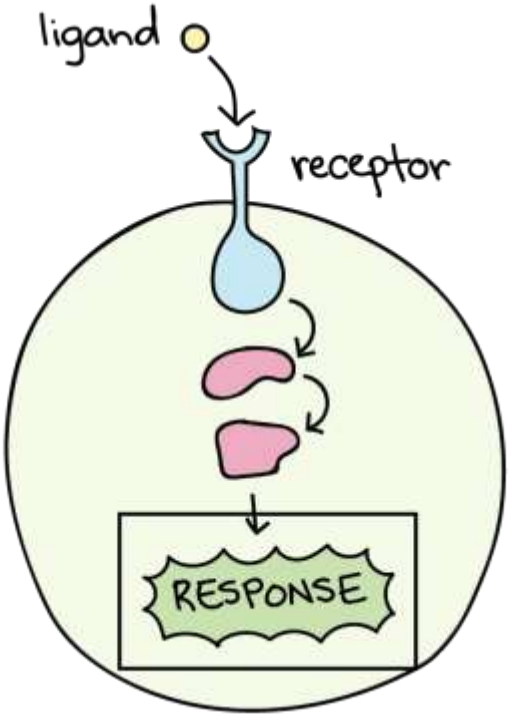
Response to a signal

The many different ways cells can change their behaviour in response to a signal.

Overview: cellular response

Cell signalling pathways vary a lot. Signals (a.k.a. ligands) and receptors come in many varieties, and binding can trigger a wide range of signal relay cascades inside the cell, from short and simple to long and complex.

Despite these differences, signalling pathways share a common goal: to produce some kind of cellular response. That is, a signal is released by the sending cell in order to make the receiving cell change in a particular way.



Generalized diagram of receptor-ligand binding, intracellular signal transduction, and cellular response. The cellular response stage is boxed.

In some cases, we can describe a cellular response at both the molecular level and the macroscopic (large-scale, or visible) level.

- At the molecular level, we can see changes such as an increase in the transcription of certain genes or the activity of particular enzymes.
- At the macroscopic level, we may be able to see changes in the outward behaviour or appearance of the cell, such as cell growth or cell death, that are caused by the molecular changes.

In this article, we'll look at examples of cellular responses to signalling that happen at both the "micro" and "macro" levels.

Gene expression

Many signalling pathways cause a cellular response that involves a change in gene expression. **Gene expression** is the process in which information from a gene is used by the cell to produce a functional product, typically a protein. It involves two major steps, transcription and translation.

- Transcription makes an RNA transcript (copy) of a gene's DNA sequence.
- Translation reads information from the RNA and uses it to make a protein.

  Here is a little more detail about how gene expression happens in eukaryotic cells:

  1. The deoxyribonucleic acid (DNA) sequence of a gene is copied (transcribed) into ribonucleic acid (RNA), a step called **transcription**. The RNA is modified in the nucleus to make a functional messenger RNA (mRNA).
  2. The mRNA leaves the nucleus and enters the cytosol. There, it directs synthesis of a protein, indicating which amino acids should be added to the chain. This step is called **translation**.

Signalling pathways can target either or both steps to alter the amount of a particular protein produced in a cell.

Example: Growth factor signalling

We can use the growth factor signalling pathway from the signal relay article as an example to see how signalling pathways alter transcription and translation.

This growth factor pathway has many targets, which it activates through a signalling cascade that involves phosphorylation (addition of phosphate groups to molecules). Some of the pathway's targets are transcription factors, proteins that increase or decrease transcription of certain genes. In the case of growth factor signalling, the genes have effects that lead to cell growth and division. One transcription factor targeted by the pathway is c-Myc, a protein that can lead to cancer when it is too active ("too good" at promoting cell division).

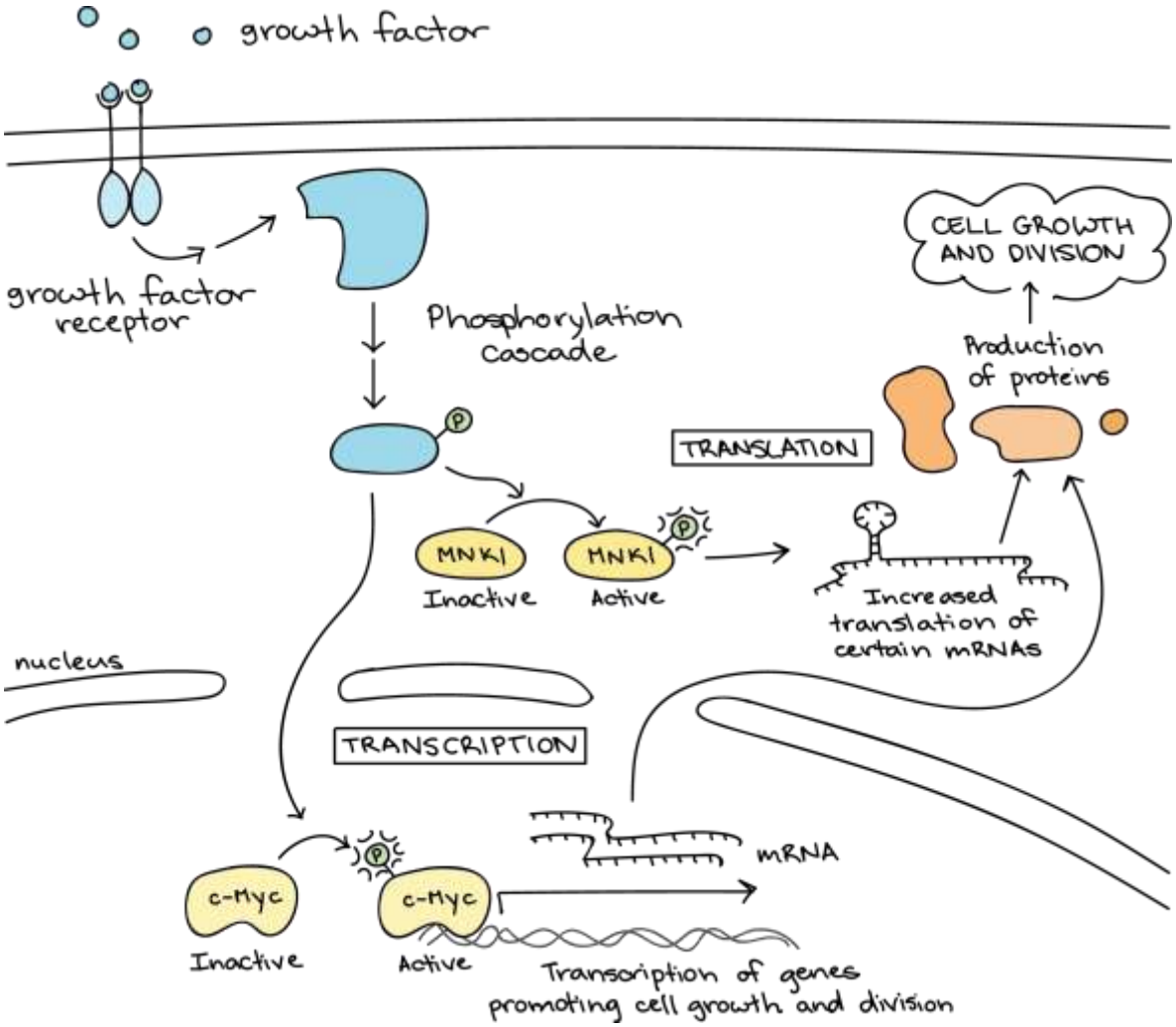


Image showing two ways in which the growth factor signalling pathway regulates gene expression to produce a cellular response of cell growth and proliferation. Growth factors signalling acts through a cascade to activate an ERK kinase, and the image shows two types of targets the ERK kinase acts on. (In reality, it has many others. We are just look at these two cases as examples.)

1) Transcriptional regulation. The ERK kinase phosphorylates and activates the transcription factor c-Myc. c-Myc binds to DNA to alter expression of target genes, activating genes that promote cell growth and proliferation. The genes are transcribed into mRNA, which can be translated in the cytosol to make proteins.

2). Translational regulation. The ERK kinase phosphorylates MNK1, a protein in the cytosol that enhances translation of mRNAs, especially ones with complex secondary structure (that form hairpins). The greater translation of these mRNAs results in higher levels of the corresponding proteins.

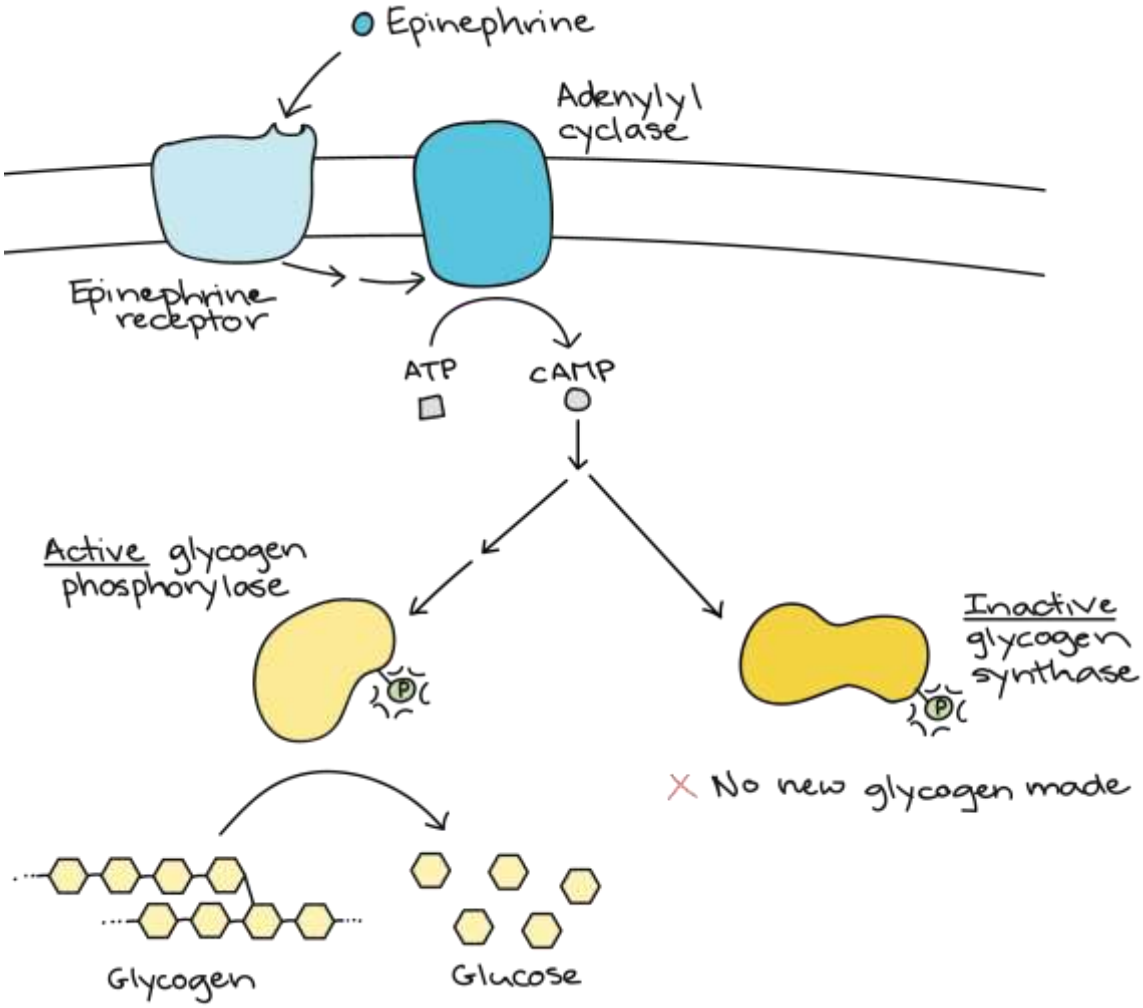
The growth factor pathway also affects gene expression at the level of translation. For instance, one of its targets is a translational regulator called MNK1. Active MNK1 increases the rate of mRNA translation, especially for certain mRNAs that fold back on themselves to make hairpin structures (which would normally block translation). Many key genes regulating cell division and survival have mRNAs that form hairpin structures, and MNK1 allows these genes to be expressed at high levels, driving growth and division.

Notably, neither c-Myc nor MNK1 is a "final responder" in the growth factor pathway. Instead, these regulatory factors, and others like them, promote or repress the production of other proteins (the orange blobs in the illustration above) that are more directly involved in carrying out cell growth and division.

Cellular metabolism

Some signalling pathways produce a metabolic response, in which metabolic enzymes in the cell become more or less active. We can see how this works by considering adrenaline signalling in muscle cells. Adrenaline, also known as epinephrine, is a hormone (produced by the adrenal gland) that readies the body for short-term emergencies. If you're nervous before a test or competition, your adrenal gland is likely to be pumping out epinephrine.

When epinephrine binds to its receptor on a muscle cell (a type of G protein-coupled receptor), it triggers a signal transduction cascade involving production of the second messenger molecule cyclic AMP (cAMP). This cascade leads to phosphorylation of two metabolic enzymes— that is, addition of a phosphate group, causing a change in the enzymes' behaviour.



The first enzyme is glycogen phosphorylase (GP). The job of this enzyme is to break down glycogen into glucose. Glycogen is a storage form of glucose, and when energy is needed, glycogen must be broken down. Phosphorylation activates glycogen phosphorylase, causing lots of glucose to be released.

The second enzyme that gets phosphorylated is glycogen synthase (GS). This enzyme is involving in building up glycogen, and phosphorylation inhibits its activity. This ensures that no new glycogen molecules are built when the current need is for glycogen to be broken down.

Through regulation of these enzymes, a muscle cell rapidly gets a large, ready pool of glucose molecules. The glucose is available for use by the muscle cell in response to a sudden surge of adrenaline—the “fight or flight” response.

Big-picture outcomes of cell signalling

The types of responses we’ve discussed above are events at the molecular level. However, a signalling pathway typically triggers a molecular event (or a whole array of molecular events) to in order to produce some larger outcome.

For instance, growth factor signalling causes a variety of molecular changes, including activation of the c-Myc transcription factor and MNK1 translational regulator, to promote the larger response of cell proliferation (growth and division). Similarly, epinephrine triggers the activation of glycogen phosphorylase and the breakdown of glycogen in order to provide a muscle cell with fuel for a rapid response.

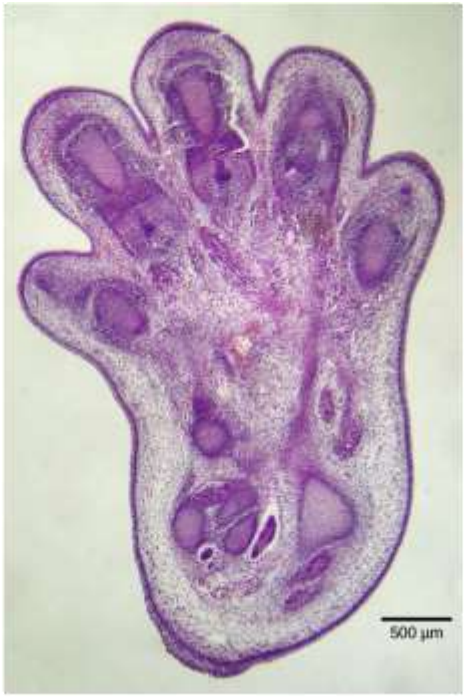
Other important large-scale outcomes of cell signalling include cell migration, changes in cell identity, and induction of apoptosis (programmed cell death).

Example: Apoptosis

When a cell is damaged, unneeded, or potentially dangerous to an organism, it may undergo 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.

Internal signals (such as those triggered by damaged DNA) can lead to apoptosis, but so can signals from outside the cell. For example, most animal cells have receptors that interact with the extracellular matrix, a supportive network of proteins and carbohydrates. If the cell moves away from the extracellular matrix, signalling through these receptors stops, and the cell undergoes apoptosis. This system keeps cells from traveling through the body and proliferating out of control (and is "broken" in cancer cells that metastasize, or spread to new sites).

Apoptosis is also essential for normal embryological development. In vertebrates, for example, early stages of development include the formation of tissue between what will become individual fingers and toes. During the course of normal development, these unneeded cells must be eliminated, enabling fully separated fingers and toes to form. A cell signalling mechanism triggers apoptosis, which destroys the cells between the developing digits.



This section of the foot of a 15-day-old mouse embryo shows areas of tissue between the toes, which apoptosis will eliminate before the mouse is born. Image credit: "Response to the signal: Figure 2," by OpenStax College, Biology, CC BY 4.0. Modification of work by Michal