

## 9.2 | Propagation of the Signal

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

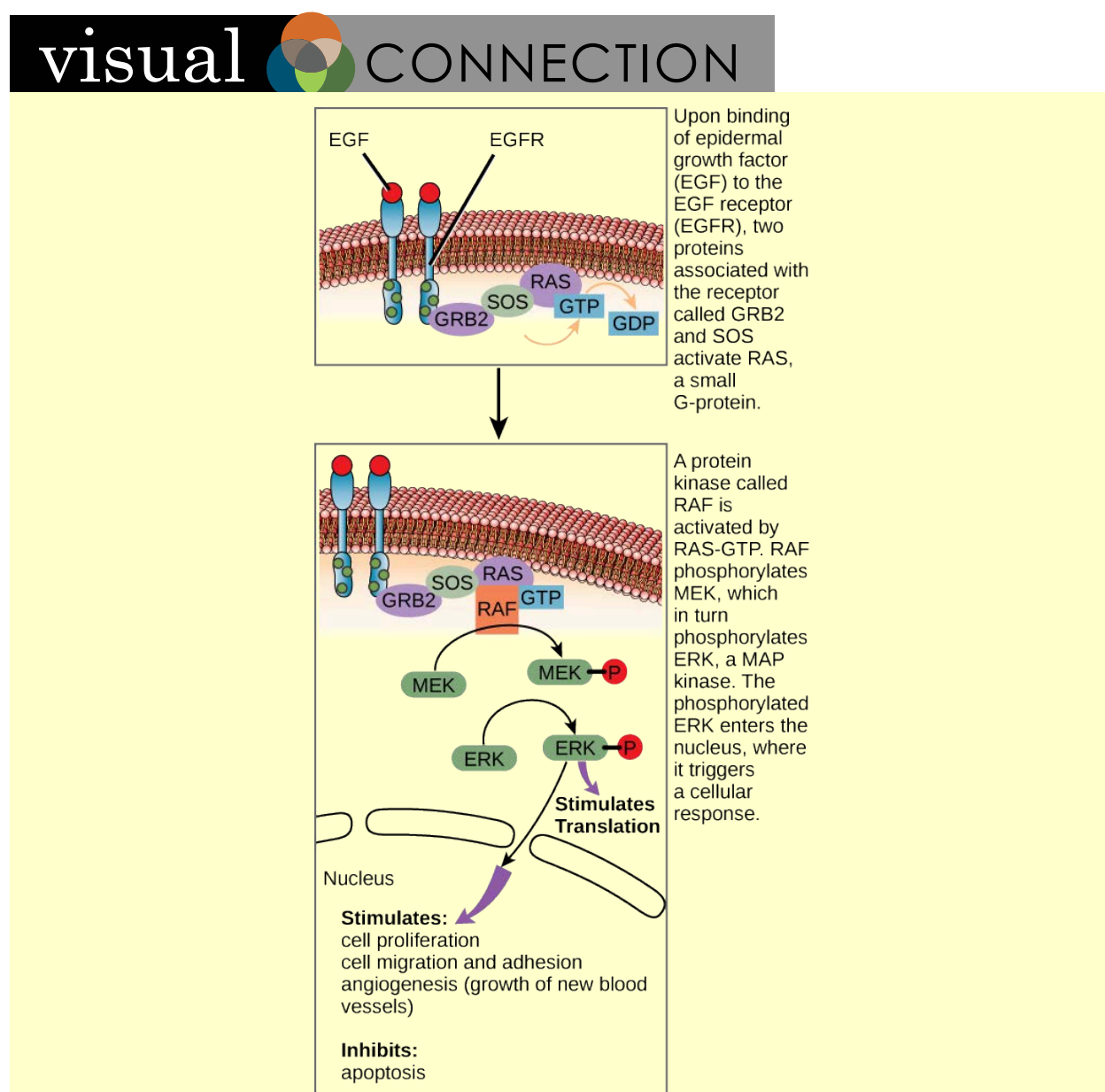
- Explain how the binding of a ligand initiates signal transduction throughout a cell
- Recognize the role of phosphorylation in the transmission of intracellular signals
- Evaluate the role of second messengers in signal transmission

Once a ligand binds to a receptor, the signal is transmitted through the membrane and into the cytoplasm. Continuation of a signal in this manner is called **signal transduction**. Signal transduction only occurs with cell-surface receptors, which cannot interact with most components of the cell such as DNA. Only internal receptors are able to interact directly with DNA in the nucleus to initiate protein synthesis.

When a ligand binds to its receptor, conformational changes occur that affect the receptor's intracellular domain. Conformational changes of the extracellular domain upon ligand binding can propagate through the membrane region of the receptor and lead to activation of the intracellular domain or its associated proteins. In some cases, binding of the ligand causes **dimerization** of the receptor, which means that two receptors bind to each other to form a stable complex called a dimer. A **dimer** is a chemical compound formed when two molecules (often identical) join together. The binding of the receptors in this manner enables their intracellular domains to come into close contact and activate each other.

### Binding Initiates a Signaling Pathway

After the ligand binds to the cell-surface receptor, the activation of the receptor's intracellular components sets off a chain of events that is called a **signaling pathway**, sometimes called a signaling cascade. In a signaling pathway, second messengers—enzymes—and activated proteins interact with specific proteins, which are in turn activated in a chain reaction that eventually leads to a change in the cell's environment (**Figure 9.10**), such as an increase in metabolism or specific gene expression. The events in the cascade occur in a series, much like a current flows in a river. Interactions that occur before a certain point are defined as upstream events, and events after that point are called downstream events.



**Figure 9.10** The epidermal growth factor (EGF) receptor (EGFR) is a receptor tyrosine kinase involved in the regulation of cell growth, wound healing, and tissue repair. When EGF binds to the EGFR, a cascade of downstream events causes the cell to grow and divide. If EGFR is activated at inappropriate times, uncontrolled cell growth (cancer) may occur.

In certain cancers, the GTPase activity of the RAS G-protein is inhibited. This means that the RAS protein can no longer hydrolyze GTP into GDP. What effect would this have on downstream cellular events?

You can see that signaling pathways can get very complicated very quickly because most cellular proteins can affect different downstream events, depending on the conditions within the cell. A single pathway can branch off toward different endpoints based on the interplay between two or more signaling pathways, and the same ligands are often used to initiate different signals in different cell types. This variation in response is due to differences in protein expression in different cell types. Another complicating element is **signal integration** of the pathways, in which signals from two or more different cell-surface receptors merge to activate the same response in the cell. This process can ensure that multiple external requirements are met before a cell commits to a specific response.

The effects of extracellular signals can also be amplified by enzymatic cascades. At the initiation of the signal,

a single ligand binds to a single receptor. However, activation of a receptor-linked enzyme can activate many copies of a component of the signaling cascade, which amplifies the signal.



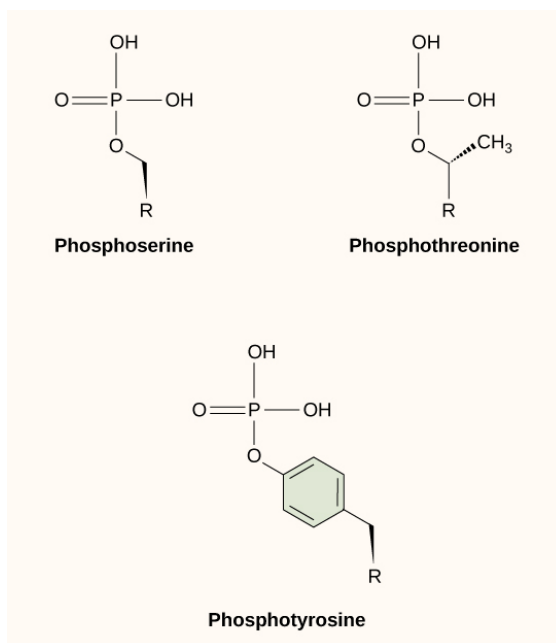
Observe an animation of cell signaling at this [site \(http://openstaxcollege.org//cell\\_signals\)](http://openstaxcollege.org//cell_signals).

## Methods of Intracellular Signaling

The induction of a signaling pathway depends on the modification of a cellular component by an enzyme. There are numerous enzymatic modifications that can occur, and they are recognized in turn by the next component downstream. The following are some of the more common events in intracellular signaling.

### Phosphorylation

One of the most common chemical modifications that occurs in signaling pathways is the addition of a phosphate group ( $\text{PO}_4^{3-}$ ) to a molecule such as a protein in a process called phosphorylation. The phosphate can be added to a nucleotide such as GMP to form GDP or GTP. Phosphates are also often added to serine, threonine, and tyrosine residues of proteins, where they replace the hydroxyl group of the amino acid (**Figure 9.11**). The transfer of the phosphate is catalyzed by an enzyme called a **kinase**. Various kinases are named for the substrate they phosphorylate. Phosphorylation of serine and threonine residues often activates enzymes. Phosphorylation of tyrosine residues can either affect the activity of an enzyme or create a binding site that interacts with downstream components in the signaling cascade. Phosphorylation may activate or inactivate enzymes, and the reversal of phosphorylation, dephosphorylation by a phosphatase, will reverse the effect.



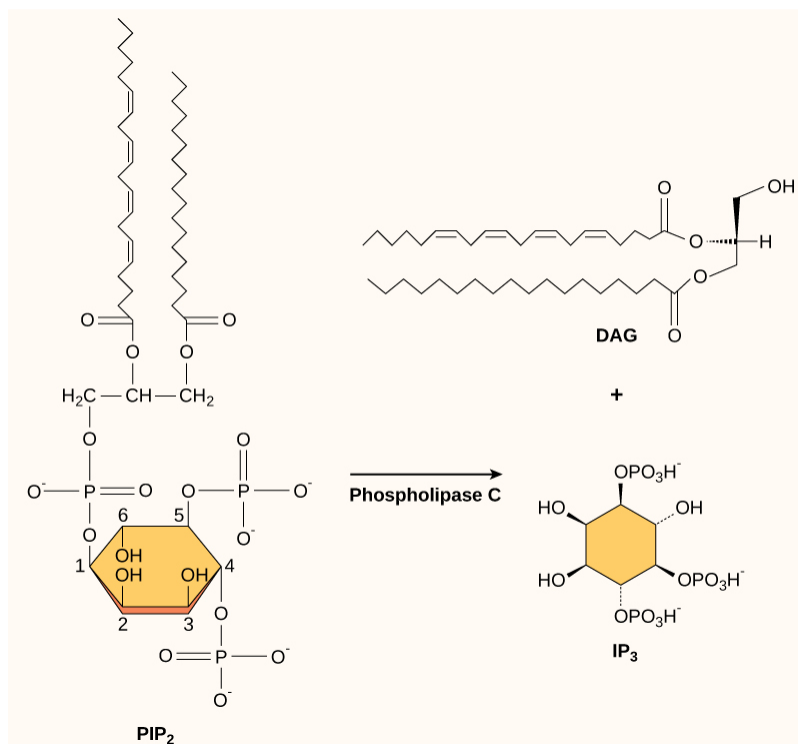
**Figure 9.11** In protein phosphorylation, a phosphate group ( $\text{PO}_4^{3-}$ ) is added to residues of the amino acids serine, threonine, and tyrosine.

### Second Messengers

**Second messengers** are small molecules that propagate a signal after it has been initiated by the binding of the signaling molecule to the receptor. These molecules help to spread a signal through the cytoplasm by altering the behavior of certain cellular proteins.

Calcium ion is a widely used second messenger. The free concentration of calcium ions ( $\text{Ca}^{2+}$ ) within a





**Figure 9.13** The enzyme phospholipase C breaks down PIP<sub>2</sub> into IP<sub>3</sub> 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**).