK enters the nucleus and activates a protein kinase that, in turn, regulates protein translation (Figure 9.14).

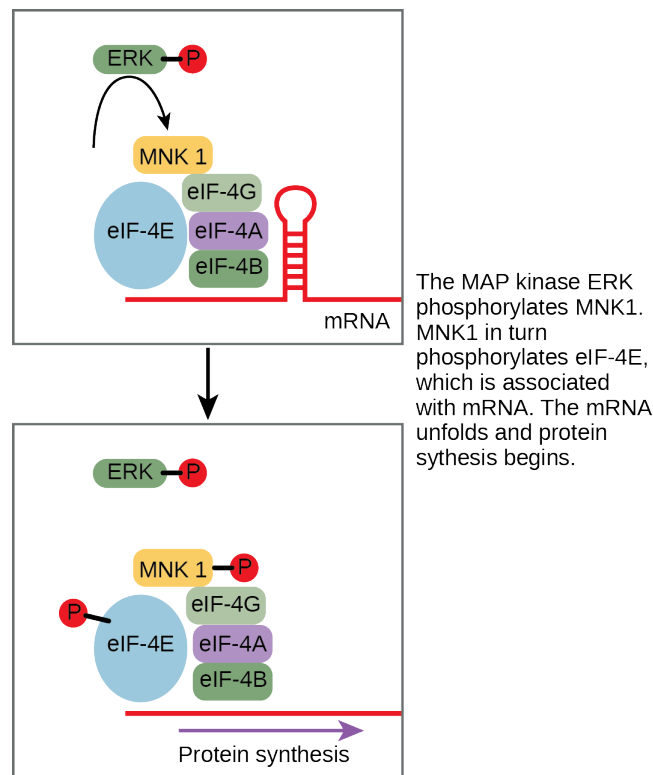


Figure 9.14 ERK is a MAP kinase that activates translation when it is phosphorylated. ERK phosphorylates MNK1, which in turn phosphorylates eIF-4E, an elongation initiation factor that, with other initiation factors, is associated with mRNA. When eIF-4E becomes phosphorylated, the mRNA unfolds, allowing protein synthesis in the nucleus to begin. (See [Figure 9.10](#) for the phosphorylation pathway that activates ERK.)

Another mechanism of gene regulation involves PKC, which can interact with a protein that acts as an inhibitor. An **inhibitor** is a molecule that binds to a protein and prevents it from functioning or reduces its function. In this case, the inhibitor is a protein called I κ -B, which binds to the regulatory protein NF- κ B. (The symbol κ represents the Greek letter kappa.) When I κ -B is bound to NF- κ B, the complex cannot enter the nucleus of the cell, but when I κ -B is phosphorylated by PKC, it can no longer bind NF- κ B, and NF- κ B (a transcription factor) can enter the nucleus and initiate RNA transcription. In this case, the effect of phosphorylation is to inactivate an inhibitor and thereby activate the process of transcription.

Increase in Cellular Metabolism

The result of another signaling pathway affects muscle cells. The activation of β -adrenergic receptors in muscle cells by adrenaline leads to an increase in cyclic AMP (cAMP) inside the cell. Also known as epinephrine, adrenaline is a hormone (produced by the adrenal gland located on top of the kidney) that readies the body for short-term emergencies. Cyclic AMP activates PKA (protein kinase A), which in turn phosphorylates two enzymes. The first enzyme promotes the degradation of glycogen by activating intermediate glycogen phosphorylase kinase (GPK) that in turn activates glycogen phosphorylase (GP) that catabolizes glycogen into its constituent glucose monomers. (Recall that your body converts excess glucose to glycogen for short-term storage. When energy is needed, glycogen is quickly reconverted to glucose.) Phosphorylation of the second enzyme, glycogen synthase (GS), inhibits its ability to form glycogen from glucose. In this manner, a muscle cell obtains a ready pool of glucose by activating its formation via glycogen degradation and by inhibiting the use of glucose to form glycogen, thus preventing a futile cycle of glycogen degradation and synthesis. The glucose is then available for use by the muscle cell in response to a sudden surge of adrenaline—the “fight or flight” reflex.

Cell Growth

Cell signaling pathways also play a major role in cell division. Cells do not normally divide unless they are stimulated by signals from other cells. The ligands that promote cell growth are called **growth factors**. Most growth factors bind to cell-surface receptors that are linked to tyrosine kinases. These cell-surface receptors are called receptor tyrosine kinases (RTKs). Activation of RTKs initiates a signaling pathway that includes a G-protein called RAS, which activates the MAP kinase pathway described

earlier. The enzyme MAP kinase then stimulates the expression of proteins that interact with other cellular components to initiate cell division.



CAREER CONNECTION

Cancer Biologist

Cancer biologists study the molecular origins of cancer with the goal of developing new prevention methods and treatment strategies that will inhibit the growth of tumors without harming the normal cells of the body. As mentioned earlier, signaling pathways control cell growth. These signaling pathways are controlled by signaling proteins, which are, in turn, expressed by genes. Mutations in these genes can result in malfunctioning signaling proteins. This prevents the cell from regulating its cell cycle, triggering unrestricted cell division and perhaps cancer. The genes that regulate the signaling proteins are one type of oncogene, which is a gene that has the potential to cause cancer. The gene encoding RAS is an oncogene that was originally discovered when mutations in the RAS protein were linked to cancer. Further studies have indicated that 30 percent of cancer cells have a mutation in the RAS gene that leads to uncontrolled growth. If left unchecked, uncontrolled cell division can lead to tumor formation and metastasis, the growth of cancer cells in new locations in the body.

Cancer biologists have been able to identify many other oncogenes that contribute to the development of cancer. For example, HER2 is a cell-surface receptor that is present in excessive amounts in 20 percent of human breast cancers. Cancer biologists realized that gene duplication led to HER2 overexpression in 25 percent of breast cancer patients and developed a drug called Herceptin (trastuzumab). Herceptin is a monoclonal antibody that targets HER2 for removal by the immune system. Herceptin therapy helps to control signaling through HER2. The use of Herceptin in combination with chemotherapy has helped to increase the overall survival rate of patients with metastatic breast cancer.

More information on cancer biology research can be found at the National Cancer Institute website (<https://www.cancer.gov/research/areas/biology> (http://openstax.org/l/cancer_research)).

Cell Death

When a cell is damaged, superfluous, or potentially dangerous to an organism, a cell can initiate a mechanism to trigger programmed cell death, or **apoptosis**. Apoptosis allows a cell to die in a controlled manner that prevents the release of potentially damaging molecules from inside the cell. There are many internal checkpoints that monitor a cell's health; if abnormalities are observed, a cell can spontaneously initiate the process of apoptosis. However, in some cases, such as a viral infection or uncontrolled cell division due to cancer, the cell's normal checks and balances fail. External signaling can also initiate apoptosis. For example, most normal animal cells have receptors that interact with the extracellular matrix, a network of glycoproteins that provides structural support for cells in an organism. The binding of cellular receptors to the extracellular matrix initiates a signaling cascade within the cell. However, if the cell moves away from the extracellular matrix, the signaling ceases, and the cell undergoes apoptosis. This system keeps cells from traveling through the body and proliferating out of control, as happens with tumor cells that metastasize.

Another example of external signaling that leads to apoptosis occurs in T-cell development. T-cells are immune cells that bind to foreign macromolecules and particles, and target them for destruction by the immune system. Normally, T-cells do not target "self" proteins (those of their own organism), a process that can lead to autoimmune diseases. In order to develop the ability to discriminate between self and non-self, immature T-cells undergo screening to determine whether they bind to so-called self proteins. If the T-cell receptor binds to self proteins, the cell initiates apoptosis to remove the potentially dangerous cell.

Apoptosis is also essential for normal embryological development. In vertebrates, for example, early stages of development include the formation of web-like tissue between individual fingers and toes ([Figure 9.15](#)). During the course of normal development, these unneeded cells must be eliminated, enabling fully separated fingers and toes to form. A cell signaling mechanism triggers apoptosis, which destroys the cells between the developing digits.



Figure 9.15 The histological section of a foot of a 15-day-old mouse embryo, visualized using light microscopy, reveals areas of tissue between the toes, which apoptosis will eliminate before the mouse reaches its full gestational age at 27 days. (credit: modification of work by Michal Mañas)

Termination of the Signal Cascade

The aberrant signaling often seen in tumor cells is proof that the termination of a signal at the appropriate time can be just as important as the initiation of a signal. One method of stopping a specific signal is to degrade the ligand or remove it so that it can no longer access its receptor. One reason that hydrophobic hormones like estrogen and testosterone trigger long-lasting events is because they bind carrier proteins. These proteins allow the insoluble molecules to be soluble in blood, but they also protect the hormones from degradation by circulating enzymes.

Inside the cell, many different enzymes reverse the cellular modifications that result from signaling cascades. For example, **phosphatases** are enzymes that remove the phosphate group attached to proteins by kinases in a process called dephosphorylation. Cyclic AMP (cAMP) is degraded into AMP by **phosphodiesterase**, and the release of calcium stores is reversed by the Ca^{2+} pumps that are located in the external and internal membranes of the cell.

9.4 Signaling in Single-Celled Organisms

By the end of this section, you will be able to do the following:

- Describe how single-celled yeasts use cell signaling to communicate with one another
- Relate the role of quorum sensing to the ability of some bacteria to form biofilms

Within-cell signaling allows bacteria to respond to environmental cues, such as nutrient levels. Some single-celled organisms also release molecules to signal to each other.

Signaling in Yeast

Yeasts are eukaryotes (fungi), and the components and processes found in yeast signals are similar to those of cell-surface receptor signals in multicellular organisms. Budding yeasts (Figure 9.16) are able to participate in a process that is similar to sexual reproduction that entails two haploid cells (cells with one-half the normal number of chromosomes) combining to form a diploid cell (a cell with two sets of each chromosome, which is what normal body cells contain). In order to find another haploid yeast cell that is prepared to mate, budding yeasts secrete a signaling molecule called **mating factor**. When mating factor binds to cell-surface receptors in other yeast cells that are nearby, they stop their normal growth cycles and initiate a cell signaling cascade that includes protein kinases and GTP-binding proteins that are similar to G-proteins.