BME 1532-CELL BIOLOGY

Cell Signaling

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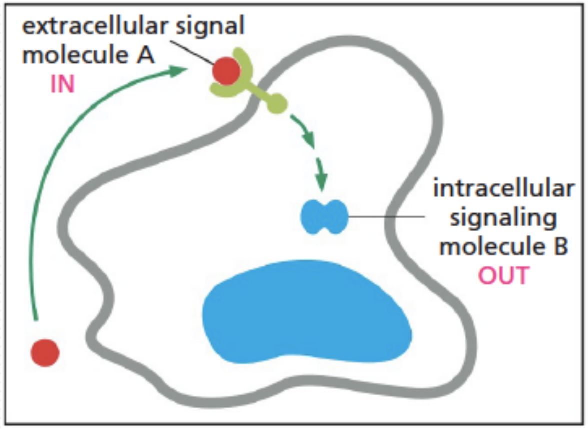
Last Week on BME 1532

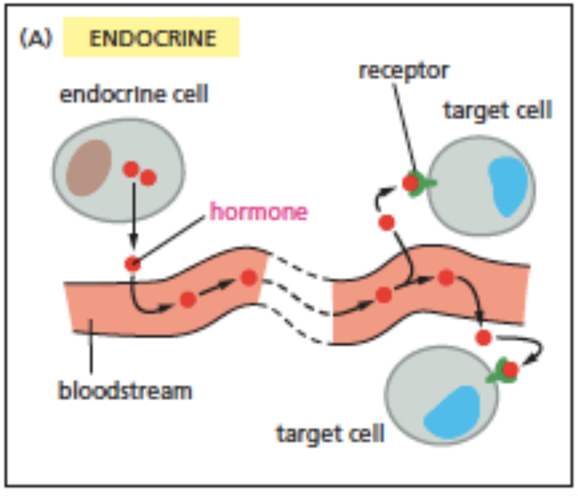
- Cytoskeleton
  - Intermediate Filaments
  - Microtubules
    - Mitotic spindle
    - MT-associated motor proteins: kinesins and dyneins
  - Actin Filaments
    - Cell Cortex
    - Contractile Ring
    - Actin-associated motor proteins: Myosin-I and Myosin-II
- Extracellular Matrix
  - Fibrous Proteins
    - Collagen
    - Fibronectin
    - Elastin
  - Glycosaminoglycans - Proteoglycans

- Individual cells, like multicellular organisms, need to sense and respond to their environment.
- During animal development, for example, cells in the embryo exchange signals to determine which specialized role each cell will adopt, what position it will occupy in the animal, and whether it will survive, divide, or die.
- Later in life, a large variety of signals coordinates the animal's growth and its day-to-day physiology and behavior.

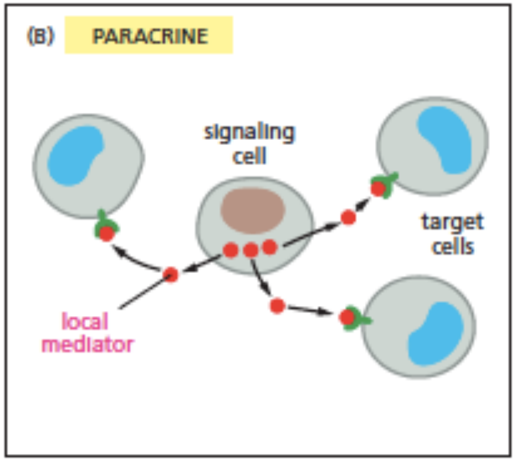
- In a typical communication between cells, the signaling cell produces a particular type of extracellular signal molecule that is detected by the target cell.
- Most animal cells both send and receive signals, and they can therefore act as both signaling cells and target cells.
- Target cells possess proteins called receptors that recognize and respond specifically to the signal molecule. Signal transduction begins when the receptor on a target cell receives an incoming extracellular signal ans converts it to the intracellular signaling molecules that alter cell behavior.



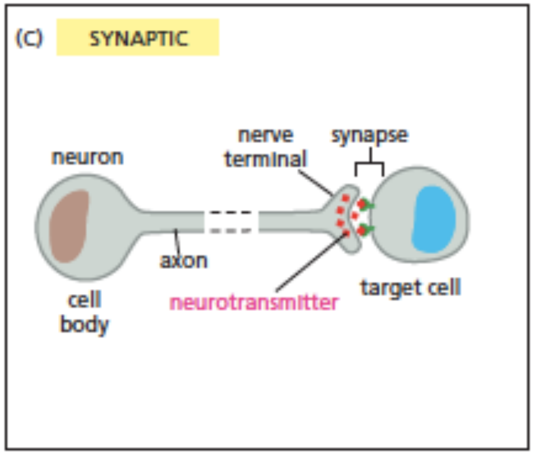
- Cells in multicellular organisms use hundreds of kinds of extracellular signal molecules to communicate with one another.
- The signal molecules can be proteins, peptides, amino acids, nucleotides, steroids, fatty acid derivatives, or even dissolved gases—but they all rely on only a handful of basic styles of communication for getting the message across.
- In animals, the most "public" style of cell-to-cell communication involves broadcasting the signal throughout the whole body by secreting it into an animal's bloodstream.
- Extracellular signal molecules used in this way are called ***hormones***, and, in animals, the cells that produce hormones are called ***endocrine cells***.



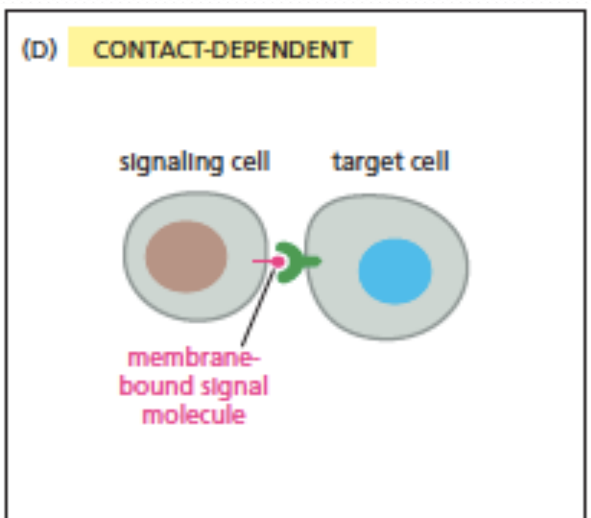
- Somewhat less public is the process known as ***paracrine signaling***.
- In this case, rather than entering the bloodstream, the signal molecules diffuse locally through the extracellular fluid, remaining in the neighborhood of the cell that secretes them.
- Thus, they act as local mediators on nearby cells.
- In some cases, cells can respond to the local mediators that they themselves produce, a form of paracrine communication called autocrine signaling; cancer cells sometimes promote their own survival and proliferation in this way.

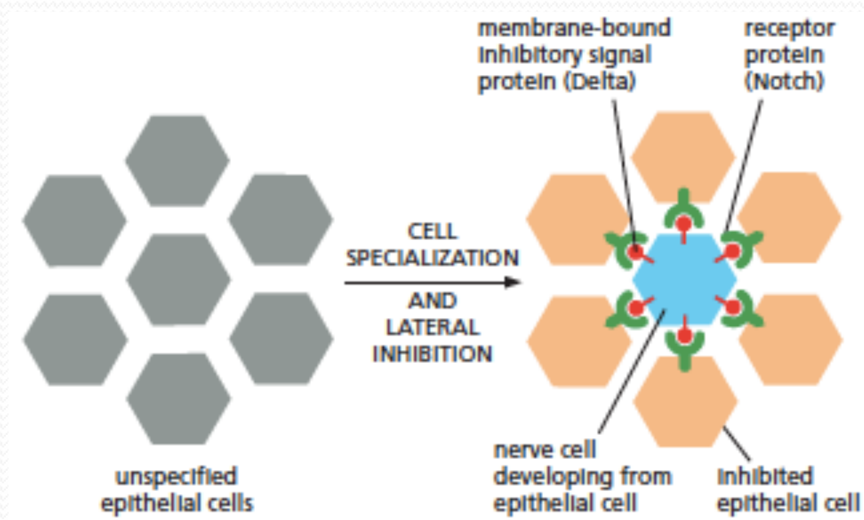


- Neuronal signaling is a third form of cell communication. Like endocrine cells, nerve cells (neurons) can deliver messages over long distances.
- In the case of neuronal signaling, however, a message is not broadcast widely but is instead delivered quickly and specifically to individual target cells through private lines.
- The axon of a neuron terminates at specialized junctions (synapses) on target cells that can lie far from the neuronal cell body.
- When activated by signals from the environment or from other nerve cells, a neuron sends electrical impulses racing along its axon.
- On reaching the axon terminal, these electrical signals are converted into a chemical form: each electrical impulse stimulates the nerve terminal to release a pulse of an extracellular signal molecule called a ***neurotransmitter***.
- The neurotransmitter then diffuses across the narrow gap that separates the membrane of the axon terminal from that of the target cell, reaching its destination very fast.



- A fourth style of signal-mediated cell-to-cell communication—the most intimate and short-range of all—does not require the release of a secreted molecule.
- Instead, the cells molecules lodged in the plasma membrane of the signaling cell and receptor proteins embedded in the plasma membrane of the target cell.
- During embryonic development, for example, such contact-dependent signaling allows adjacent cells that are initially similar to become specialized to form different cell types make direct physical contact through signal.



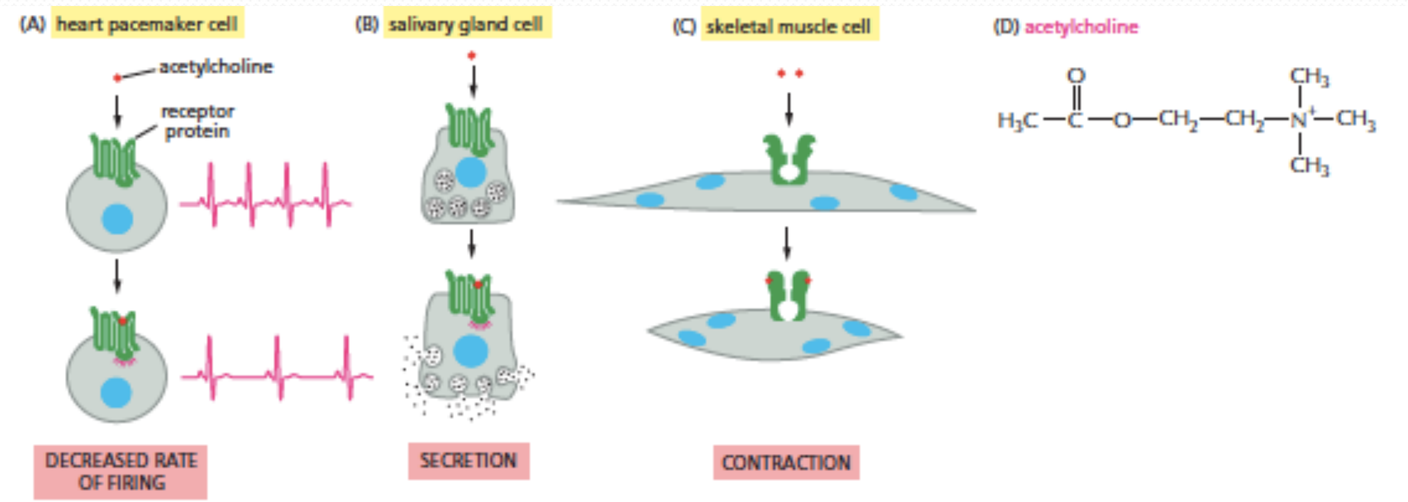


Signal Molecule	Site of Origin	Chemical Nature	Some Actions
Hormones			
Adrenaline (epinephrine)	adrenal gland	derivative of the amino acid tyrosine	increases blood pressure, heart rate, and metabolism
Cortisol	adrenal gland	steroid (derivative of cholesterol)	affects metabolism of proteins, carbohydrates, and lipids in most tissues
Estradiol	ovary	steroid (derivative of cholesterol)	induces and maintains secondary female sexual characteristics
Insulin	β cells of pancreas	protein	stimulates glucose uptake, protein synthesis, and lipid synthesis in various cell types
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 in 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 their survival and growth of their axons
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

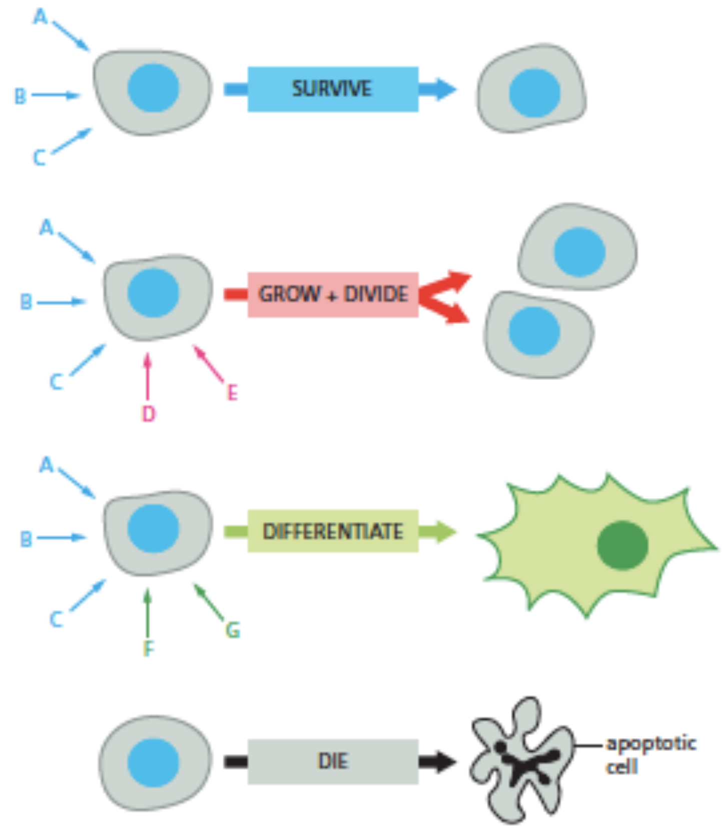
Receptors

- A typical cell in a multicellular organism is exposed to hundreds of different signal molecules in its environment.
- Each cell must respond very selectively to this mixture of signals, disregarding some and reacting to others, according to the cell's specialized function.
- Whether a cell responds to a signal molecule depends first of all on whether it possesses a ***receptor*** for that signal.
- Each receptor is usually activated by only one type of signal. Without the appropriate receptor, a cell will be deaf to the signal and will not respond to it.
- By producing only a limited set of receptors out of the thousands that are possible, a cell restricts the types of signals that can affect it.

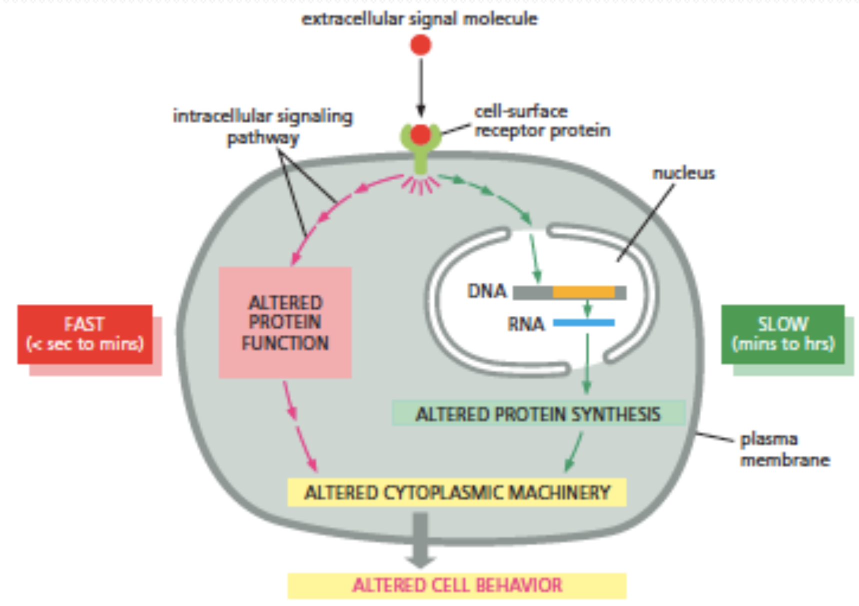
- Different types of cells respond to the same signal in different ways.
- The signal from a cell surface receptor is generally conveyed into the target cell interior via a set of intracellular signaling molecules.
- These molecules act in sequence and ultimately alter the activity of effector proteins, those that have some direct effect on the behavior of the target cell.



- A typical cell possesses many sorts of receptors—each present in tens to hundreds of thousands of copies.
- Such variety makes the cell simultaneously sensitive to many different extracellular signals and allows a relatively small number of signal molecules, used in different combinations, to exert subtle and complex control over cell behavior.
- A combination of signals can evoke a response that is different from the sum of the effects that each signal would trigger on its own.

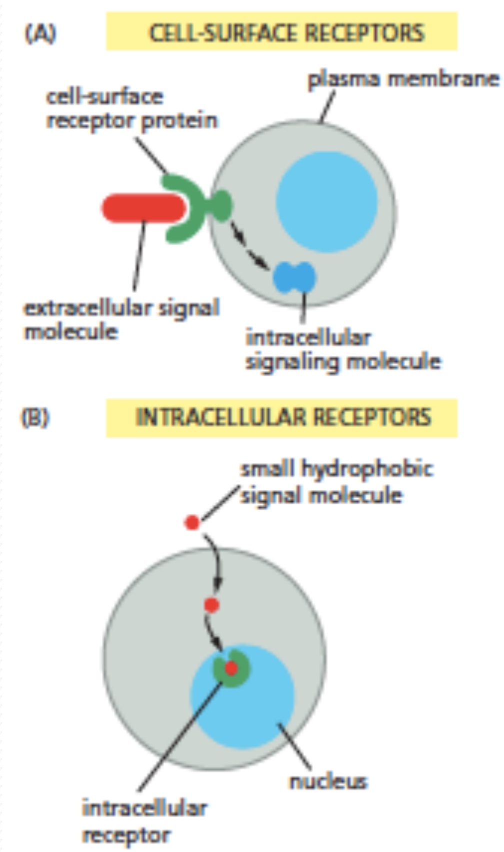


- The length of time a cell takes to respond to an extracellular signal can vary greatly, depending on what needs to happen once the message has been received.
- Some extracellular signals act swiftly: acetylcholine can stimulate a skeletal muscle cell to contract within milliseconds and a salivary gland cell to secrete within a minute or so. Such rapid responses are possible because, in each case, the signal affects the activity of proteins that are already present inside the target cell, awaiting their marching orders.

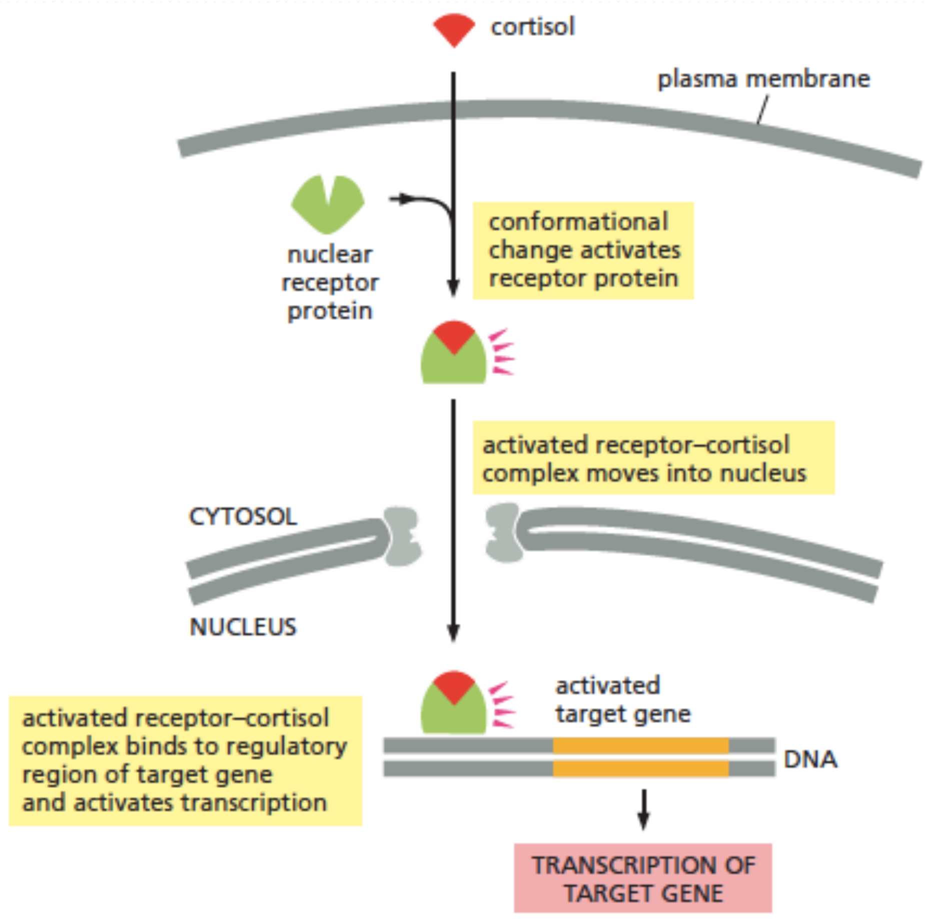


- Other responses take more time. Cell growth and cell division, when triggered by the appropriate signal molecules, can take many hours to execute. This is because the response to these extracellular signals requires changes in gene expression and the production of new proteins

- Extracellular signal molecules generally fall into two classes. The first and largest class consists of molecules that are too large or too hydrophilic to cross the plasma membrane of the target cell. They rely on receptors on the surface of the target cell to relay their message across the membrane.
- The second, and smaller, class of signals consists of molecules that are small enough or hydrophobic enough to pass through the plasma membrane and into the cytosol.
- Once inside, these signal molecules usually activate intracellular enzymes or bind to intracellular receptor proteins that regulate gene expression.



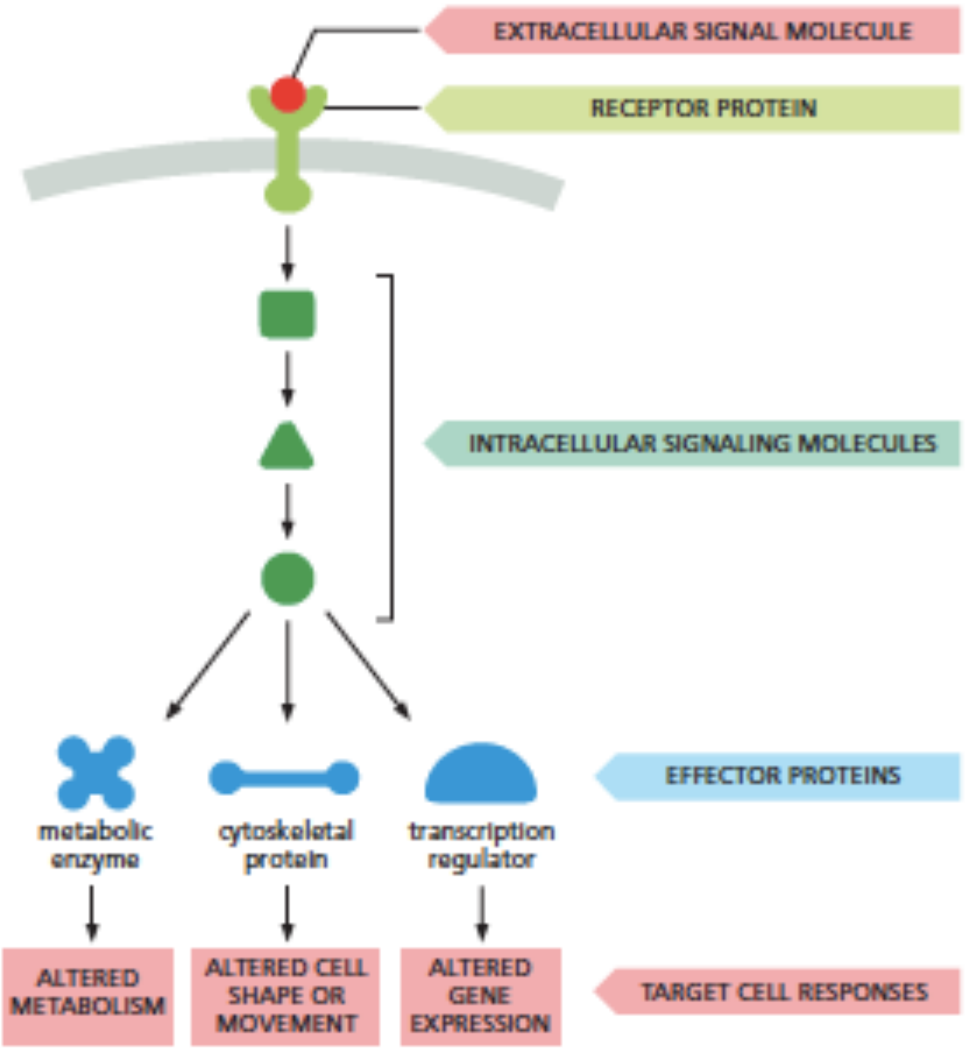
- Steroid hormones—including cortisol, estradiol, and testosterone—and the thyroid hormones can pass through the cell membrane and rely on intracellular receptor proteins.
- These hydrophobic molecules pass through the plasma membrane of the target cell and bind to receptor proteins located in either the cytosol or the nucleus. Both the cytosolic and nuclear receptors are referred to as nuclear receptors, because, when activated by hormone binding, they act as transcription regulators in the nucleus.



- Steroid hormones and thyroid hormones are not the only extracellular signal molecules that can pass through the plasma membrane.
- Some dissolved gases can diffuse across the membrane to the cell interior and directly regulate the activity of specific intracellular proteins.
- The gas nitric oxide (NO) acts in this way.
- Endothelial cells—the flattened cells that line every blood vessel—release NO in response to neurotransmitters secreted by nearby nerve endings.
- This NO signal causes smooth muscle cells in the adjacent vessel wall to relax, allowing the vessel to dilate, so that blood flows through it more freely.

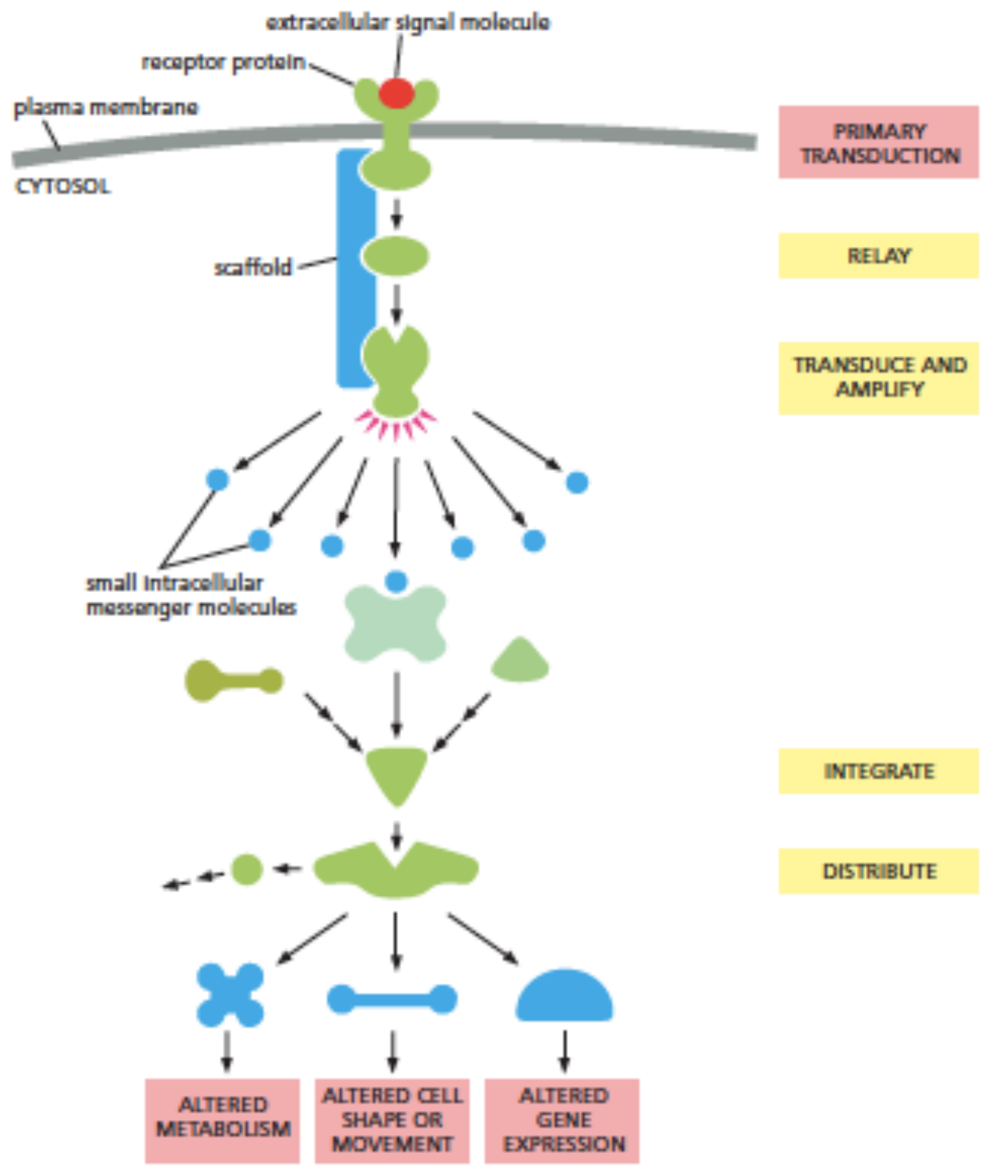
- The vast majority of signal molecules are too large or hydrophilic to cross the plasma membrane of the target cell.
- These proteins, peptides, and small hydrophilic molecules bind to cell-surface receptor proteins that span the plasma membrane.
- Transmembrane receptors detect a signal on the outside and relay the message, in a new form, across the membrane into the interior of the cell.

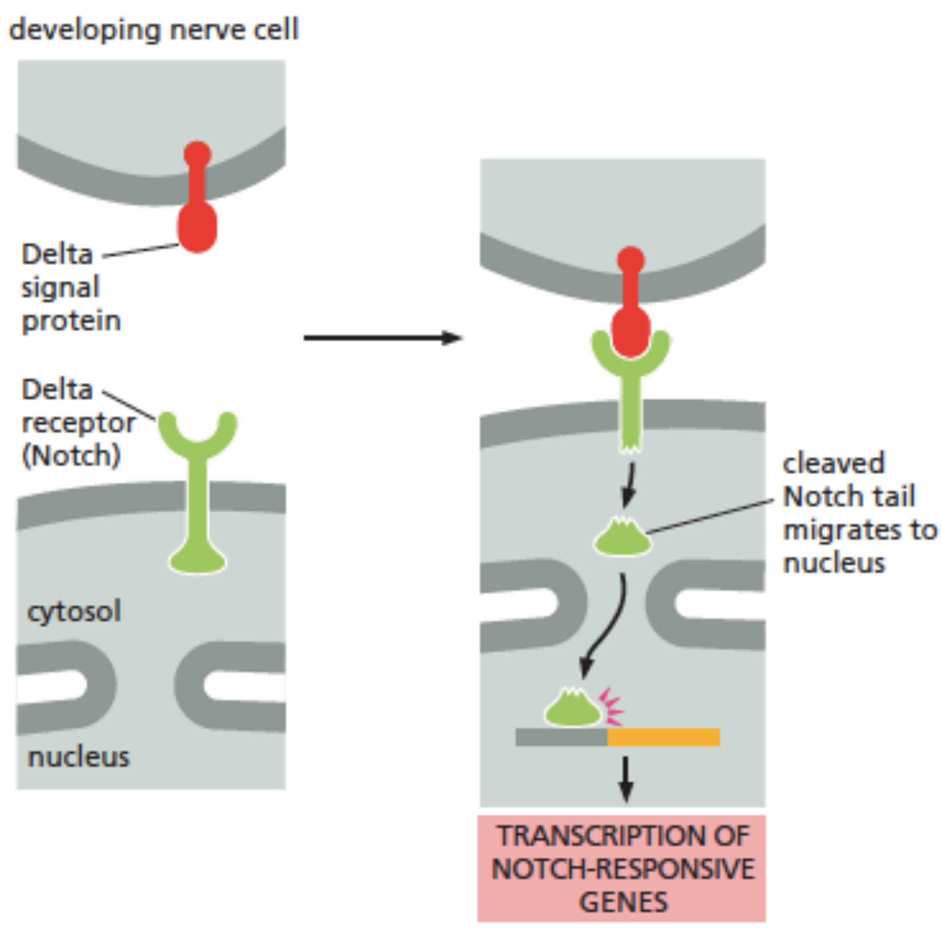
- The receptor protein performs the primary step in signal transduction: it recognizes the extracellular signal and generates new intracellular signals in response.
- The resulting intracellular signaling process usually works like a molecular relay race, in which the message is passed "downstream" from one intracellular signaling molecule to another, each activating or generating the next signaling molecule in the pathway, until a metabolic enzyme is kicked into action, the cytoskeleton is tweaked into a new configuration, or a gene is switched on or off.
- This final outcome is called the response of the cell.



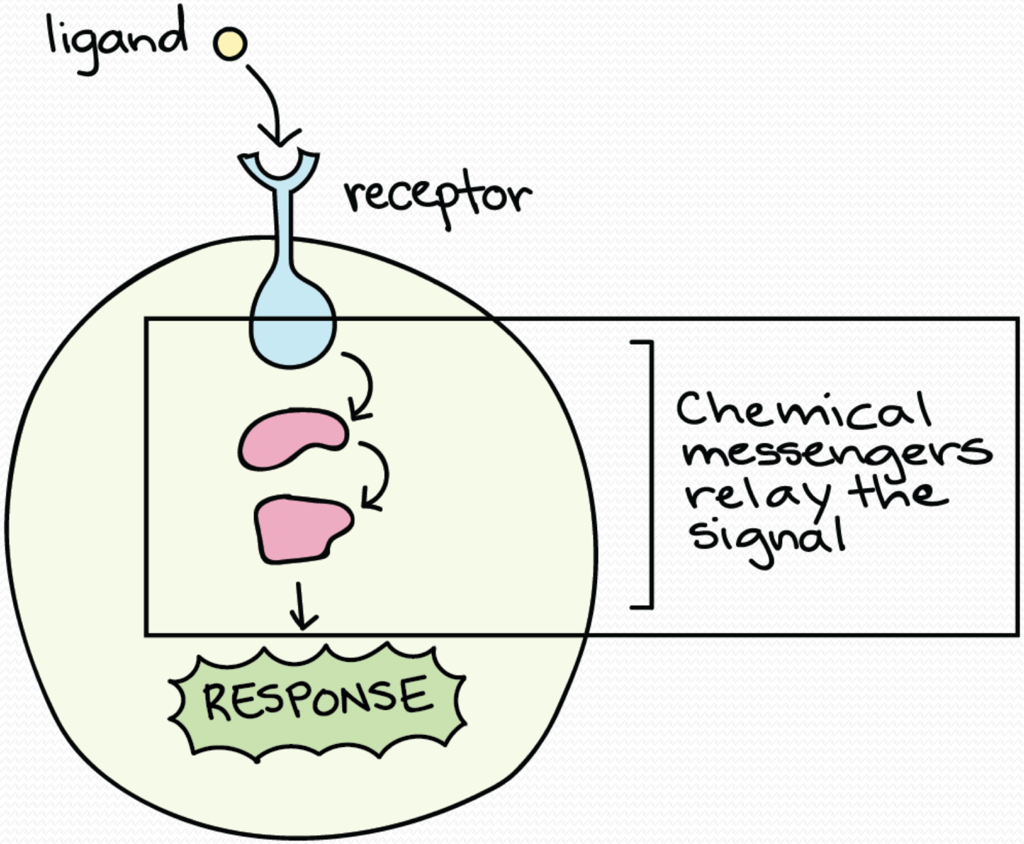
The components of these intracellular signaling pathways perform one or more crucial functions:

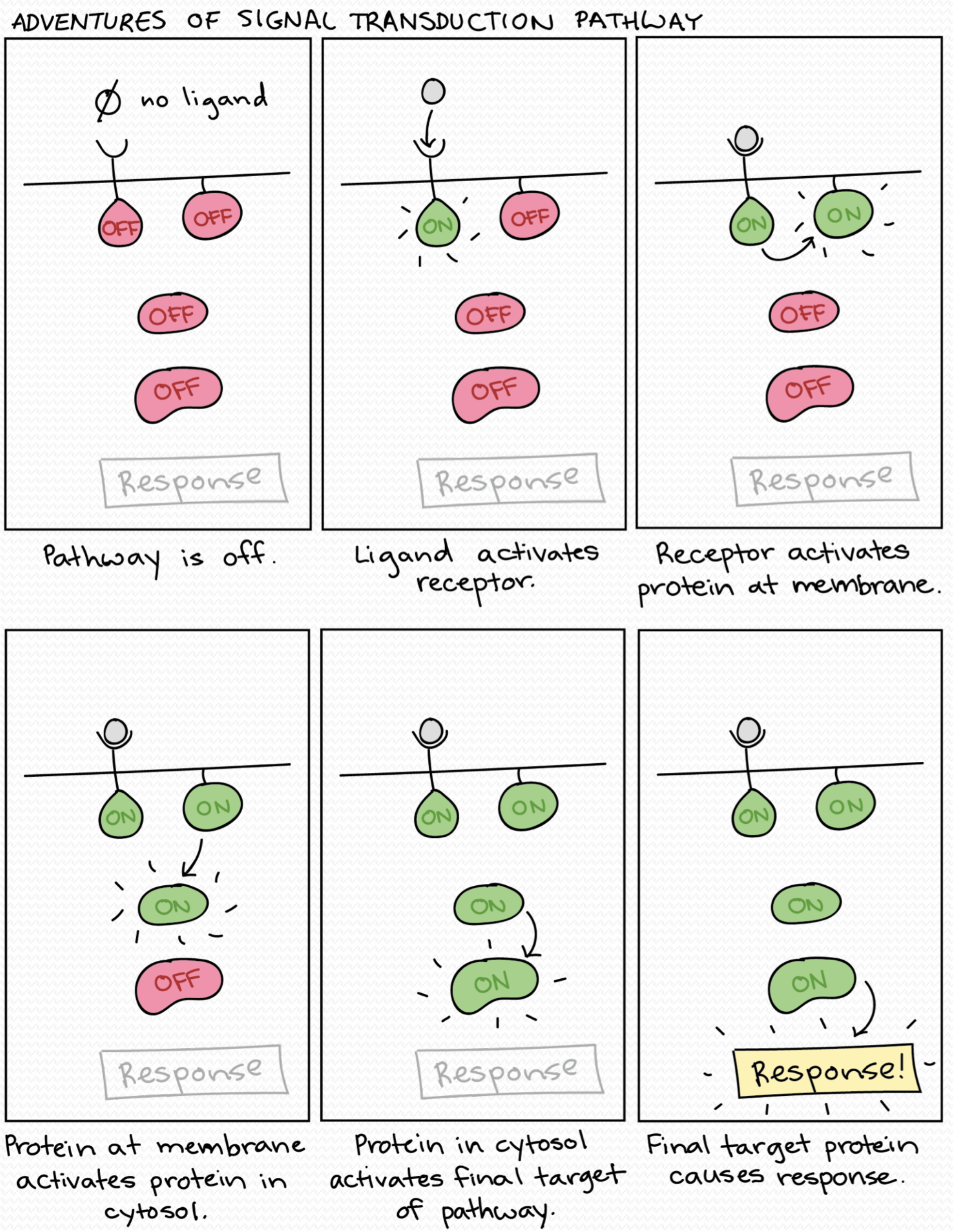
1. They can simply relay the signal onward and thereby help spread it through the cell.
2. They can amplify the signal received, making it stronger, so that a few extracellular signal molecules are enough to evoke a large intracellular response.
3. They can detect signals from more than one intracellular signaling pathway and integrate them before relaying a signal onward.
4. They can distribute the signal to more than one effector protein, creating branches in the information flow diagram and evoking a complex response.

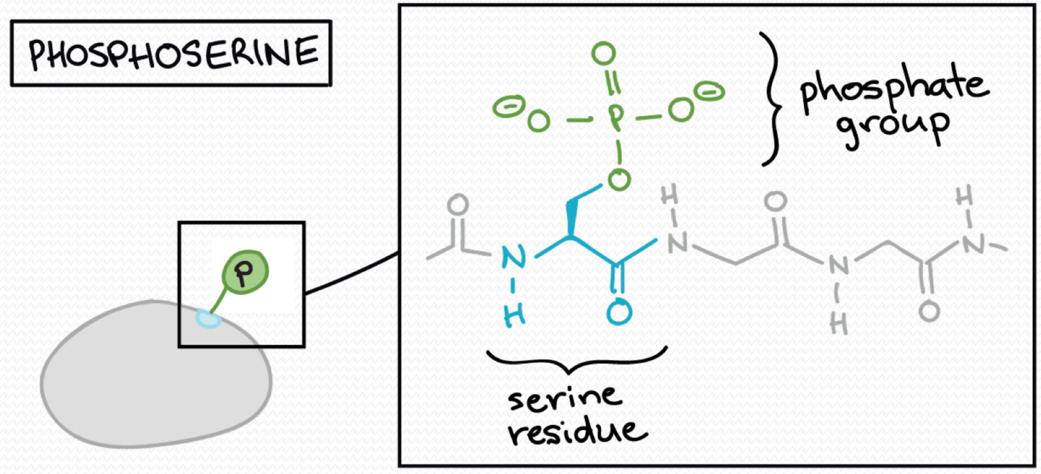


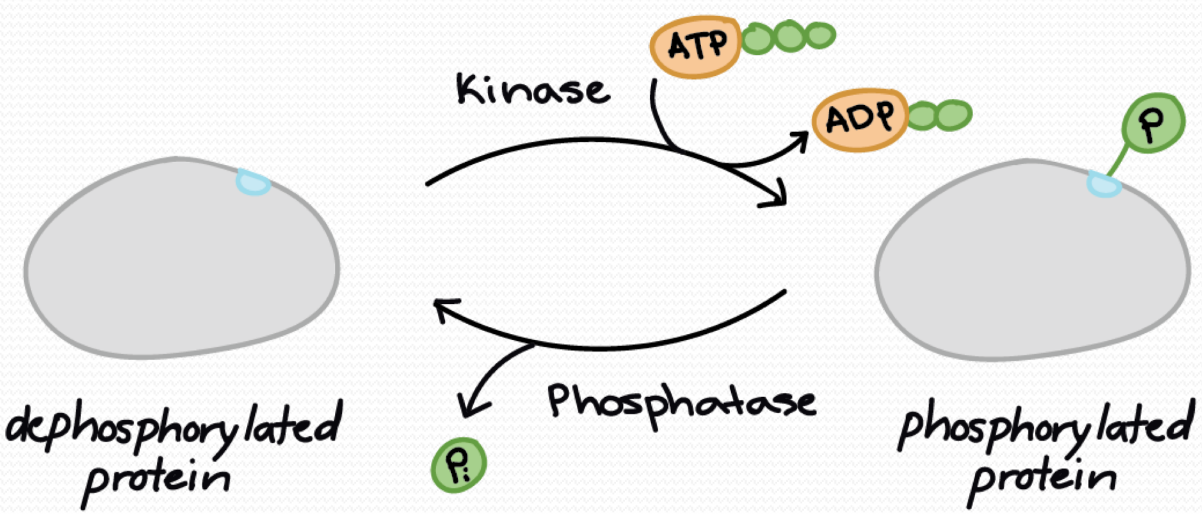


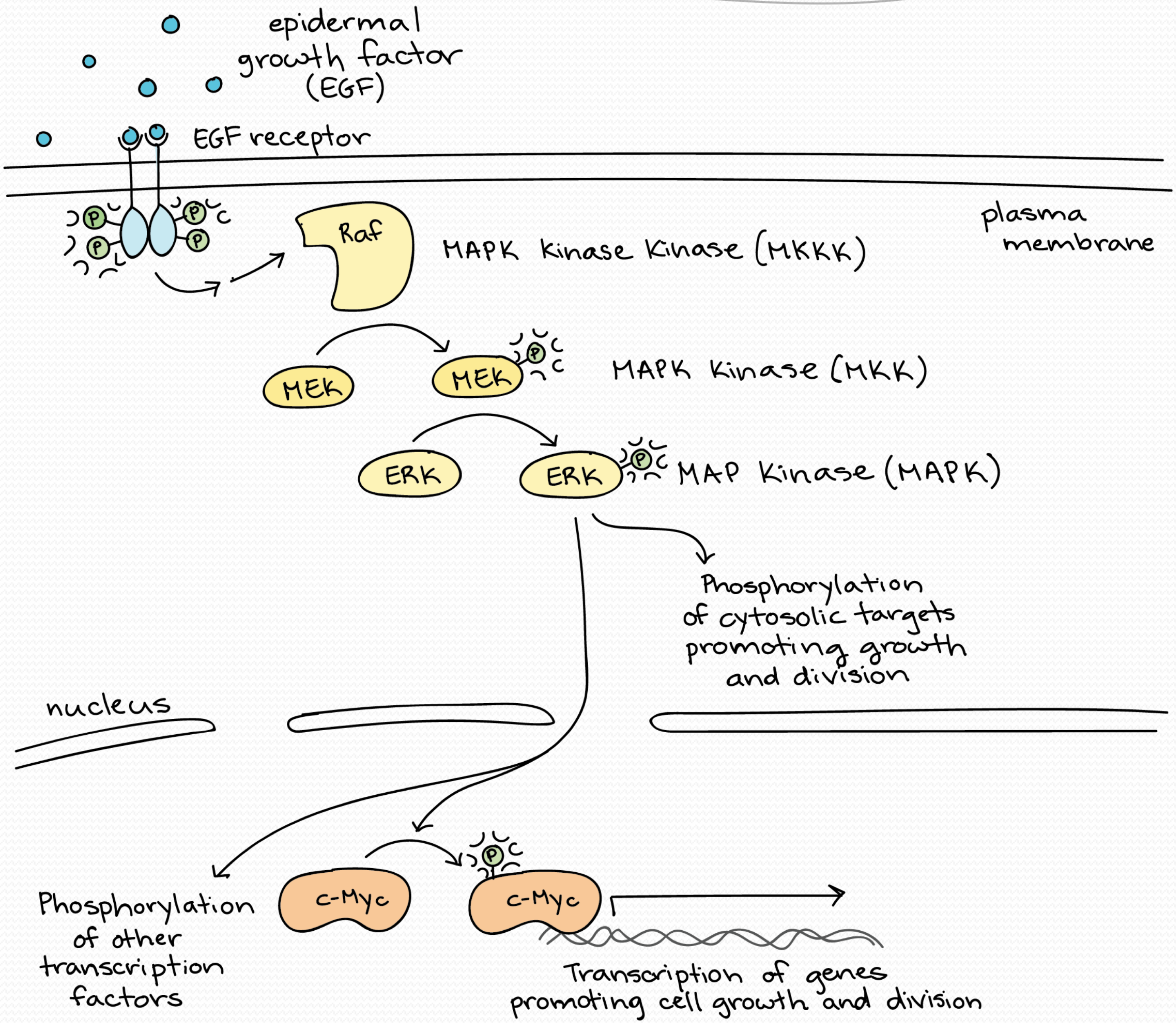
- Not all receptors trigger complex signaling cascades to carry a message to the nucleus. Some use a more direct route to control gene expression.
- One such receptor is the protein Notch.
- Notch is a crucially important receptor in all animals, both during development and in adults.
- In this simple signaling pathway, the receptor itself acts as a transcription regulator.
- When activated by the binding of Delta, which is a transmembrane signal protein on the surface of a neighboring cell, the Notch receptor is cleaved. This cleavage releases the cytosolic tail of the receptor, which is then free to move to the nucleus where it helps to activate the appropriate set of Notch-responsive genes.

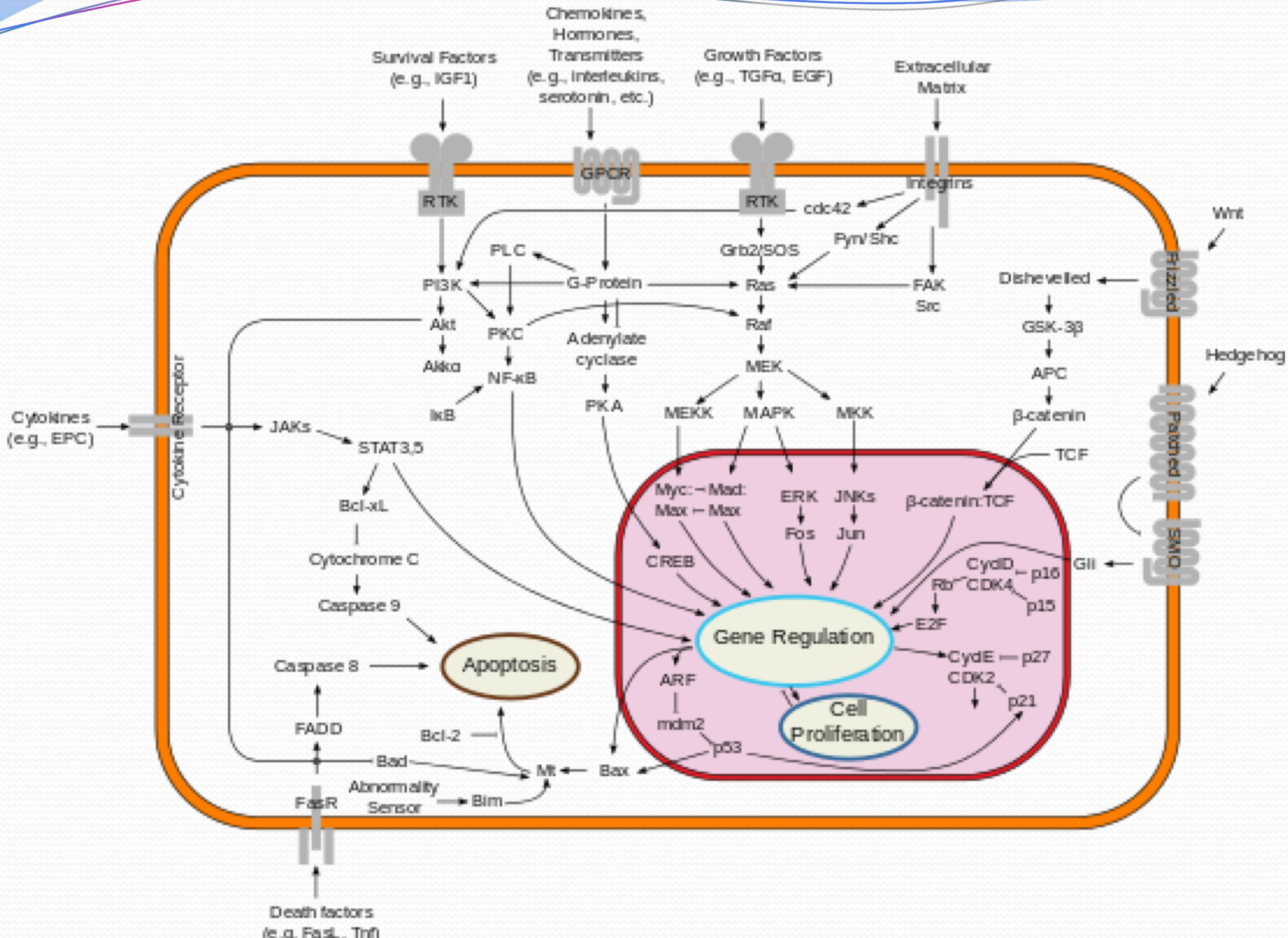

ligand
receptor
Chemical messengers relay the signal
RESPONSE


ADVENTURES OF SIGNAL TRANSDUCTION PATHWAY
no ligand
OFF
OFF
OFF
OFF
Response
Pathway is off.
ON
OFF
OFF
OFF
Response
Ligand activates receptor.
ON
ON
OFF
OFF
Response
Receptor activates protein at membrane.
ON
ON
ON
OFF
Response
Protein at membrane activates protein in cytosol.
ON
ON
ON
ON
Response
Protein in cytosol activates final target of pathway.
ON
ON
ON
ON
Response!
Final target protein causes response.


PHOSPHOSERINE
P
phosphate group
serine residue


Kinase
ATP
ADP
P
Phosphatase
P
dephosphorylated protein
phosphorylated protein


epidermal growth factor (EGF)
EGF receptor
plasma membrane
Raf
MAPK Kinase Kinase (MKKK)
MEK
MEK
P
MAPK Kinase (MKK)
ERK
ERK
P
MAP Kinase (MAPK)
Phosphorylation of cytosolic targets promoting growth and division
nucleus
c-Myc
c-Myc
P
Phosphorylation of other transcription factors
Transcription of genes promoting cell growth and division


Chemokines,
Hormones,
Transmitters
(e.g., interleukins,
serotonin, etc.)
Survival Factors
(e.g., IGF1)
Growth Factors
(e.g., TGFα, EGF)
Extracellular
Matrix
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Wnt
Frizzled
Dishevelled
GSK-3β
APC
β-catenin
TCF
Hedgehog
Patched
SMO
Gli
Akt
PKC
Adenylate
cyclase
Raf
Akkα
NF-κB
IκB
PKA
MEK
MEKK
MAPK
MKK
Cytokines
(e.g., EPC)
Cytokine Receptor
JAKs
STAT3,5
Bcl-xL
Cytochrome C
Caspase 9
Caspase 8
Apoptosis
FADD
Bcl-2
Bad
Mt
Bax
FasR
Abnormality
Sensor
Bim
Death factors
(e.g. FasL, Tnf)
Myc:
Max
Mad:
Max
ERK
JNKs
β-catenin:TCF
Fos
Jun
CREB
CycD
p16
Rb
CDK4
p15
E2F
Gene Regulation
ARF
mdm2
p53
Cell
Proliferation
CycE
p27
CDK2
p21

MAPK Pathway