Cells communicate through "signaling"

- *Signaling cell* = cell sending the signal (if signal is cellular in origin)
- Cell that detects the signal = *target cell*
- Signal is detected by a *receptor*
- Conversion of the information in the signal from one form to another = *signal transduction*
- **Example of signal transduction:** Conversion of a chemical signal (e.g., a neurotransmitter) to an electrical signal (change in membrane electric potential) during nerve impulse conduction
- Signaling controls cell fate

Figure 11.5 Overview of cell signaling (Layer 1)

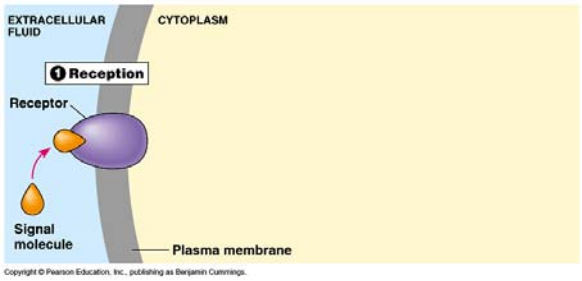


Figure 11.5 Overview of cell signaling (Layer 2)

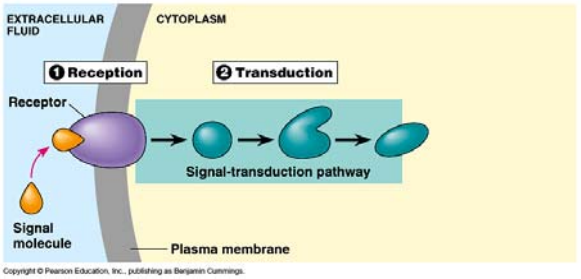
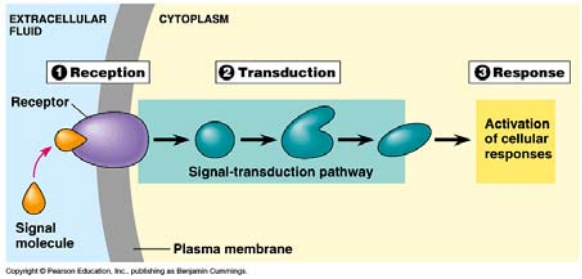
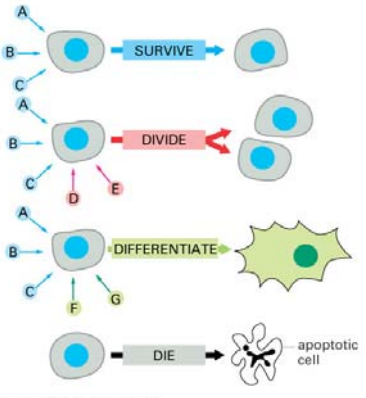


Figure 11.5 Overview of cell signaling (Layer 3)





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Signals may be chemical or physical

- Signaling molecules include: amino acids, peptides, proteins, nucleotides, fatty acid derivatives, and dissolved gases
- Physical signals include: heat, cold, light quantity or quality, etc.

SIGNAL MOLECULE	SITE OF ORIGIN	CHEMICAL NATURE	SOME ACTIONS
Hormones			
Adrenaline (epinephrine)	adrenal gland	derivative of the amino acid tyrosine	increases blood pressure, heart rate, and metabolism
Cortisol	adrenal gland	steroid (derivative of cholesterol)	affects metabolism of proteins, carbohydrates, and lipids in most tissues
Estradiol	ovary	steroid (derivative of cholesterol)	induces and maintains secondary female sexual characteristics
Glucagon	α cells of pancreas	peptide	stimulates glucose synthesis, glycogen breakdown, and lipid breakdown, e.g., in liver and fat cells
Insulin	β cells of pancreas	protein	stimulates glucose uptake, protein synthesis, and lipid synthesis, e.g., in liver cells
Testosterone	testis	steroid (derivative of cholesterol)	induces and maintains secondary male sexual characteristics
Thyroid hormone (thyroxine)	thyroid gland	derivative of the amino acid tyrosine	stimulates metabolism of many cell types
Local Mediators			
Epidermal growth factor (EGF)	various cells	protein	stimulates epidermal and many other cell types to proliferate
Platelet-derived growth factor (PDGF)	various cells, including blood platelets	protein	stimulates many cell types to proliferate
Nerve growth factor (NGF)	various innervated tissues	protein	promotes survival of certain classes of neurons; promotes growth of their axons
Transforming growth factor-β (TGF-β)	many cell types	protein	inhibits cell proliferation; stimulates extracellular matrix production
Histamine	mast cells	derivative of the amino acid histidine	causes blood vessels to dilate and become leaky, helping to cause inflammation
Nitric oxide (NO)	nerve cells; endothelial cells lining blood vessels	dissolved gas	causes smooth muscle cells to relax; regulates nerve cell activity
Neurotransmitters			
Acetylcholine	nerve terminals	derivative of choline	excitatory neurotransmitter at many nerve-muscle synapses and in central nervous system
γ-Aminobutyric acid (GABA)	nerve terminals	derivative of the amino acid glutamic acid	inhibitory neurotransmitter in central nervous system
Contact-dependent Signal Molecules			
Delta	prospective neurons; various other developing cell types	transmembrane protein	inhibits neighboring cells from becoming specialized in same way as the signaling cell

Signals may act over long or short distances

- *Endocrine signaling* hormones of animals and water stress hormones of plants (e.g. ABA) may travel long distances
- *Paracrine signaling* is exemplified by secretion of local mediators during the inflammatory response of the animal immune system
- In *neuronal signaling*, neurotransmitters signal over very short distances
- *Contact-dependent signaling* involves cell contact, e.g., contact between delta and Notch in developing neurons

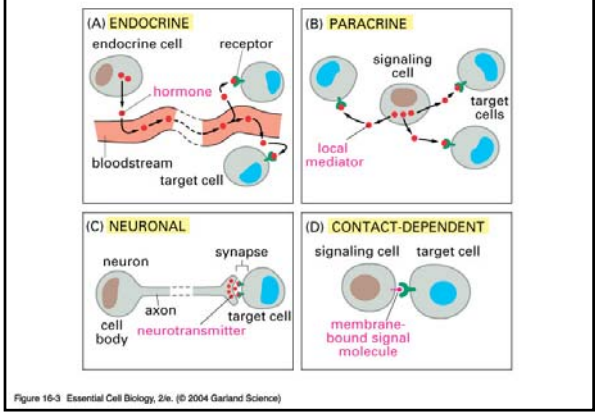


Figure 16-3 Essential Cell Biology, 2/e. (© 2004 Garland Science)

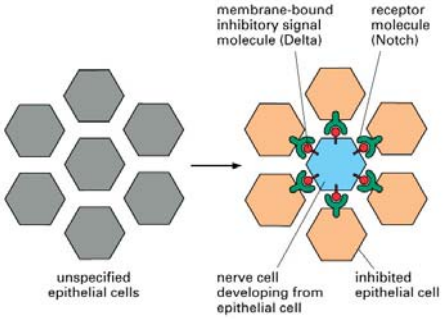


Figure 16-4 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Figure 11.3 Local and long-distance cell communication in animals

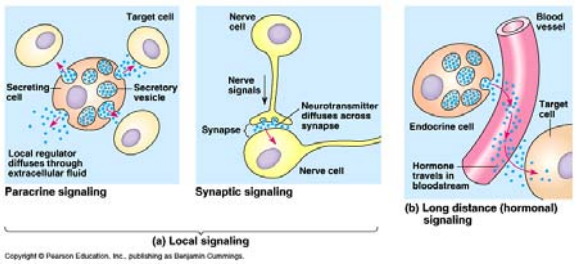
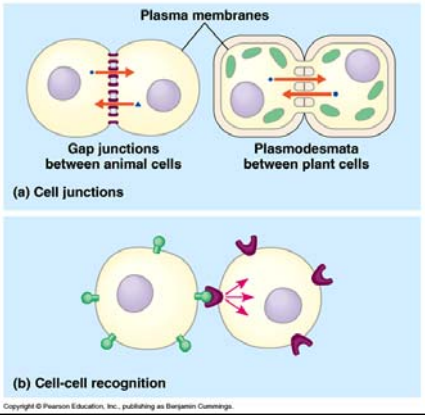


Figure 11.4 Communication by direct contact between cells



You are what you "perceive"

- Each cell type has a unique collection of different receptors; therefore, each cell type responds to a limited set of signals
- A single type of signaling molecule (= *ligand*) binding to one type of receptor can trigger a variety of effects in a single cell – e.g., a change in metabolism, gene expression, cell shape, etc.
- Some signal effects are fast; some are slow
- The effects of multiple signals may be interactive
- The same signal may affect different cell types differently

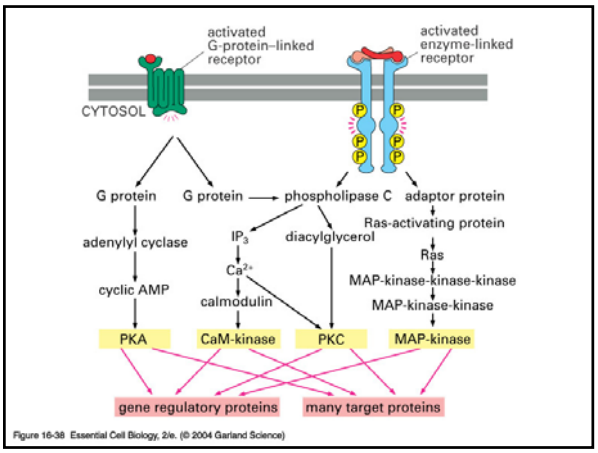


Figure 16-38 Essential Cell Biology, 2/e. (© 2004 Garland Science)

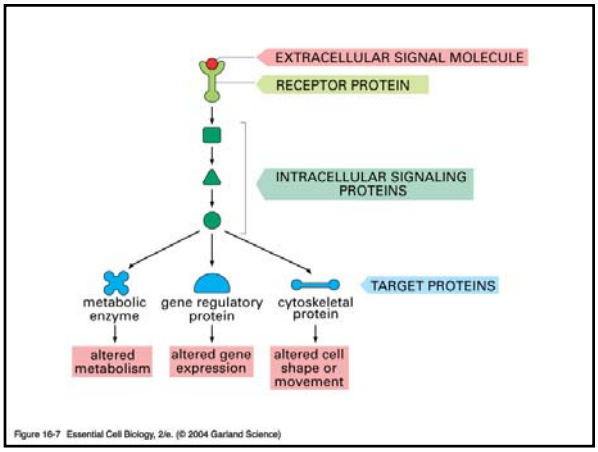
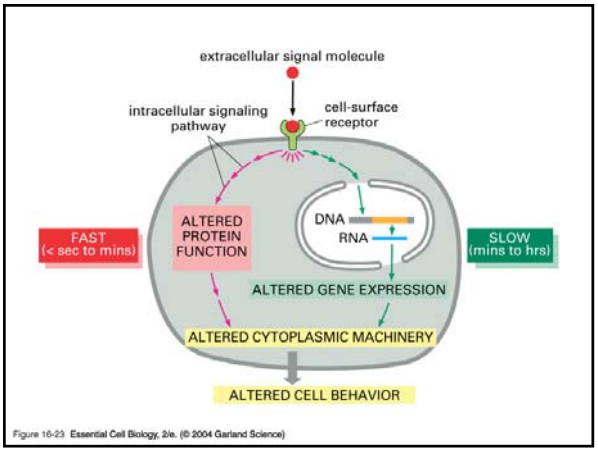


Figure 16-7 Essential Cell Biology, 2/e. (© 2004 Garland Science)



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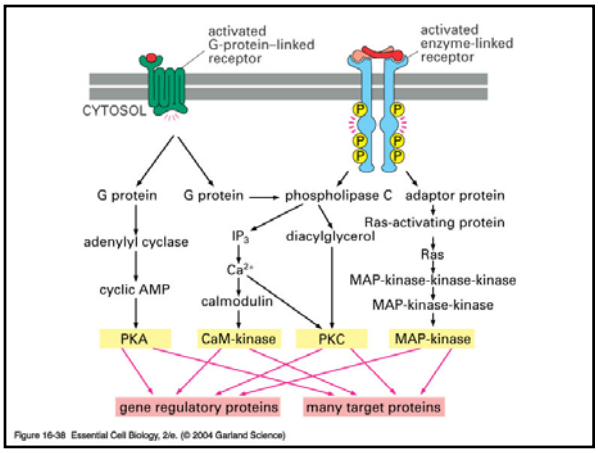

Figure 16-38 Essential Cell Biology, 2/e. (© 2004 Garland Science)

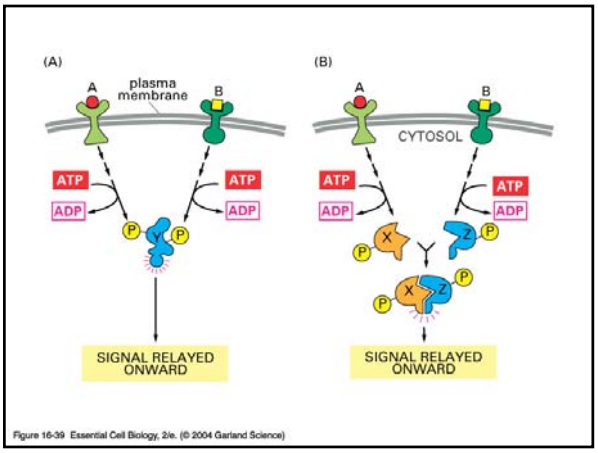

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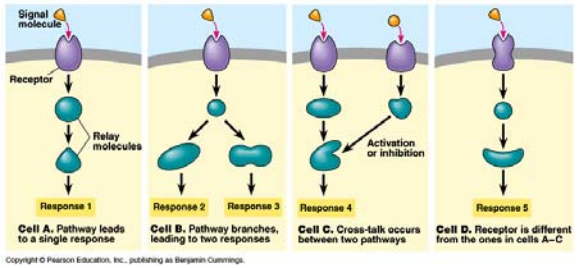
Figure 11.18 The specificity of cell signaling



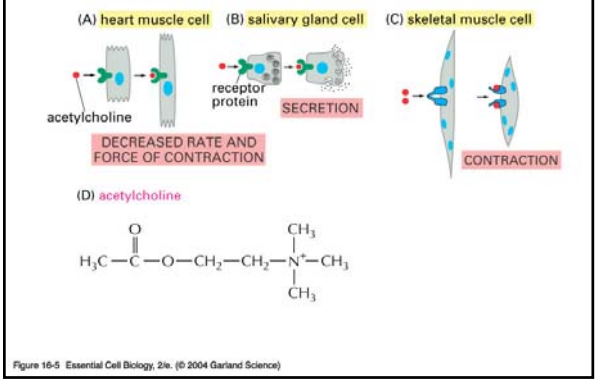
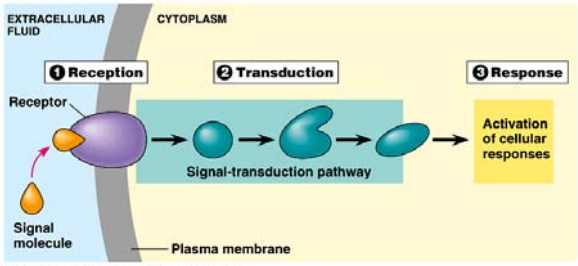


Figure 16-5 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Binding of ligand to receptor triggers a signaling "cascade" in which information is passed from the primary receptor to and through a chain of sequential intracellular signaling molecules.

Figure 11.5 Overview of cell signaling (Layer 3)



Functions of a signaling cascade

- Transfer of signal to response machinery of cell
- Transformation of signal into a molecular form that can evoke the desire response
- Amplification of the signal
- Distribution of the signal to divergent response mechanisms
- Capacity for "modulation" by internal or external factors

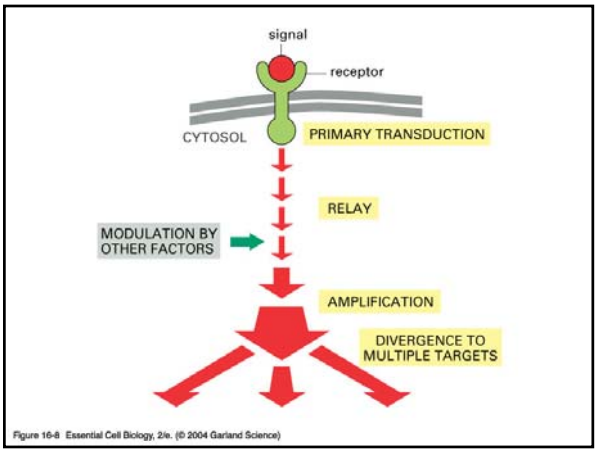
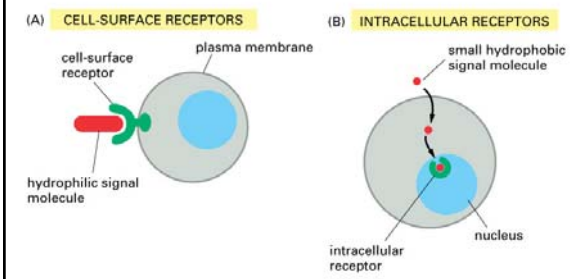


Figure 16-8 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Some signaling molecules can cross the plasma membrane, others can not.

- Large, hydrophilic signaling molecules bind to receptors in the plasma membrane = *extracellular receptors*
- For hydrophilic signaling molecules, the signal must be relayed across the membrane, often by a "second messenger"
- The five most common second messengers are: 3',5' cyclic AMP (cAMP); 3',5' cyclic GMP; 1,2-Diacylglycerol (DAG); inositol 1,4,5-triphosphate (IP_3); and calcium ion



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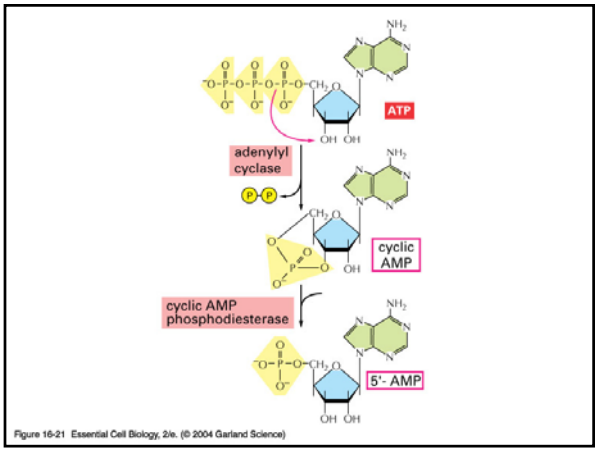

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Figure 11-12x cAMP

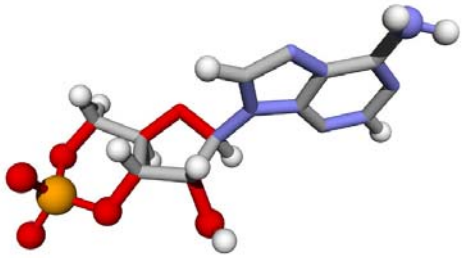
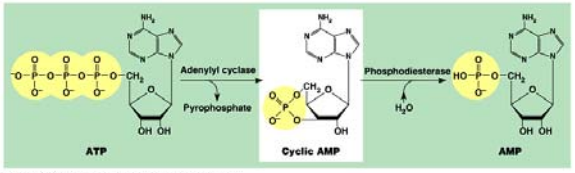


Figure 11.12 Cyclic AMP



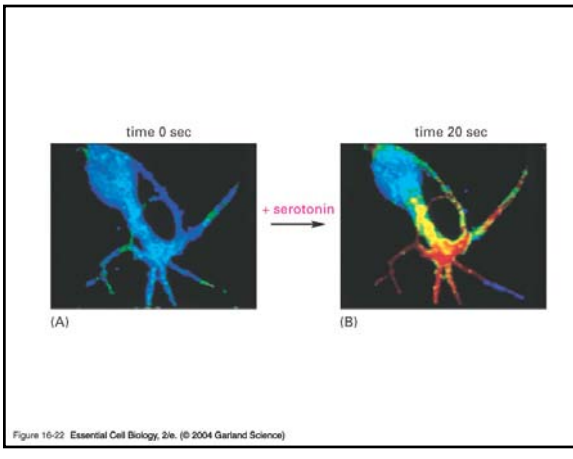
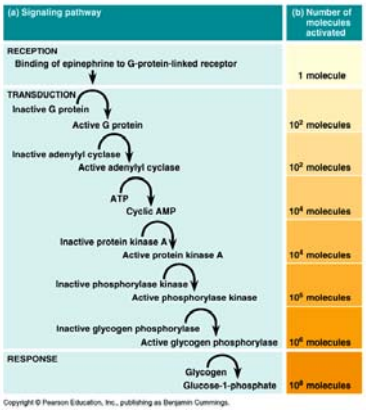


Figure 16-22 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Figure 11.16 Cytoplasmic response to a signal: the stimulation of glycogen breakdown by epinephrine



Some signaling molecules can cross the plasma membrane, others can not. (cont.)

- Hydrophobic signaling molecules often cross the membrane and bind to *intracellular receptors*
- Steroid hormones are good examples

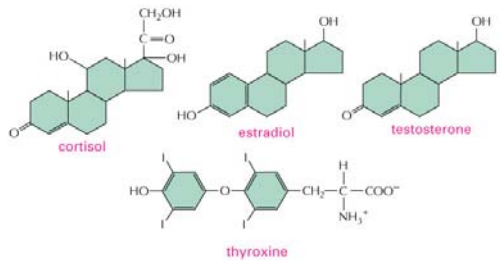
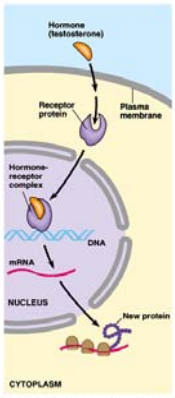


Figure 16-11 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Figure 11.10 Steroid hormone interacting with an intracellular receptor



Some signaling molecules are gases that readily diffuse across membranes.

- Nitric oxide (NO) can enter cells to activate enzymes directly
- NO causes relaxation of smooth muscle
- Both NO and the plant hormone ethylene are important signaling molecules in plants

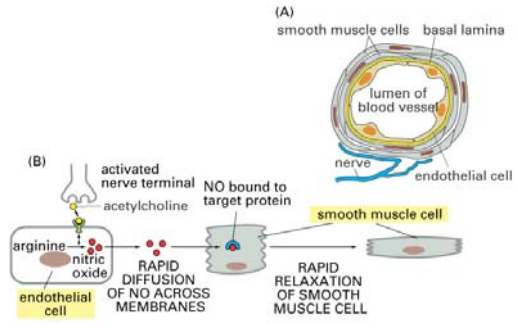


Figure 16-10 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Three main types of extracellular (cell surface; plasma membrane) receptors for large, hydrophilic signaling molecules

- G-protein-linked (coupled) receptors
- Enzyme-linked receptors
- Ion channel-linked receptors

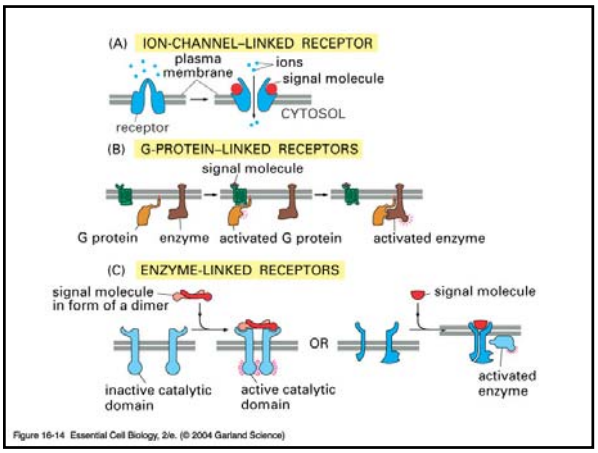


Figure 16-14 Essential Cell Biology, 2/e. (© 2004 Garland Science)

REMINDER: There are two main types of receptors

- Extracellular (plasma membrane; cell surface)
- Intracellular

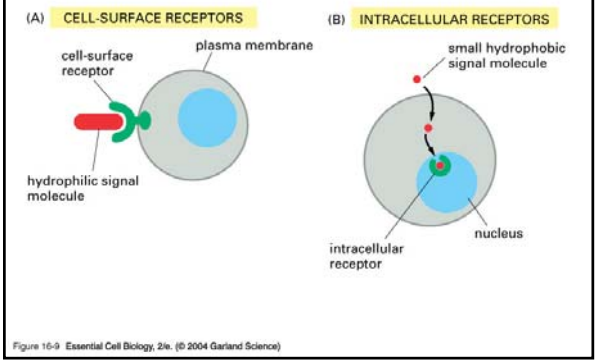
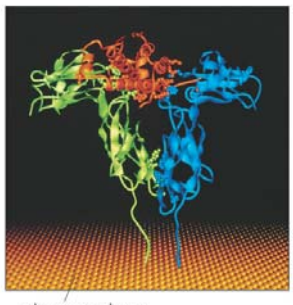


Figure 16-9 Essential Cell Biology, 2/e. (© 2004 Garland Science)



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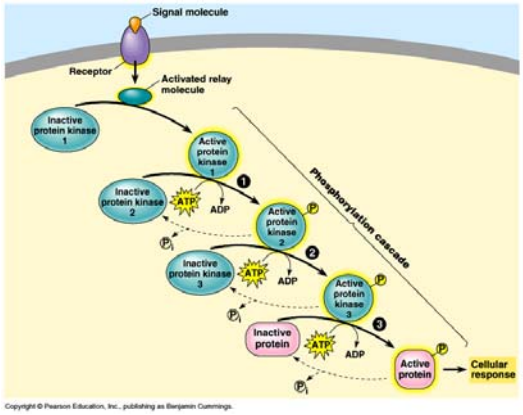
REMINDER:

Extracellular receptors often trigger signal transduction cascades through second messengers.

Figure 11.11 A phosphorylation cascade



Protein phosphorylation by kinases and protein de-phosphorylation by phosphatases is a major mechanism of signal transduction in all cells.

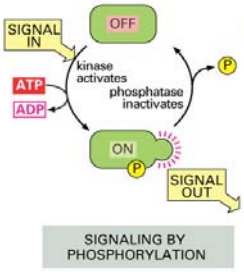


Figure 11.17 Nuclear response to a signal: the activation of a specific gene by a growth factor

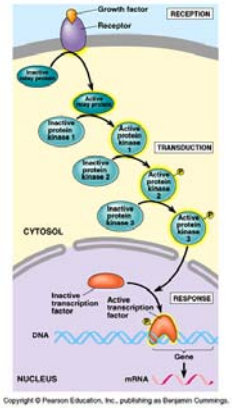
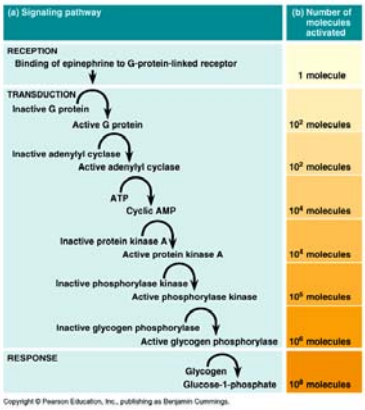


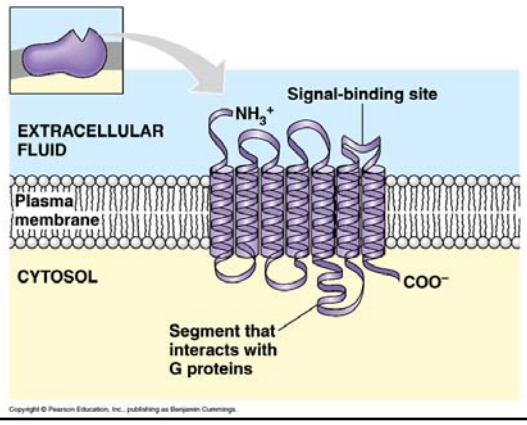
Figure 11.16 Cytoplasmic response to a signal: the stimulation of glycogen breakdown by epinephrine



G-protein-linked (coupled) receptors

- Largest family of extracellular receptor in animals
- Regulate a wide variety of processes
- Receptor spans the membrane 7 times = seven-pass transmembrane receptor proteins
- Ligand binding changes receptor shape (conformation) – then receptor binds to "G-protein"
- G-protein is on the inside of the membrane (NOTE: G-protein ≠ G-protein-linked receptor

Figure 11.6 The structure of a G-protein-linked receptor



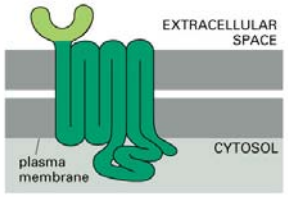


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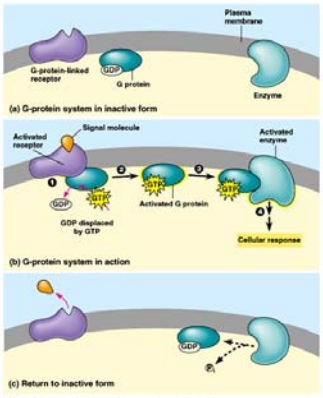
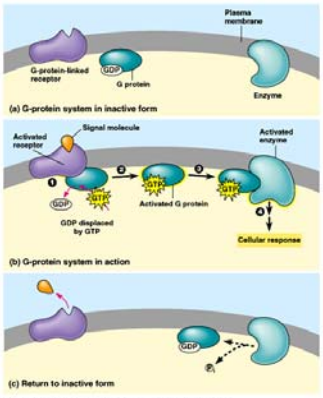
Figure 11.7 The functioning of a G-protein-linked receptor



There are two types of G proteins

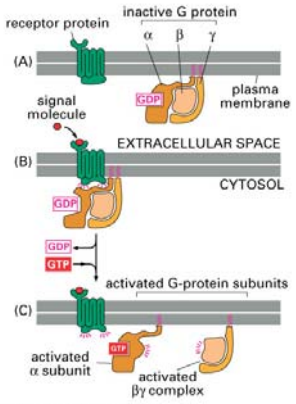
- Monomeric = single polypeptide
- Trimeric = 3 polypeptides
- Trimeric are most common
- Trimeric G proteins are "heterotrimeric" = 3 different polypeptides = subunits = α,β, and γ
- "Unstimulated" G protein has GDP bound to α subunit = G protein is "quiet"

Figure 11.7 The functioning of a G-protein-linked receptor



Signaling through heterotrimeric G proteins - THE BEGINNING

- Ligand binds to G-protein-linked receptor; changes its conformation (shape)
- Activated receptor binds to G protein
- G protein ejects GDP; replaces it with GTP
- G protein breaks up into α subunit and (β + γ) complex
- α and (β + γ) diffuse freely beneath membranes to interact with other target proteins to relay signals to other destinations



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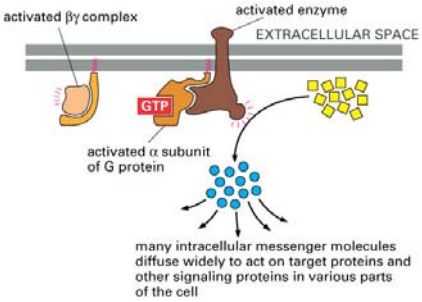

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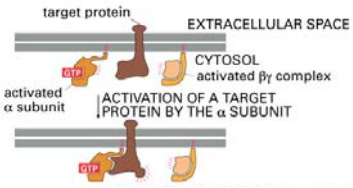

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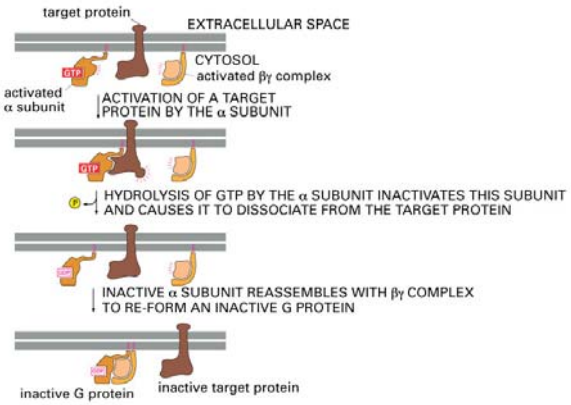
Signaling through heterotrimeric G proteins- THE END

- α subunit is a GTPase
- GTPase hydrolyzes GTP to GDP and Pi (inorganic phosphate)
- Hydrolysis leads to reassociation of α subunit and (β + γ)
- Signal ends
- Duration is determined by how long GTP is bound to α subunit before GTPase catalyzes GTP hydrolysis



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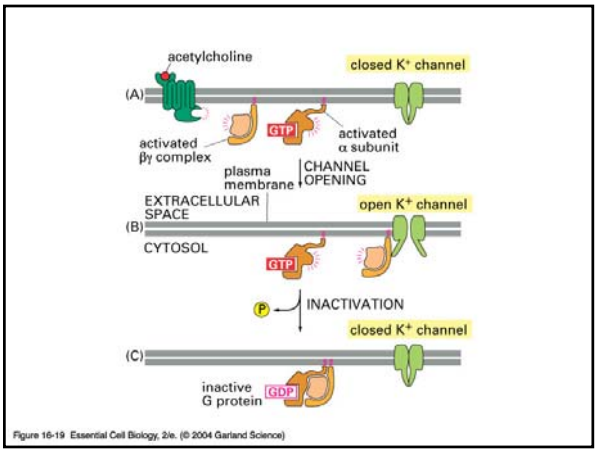
Ion channels are common targets of G proteins

EXAMPLE:

Acetylcholine inhibits contraction of heart muscle via a G-protein-linked receptor that regulates potassium ion channel activity

CAUTION:

Acetylcholine does not act through a G-protein-linked receptor in skeletal muscle



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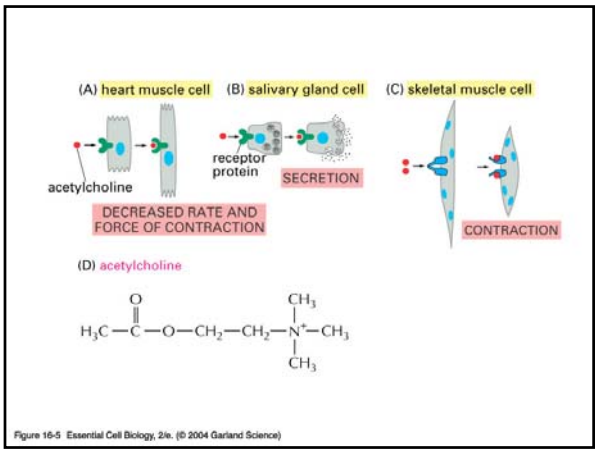

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Enzymes that catalyze production or release of second messenger are common targets of G proteins

- Adenylyl cyclase catalyzes formation of cAMP
- cAMP can activate cyclic-AMP-dependent kinase = A-kinase = protein kinase A (PKA)
- PKA can catalyze phosphorylation of other proteins
- Effects of PKA may be fast or slow
- Effects of PKA are tissue-specific

Figure 11.13 cAMP as a second messenger

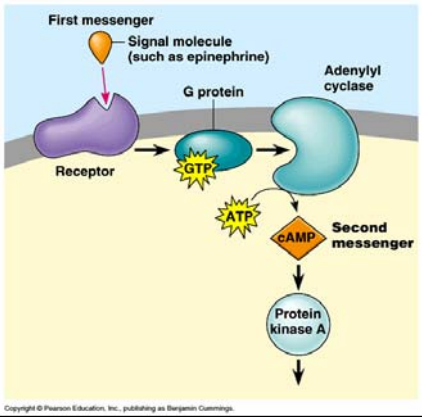

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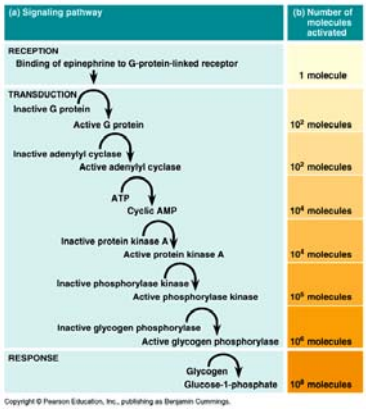
Figure 11.16 Cytoplasmic response to a signal: the stimulation of glycogen breakdown by epinephrine



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Enzymes that catalyze production or release of second messenger are common targets of G proteins (cont.)

- Phospholipase C catalyzes hydrolysis of plasma membrane inositol phospholipid to IP_3 and DAG
- IP_3 opens calcium ion channels of endoplasmic reticulum (ER) to increase cytosolic calcium
- Calcium may bind to calmodulin or CaM kinases to affect many processes
- DAG activates C-kinase = protein kinase C (PKC)
- PKC can also cause calcium ion release from ER

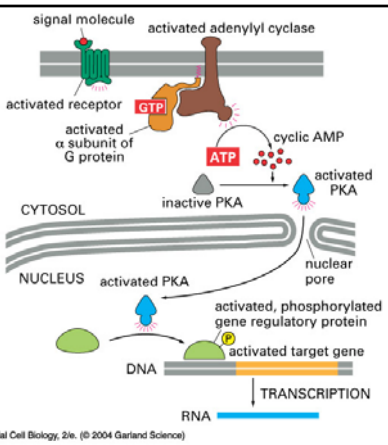

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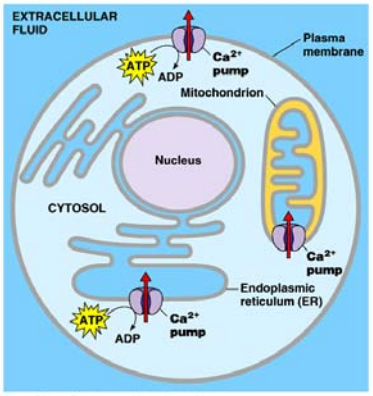
Figure 11.14 The maintenance of calcium ion concentrations in an animal cell



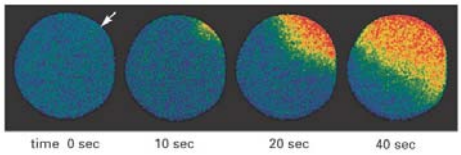


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Figure 11.15 Calcium and inositol triphosphate in signaling pathways (Layer 1)

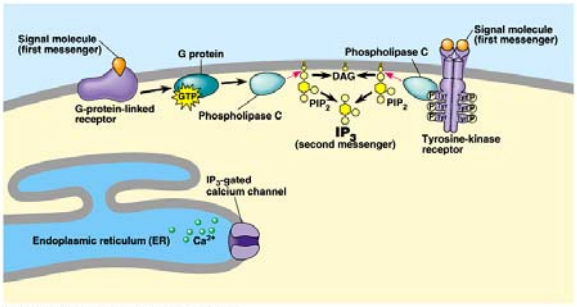


Figure 11.15 Calcium and inositol triphosphate in signaling pathways (Layer 2)

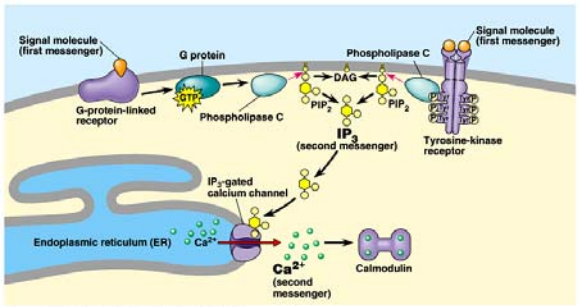
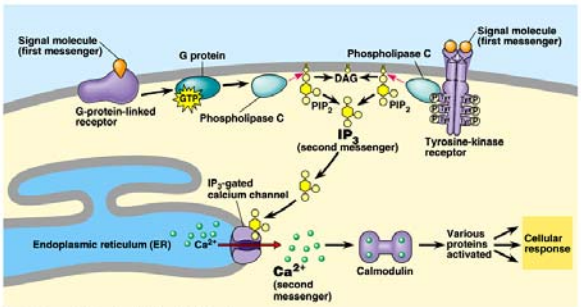
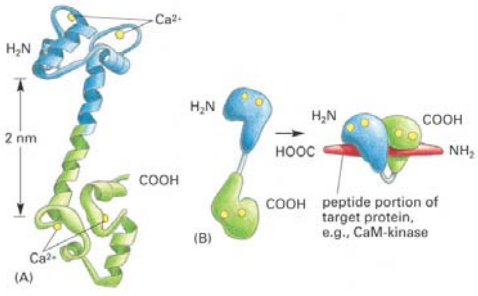


Figure 11.15 Calcium and inositol triphosphate in signaling pathways (Layer 3)





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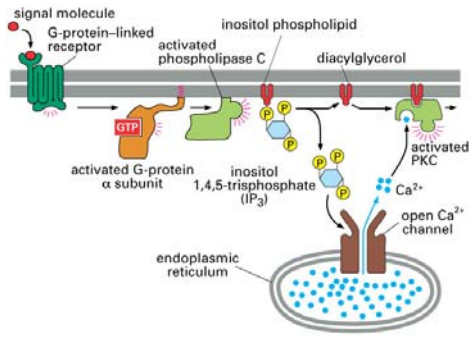

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Enzyme-linked receptors

- Transmembrane proteins
- All have extracellular ligand binding "domain"
- All have cytoplasmic domain with enzyme activity
- Largest class = receptor tyrosine kinases = RTK

RTK – THE BEGINNING

- Ligand binding causes dimerization of RTK monomers
- Each monomer phosphorylates tyrosines in the other = autophosphorylation
- Many types of intracellular signaling proteins bind to phosphorylated cytoplasmic domains of activated RTK to carry signals forward

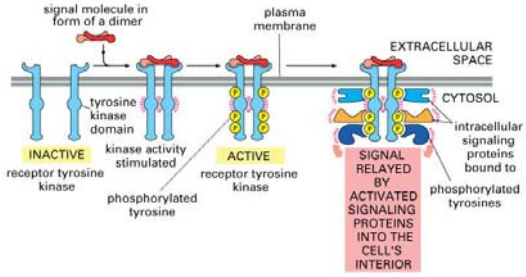

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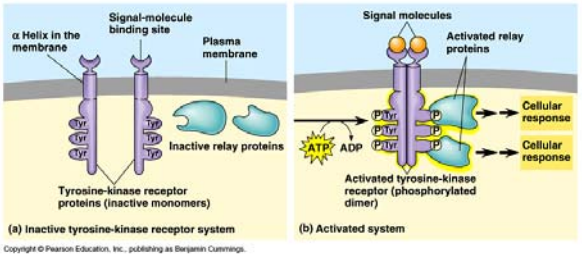
Figure 11.8 The structure and function of a tyrosine-kinase receptor



RTK – THE END

- Protein phosphatases remove phosphates to end signaling
- Signal duration depends on phosphatase activity

Famous RTK targets

- A phosholipase equivalent in action to phospholipase C
- A monomeric GTP-binding protein called Ras

Characteristics/targets of Ras

- Binds GTP; similar to a monomeric G protein
- Activates phosphorylation of several important protein kinases
- Ras activates Raf (a ser/thr kinase)
- Ras activates MAP kinases (MAPK) = microtubule- associated protein or mitogen-activated protein kinases (also a ser/thr kinase);
- Ras activates MEK (= "M" from MAP and "E" and "K" from ERK = extracellular regulating kinase = another acronym for MAP); MEK is a thr/tyr kinase

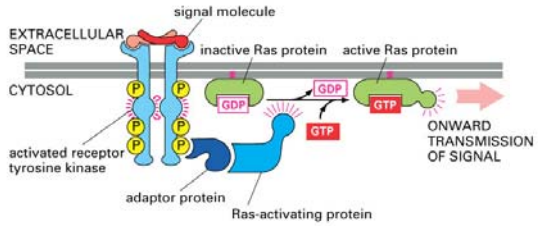
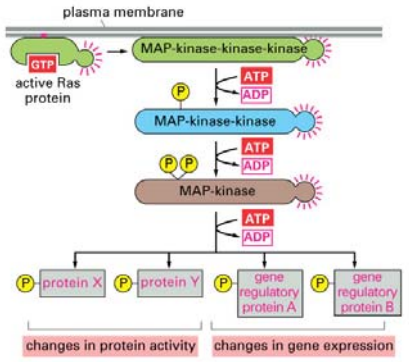


Figure 16-31 Essential Cell Biology, 2/e. (© 2004 Garland Science)



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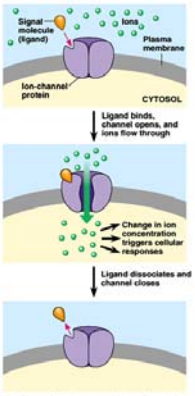
Molecules/processes connected to Ras

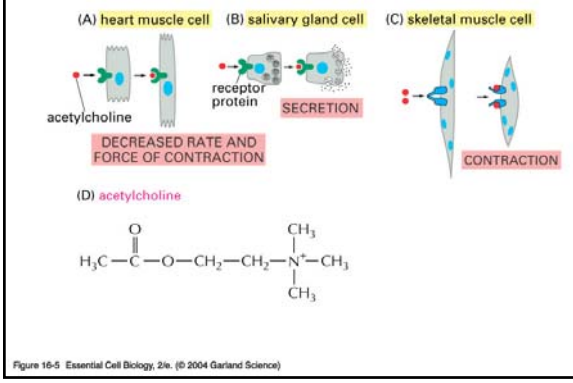
- Platelet-derived growth factor (PDGF)- promotes cell proliferation at healing wound
- Nerve growth factor (NGF) prevents death of neurons in developing nervous system
- 30% of human cancers; mutations in Ras or Ras signaling proto-oncogenes lead to "constitutive" (uncontrolled) cell division
- NOTE: mutated gene that causes cancer = oncogene; non-mutated form = proto-oncogene

Ion-channel-linked receptors

- Also called transmitter-gated ion channels
- Found in membranes
- Transduce chemical signals into electrical signals
- Best ligand examples are neurotransmitters
- Binding of neurotransmitter causes change in membrane electric potential by changing membrane permeability to certain ions
- Used for rapid transmission of nerve impulse; may be used for other rapid responses such as altering enzyme activity in cells

Figure 11.9 A ligand-gated ion-channel receptor





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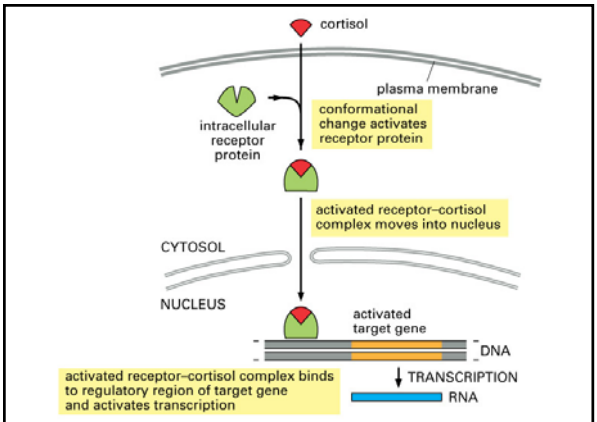
Intracellular receptors are exemplified by the steroid hormone receptors of animals.



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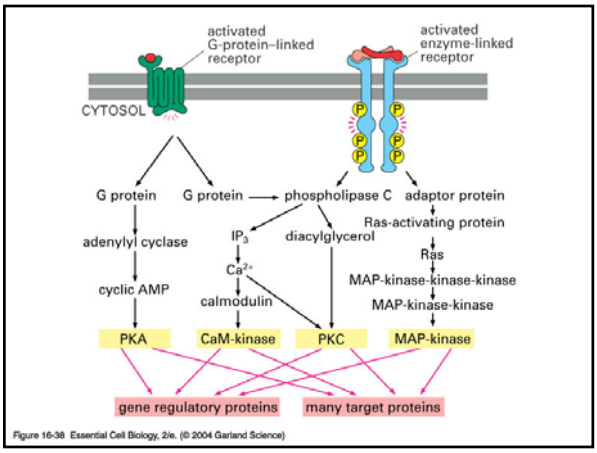
Signaling networks

- Multiple signal transduction pathways operate simultaneously in every cell.
- Signaling pathways interact.
- Cell signaling is integrated.



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