CELL SIGNALING

How the cells communicate with the environment

Impact of the topic for cell biology

The Nobel Prize in Physiology or Medicine 2000
Arvid Carlsson, Paul Greengard, Eric R. Kandel

The Nobel Prize in Physiology or Medicine 2000
Nobel Prize Award Ceremony
Arvid Carlsson
Paul Greengard
Eric R. Kandel



Arvid Carlsson | Paul Greengard | Eric R. Kandel

The Nobel Prize in Physiology or Medicine 2000 was awarded jointly to Arvid Carlsson, Paul Greengard and Eric R. Kandel *"for their discoveries concerning signal transduction in the nervous system"*.

The Nobel Prize in Physiology or Medicine 2004
Richard Axel, Linda B. Buck

The Nobel Prize in Physiology or Medicine 2004
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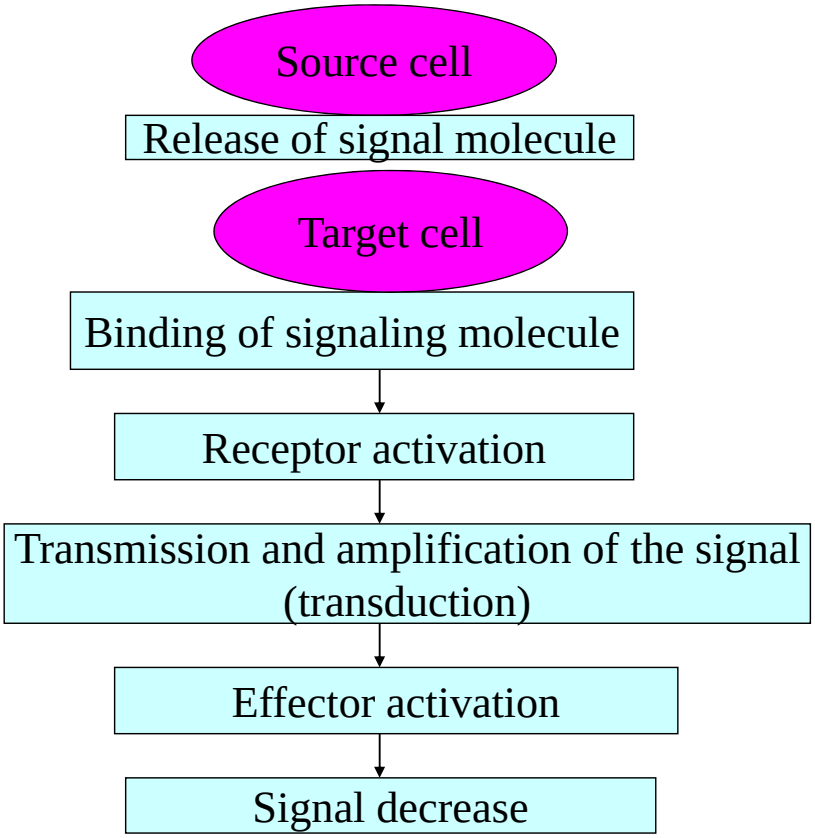
Richard Axel
Linda B. Buck


Richard Axel | Linda B. Buck

The Nobel Prize in Physiology or Medicine 2004 was awarded jointly to Richard Axel and Linda B. Buck *"for their discoveries of odorant receptors and the organization of the olfactory system"*

A standard pathway in cell signaling



Events in cell signaling

In the membrane

✓ Signaling molecule binds to receptor in membrane; activating an intracellular pathway with a series of signaling proteins; one or more signaling proteins interact with target protein, altering TP, which changes its behavior

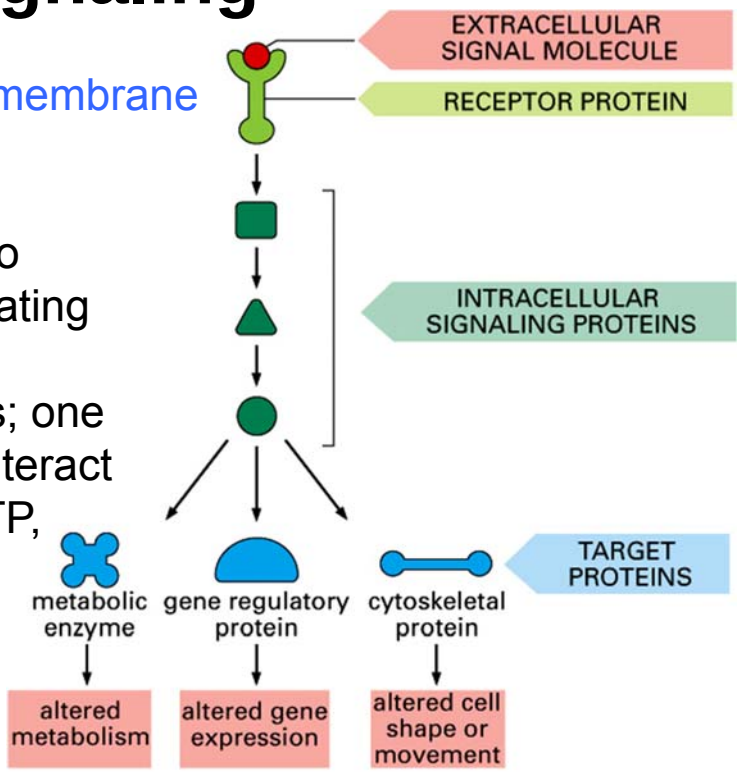


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

Communication distance

- Endocrine – signal molecule → blood → target cell
- Paracrine – local communication mechanism
- Autocrine – cell elaborates a self-addressed message
- Juxtacrine – two cells in direct contact
- Junctional – by gap junction
- Synaptic – through a synaptic cleft

Coordination of response *via* autocrine signals

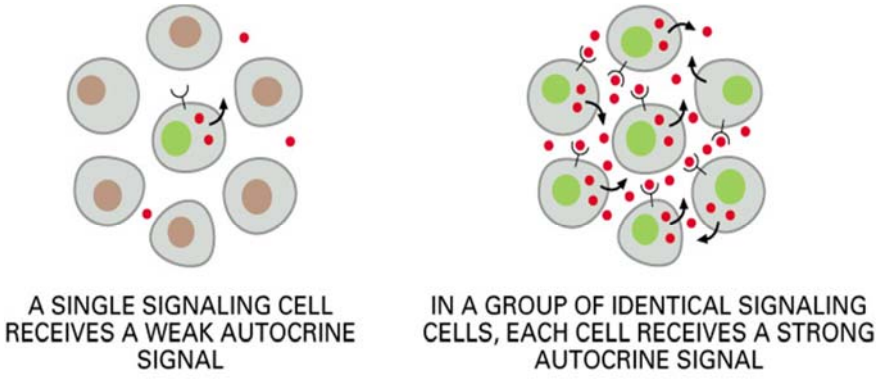


Figure 15–6. Molecular Biology of the Cell, 4th Edition.

- Cell producing hormone and target cell are same cell type
- Common in embryological development where, early in development, a group of cells can respond to a differentiation-inducing signal, but a single isolated cell of the same type cannot
- Cancer cells often use autocrine signaling to overcome controls on cell proliferation and survival

Types of communication

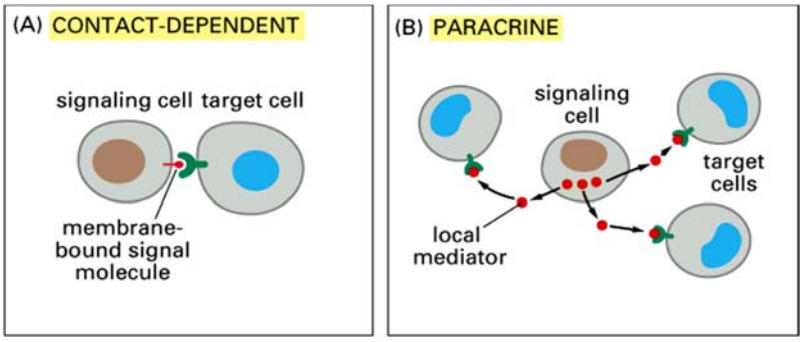
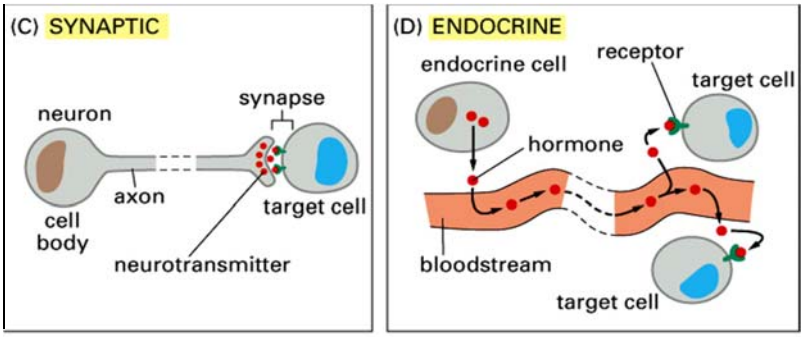


Figure 15–4 part 1 of 2. Molecular Biology of the Cell, 4th Edition.



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Communication *via* gap junctions

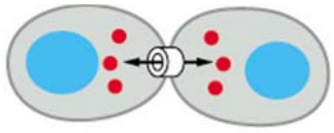
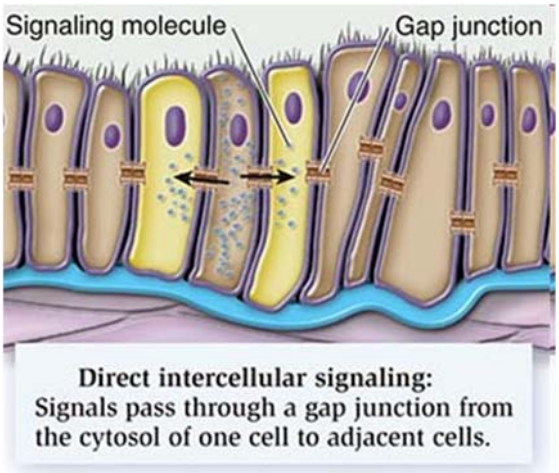


Figure 15–7. Molecular Biology of the Cell, 4th Edition.



- Signaling via gap junctions coordinates response of adjacent cells that are in direct contact
- Ca^{++} and c-AMP are 2 signals commonly passed by gap junctions; macromolecules such as proteins and nucleic acids cannot pass
- Cells in embryos form and break gap junction connections throughout development
- Animals with a defective gap junction protein have severe defects in heart development

Signaling molecules

- Steroid hormones: glucocorticoids, estrogen
- Gas molecules: NO, CO
- small hidrophilic molecules e.g. neurotransmitters: (adrenaline, noradrenaline, serotonine, histamine, glutamate, GABA)
- Peptides
  - hormones: insulin, glucagon, GH, FSH, prolactin
  - Growth factors: NGF, EGF, PDGF, cytokines
- Eicosanoids: prostaglandins, tromboxanes, leukotrienes

Classification of the receptors

- According to their localization
- According to the physical /chemical features of their ligands

Receptors (1)

➢ Intracellular receptors :

- receptors for thyroid hormones
- superfamily of receptors for lipophilic signaling molecules
  - steroid hormones
  - liposoluble vitamins: vit. A, D
- intracellular proteins that bind small, nonpolar molecules: NO, CO

Receptors (2)

➢ Membrane receptors

- The superfamily of receptors for hydrophilic molecules (integral proteins – ligand specific)
- families: - ion channel receptors
  - receptors coupled with G proteins
  - receptors with intrinsic enzymatic activity:
    - tyrosine kinase receptors
      - tyrosine kinase associated receptors
    - *serine-threonine kinase associated receptors*
    - *guanylyl cyclase associated receptors*
    - *tyrosine phosphatase associated receptors*

Signalling *via* hydrophilic /hydrophobic molecules

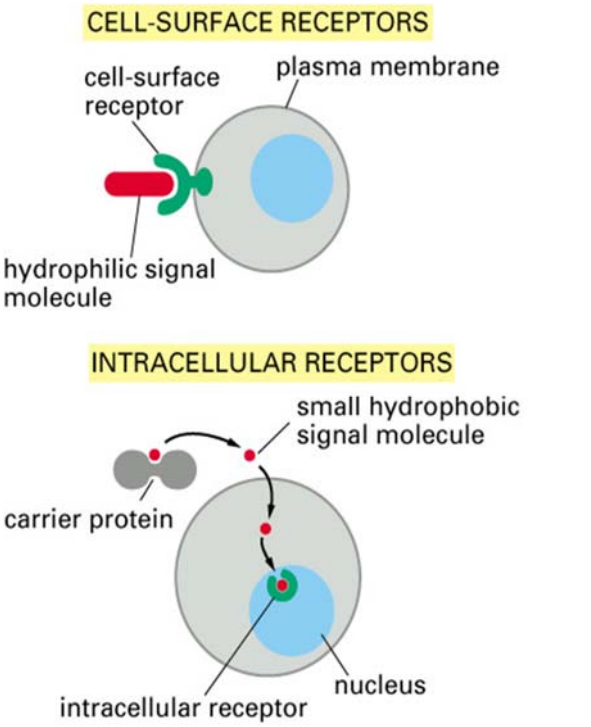
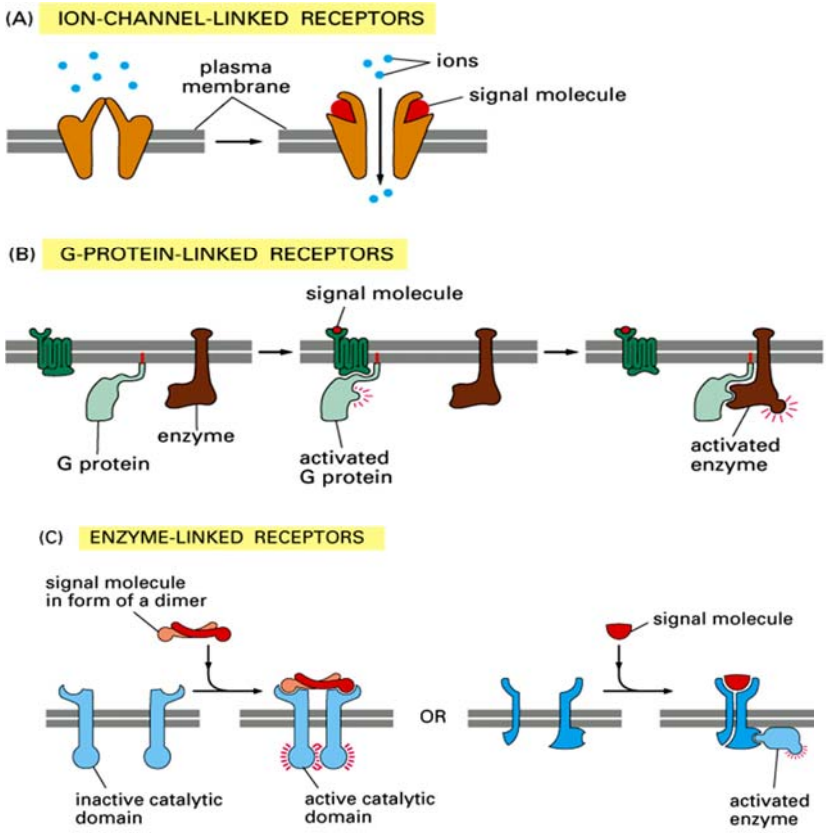


Figure 15–3. Molecular Biology of the Cell, 4th Edition.

- Most chemical signals are hydrophilic
- Hydrophilic signals cannot cross membrane and bind to a cytoplasmic receptor, so receptors exposed on the outer cell surface are required
- Some small signal molecules are hydrophobic and are bound to a carrier protein

✓ Signal molecules often act at very low concentrations!

Cell surface receptors



Downstream mechanisms

- Adenilate cyclase→cAMP
- Guanilate cyclase→cGMP
- Phospholipase C→diacylglycerol
  →IP3→Ca^{++}
- MAP kinase
- JAK-STAT

Time needed for cell to cell talk (1)

- Signaling *via* receptors = ion channels
  - mechanism: hyperpolarization or depolarization
  - *time: milliseconds*
- Signaling via receptors coupled with G proteins
  - mechanisms:
    - modifying excitability of membrane components (e.g. ion channels)
    - production of second messengers
  - *time: seconds*

Time needed for cell to cell talk (2)

- Signaling *via* receptors with enzymatic activity
  - mechanism: protein phosphorylation and modifying of transcription
  - *time: minutes*
- Signaling *via* intracellular (nuclear) receptors
  - mechanism: modifying of DNA transcription
  - *time: hours*

Signaling effects on cells

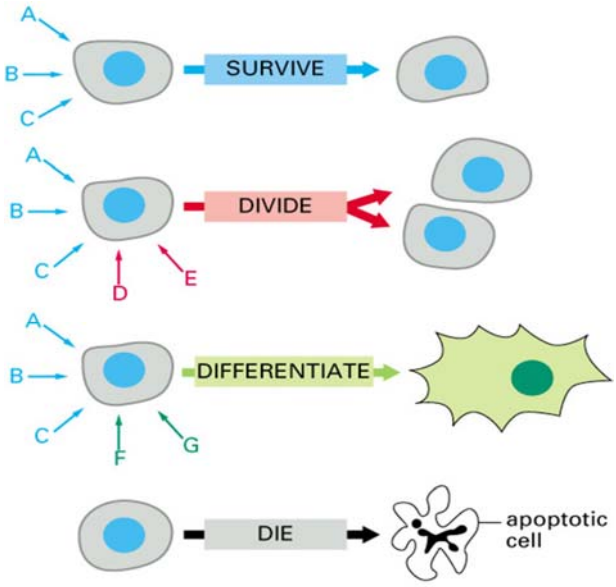


Figure 15–8. Molecular Biology of the Cell, 4th Edition.

- Each cell is programmed to respond to specific combinations of signals
- Multiple signals bind to receptors and trigger cell responses; presence of receptor determines if cell will respond
- Deprivation of signals can cause cell death

Ligand *versus* cell *versus* effect

Acetylcholine

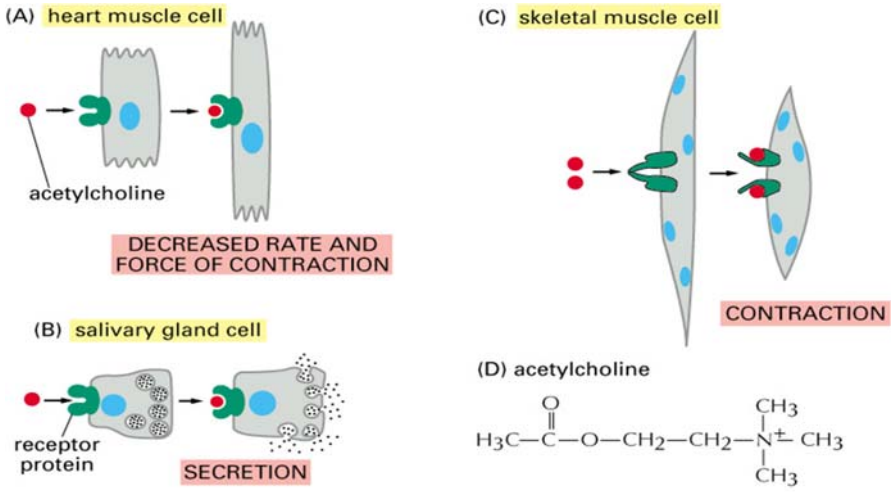


Figure 15–9. Molecular Biology of the Cell, 4th Edition.

✓Same signal can have more than one receptor; even the same receptor can produce different responses in different cells depending on the intracellular path activated by the receptor.

Signal decrease (1)

✓Concentration of signal molecule can be adjusted quickly only if the life of the molecule is short

- Effects of signal molecules are typically transitory because the signal molecule concentration decreases rapidly after a quick increase

- Signal molecules undergo rapid turnover and are broken down in the extracellular space; enzymatic degradation, uptake, diffusion

- Intracellular proteins that are part of the signal cascade are activated, then inactivated rapidly

- New proteins may be made and then have short half-lives, just a few minutes

- The most common alteration of intracellular signal path proteins is phosphorylation / dephosphorylation

Acknowledging contributions

The Nobel Prize in Physiology or Medicine 1992
Edmond H. Fischer, Edwin G. Krebs

The Nobel Prize in Physiology or Medicine 1992

Nobel Prize Award Ceremony

Edmond H. Fischer

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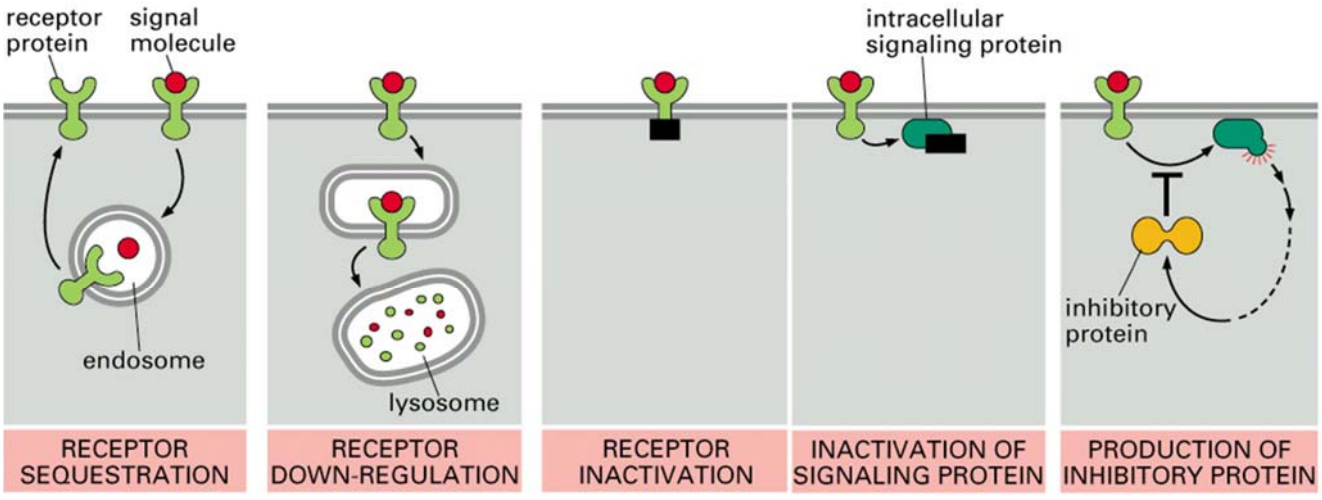
Signal decrease (2)



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Water soluble *versus* water insoluble signaling molecules

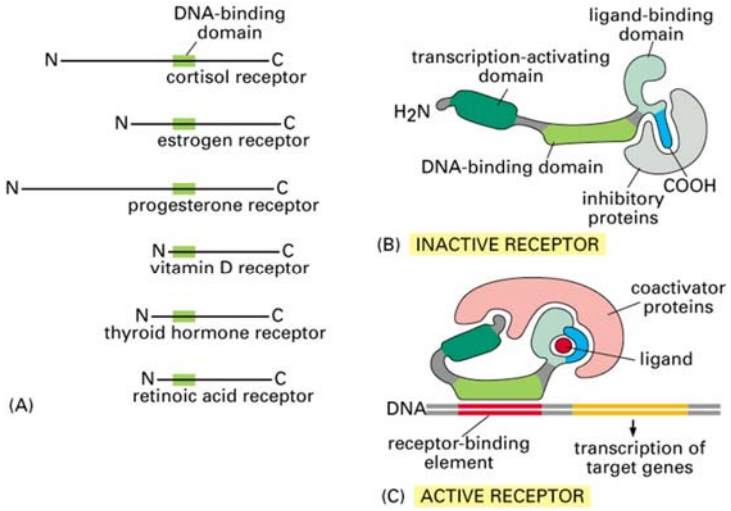
• Water soluble molecules are broken down or removed rapidly giving quick and short-lived responses.

• Water insoluble molecules persist in blood for hours or even days and mediate longer lasting effects.

✓Cortisol receptors are in the cytosol and enter the nucleus to bind to DNA after binding cortisol.
✓Thyroid hormone receptors and retinoid receptors are bound to DNA in the nucleus in an inactive form; they are activated with ligand binding.

Signaling by lipophilic molecules

- Receptor typically has inhibitory protein bound, making it inactive
- Signal binds to receptor, leading to dissociation of inhibitory protein from receptor
- Activated receptor binds to specific DNA region, that regulates transcription of specific genes



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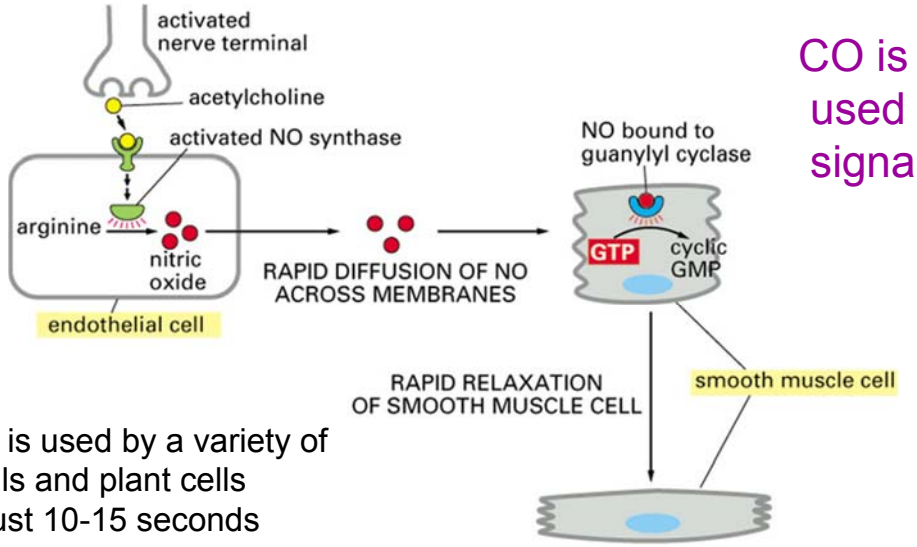
Signaling by small, nonpolar molecules



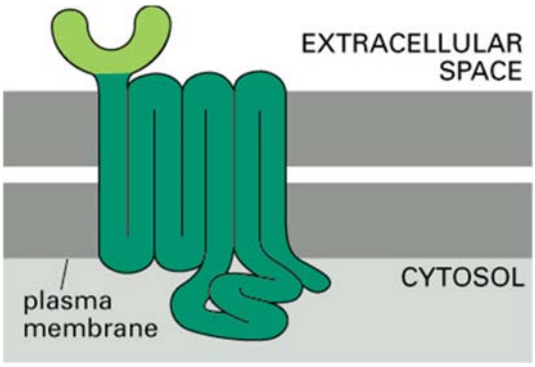
CO is also used as a signal

- Nitric Oxide is used by a variety of animal cells and plant cells
- Half-life is just 10-15 seconds

Figure 15–11. Molecular Biology of the Cell, 4th Edition.

Role of nitric oxide in vascular smooth muscle relaxation

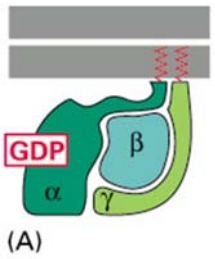
G-protein linked receptors



- ✓Largest family of cell-surface receptors
- ✓"G" refers to GTP/GDP binding
- ✓Over 2 thousand in most mammals
- ✓Most drugs work through G-protein receptors
- ✓7 membrane-spanning regions

Figure 15–26. Molecular Biology of the Cell, 4th Edition.

Trimeric G protein with alpha, beta and gamma subunits



Acknowledging contributions

The Nobel Prize in Physiology or Medicine 1994
Alfred G. Gilman, Martin Rodbell

The Nobel Prize in Physiology or Medicine 1994
Nobel Prize Award Ceremony
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Martin Rodbell

Alfred G. Gilman Martin Rodbell

The Nobel Prize in Physiology or Medicine 1994 was awarded jointly to Alfred G. Gilman and Martin Rodbell *"for their discovery of G-proteins and the role of these proteins in signal transduction in cells"*

The Nobel Prize in Chemistry 2012
Robert J. Lefkowitz, Brian K. Kobilka

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Brian K. Kobilka

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Robert J. Lefkowitz Brian K. Kobilka

The Nobel Prize in Chemistry 2012 was awarded jointly to Robert J. Lefkowitz and Brian K. Kobilka *"for studies of G-protein-coupled receptors"*

G-protein coupled receptors (1)

- Disassembly of activated G-protein into 2 signaling components
- Following dissociation, both the alpha and beta/gamma complexes can activate different membrane proteins

✓ Receptor stays activated as long as ligand is bound, so receptor can activate many G-proteins

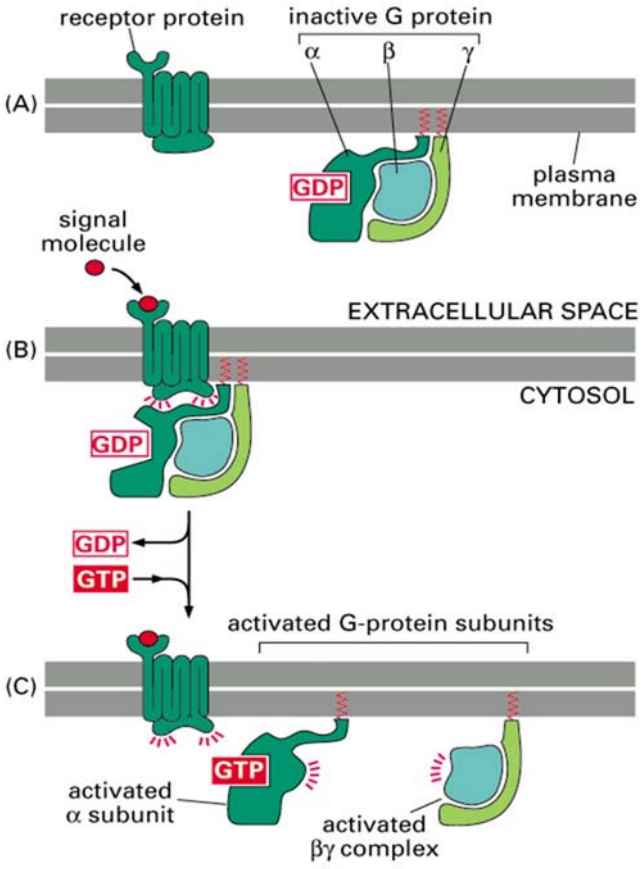

Figure 15–28. Molecular Biology of the Cell, 4th Edition.

G-protein coupled receptors (2)

- ✓ Activation of the target protein by the activated alpha subunit followed by switching off of the G-protein alpha subunit by the hydrolysis of its bound GTP

- ✓ Reassembly of 3 G-protein subunits into inactive complex

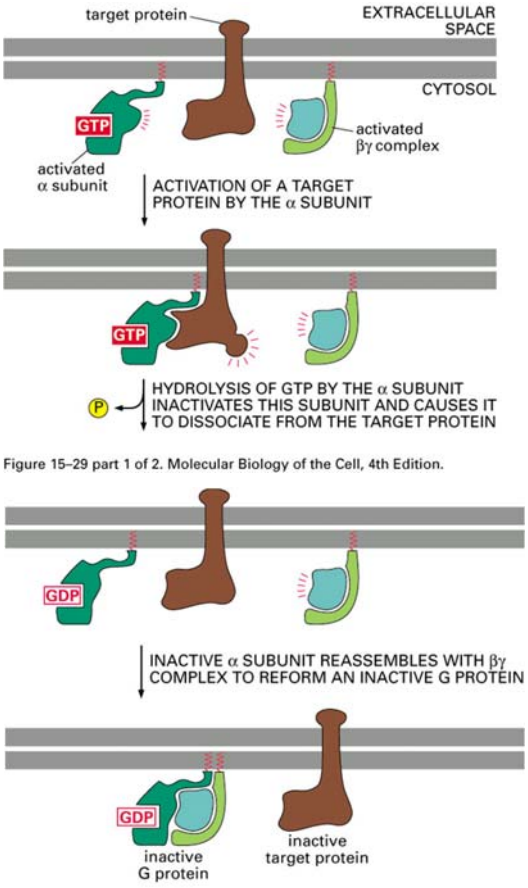

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Figure 15–29 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Adenilate cyclase pathway

- Some G-proteins signal by regulating production of c-AMP

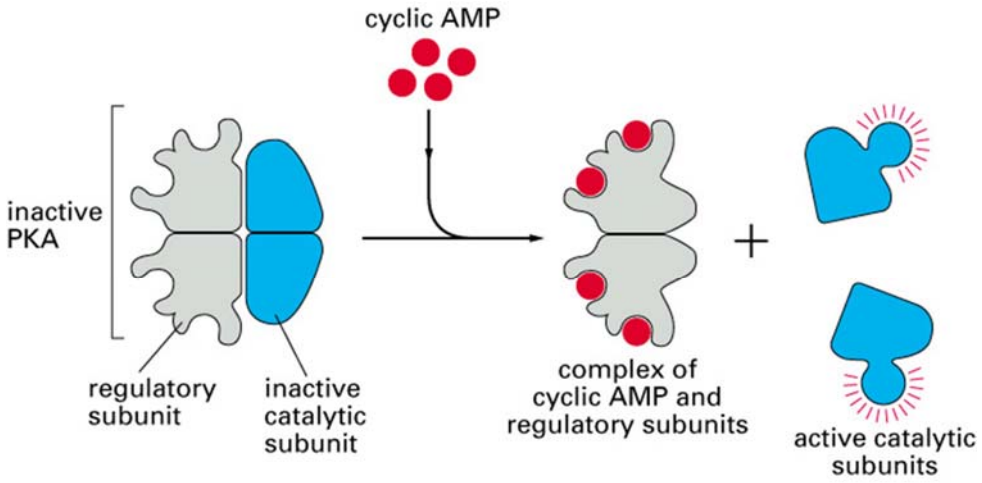
- Some G proteins are stimulatory (Gs) and other are inhibitory (Gi)

❑ Adenylyl cyclase is a plasma membrane enzyme controlled by G-proteins; leads to increased c-AMP

❑ c-AMP phosphodiesterase breaks down c-AMP, stopping signaling

cAMP action (1)

- c-AMP activates protein kinase A, which phosphorylates other proteins, regulating their activity
- Hormones using c-AMP: TSH, ACTH, LH, adrenaline, parathyroid hormone, glucagon, vasopressin



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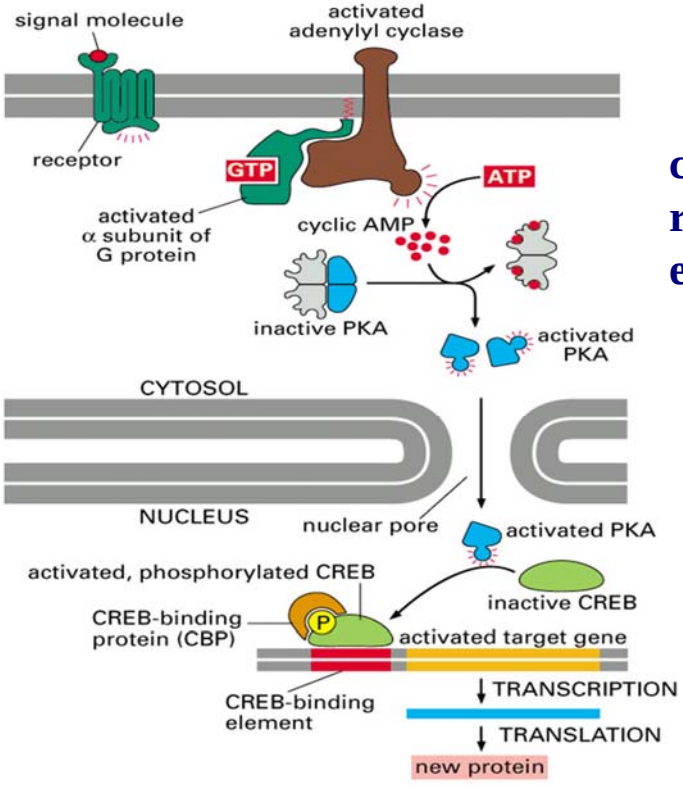
cAMP action (2)



c-AMP can regulate gene expression

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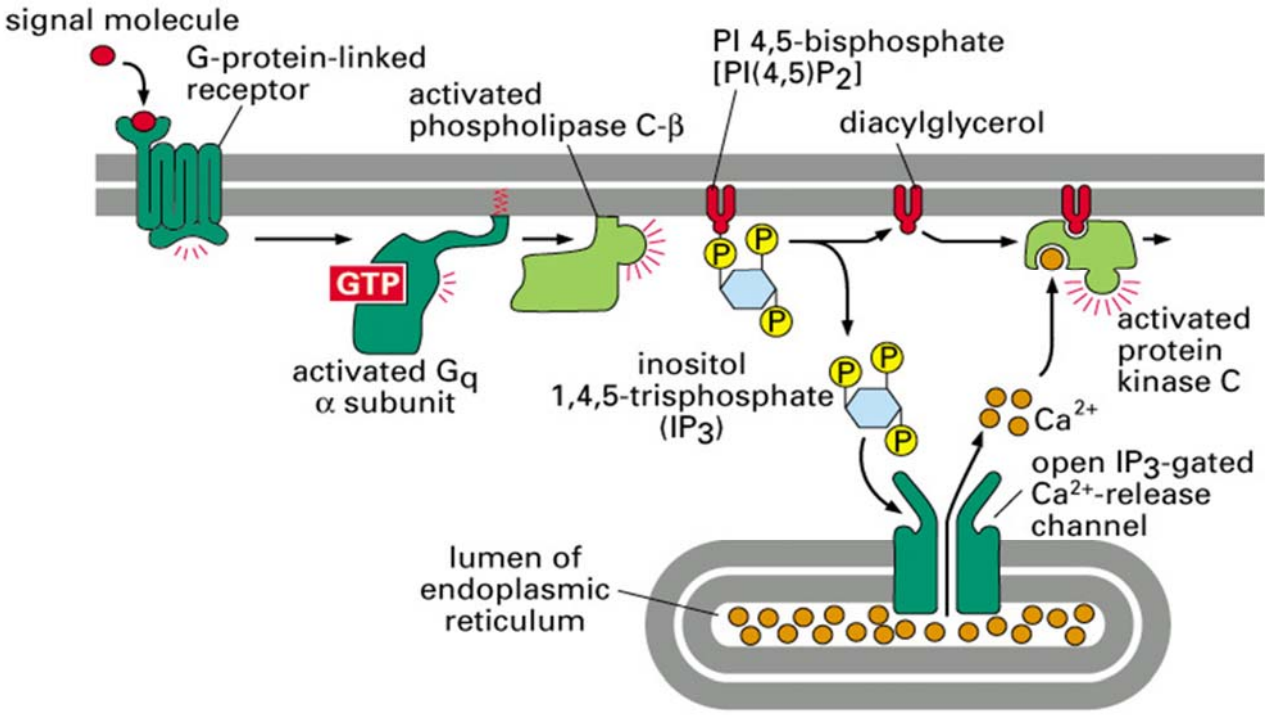
Phospholipase C pathway



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DAG effects

- Diacylglycerol can be cleaved to release arachidonic acid, which can act on its own, or be converted to prostaglandins, which have a variety of biological activities

- PGs participate in pain and inflammatory responses
- Drugs such as aspirin, ibuprofen and cortisone act in part by inhibiting synthesis of PGs

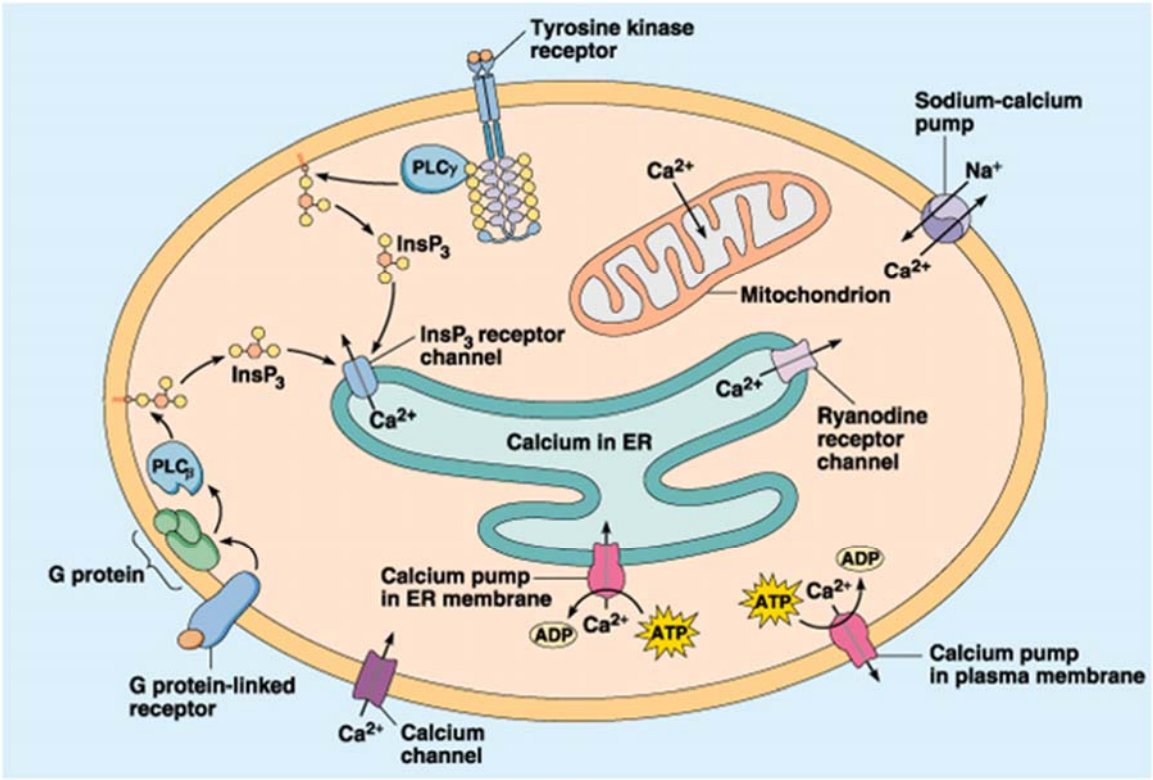
✓ DAG's most important role is in activation of PKC

Ca^{++} regulation (1)

✓ 3 types of Ca^{++} channels function in signaling in different cells:

- Voltage-gated Ca^{++} channels open in response to membrane depolarization
- IP3-gated Ca^{++} channels are found in ER and lead to Ca^{++} increase in the cytoplasm
- Ryanodine receptors in muscle SR react to changes in membrane potential, leading to increased cytosolic Ca^{++}, that causes muscle contraction
- Ryanodine receptors are also found in the ER of many non-muscle cells, where they function in Ca^{++} signaling

Ca^{++} regulation (2)



Ca^{++} regulation (3)

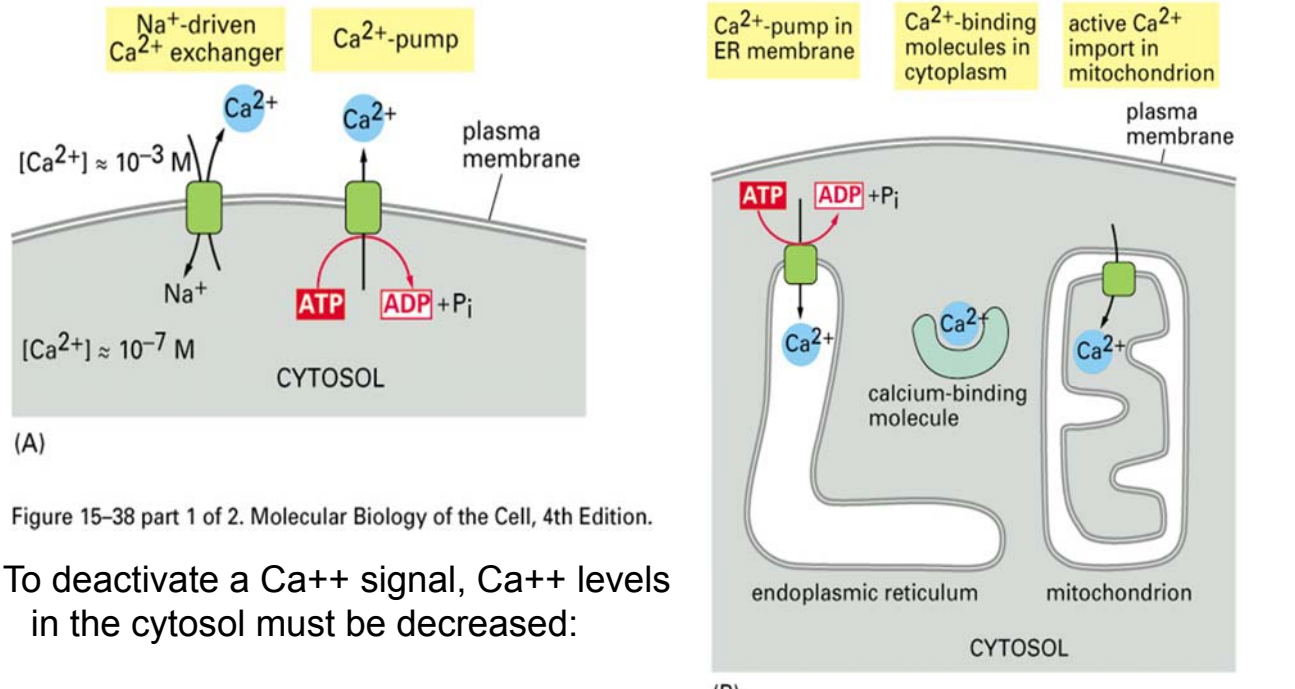


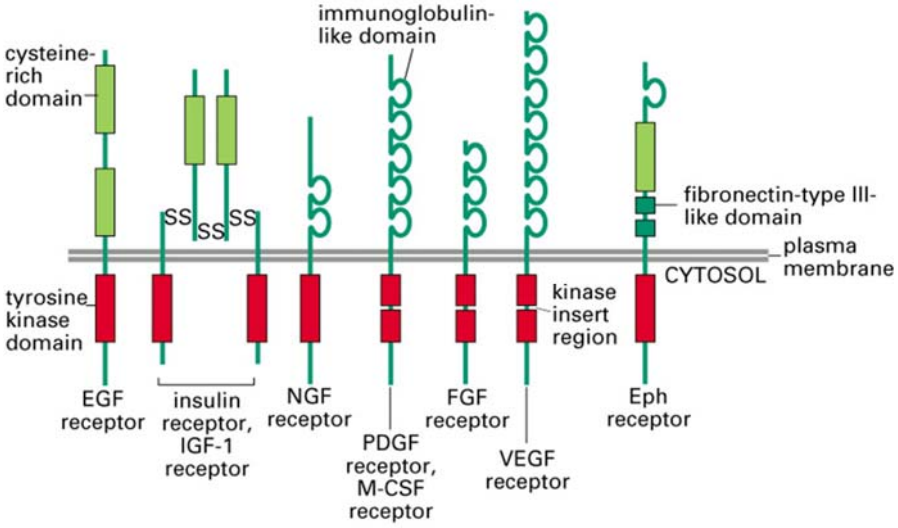
Figure 15–38 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Figure 15–38 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

- To deactivate a Ca++ signal, Ca++ levels in the cytosol must be decreased:
- Ca is pumped out of the cell, bound to Ca-binding molecules in cytoplasm, or Ca is pumped into ER or mitochondria

Enzyme-linked Cell Surface Receptors

- Examples of the 7 subfamilies of receptors
- Functions of some extracellular domains is not known.



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Functions of Tyrosine Kinase-Type Receptors

Epidermal Growth Factor	proliferation of cells
Insulin	glucose uptake and protein synthesis
Insulin-like Growth Factor 1 & 2	cell growth & survival
Nerve Growth Factor	survival and growth of neurons
Platelet-derived Growth Factor	survival, growth and proliferation of different cells
Macrophage colony stimulating factor	monocyte/macrophage proliferation & differentiation
Fibroblast Growth Factors	proliferation of various cells
Vascular Endothelial Growth Factor	stimulates angiogenesis

Small /monomeric G proteins

•Small /monomeric G proteins (e.g. Ras) – signal transduction for tyrosine kinase receptors

•Ras proteins function in conjunction with tyrosine kinases to regulate cell proliferation and differentiation.
•Ras was first discovered in a mutant form that was hyperactive and promoted cancerous transformation of cells.
•Ras acts as a switch alternating between 2 conformations, active (GTP bound) and inactive (GDP bound).
•2 classes of signaling proteins regulate Ras activity by regulating its transition between active and inactive states; inactivation is achieved by GTP hydrolysis.
•In most of the cells, monomeric G proteins are generally maintained inactive.

G proteins – Bind to GTP; Hydrolyze GTP to GDP

Heterotrimeric G proteins	Ras superfamily G proteins
Three subunits, α, β, γ	Monomers resemble α subunit of heterotrimeric G proteins
Use G-protein linked receptors	Use catalytic receptors
Regulate second messengers	

Activation of small G proteins by an activated tyrosine kinase receptor

- Tyrosine kinase receptor dimerization, followed by cross phosphorylation of the cytosolic domain
- an adaptor protein binds to phospho-tyrosine on receptor and binds a protein which stimulates Ras to exchange its bound GDP for GTP

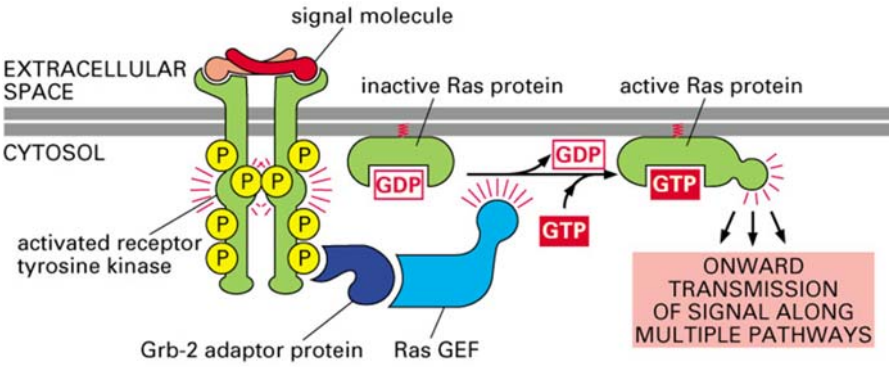


Figure 15–55. Molecular Biology of the Cell, 4th Edition.

- Activated Ras then activates several downstream signaling pathways, including the MAP-kinase pathway
- The monomeric G protein (Ras) inactivates itself by hydrolyzing the GTP

MAP-kinase serine/threonine phosphorylation pathway activated by Ras

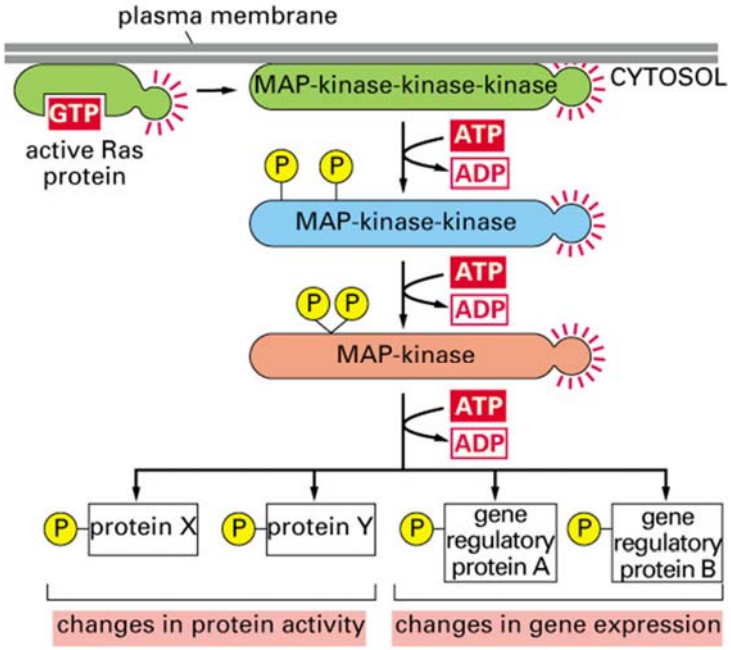
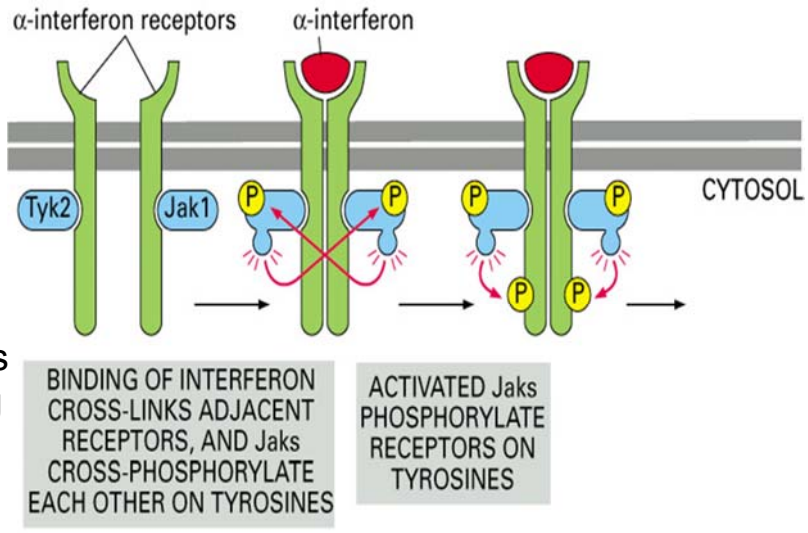


Figure 15–56. Molecular Biology of the Cell, 4th Edition.

Jak-STAT signaling pathway (1)

- signaling molecule: α-interferon
- Interferons are cytokines secreted by cells (especially WBC) in response to viral infection
- Interferons bind to receptors on non-infected neighboring cells and induce synthesis of proteins that increase resistance to virus
- Hormones that use this pathway: GH, prolactin



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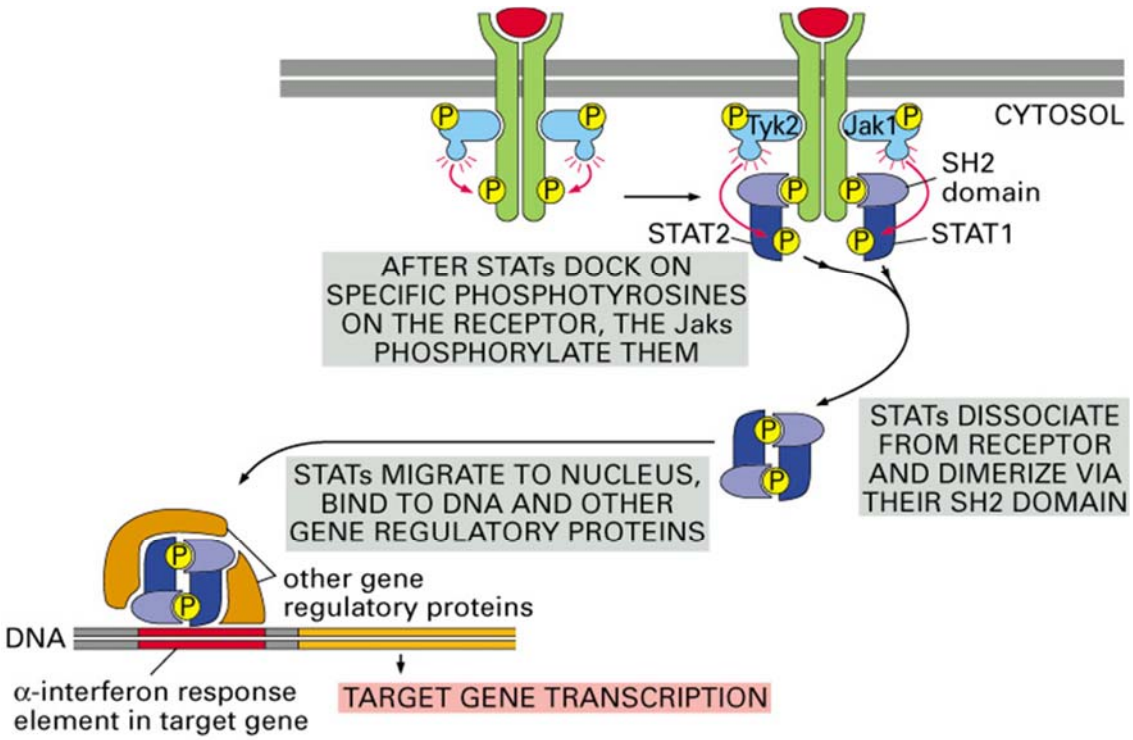
Jak-STAT signaling pathway (2)



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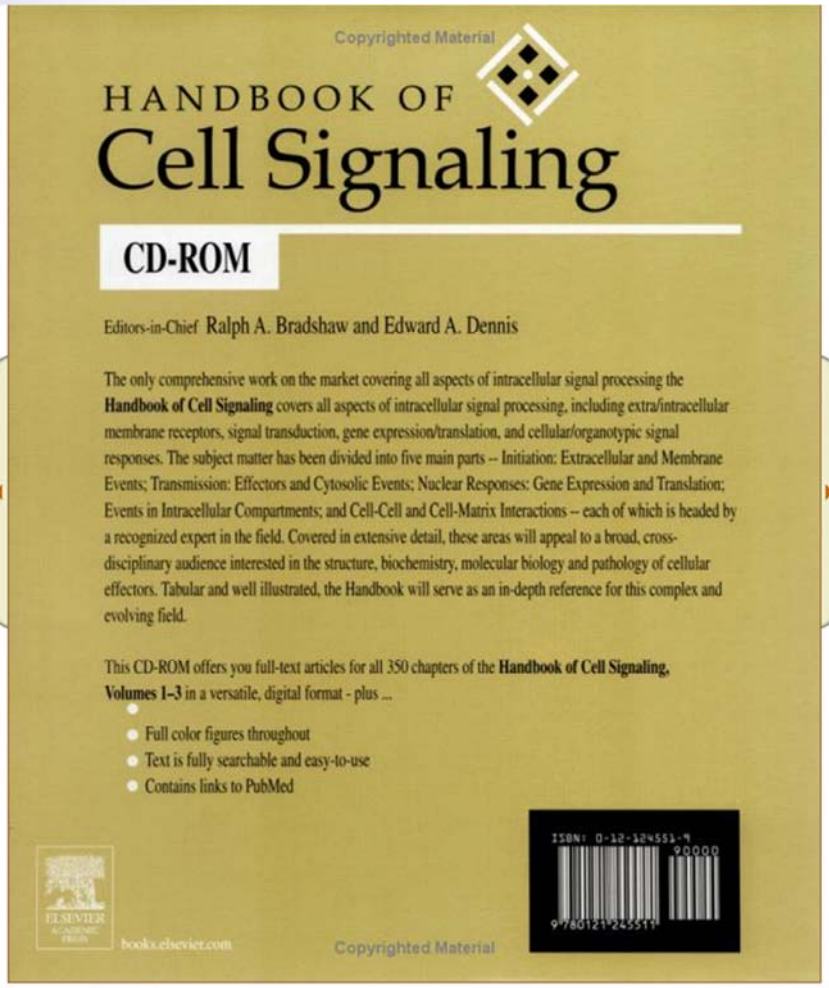
Conclusions (1)

- Communication allows functional integration
- Signaling molecules can be secreted or bound to the cell surface
- In pathology communication is altered
- Some signaling molecules act at the cell surface, others have intracellular receptors

Conclusions (2)

- Information transfer is performed on predetermined pathways
- The pathways can intersect (communication nods)
- Pharmacology means exploiting signaling pathways
- Very wide cell communication literature – mostly free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HANDBOOK OF
Cell Signaling
CD-ROM
Editors-in-Chief Ralph A. Bradshaw and Edward A. Dennis
The only comprehensive work on the market covering all aspects of intracellular signal processing the Handbook of Cell Signaling covers all aspects of intracellular signal processing, including extra/intracellular membrane receptors, signal transduction, gene expression/translation, and cellular/organotypic signal responses. The subject matter has been divided into five main parts -- Initiation: Extracellular and Membrane Events; Transmission: Effectors and Cytosolic Events; Nuclear Responses: Gene Expression and Translation; Events in Intracellular Compartments; and Cell-Cell and Cell-Matrix Interactions -- each of which is headed by a recognized expert in the field. Covered in extensive detail, these areas will appeal to a broad, cross-disciplinary audience interested in the structure, biochemistry, molecular biology and pathology of cellular effectors. Tabular and well illustrated, the Handbook will serve as an in-depth reference for this complex and evolving field.
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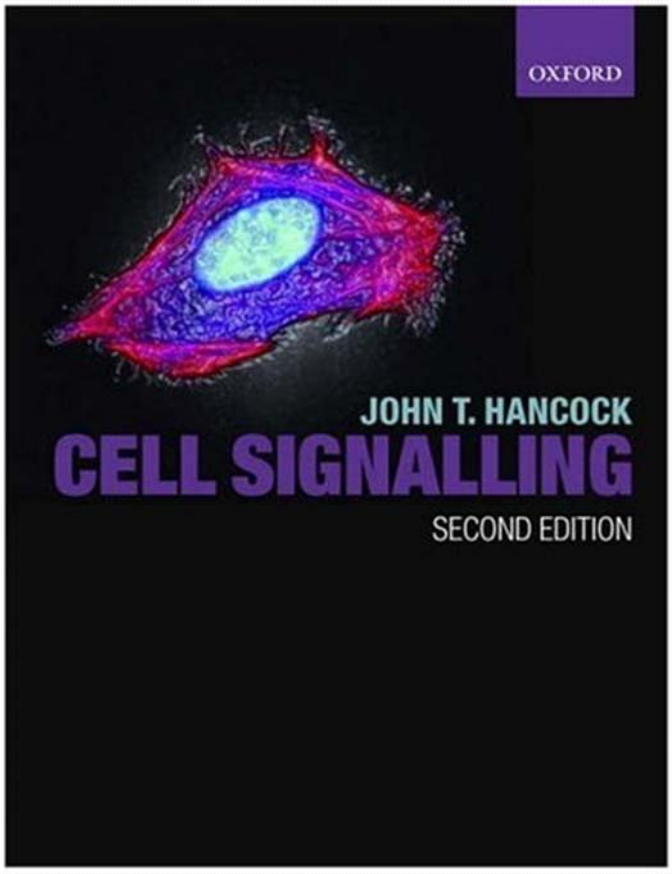
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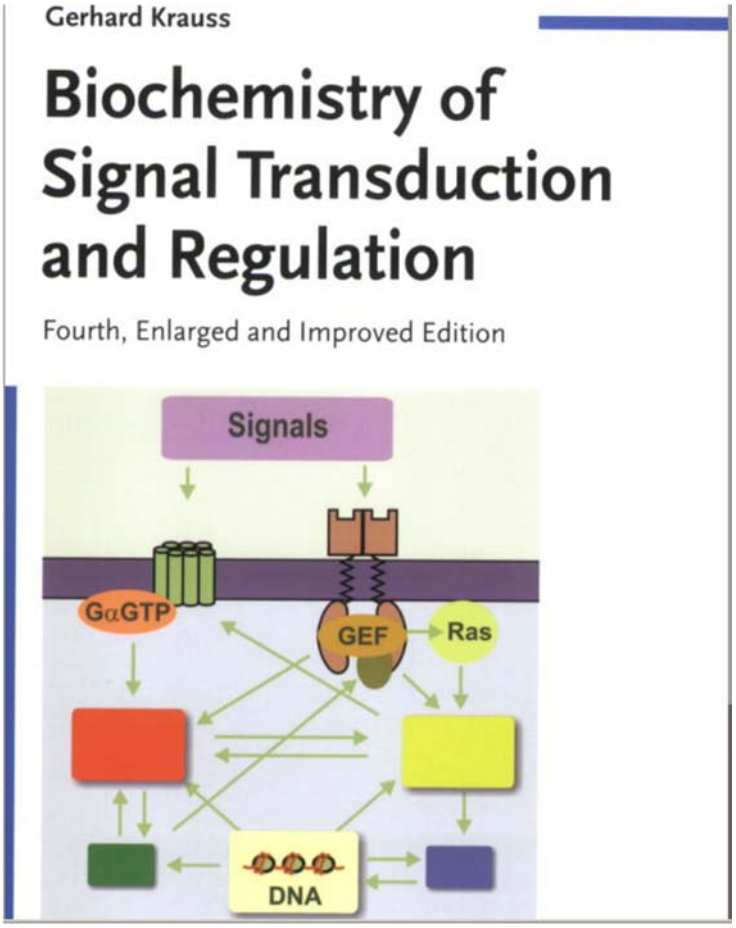
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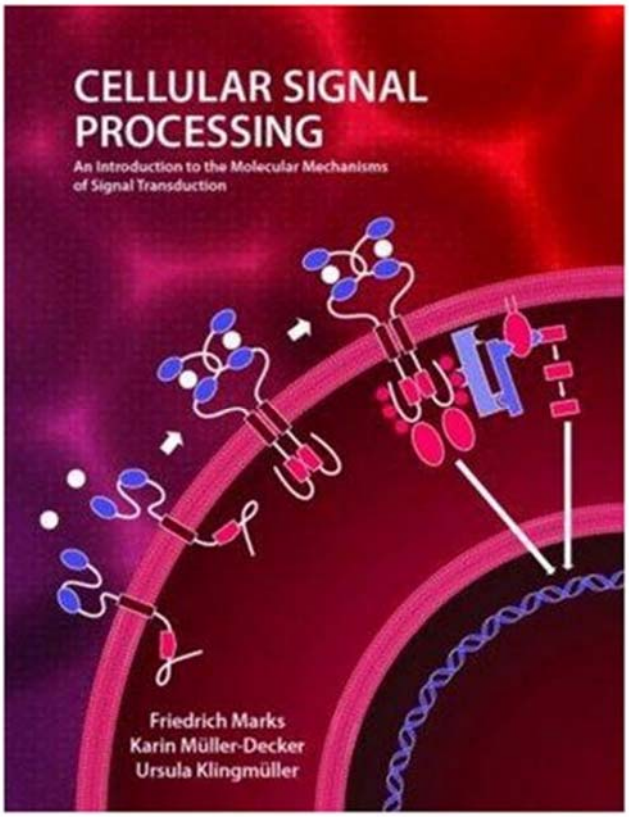
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