

1. Specific carbohydrate residues on the surface glycoproteins of blood cells are binding targets for hemagglutinin proteins on the surface of flu viruses. To enter a cell, the virus must cleave the sialic acid off with a neuraminidase enzyme (also on the flu virus's surface). Anti-flu drugs like tamiflu act by inhibiting the action of the neuraminidase.

Signaling Highlights

1. Signaling is essential for cells in multicellular organisms to communicate with each other.
2. A common signaling system is that of the beta-adrenergic receptor, which works as follows. A ligand, such as epinephrine (also called adrenalin) is released into the bloodstream in response to a stimulus. This molecule is called the first messenger. When it arrives at the target cell, it binds to the receptor, causing the receptor to change shape slightly. The result of this shape change is that on the inside of the cell, the receptor acts on a G protein (see below) to activate it. The activated G protein, in turn, activates the enzyme adenylate cyclase (previously written incorrectly as adenylate kinase), which, in turn, begins to synthesize cAMP. cAMP is a so-called second messenger, which acts by binding to Protein Kinase A (PKA) to activate it. The activated PKA begins phosphorylating a set of enzymes, turning them on or off (depending on the enzyme).
3. Phosphorylation of proteins known as transcription factors can activate or inactivate them. When activated they will turn on transcription of specific genes in the DNA.
4. Thus, signaling can have rapid effects (controlling enzyme activities) or slower effects (controlling gene expression by controlling transcription)
5. Receptors of the first messenger have similarity in structure, consisting of a polypeptide chain that spans the cell membrane 7 times. Such proteins are called 7TM proteins.
6. G proteins get their name from the fact that they bind guanine nucleotides (GDP and GTP). G protein complexes have three subunits - alpha, beta, gamma. Cells have 'families' of G protein complexes arising from the fact that there are multiple, slightly different versions of the individual subunits in the genome and these can be paired in many ways. The alpha subunit binds to GDP or GTP. When the alpha subunit is bound to GDP, it also binds the beta and gamma subunits. The G protein complex is thus inactivated. When the beta-adrenergic receptor binds its ligand, the receptor stimulates the 'loading' of GTP onto the alpha subunit, displacing GDP in the process. Upon binding GTP, the alpha subunit dissociates from the beta and gamma units. The alpha subunit is then free to bind other target proteins and is thus 'active' when bound to GTP.
7. G proteins have an enzymatic activity that slowly breaks down GTP to GDP within the alpha subunit. This activity is very important because it ensures that the G protein will not be left in the 'on' state permanently. When the alpha subunit is bound with GTP, it can bind to adenylate cyclase (an enzyme embedded in the cell membrane) and activate it. When the alpha subunit has GDP, it is bound with the beta/gamma subunits and CANNOT bind to adenylate cyclase.

8. Cells have two ways of turning off the beta adrenergic receptor. The first involves simple dissociation of the epinephrine ligand from the receptor. This leaves the receptor in the 'off' state. The second method involves phosphorylation of the receptor (by a receptor kinase). The phosphorylated receptor is then bound by the protein called beta-arrestin that binds the receptor and inhibits the activation of G proteins.
9. cAMP in cells acts on a kinase known as Protein Kinase A (PKA). PKA is composed of four subunits - two identical catalytic subunits (C) and two identical regulatory subunits (R). When the complex is present as C_2R_2 , the PKA is inactive. Binding of cAMP to the R subunits causes them to dissociate from the C subunits. The freed C subunits are therefore active.
10. Signaling through the adrenergic receptor has the effect of increasing blood glucose. Insulin is a hormone that counters the effect of epinephrine. It should be noted that increasing concentration of cAMP in cells results in an increase of blood glucose. Phosphodiesterase breaks down cAMP. Inhibitors of phosphodiesterase, such as caffeine, have the effect of increasing blood glucose.
11. Other receptors involved in signal transduction (signaling) act in different ways. For example, some receptors stimulate the activity of the enzyme Phospholipase C. This enzyme acts on a membranous molecule called phosphatidyl inositol (or PIP_2). Cleavage of PIP_2 by phospholipase C results in production of TWO second messengers. One of these, diacylglycerol (DAG) remains near or in the lipid bilayer where it stimulates another kinase, Protein Kinase C. Protein Kinase C acts to phosphorylate numerous proteins/enzymes to activate/inactivate them, depending upon the enzyme. The other second messenger produced by phospholipase C cleavage is inositol 1,4,5 triphosphate (also called IP_3). IP_3 is soluble in the cytoplasm and it acts there to stimulate the release of calcium from intracellular storage areas holding calcium.
12. Calcium may be thought of as a kind of 'third' messenger in the process of signaling. Cells normally must keep the concentration of the ion low so as to prevent it from binding to proteins and precipitating DNA. Calcium is essential for muscular contraction.
13. EF Hands are important structural domains of calcium binding proteins. Calmodulin is one such protein.
14. Calmodulin binds calcium, helping to keep its concentration relatively low. Upon binding calcium, calmodulin changes shape and this change in shape allows it to bind to other proteins that it wouldn't otherwise be able to bind to. One class of these are the CaM kinases that are stimulated to phosphorylate proteins when calmodulin binds.