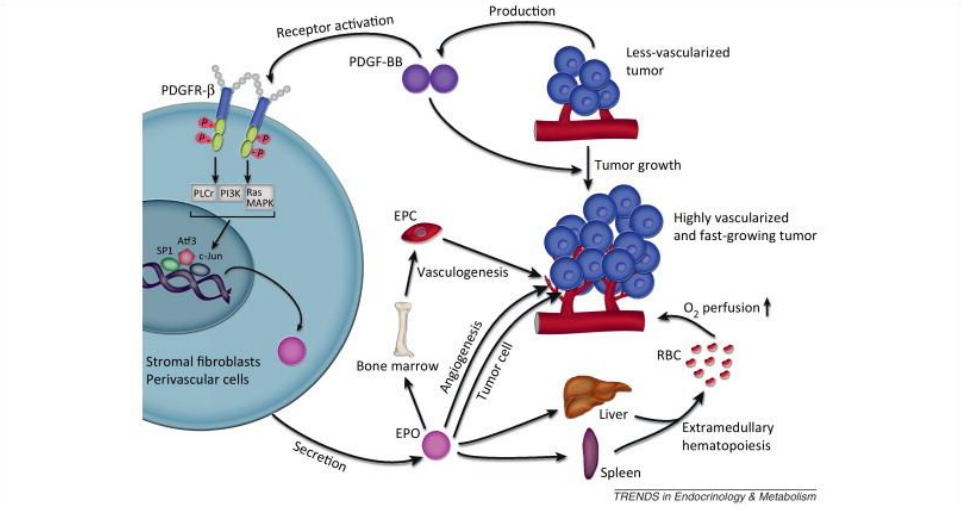
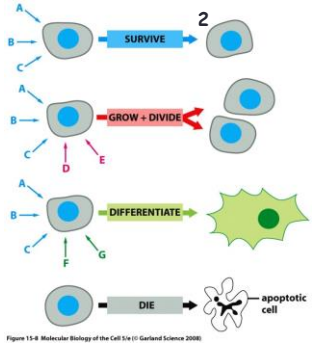
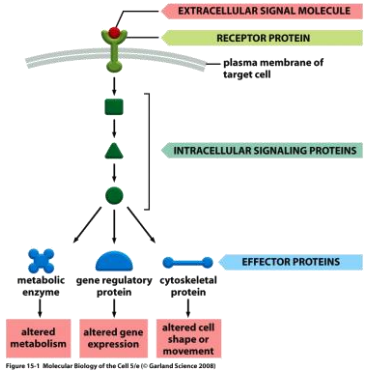
CELL COMMUNICATION : G-COUPLE RECEPTOR PROTEIN



- **Extracellular signal molecules**
  - Unicellular organisms
    - Response to extracellular signal molecules→ altered cell behavior
  - Multicellular organism
    - Response to signal molecules:
      - Altered metabolism
      - Altered tissue growth and differentiation
      - Protein synthesis and secretion
      - Altered intracellular and extracellular composition

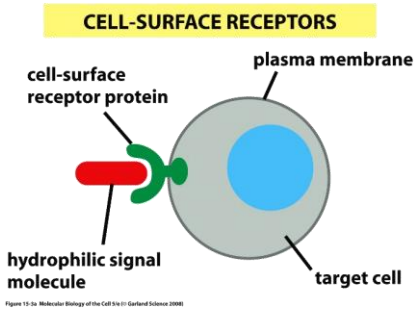


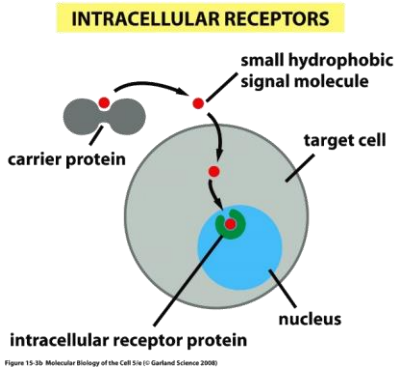
- Signal molecules : ligand bind to specific receptor - on/in target cell
- cell-surface receptors act as ***signal transducers*** by converting an extracellular ligand-binding event into intracellular signals that alter the behavior of the target cell



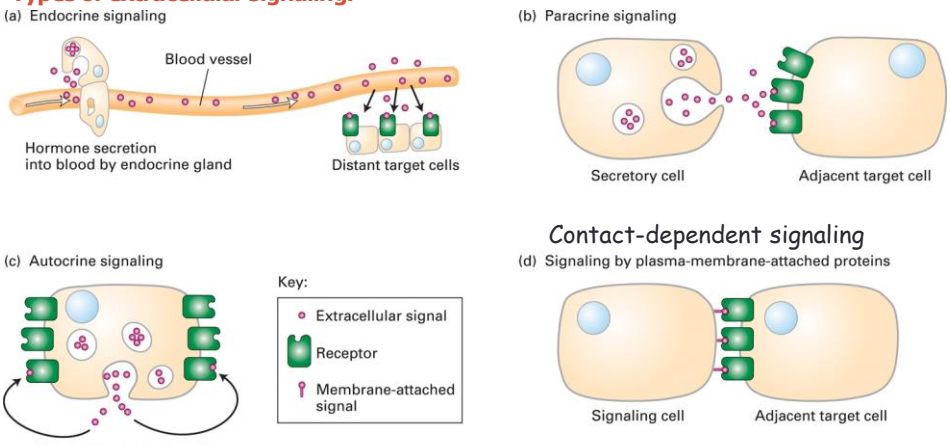
- Signal molecules ≤10^{-8}M → activate cell signalling & alter cell behavior

- Receptor :
  - Intracellular → hidrophobic/small signal molecules
  - Extracellular → hidrophilic signal molecules

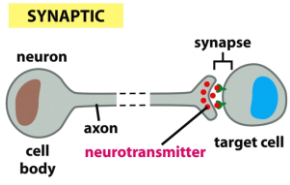




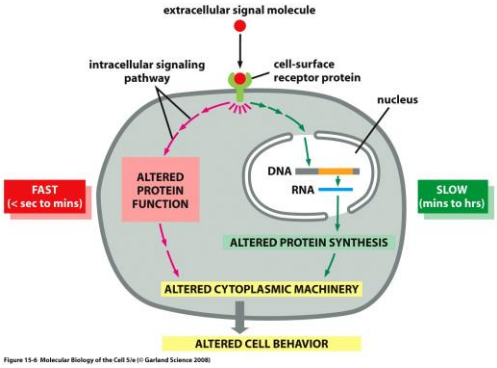
Types of extracellular signaling.



a) Endocrine signaling depends on endocrine cells, which secrete hormones into the bloodstream for distribution throughout the body.
b) Paracrine signaling depends on signals that are released into the extracellular space and act locally on neighboring cells.
c) Autocrine signaling: cells may also produce signals that they themselves respond to
d) Contact-dependent signaling requires cells to be in direct membrane–membrane contact.
e) Synaptic signaling is performed by neurons that transmit signals electrically along their axons and release neurotransmitters at synapses, which are often located far away from the neuronal cell body.

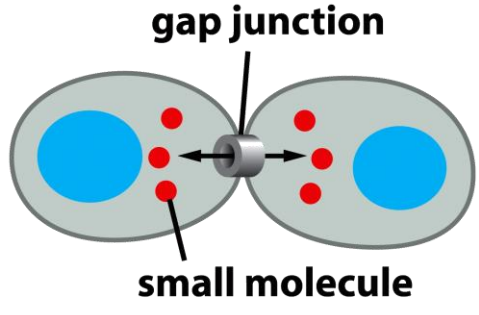


- Speed of a response to an extracellular signal depends on:
  - The mechanism of signal delivery
  - the nature of the target cell's response.



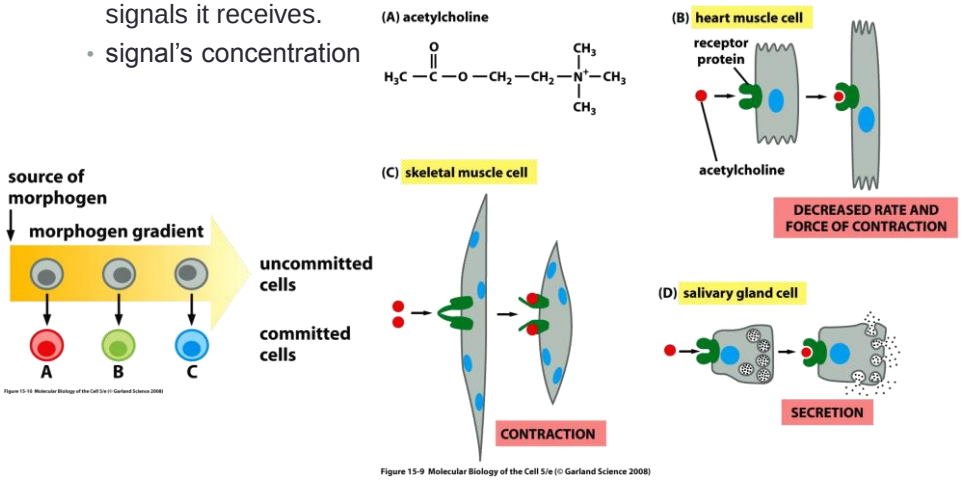
- Response :
  - rapid response:
    changes in proteins already present in the cell:
    - an allosteric change in a neurotransmitter-gated ion channel
    - protein phosphorylation
  - Slow response
    - changes in gene expression and the synthesis of new proteins

- Gap junction
  - Sharing signalling information
  - exchange of inorganic ions and other small watersoluble molecules : Ca^{2+}, cAMP
  - homogenize conditions in the communicating cells
    - nerve-muscle



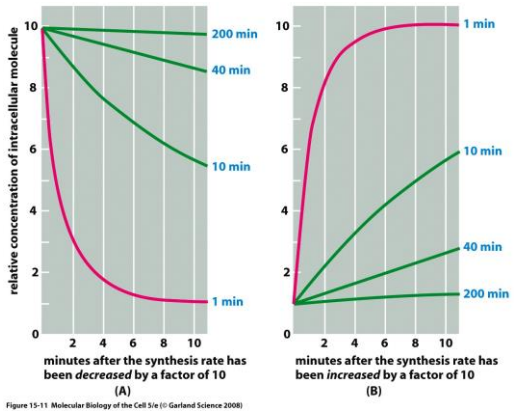
Different Types of Cells Usually Respond Differently to the Same Extracellular Signal Molecule

- A cell's response to extracellular signals depends on:
  - the receptor proteins
  - the intracellular machinery by which it integrates and interprets the signals it receives.
  - signal's concentration



A Cell Can Alter the Concentration of an Intracellular Molecule Quickly Only If the Lifetime of the Molecule Is Short

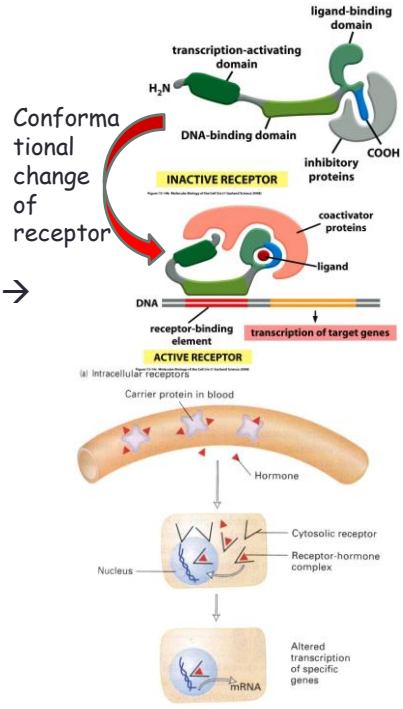
- During development ➔ transient extracellular signals →lasting effects
  - trigger a change in the cell's development through cell memory mechanisms.
- adult tissues
  - the response fades when a signal ceases.
  - effect is transient → signal effects by altering the concentrations of short-lived (unstable) intracellular molecules → undergoing continual turnover.
  - turnover rate can determine the promptness of the response when an extracellular signal arrives

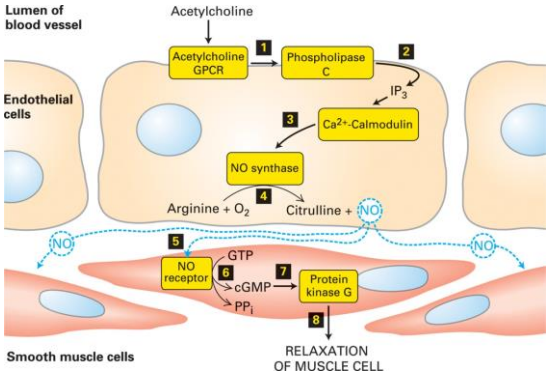


- Example : X and Y molecules are maintained by 1000 molecules
  - Y : synthesized and degraded every 100 mol/sec and lifetime each mole : 10 sec
  - X turnover rate: every 10 mol/sec. average lifetime:100 sec.
  - Activating Signal: 10 x fold increase synthesis of both x and Y ➔ Y 900; X 90

Intracellular Receptor

- Signal molecules:
  - small molecules (CO, NO),
  - hydrophobic molecules: estrogen, progesterone, testosterone, retinoic acid, vitamin D
- receptor: in cytoplasm or nucleus
- Intracellular receptor without ligand → inactive

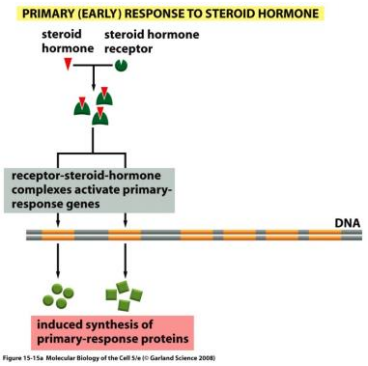


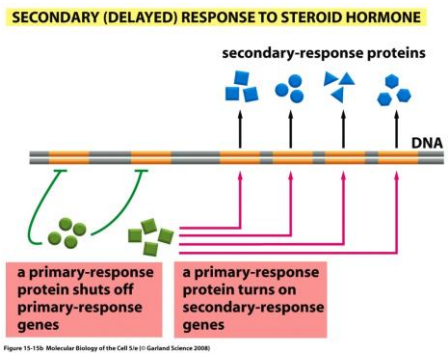


- The transcriptional response → multiple steps. :
  - direct stimulation of a small number of specific genes -~ ± 30 minutes ➔ ***primary response***;

protein products – primary response

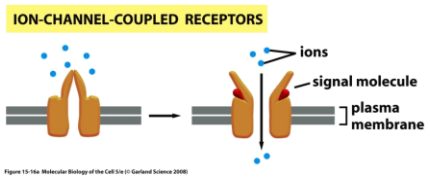
  - a delayed, ***secondary response***;
- some of the proteins from primary response → inhibit transcription of primary response genes→ **negative feedback**



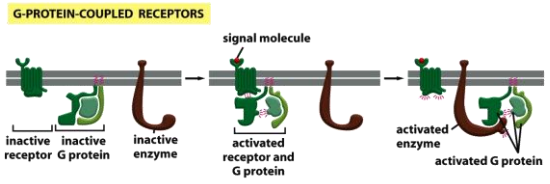


3 types of Cell-Surface Receptor Proteins

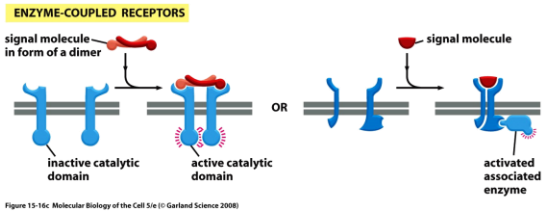
- **Ion-channel-coupled receptors**,
  - *transmitter-gated ion channels* or *ionotropic receptors*,



- **G-protein-coupled receptors**
  - act by indirectly regulating the activity of a separate plasma-membrane-bound target protein, which is generally either an enzyme or an ion channel.



- **Enzyme-coupled receptors**
  - either function directly as enzymes or associate directly with enzymes that they activate



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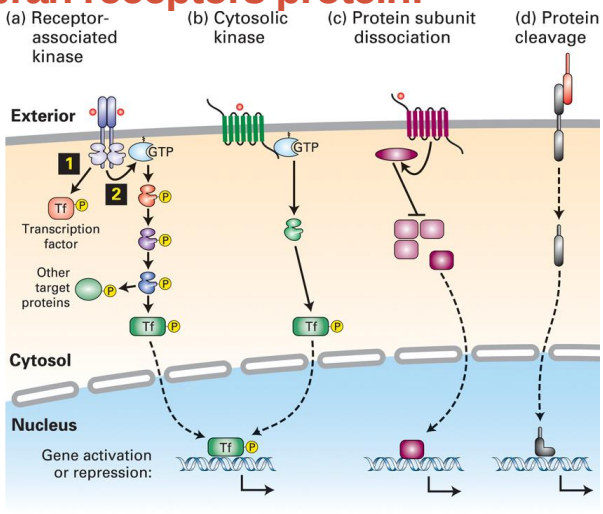
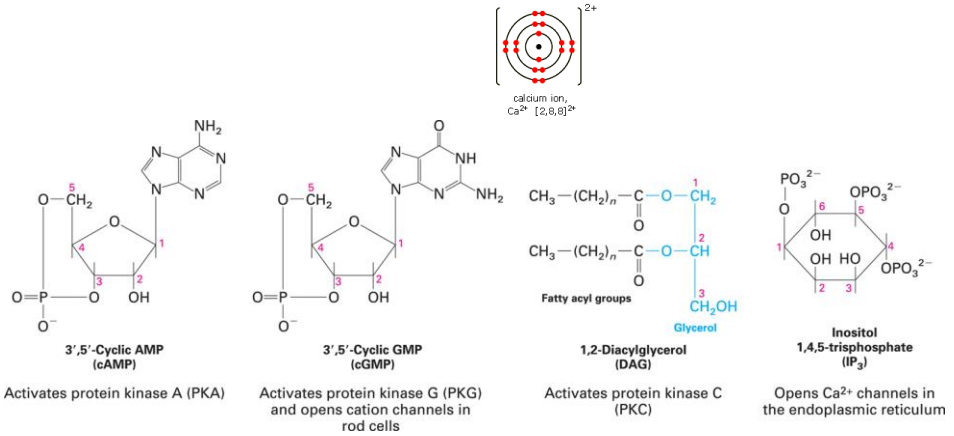
Transmembran receptors protein:



	(a) Receptor-associated kinase	(b) Cytosolic kinase	(c) Protein subunit dissociation	(d) Protein cleavage
Representative receptors and *pathways*	RTKs TGF-β receptors Cytokine receptors *JAK-STAT* *Ras/MAP Kinase*	GPCRs *cAMP/PKA/CREB*	*Wnt* *Hedgehog* *NF-kB*	*Notch/Delta*

Relay signals from cell surface

- Relay signals from cell surface via :
  1. Small molecules : second messenger



Relay signals from cell surface

- Relay signals from cell surface via :
  2. Network of intracellular signaling proteins
     - ***relay*** the signal
     - ***scaffold*** to bring two or more signaling proteins together
     - transform, or ***transduce***, the signal
     - ***amplify*** the signal it receives, :➔ chain reaction : signalling cascase
       - producing large amounts of a small intracellular mediator or
       - activating many copies of a downstream signaling protein.
     - ***Integrate*** *two or more signaling pathway*
     - ***spread*** the signal ➔ branches signalling stream
     - ***anchor*** one or more signaling proteins
     - ***modulate*** the activity of other signaling proteins ➔regulate the strength of signaling along a pathway.

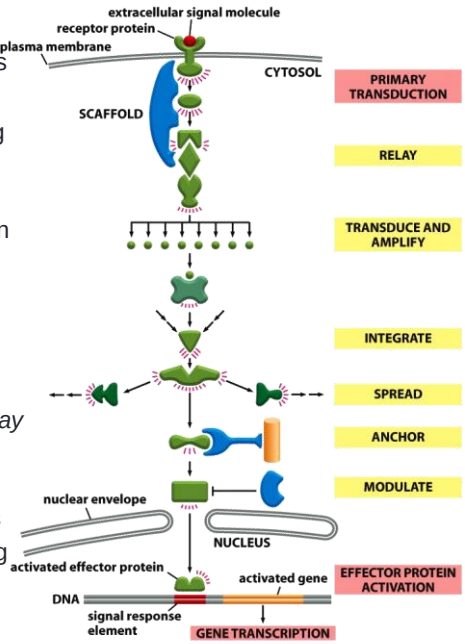


Figure 15-17 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Two important Molecular switches

- **Phosphorylation :**
  - **protein kinase & protein phosphatase**
- **GDP/GTP binding**
  - **GTPase-activating proteins (GAPs) & guanine nucleotide exchange factors (GEFs)**

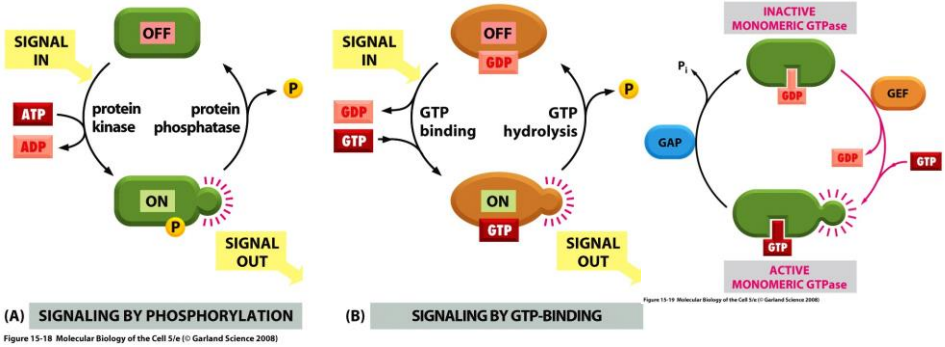
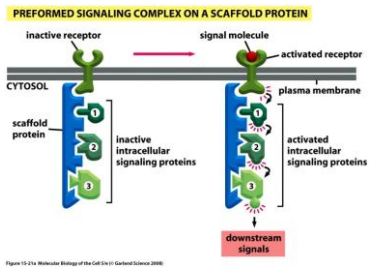
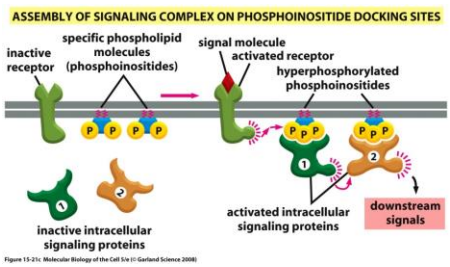


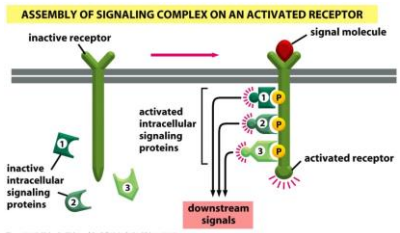
Figure 15-18 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Intracellular Signaling Complexes Enhance the Speed, Efficiency, and Specificity of the Response

- Scaffold protein
- Assembly of signaling complex on an activated receptor
- Assembly of signaling complex on phosphoinositide docking sites

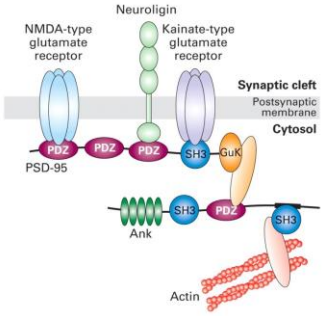


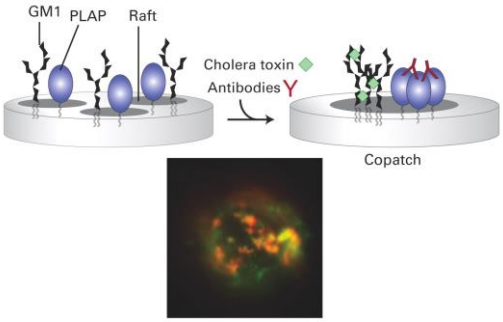


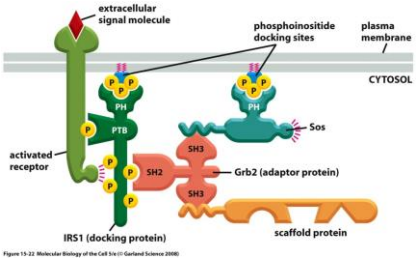


Receptor and signalling protein locallization

1. Clustering protein using adaptor protein domain
   - *Src homology 2 (SH2) or 3 (SH3) domains*
   - *phosphotyrosine-binding (PTB) domains*
   - *Pleckstrin homology (PH)* domains
2. Clustering protein using lipid raft

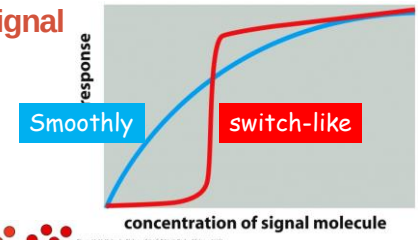




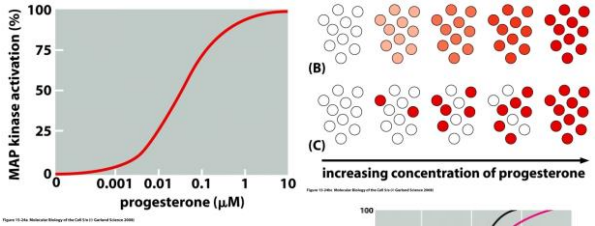


Multiple Mechanisms to Respond to a Gradually Increasing Concentration of an Extracellular Signal

- Smoothly graded vs switch-like signaling responses



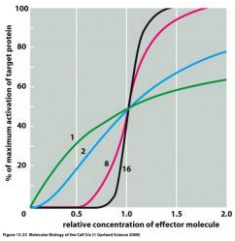
  - discontinuous or all-or-none



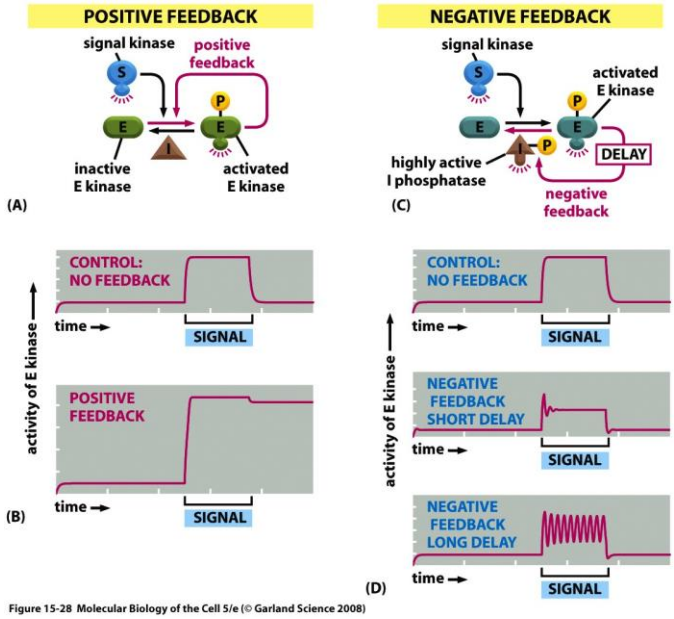
increased gradually in each individual cells

all-or-none way

  - Cooperative response



Feedback loops of intracellular signaling network



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Desensitization of a signal

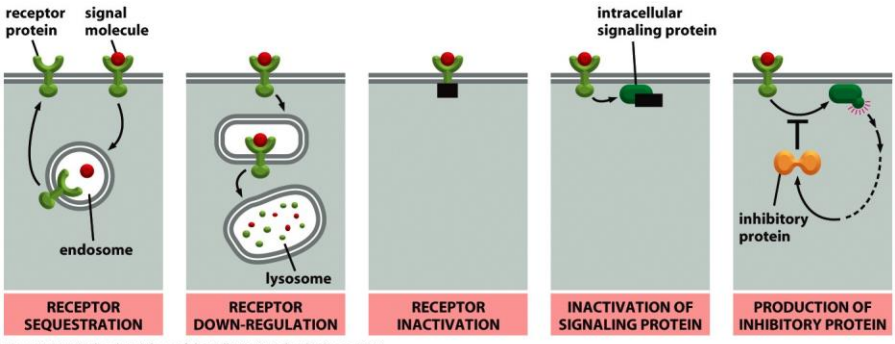

Figure 15-29 Molecular Biology of the Cell 5/e (© Garland Science 2008)