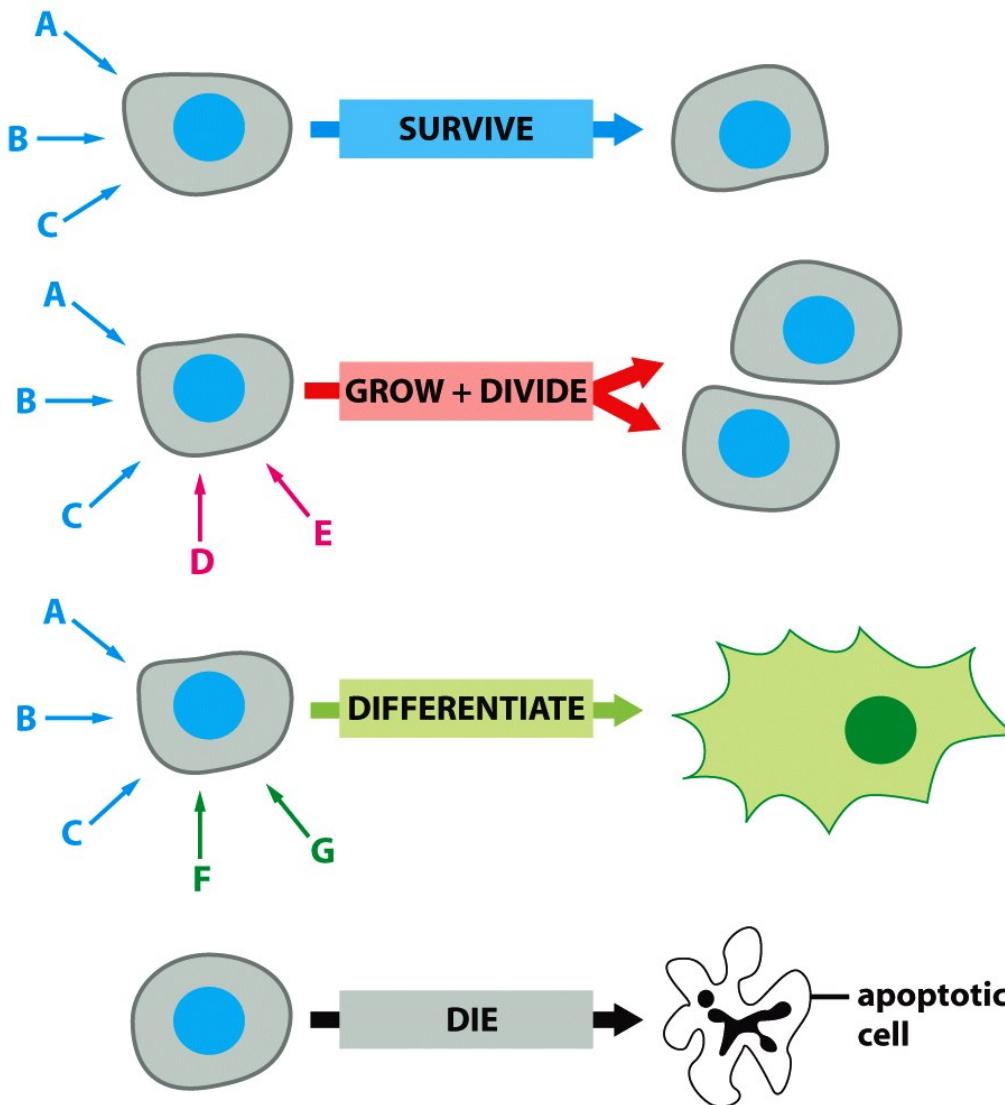
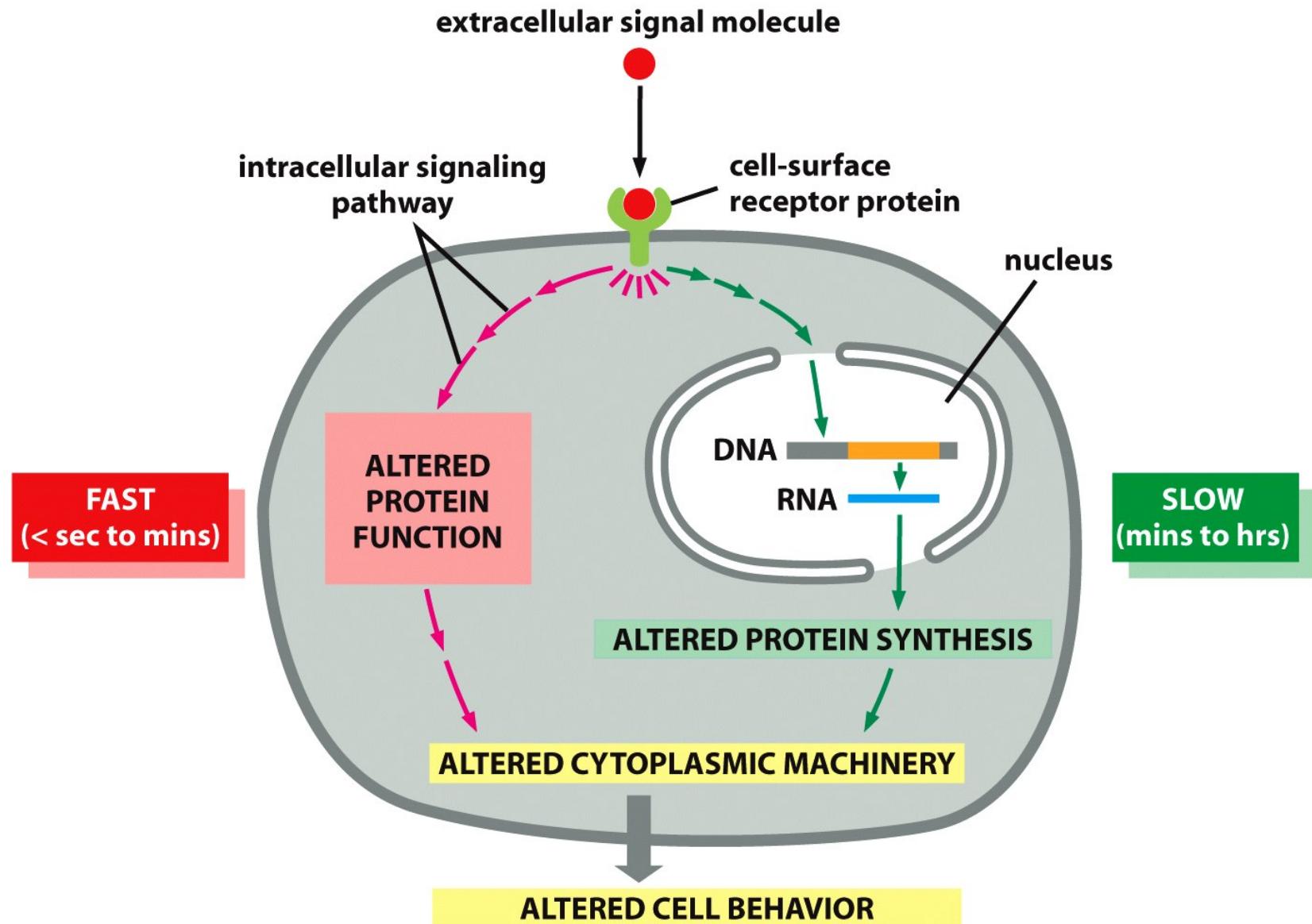


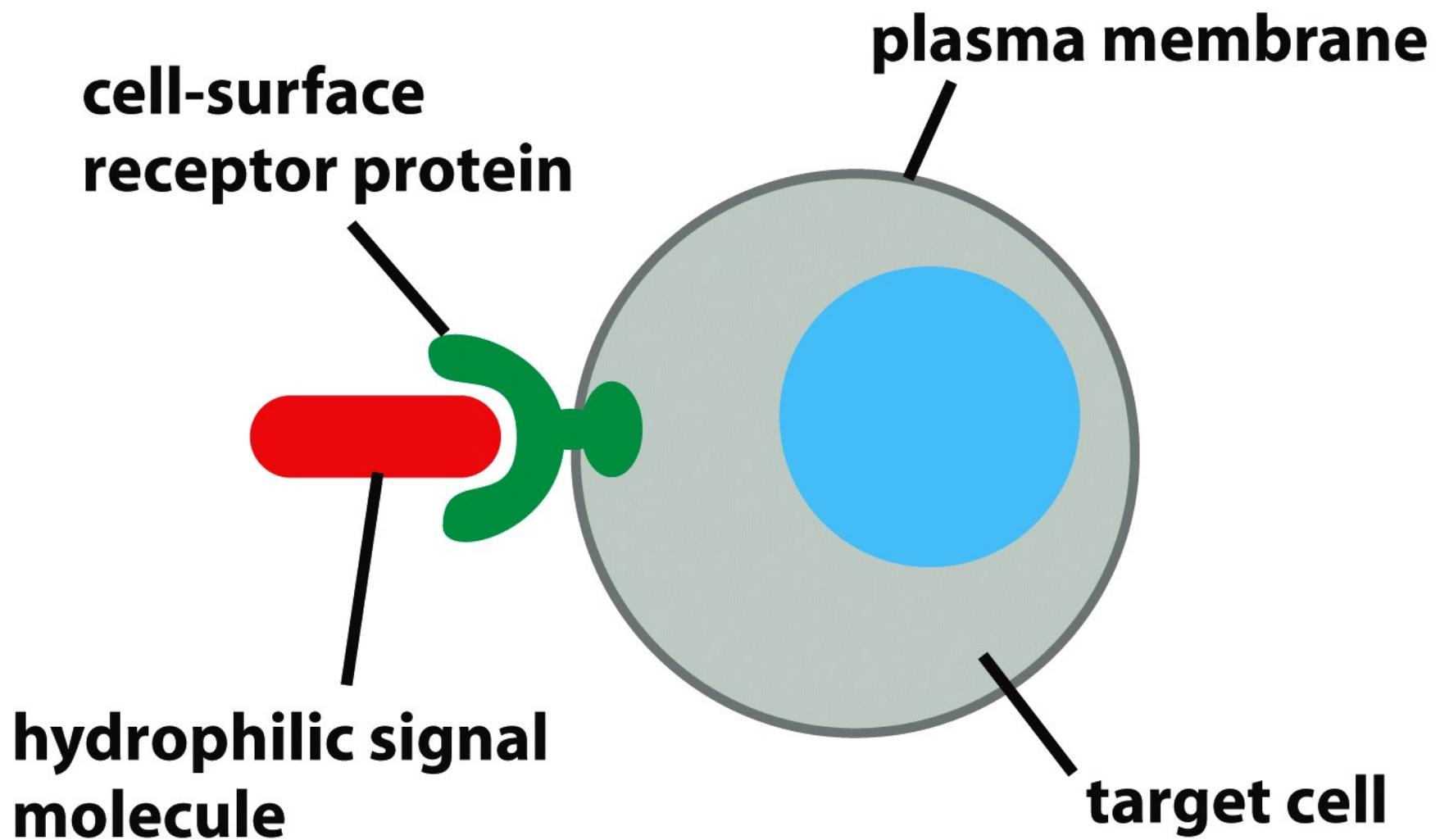
Basic Cell Responses to Stimuli

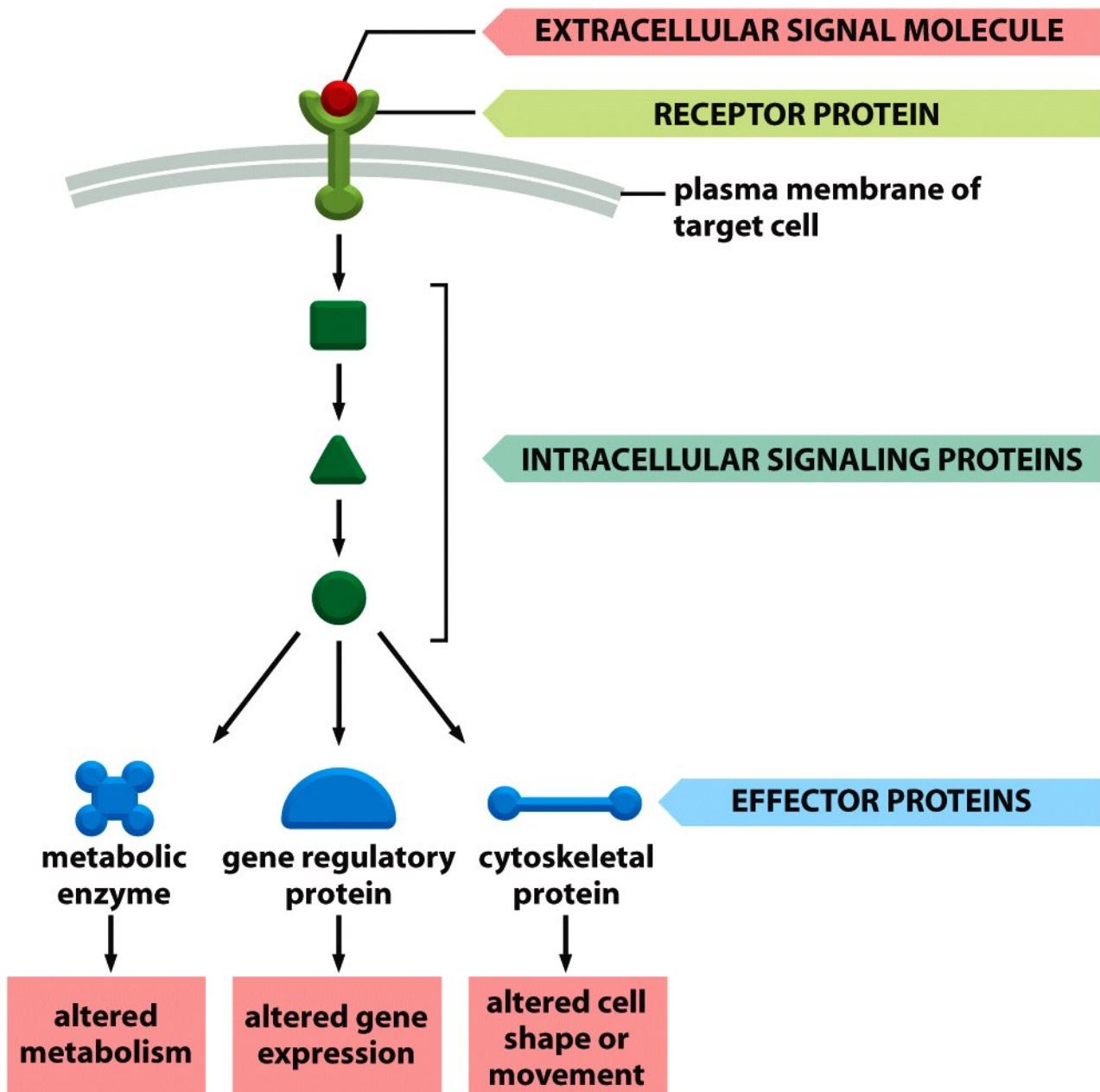


Fast and Slow Response Systems in Cell Signaling

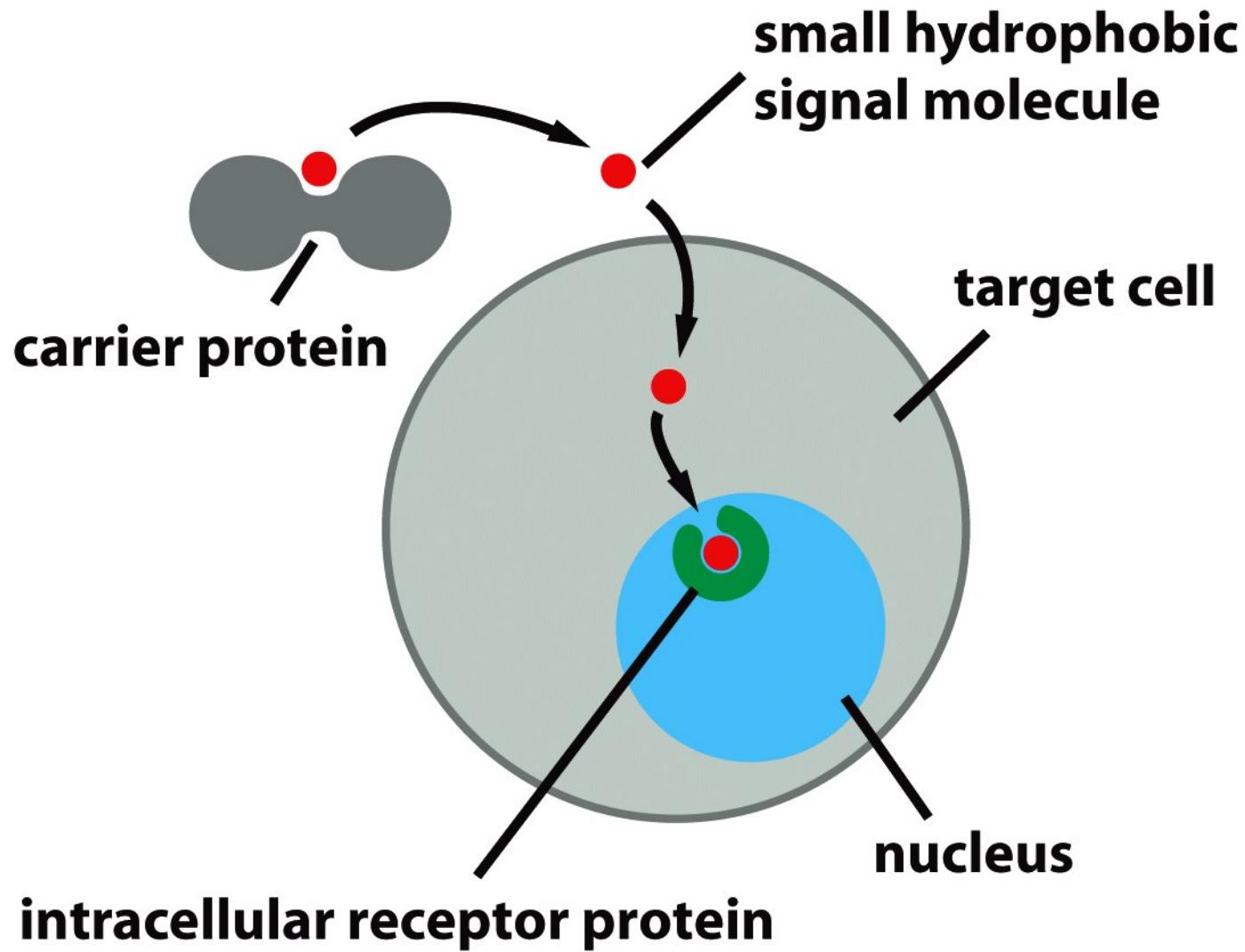


CELL-SURFACE RECEPTORS





INTRACELLULAR RECEPTORS



Mechanisms / Types of Cell Signaling

Contact-Dependent

Paracrine

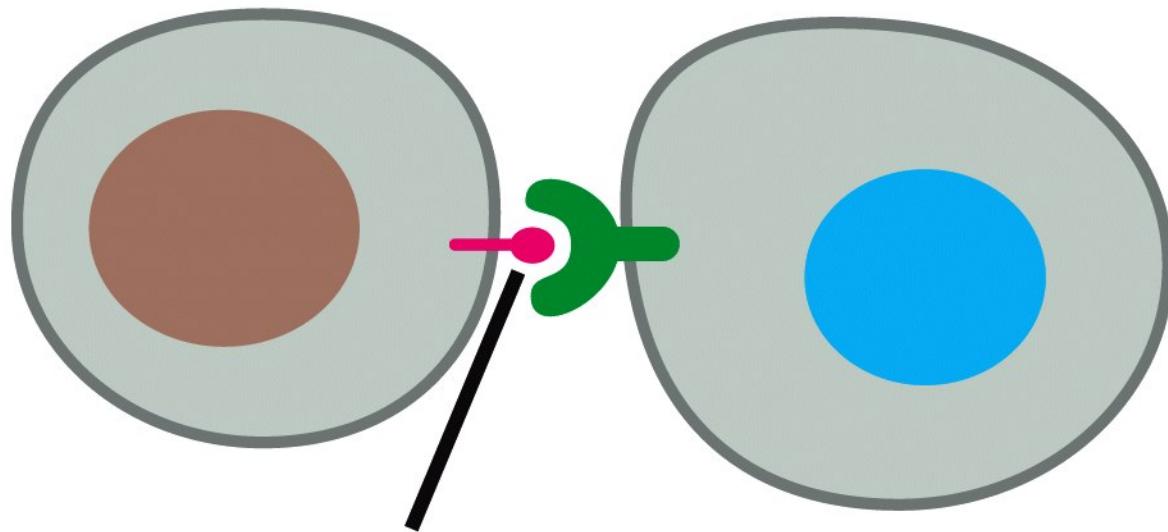
Endocrine

Autocrine

Synaptic

CONTACT-DEPENDENT

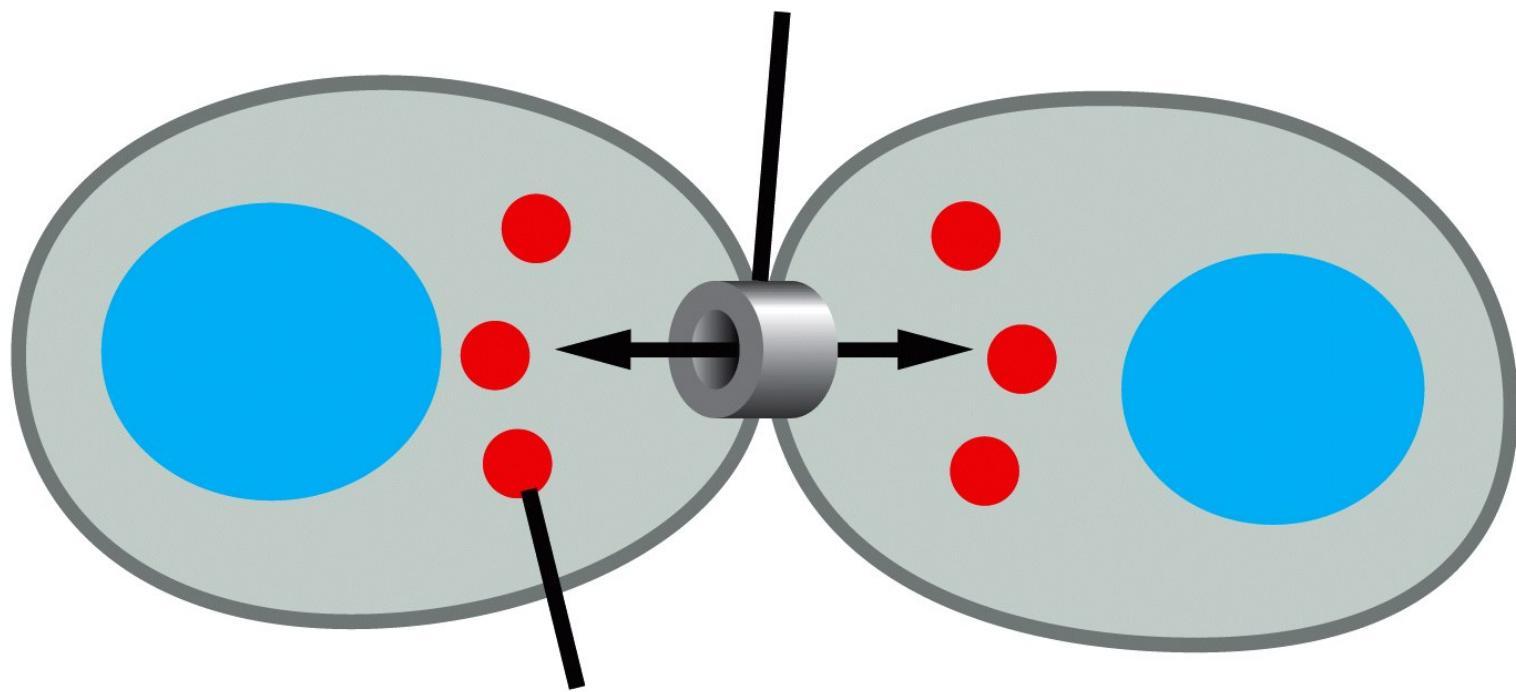
signaling cell target cell



**membrane-
bound signal
molecule**

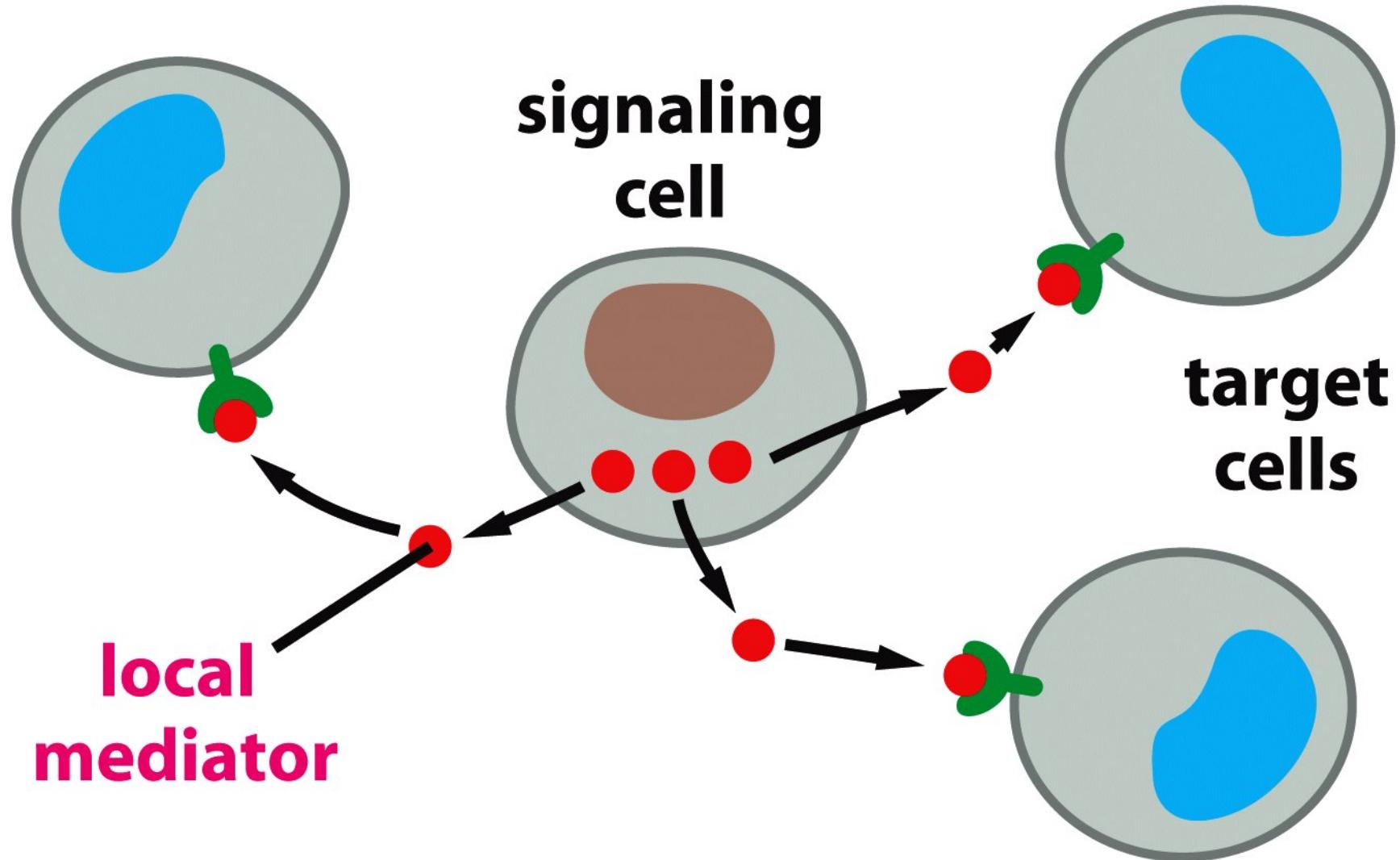
Also Contact-Dependent

gap junction

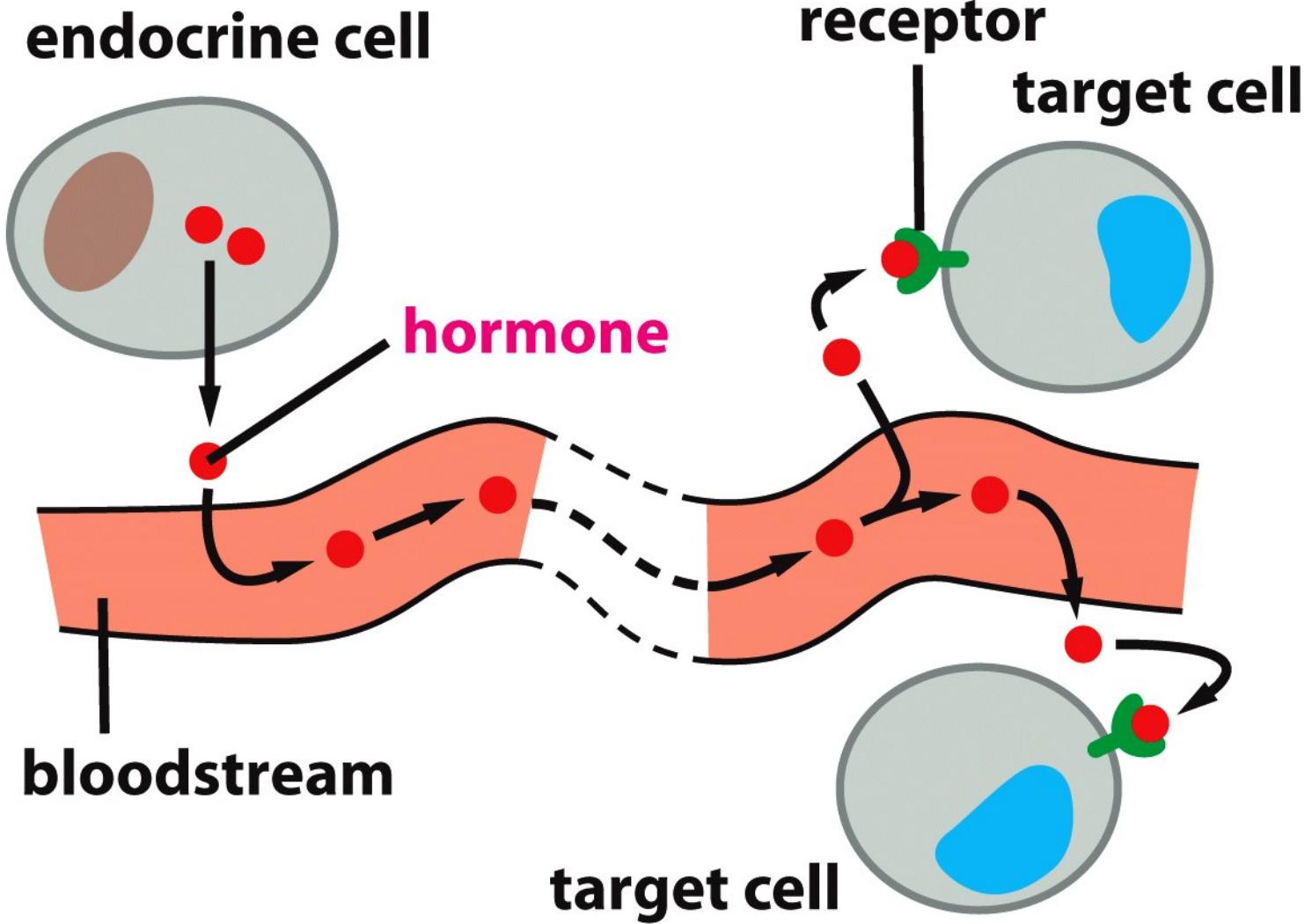


small molecule

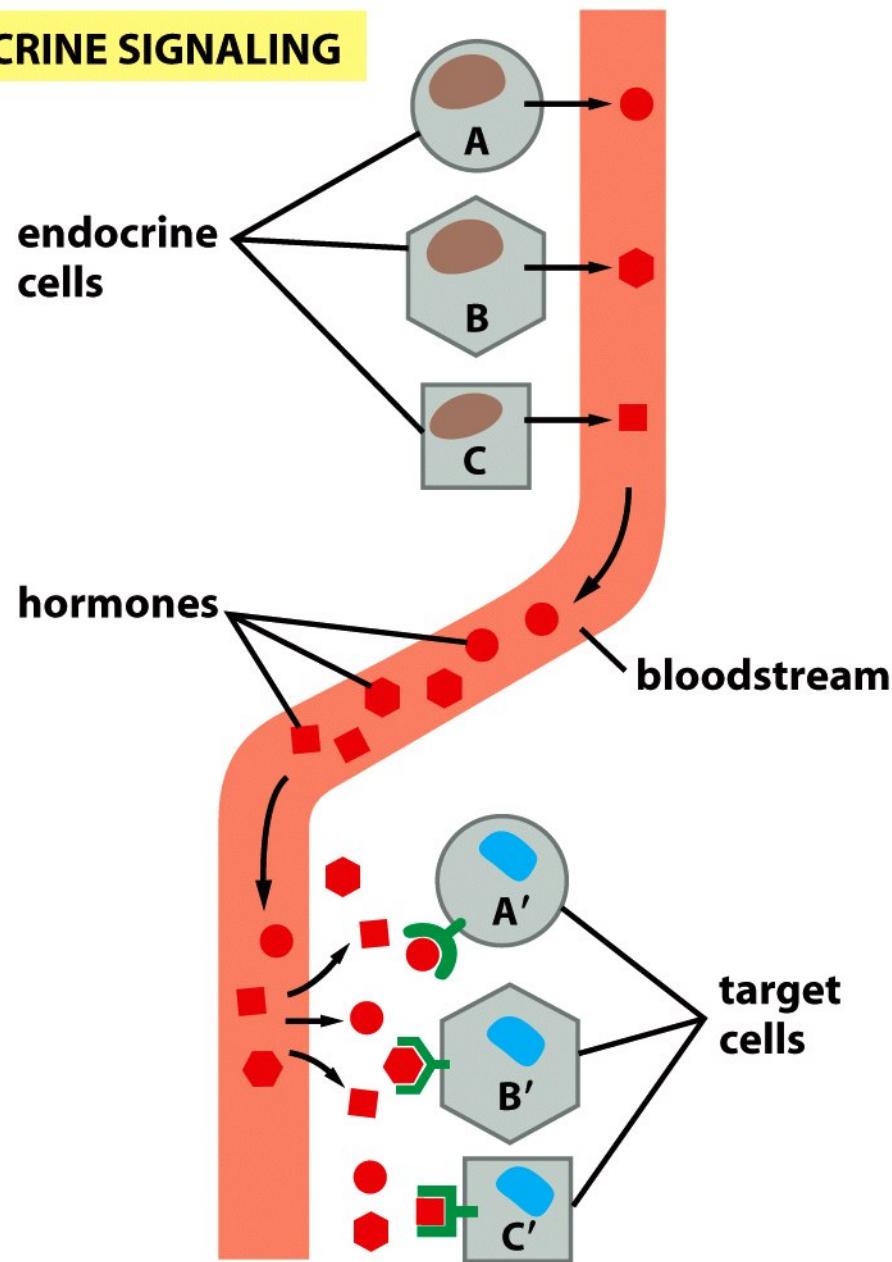
PARACRINE



ENDOCRINE

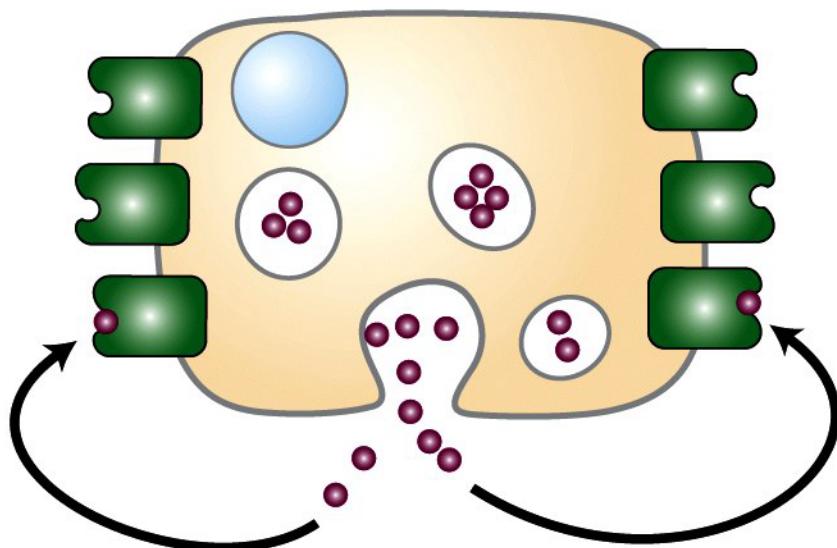


ENDOCRINE SIGNALING



AUTOCRINE

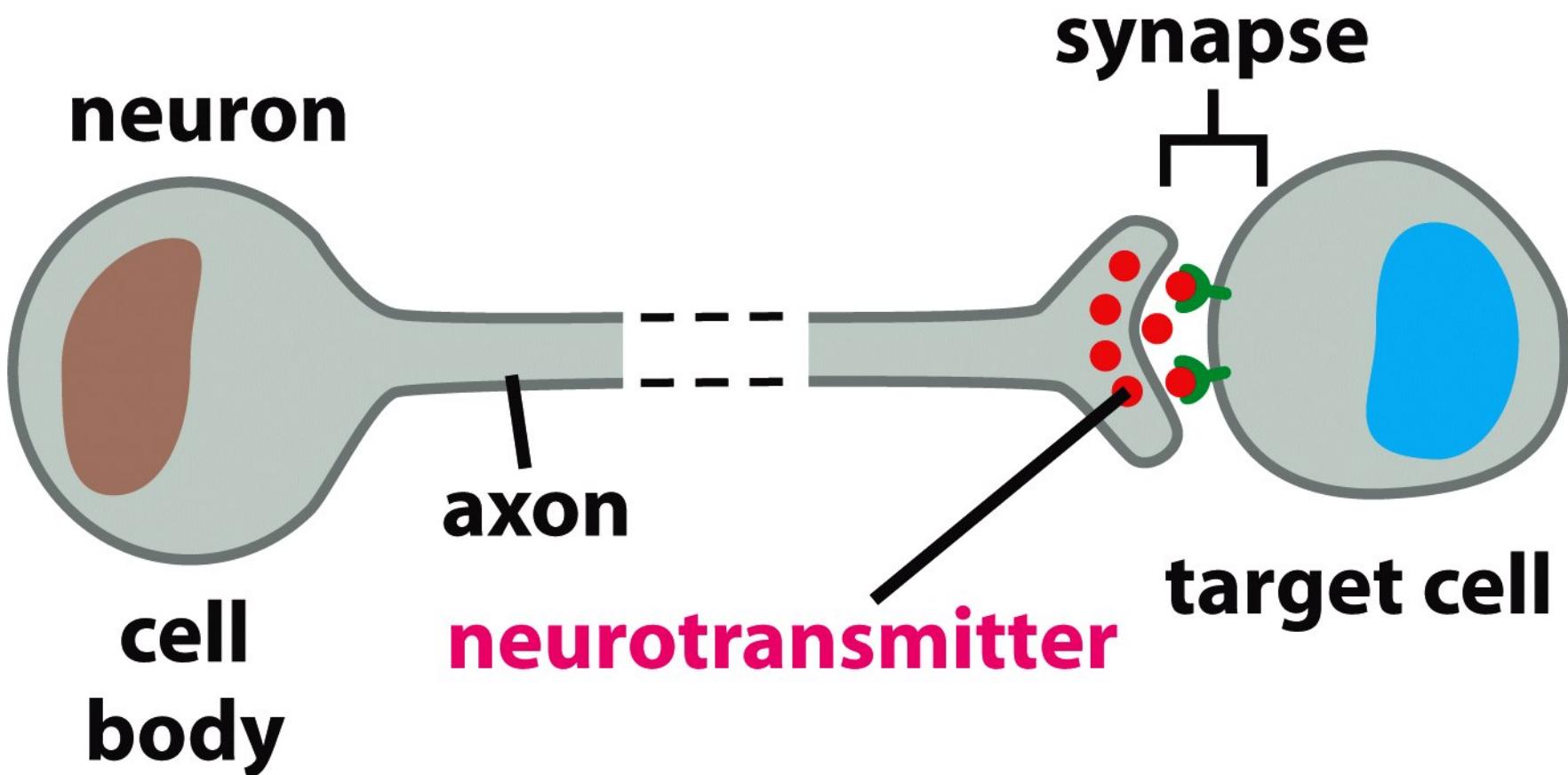
Autocrine signaling



- Extracellular signal
- Receptor

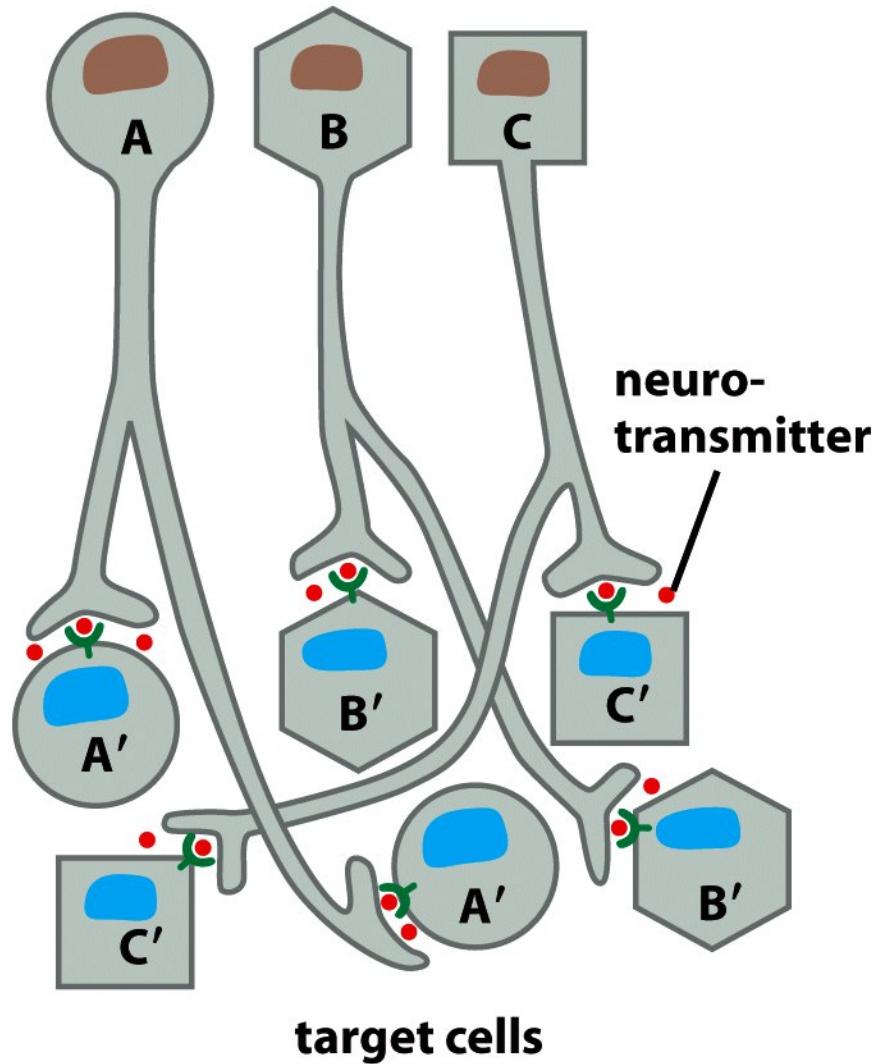
Target sites on same cell

SYNAPTIC



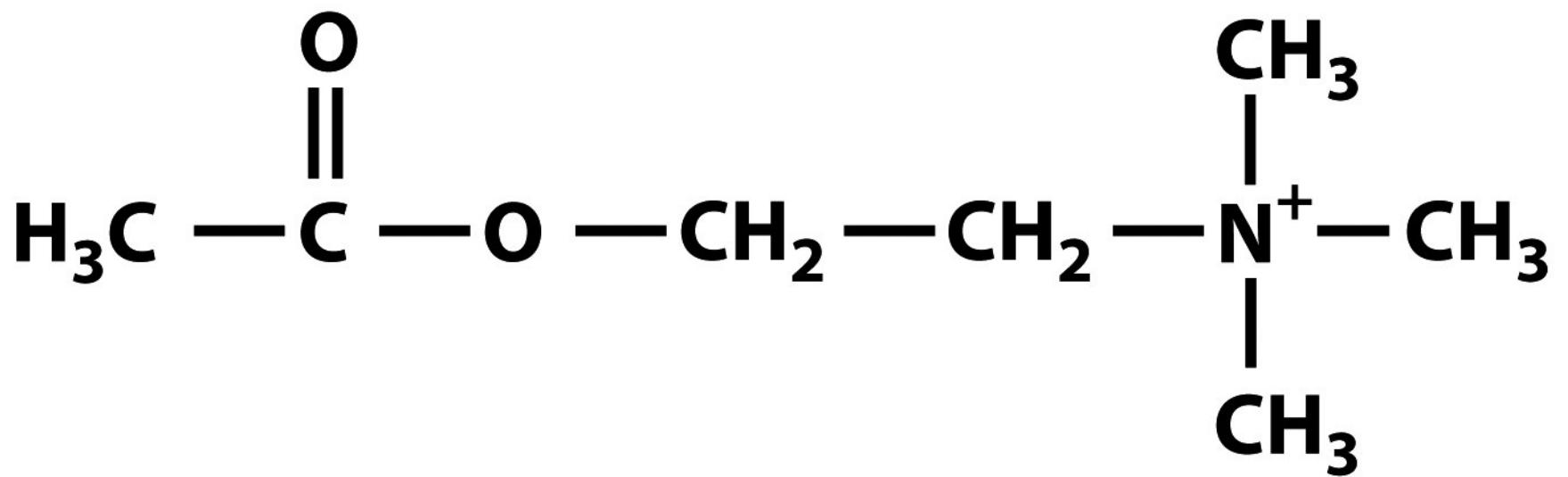
SYNAPTIC SIGNALING

neurons

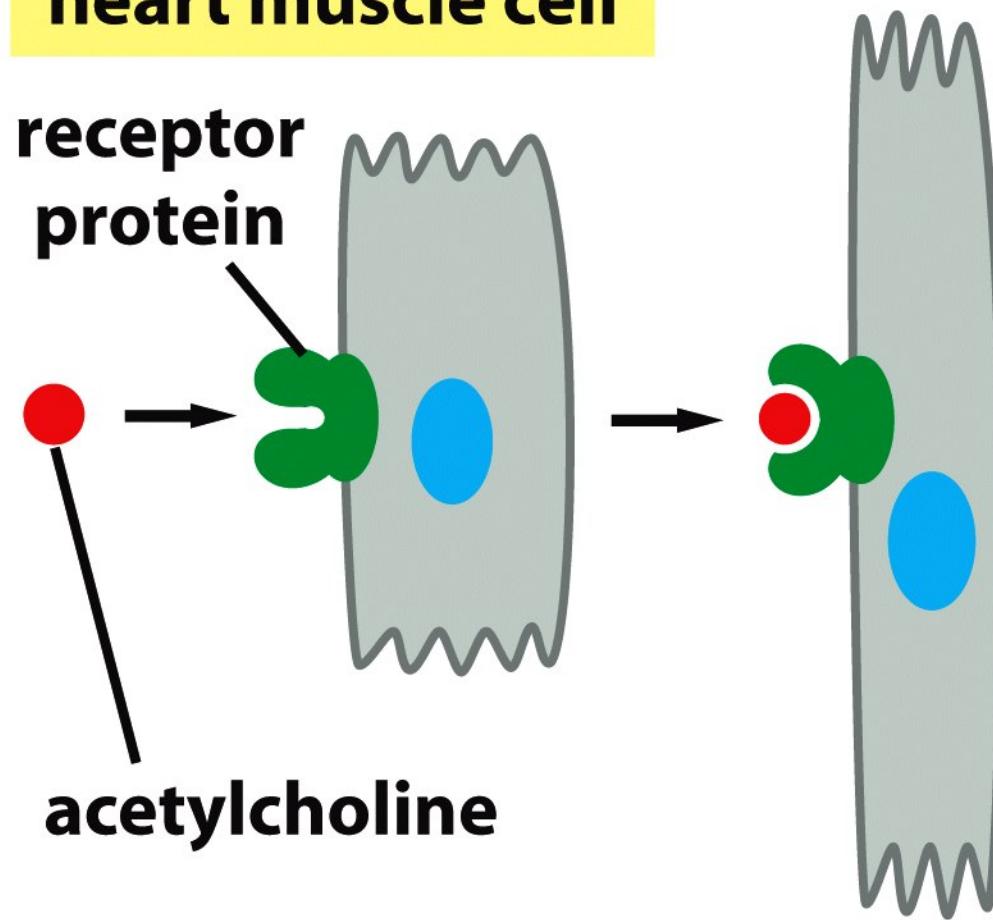


A single small molecule can exert different effects among different cells: example of acetylcholine

acetylcholine



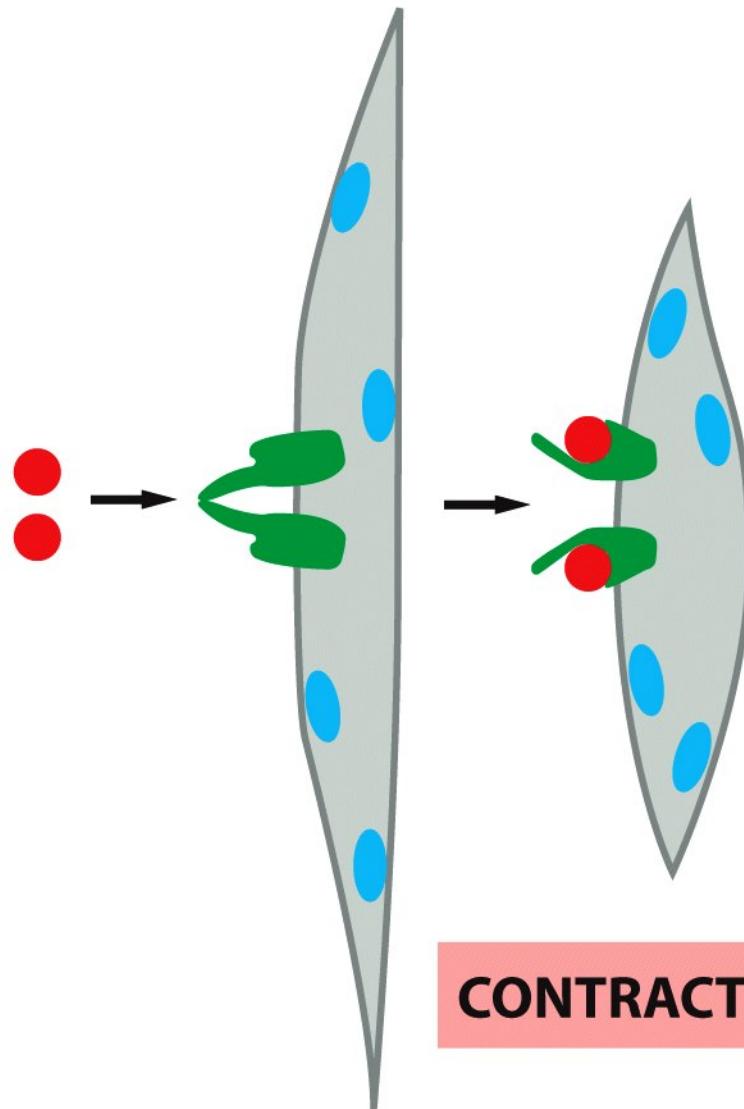
heart muscle cell



**DECREASED RATE AND
FORCE OF CONTRACTION**

skeletal muscle cell

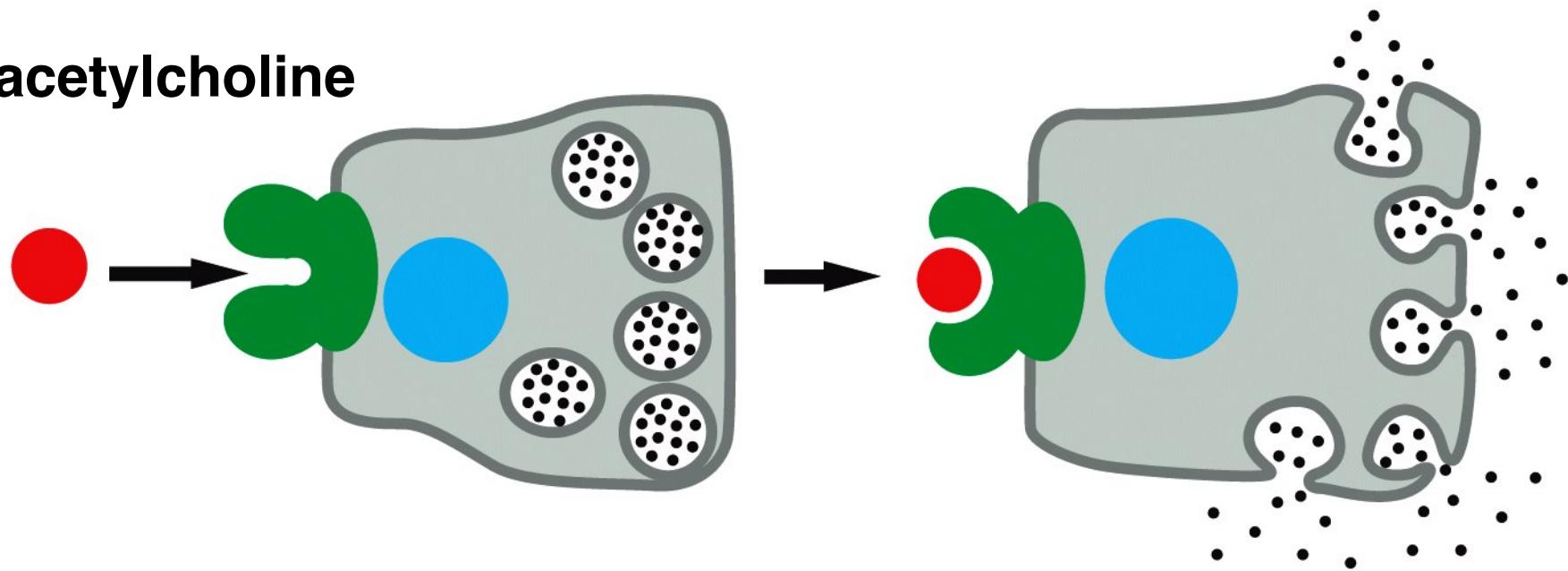
acetylcholine



CONTRACTION

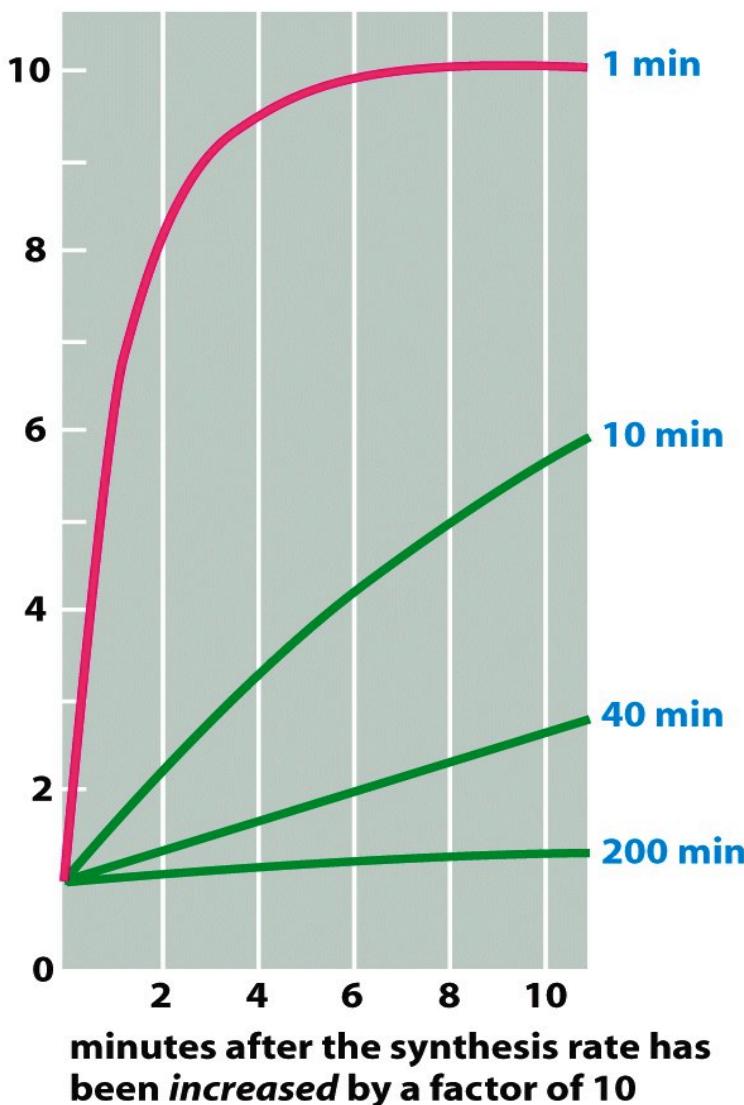
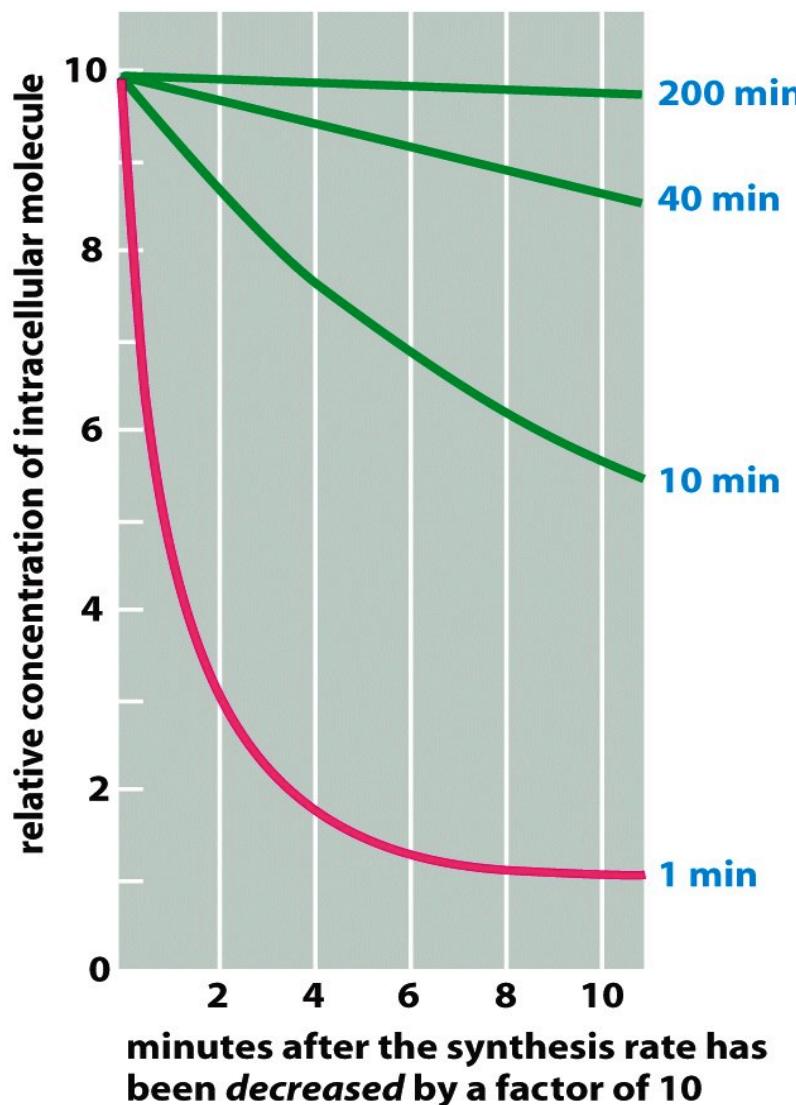
salivary gland cell

acetylcholine

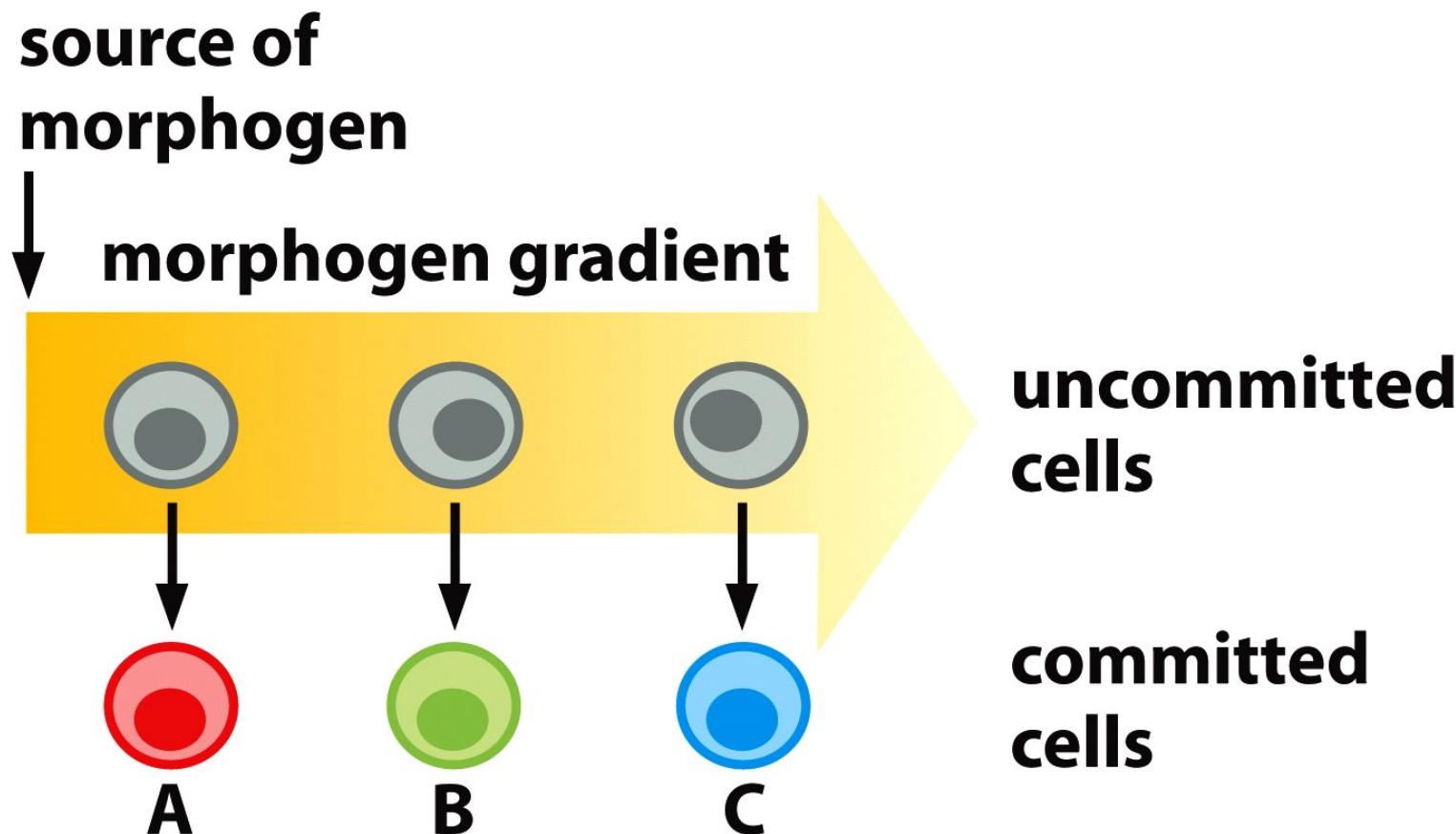


SECRETION

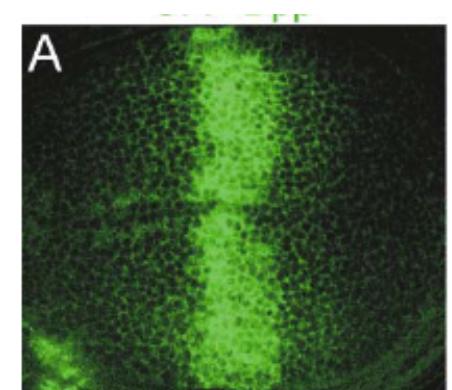
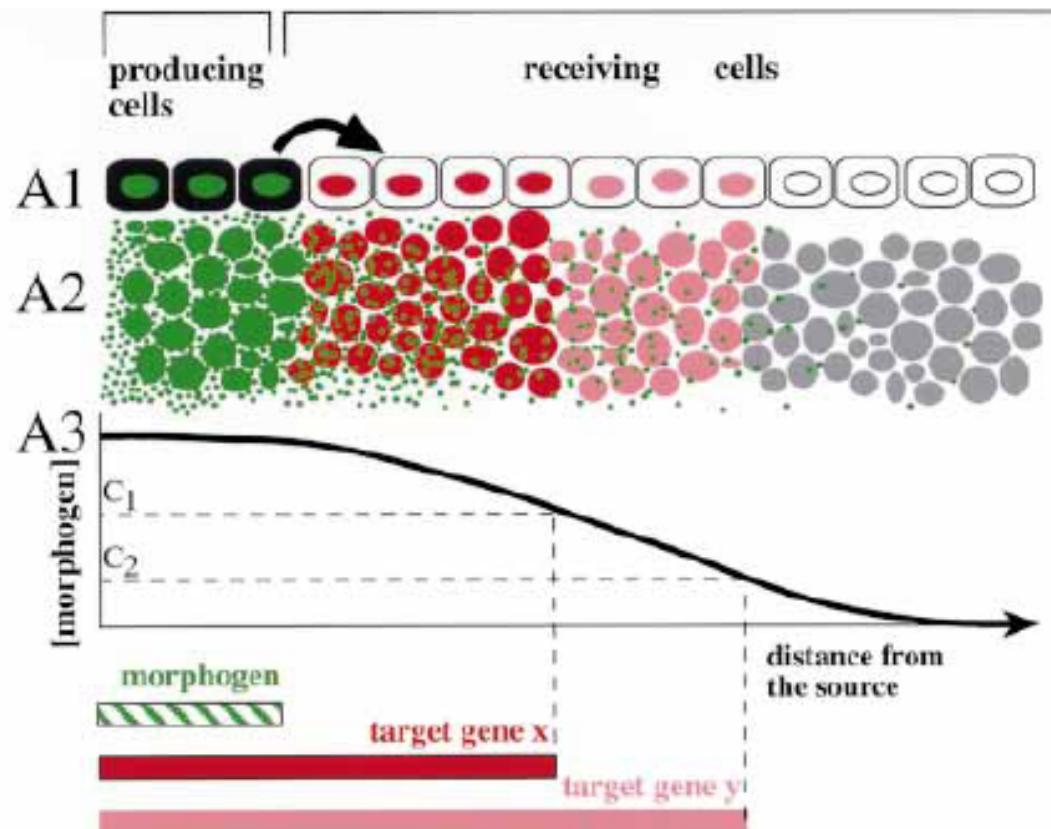
Controlling Molecules (and Hence Signaling) by Turnover: the importance of molecular half-lives (shown in blue)



Different Concentrations of Signaling molecules can Differentially Alter Cell Responses: Example of molecular gradients

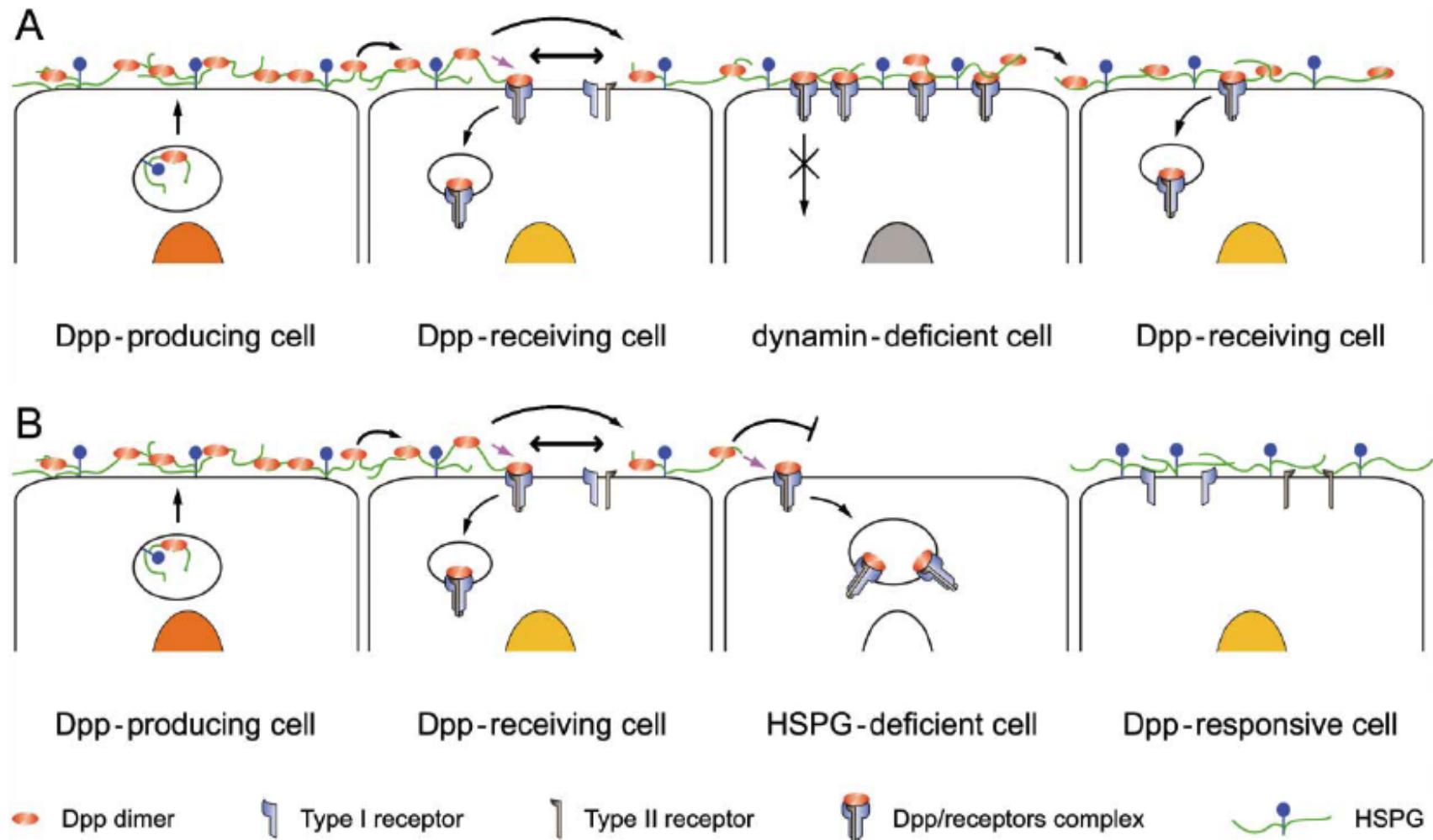


Morphogen gradients in receptor signaling and cell fate

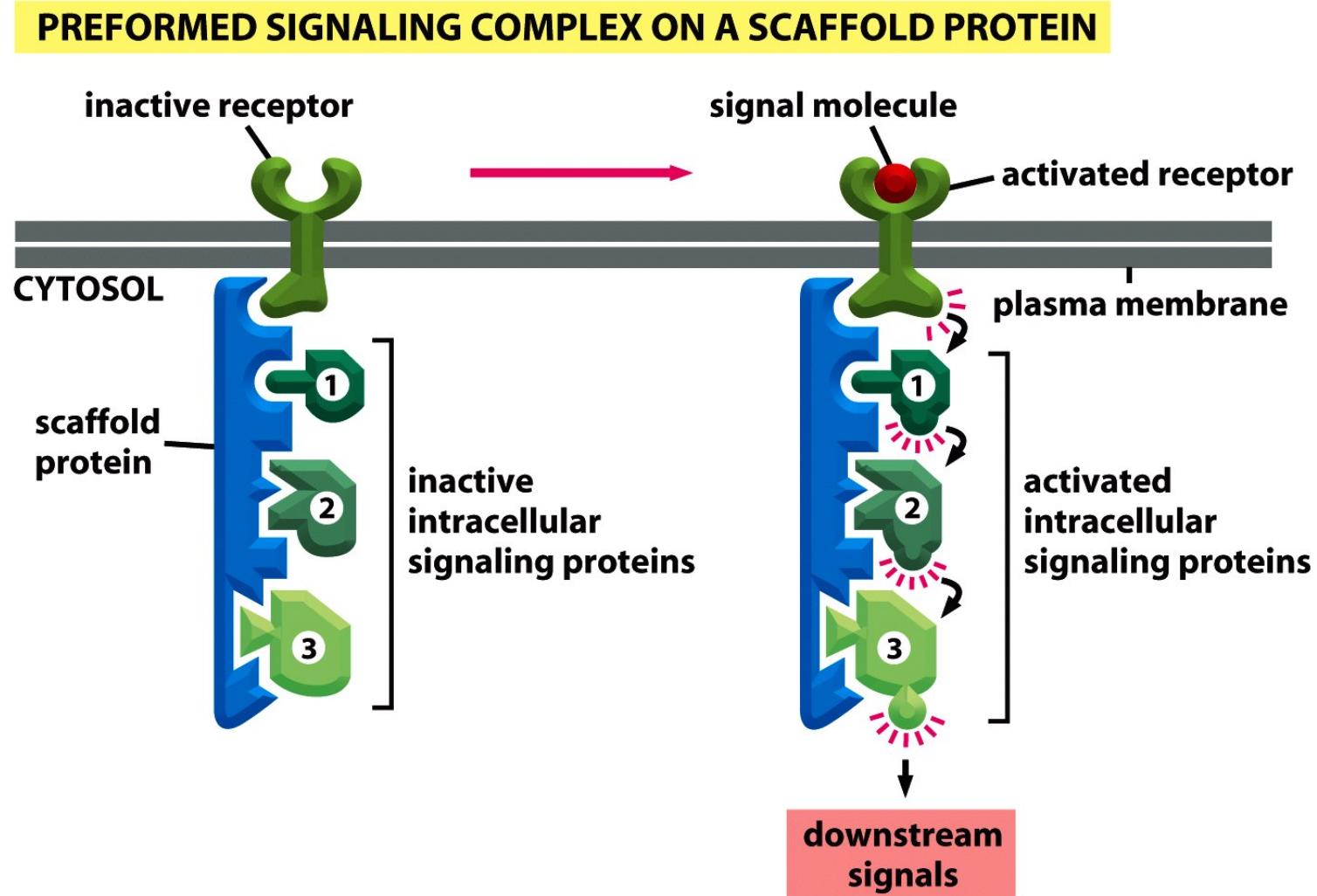


Dpp gradient

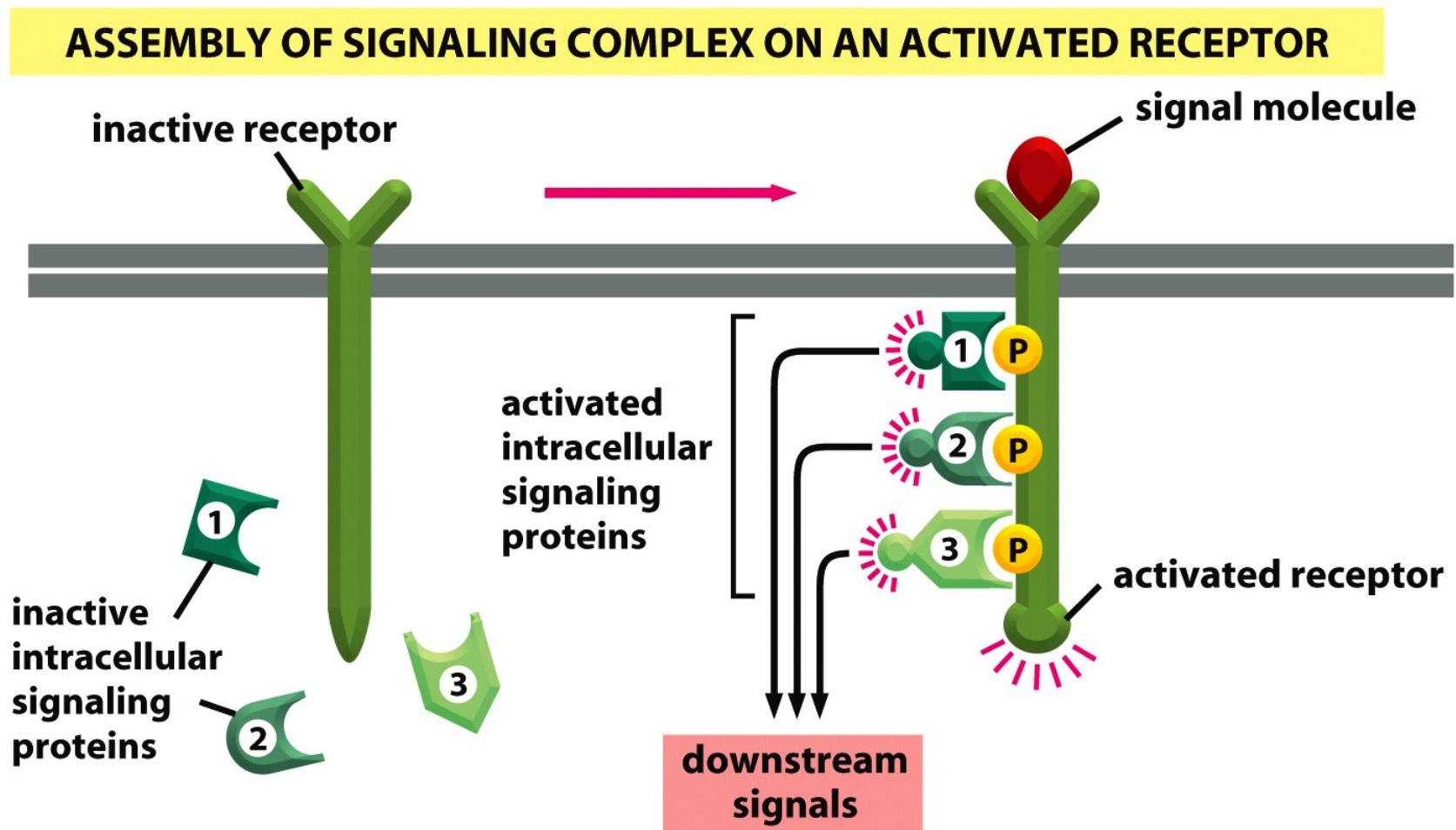
Glycosaminoglycans in Dpp morphogen movement



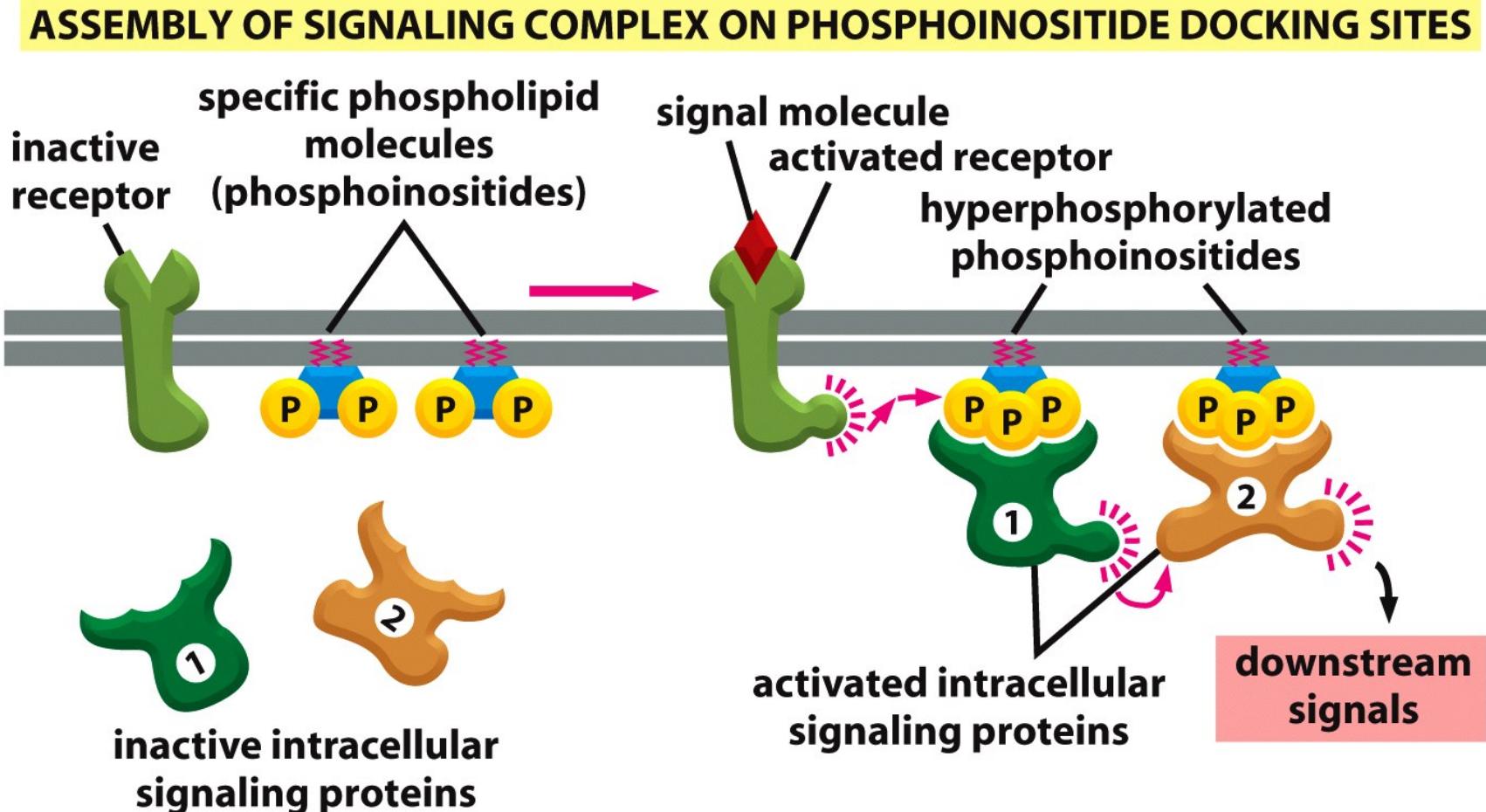
Signaling Complex Assembly: Pre-Activation



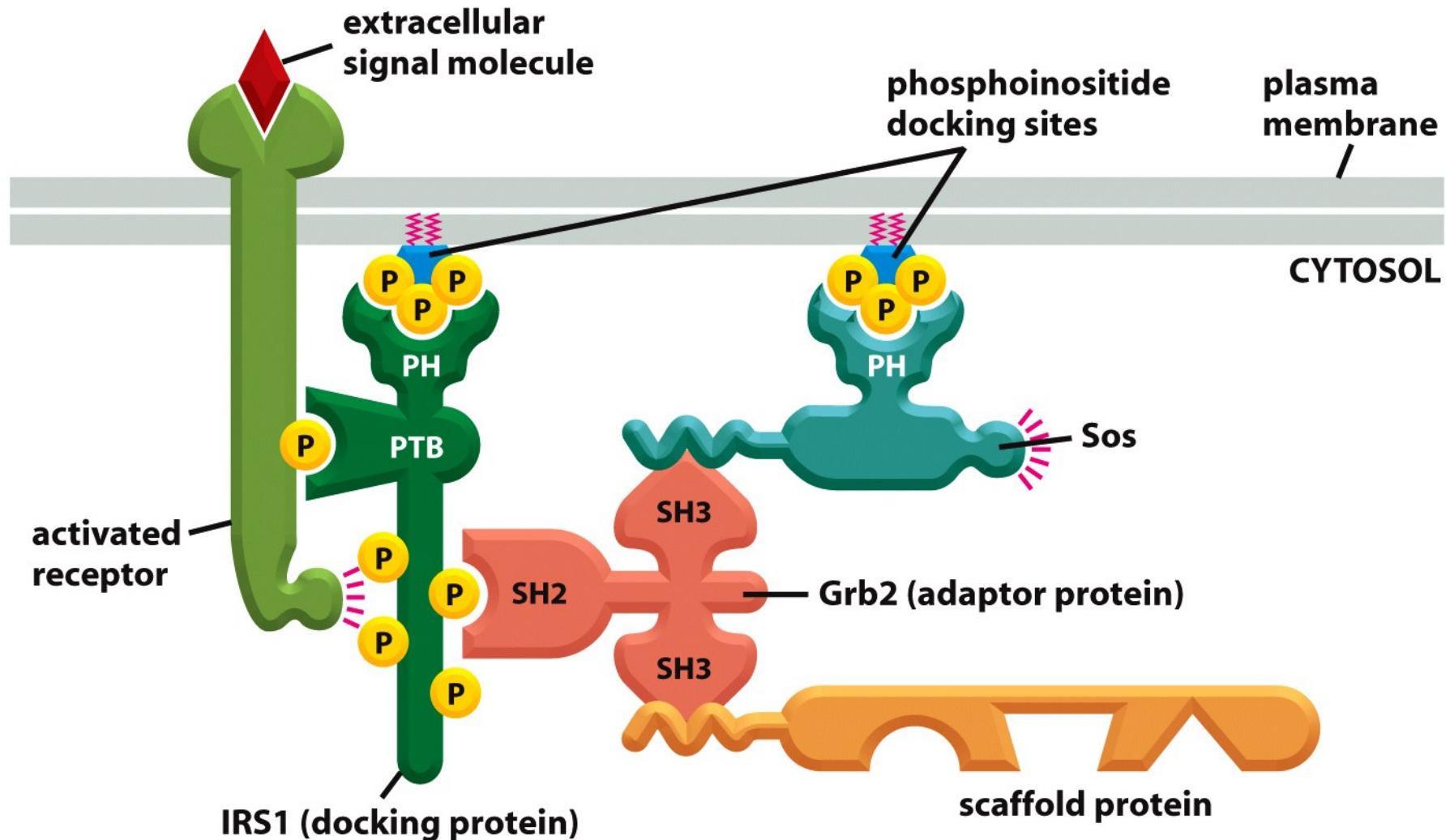
Signaling Complex Assembly: Post-Activation



Signaling Complex Assembly: Post-Activation



Signaling Complex Assembly: Modular Interactions



Signaling by Proteolysis

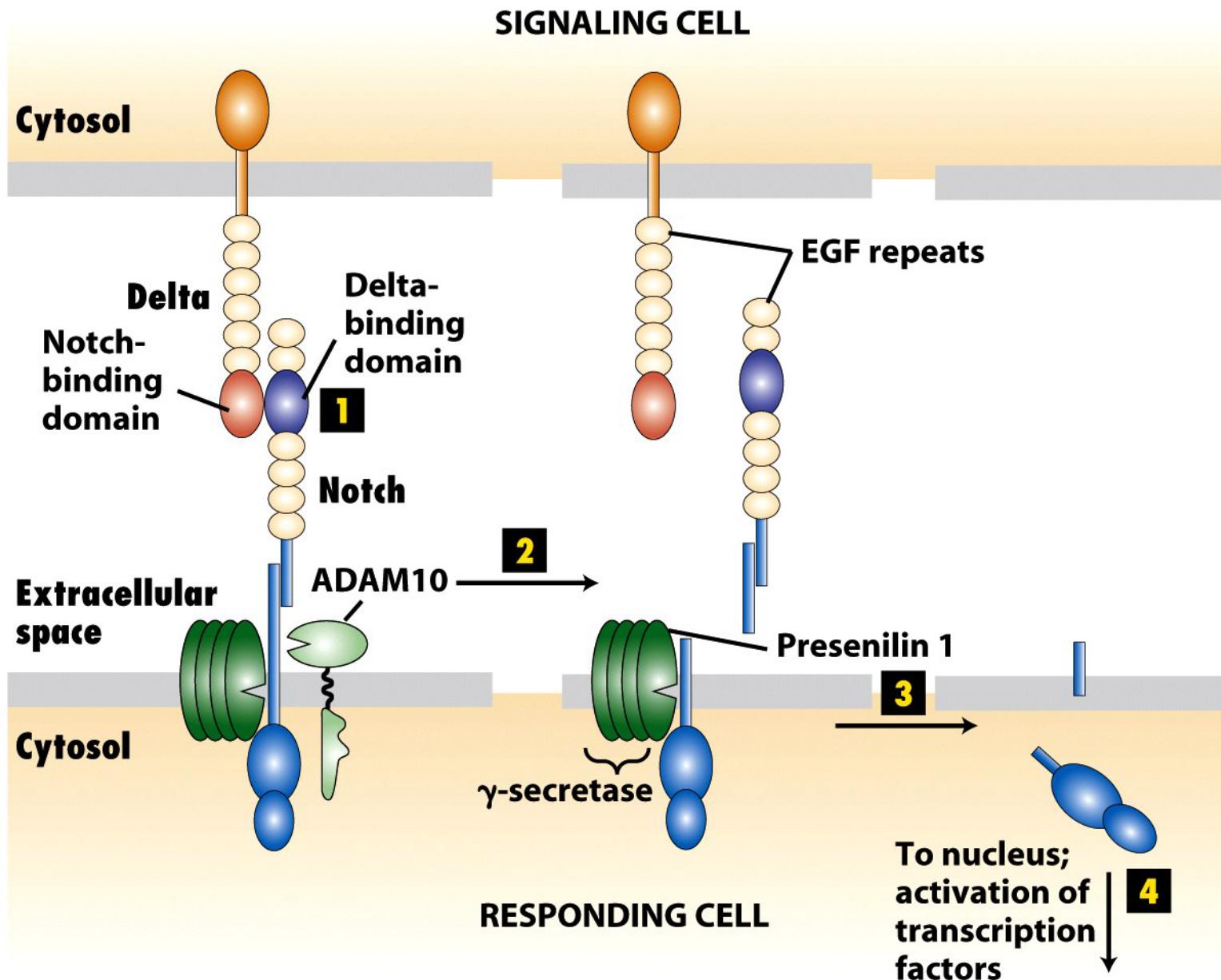
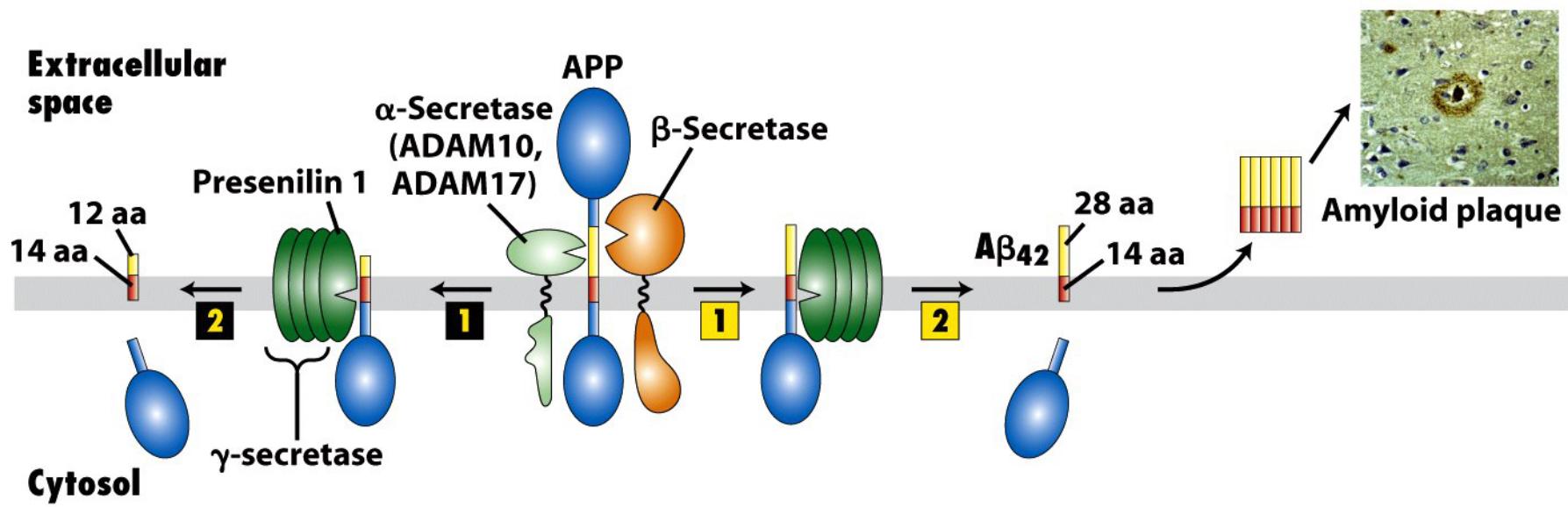


Figure 16-36
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Pathogenesis by Proteolysis - in Alzheimer's Disease



Protein Modifications in Mechanisms of Cellular Signaling: There are Many Different Types of Protein Modifications

Protein Modifications (most studied to least studied)

Phosphorylation (184,220 PubMed entries)

Glycosylation (38,426)

Acetylation (20,076)

Ubiquitination/Ubiquitin (5,605)

(Sumoylation 1326, Neddylation 129, ISGylation 56)

Sulfation (3,885)

Palmitoylation (1393) Myristoylation (1084)

Methylation: arginine (1055), lysine (2985)

S-Nitrosylation (786)

Protein Modifications (mammalian genomic investment)

Phosphorylation (kinases) ~1.5%, 510 active in humans

Glycosylation (glycosyltransferases) ~1% 250+

Ubiquitination (few E1, tens of E2, hundreds of E3) ~2%

Sulfation (sulfotransferases) ~0.2%

Acetylation (acetyltransferases) ~0.1%

Lipidation ~0.1%

Methylation ~0.1%

S-Nitrosylation ~0.1%?

No need to memorize these

There are Many Different Types of Protein Modifications

Protein Hydroxylation
(Scurvy - insufficient hydroxylation of collagen)

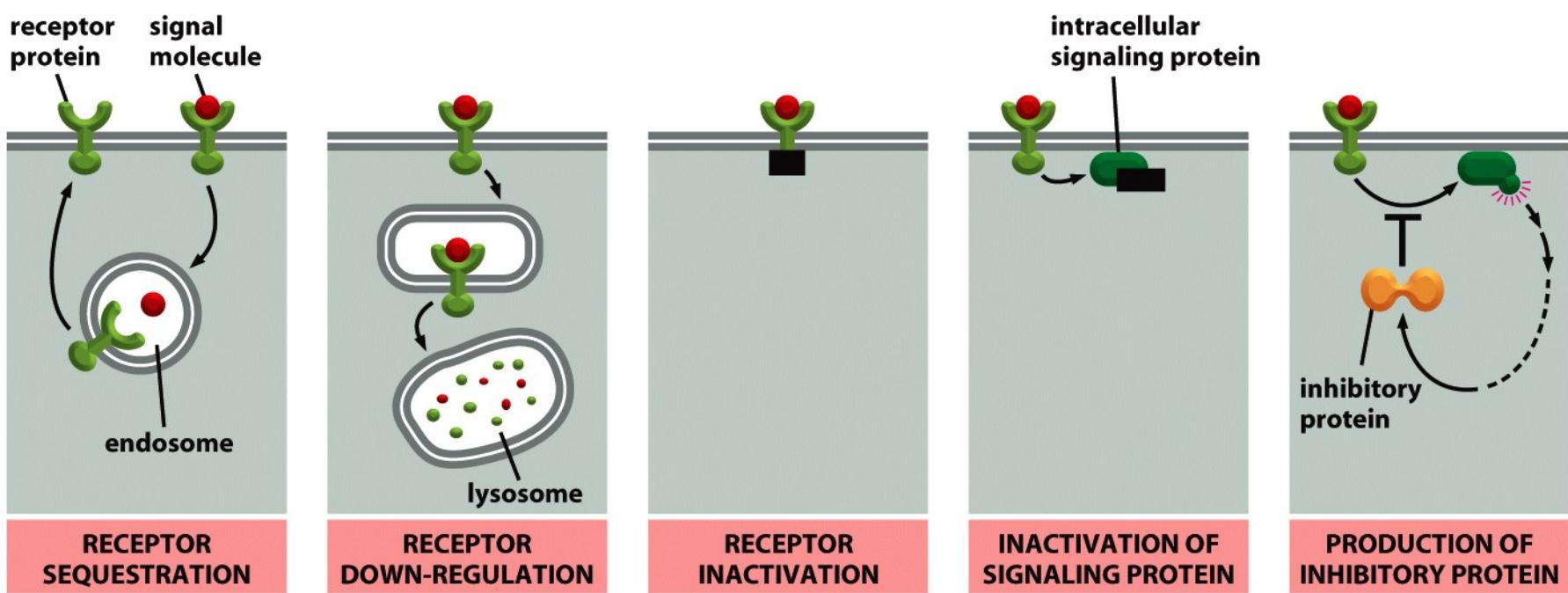
Protein Carboxylation
(Vit. K deficiency - insufficient carboxylation of prothrombin)

and many more....

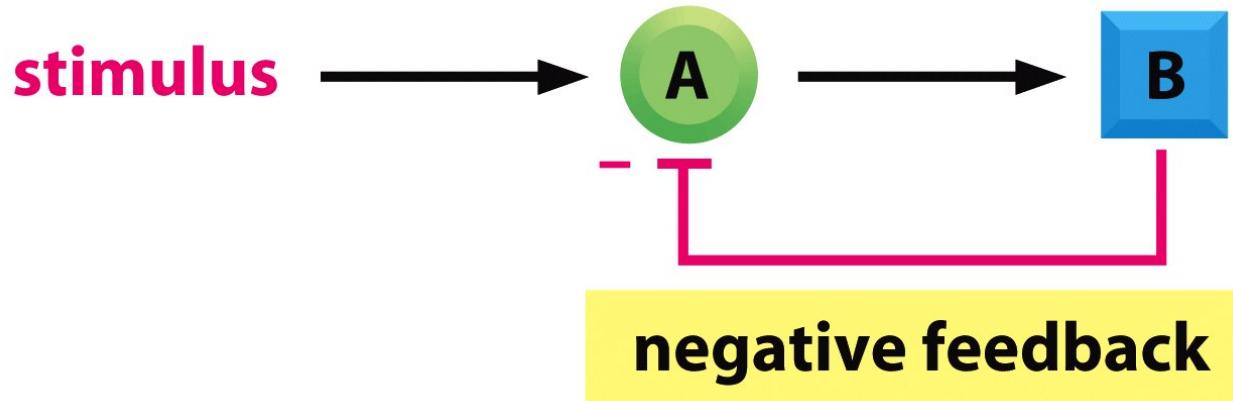
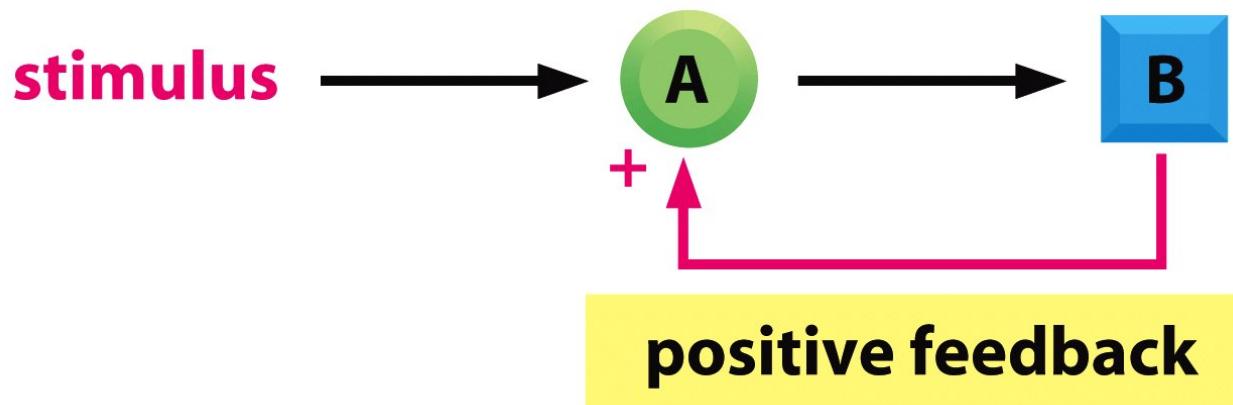
protein amino acid ADP-ribosylation
protein amino acid alkylation
protein amino acid amidation
protein amino acid biotinylation
protein amino acid carbamoylation
protein amino acid carboxyethylation
protein amino acid dehydration
protein amino acid esterification
protein amino acid flavinylation
protein amino acid glucuronidation
protein amino acid halogenation

No need to
memorize these

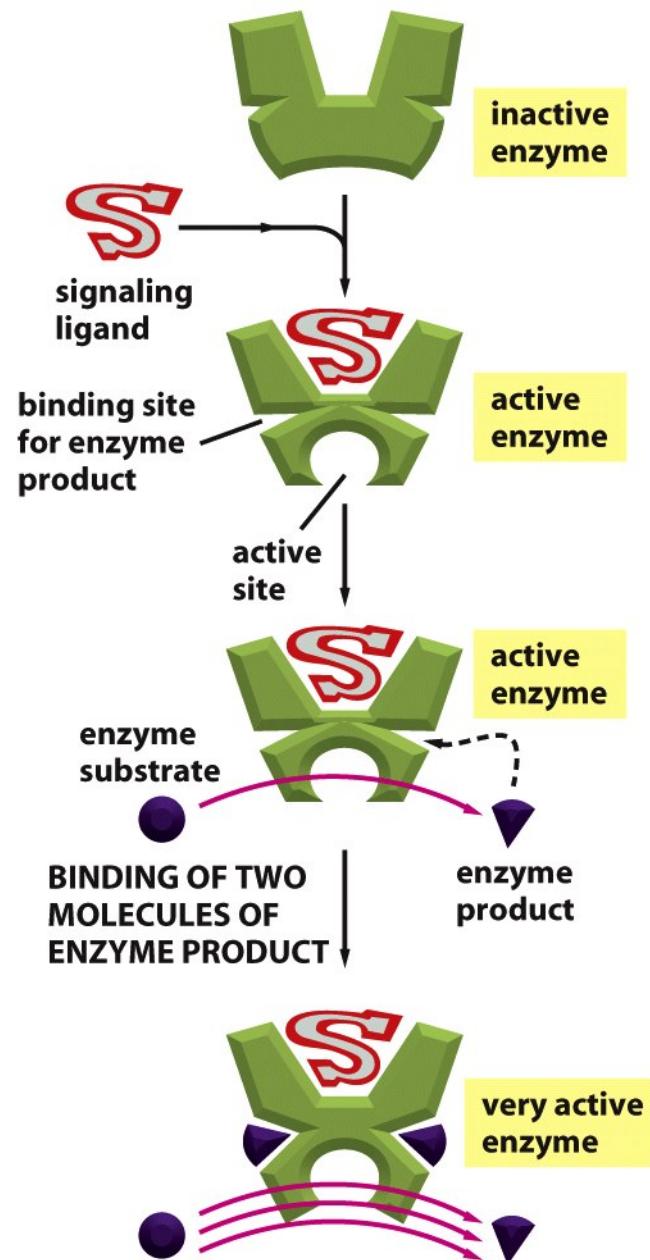
Mechanisms that Stop Signaling



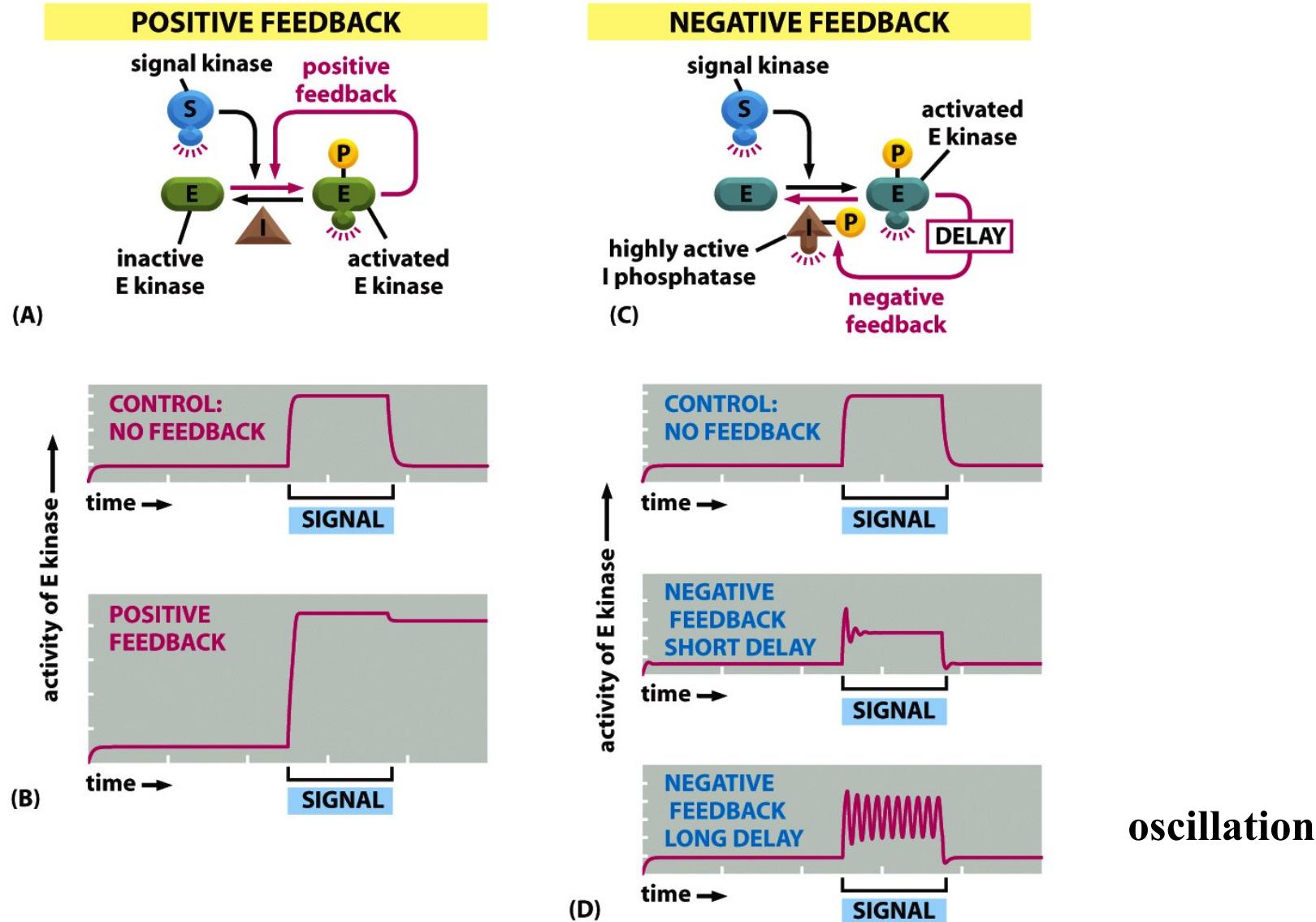
Positive and Negative Feedback in Signaling



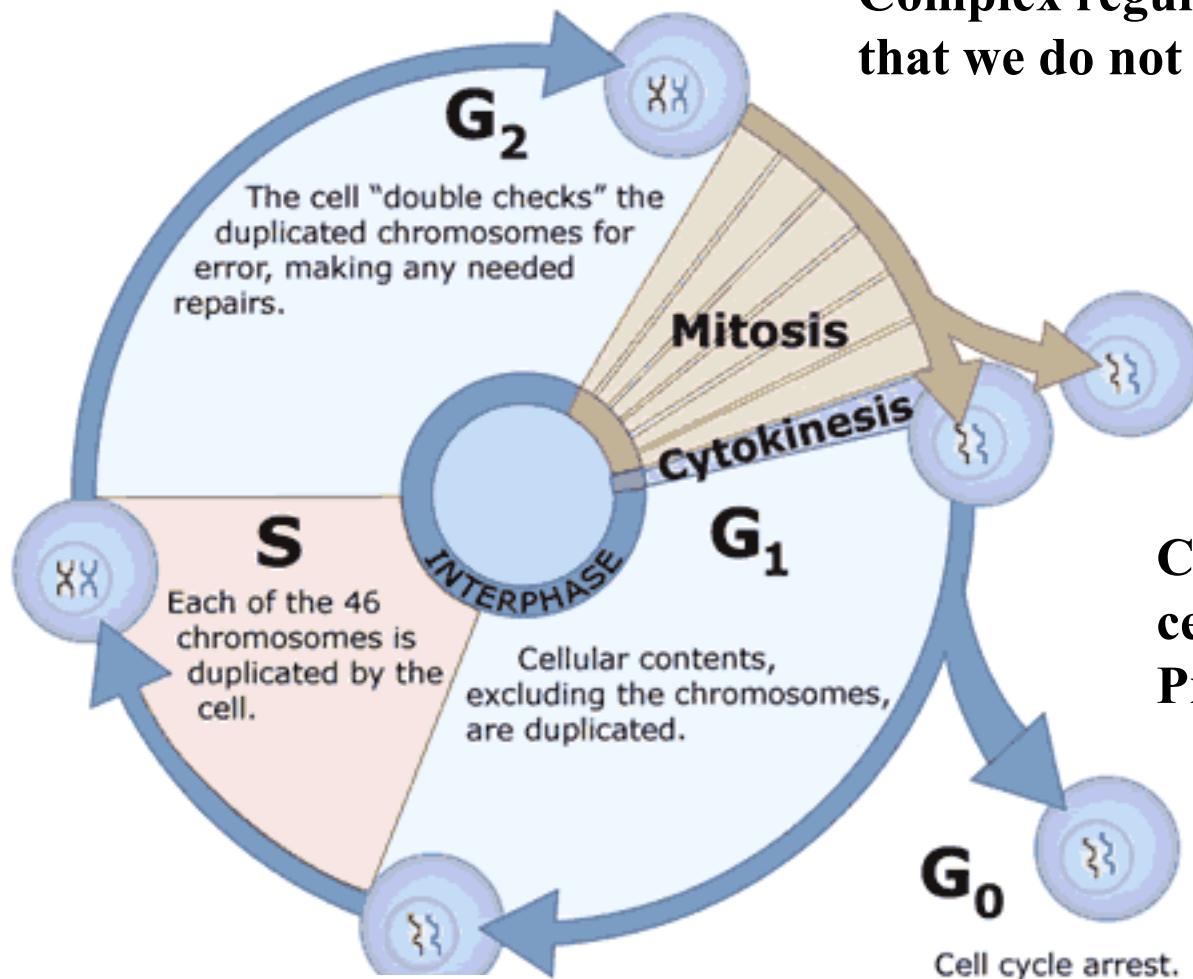
Positive Feedback in Switch-Like Behavior In Signaling



Effects of Feedback



The Cell Cycle

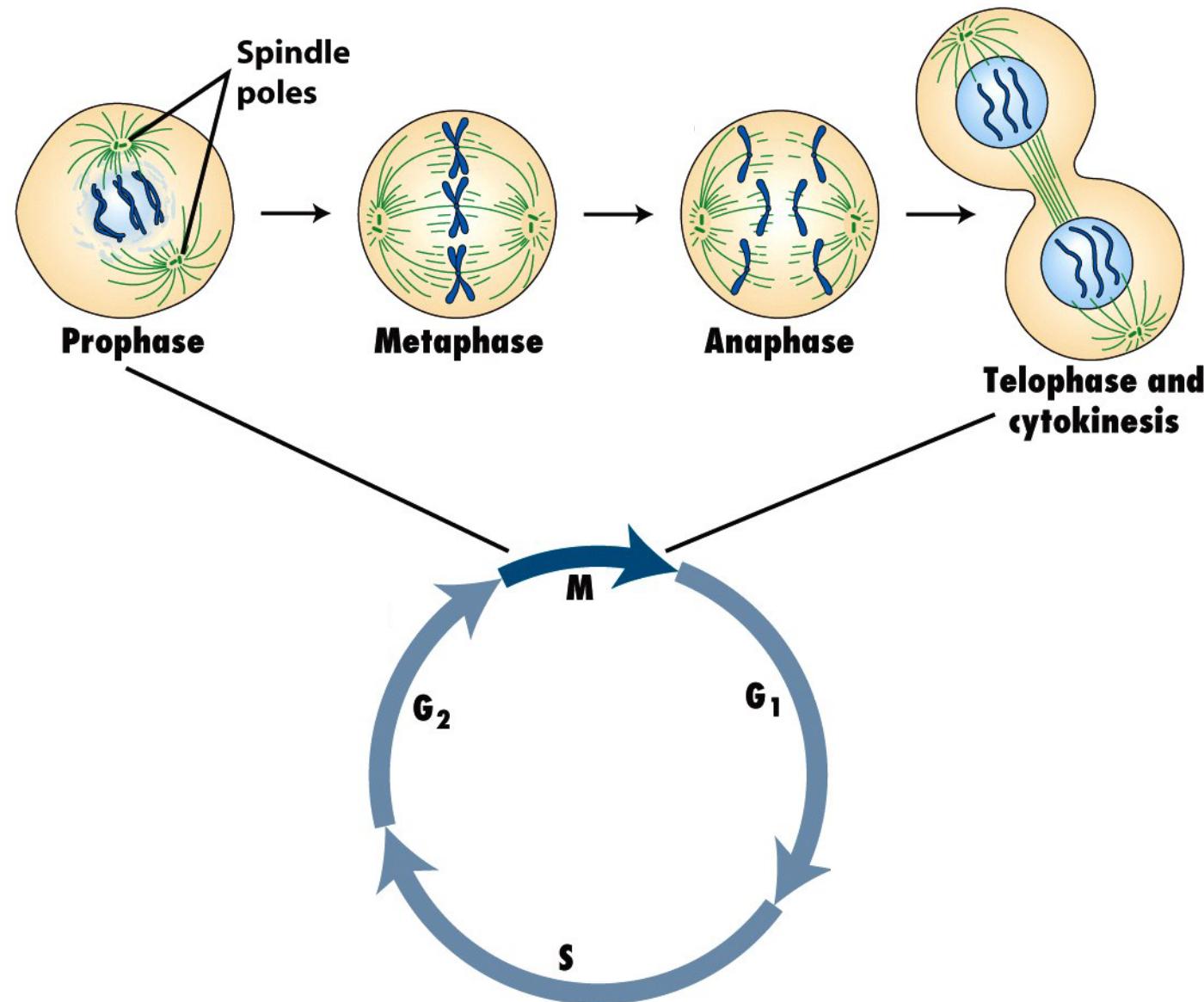


Complex regulatory mechanisms involved that we do not have time to discuss.

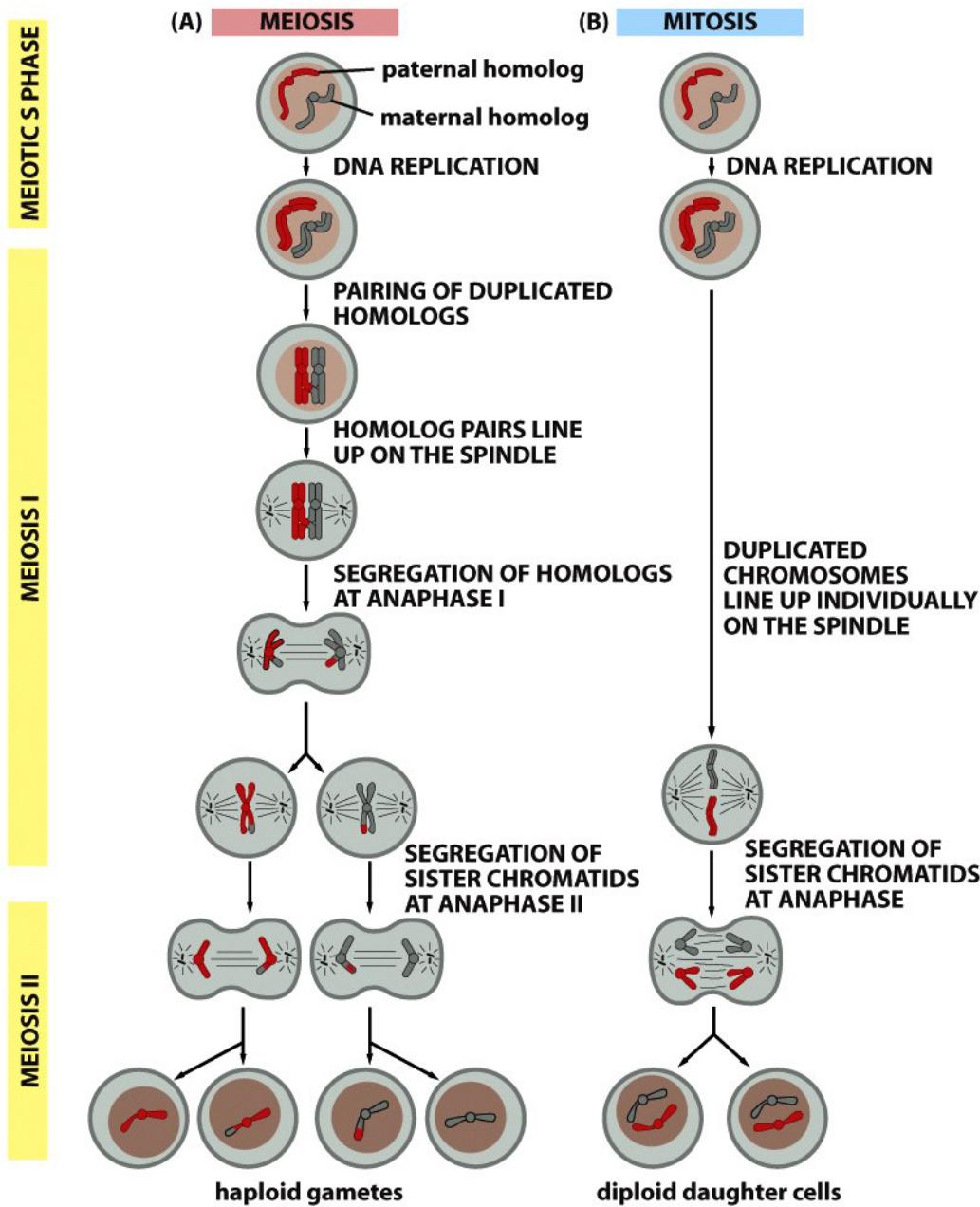
Cells in G₀ can re-enter the cell cycle by a regulated Process.

A major area of current research is to more fully understand and modulate mitosis, which could lead to better drugs for cancer therapy.

M-Phase of the Cell Cycle is Further Sub-Divided Visually



Comparing Meiosis and Mitosis



Apoptosis

Sometimes death is needed for life

Multiple Forms of Cell Death

Apoptosis



(A)

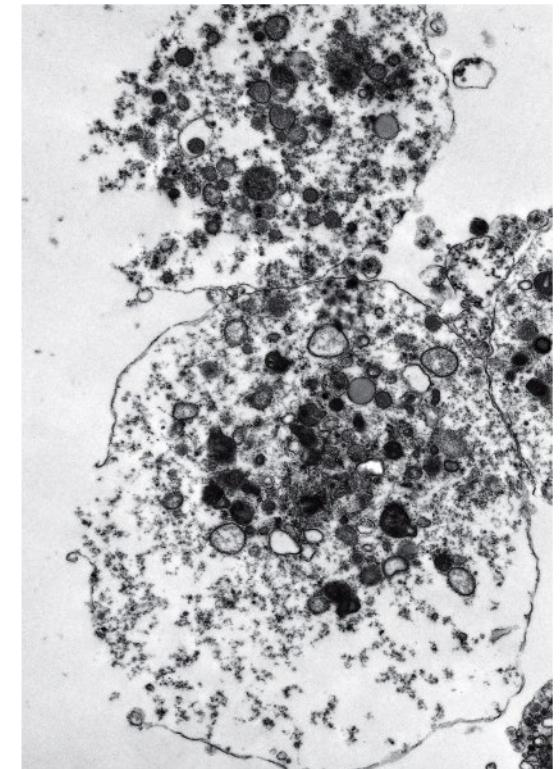
10 μm



(B)

engulfed dead
cell phagocytic
cell

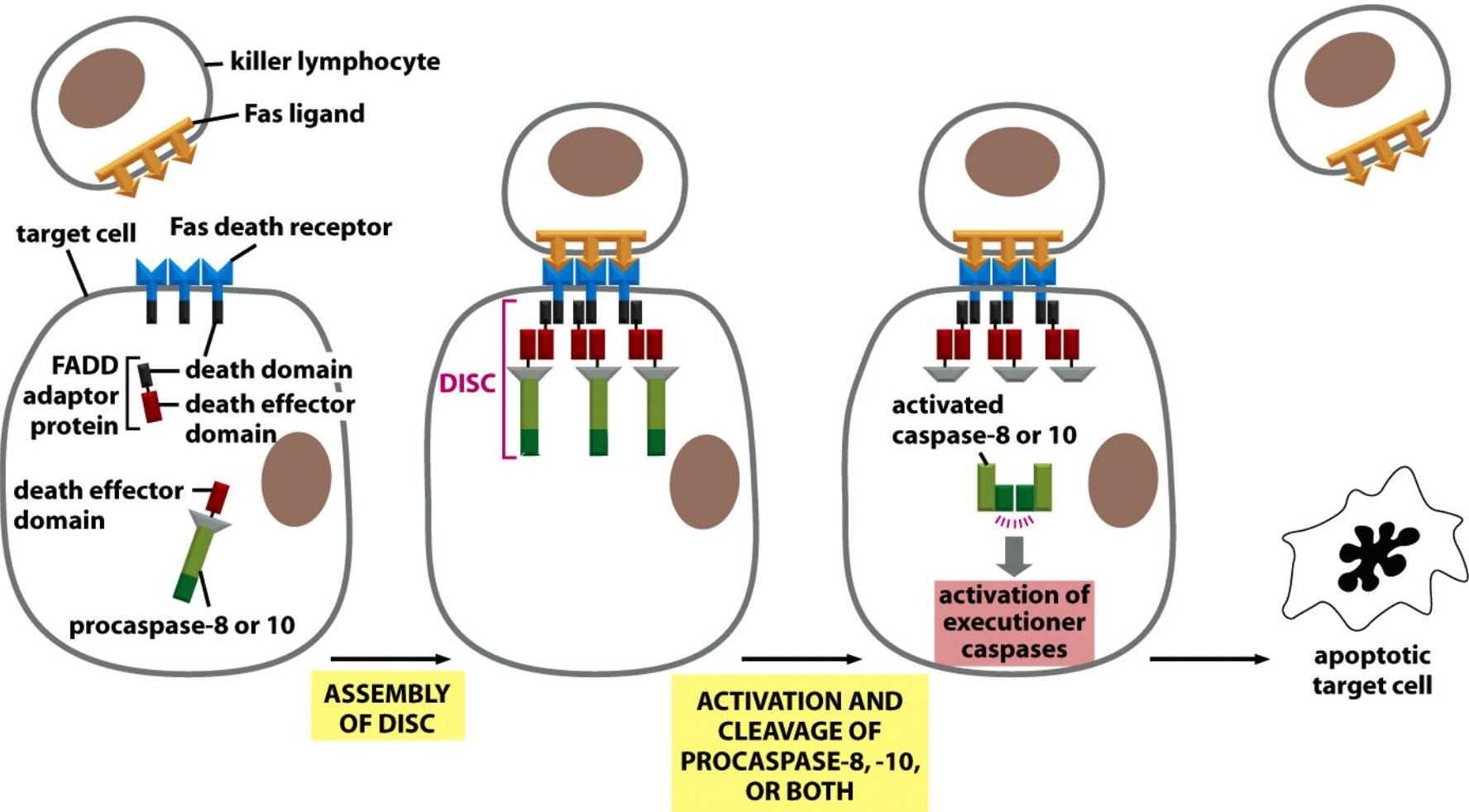
Necrosis



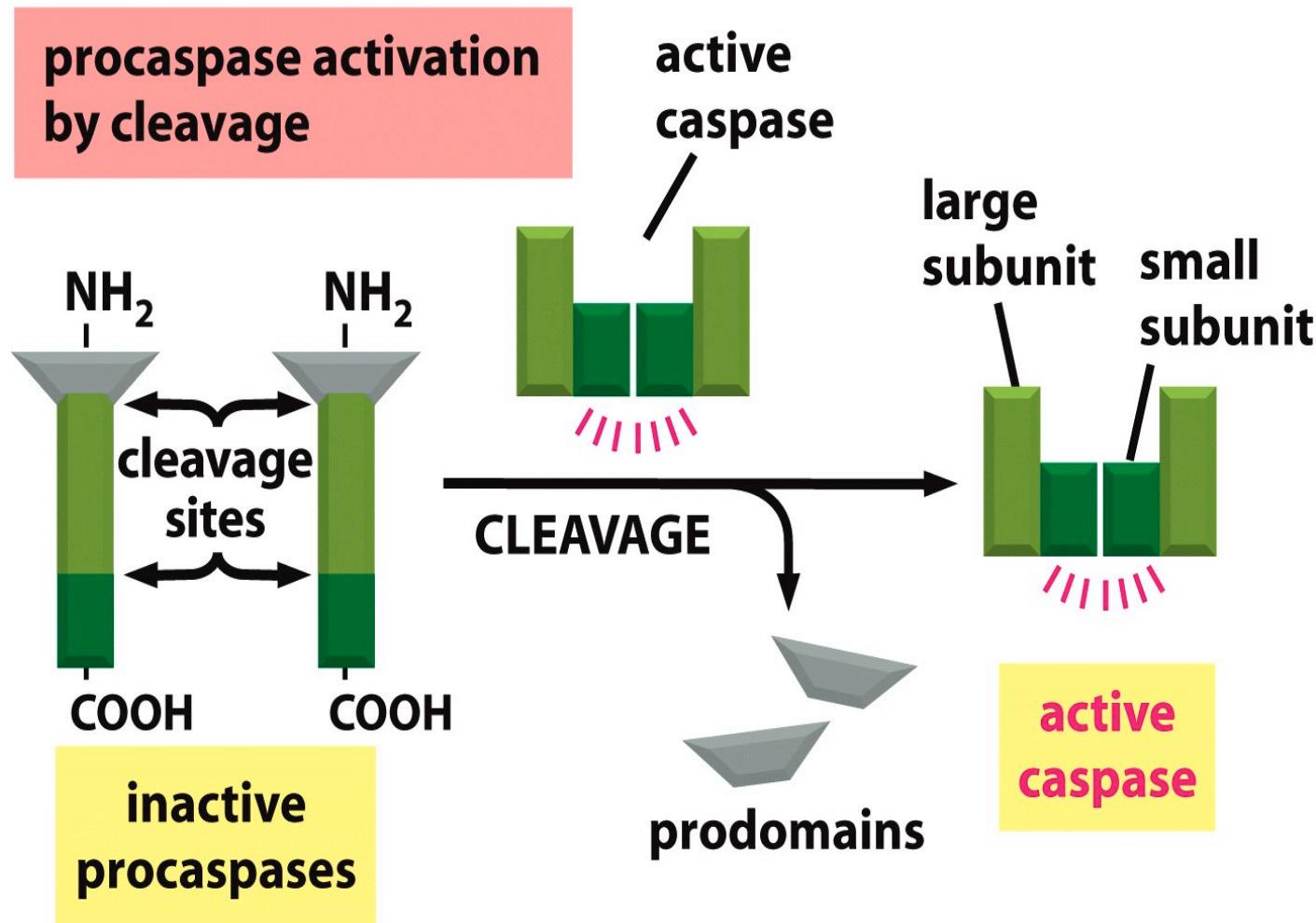
(C)

Necrosis can result from cell infection, toxins, and trauma

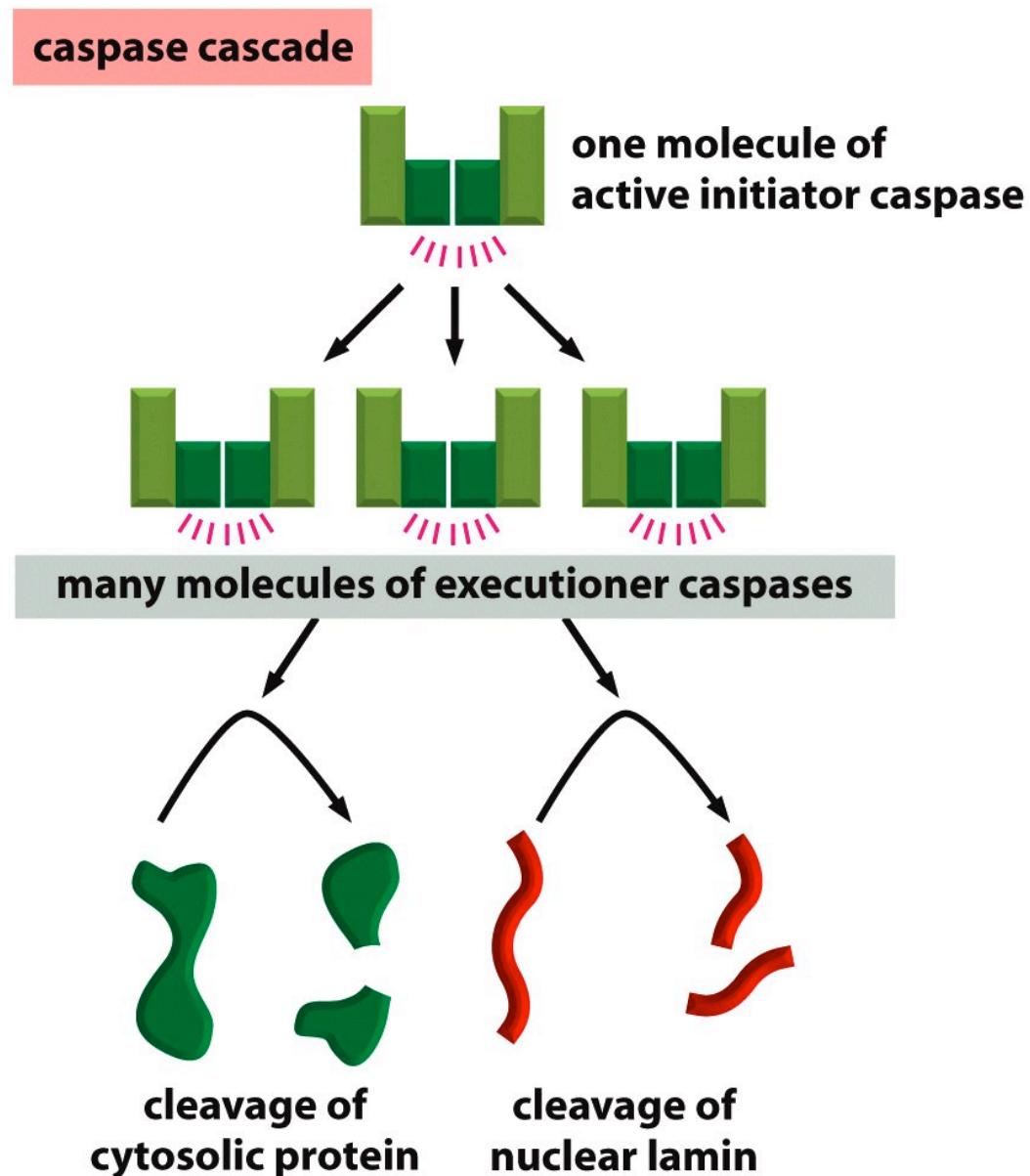
Apoptosis is Regulated and Induced by Extracellular Signals

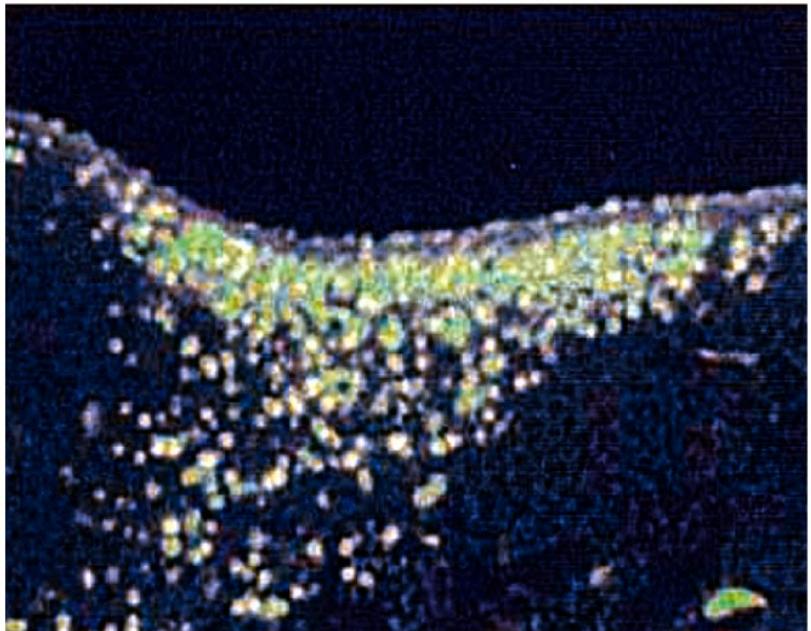


Caspases are the Proteolytic Executioners of Apoptosis



A Caspase Cascade is Activated in Apoptosis





Detecting Apoptosis

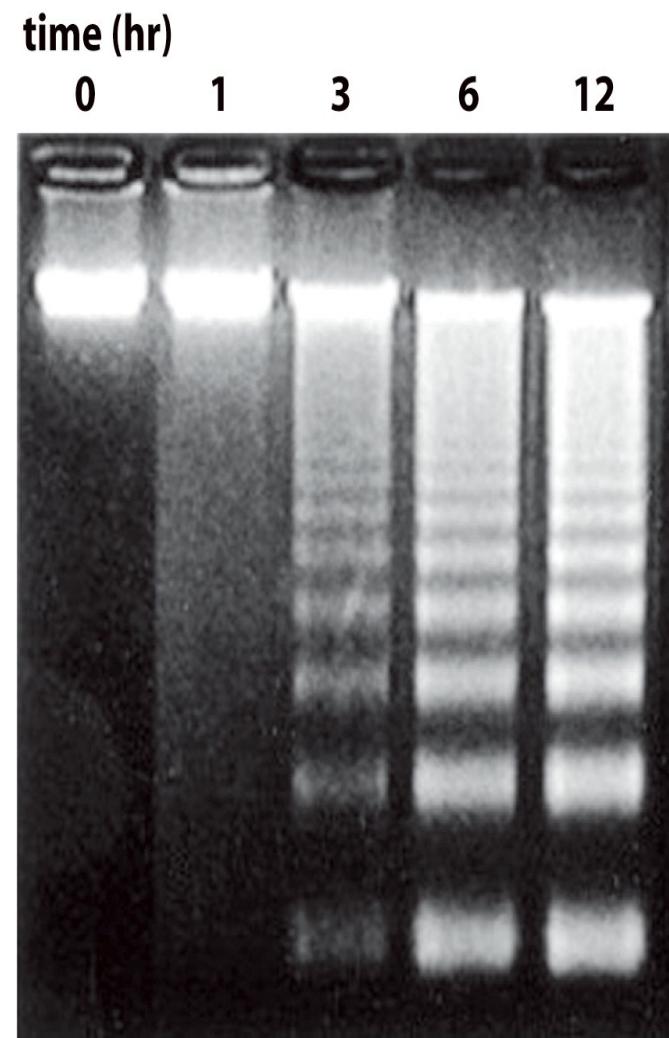
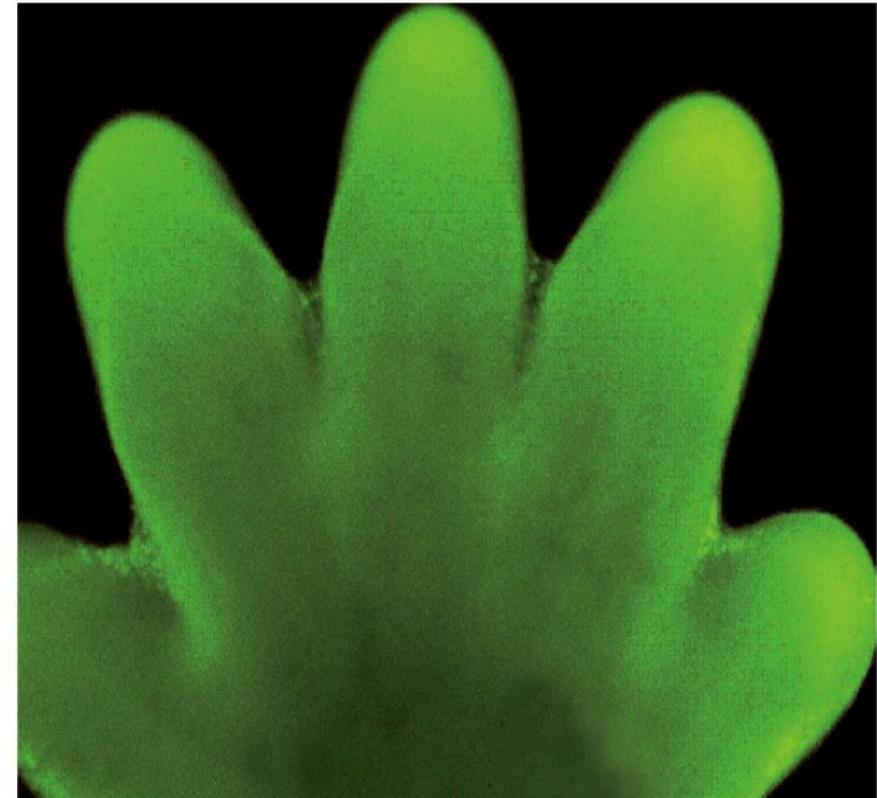
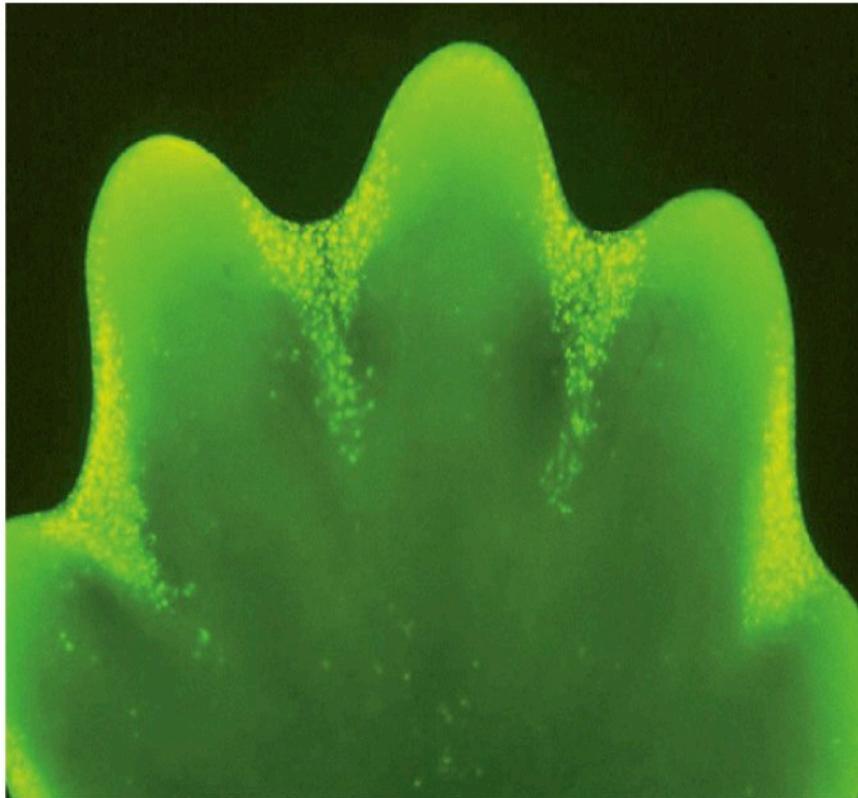


Figure 18-4a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Apoptosis in Development: How to Make Digits of a Hand



1 mm

The Proteosome and Ubiquitination

General concepts

Lysosomes and proteasomes are two major protein degradation compartments within a cell.

They recognize different substrates by different mechanisms.

Eukaryotic organisms possess two basic proteolytic pathways. One consists of an endocytotic lysosomal-based degradation of proteins. The other is adenosine triphosphate (ATP)-dependent and non-lysosomal pathway.

Ubiquitination of intracellular proteins is involved in these pathways and is required for the cytosolic pathway in normal metabolic conditions.

Ubiquitin, a highly conserved 76 amino acid polypeptide, was the first protein shown to be covalently attached to other proteins.

Mono-ubiquitination has been shown to be involved in the regulation of a wide variety of cellular processes including receptor internalization, gene transcription, and virus budding.

N-End Rule: Proteins with basic or large hydrophilic residues at N-terminus are substrates.

Through a multi-enzyme cascade, polyubiquitin chains are added to a variety of different proteins that are then ultimately degraded by the 26S proteasome.

Ubiquitin and ubiquitin-like modifications are increasingly recognized as key regulatory events in many basic cell biology processes that impact the development of cancer, such as regulation of the cell cycle, protein trafficking, and cell survival versus cell death decisions.

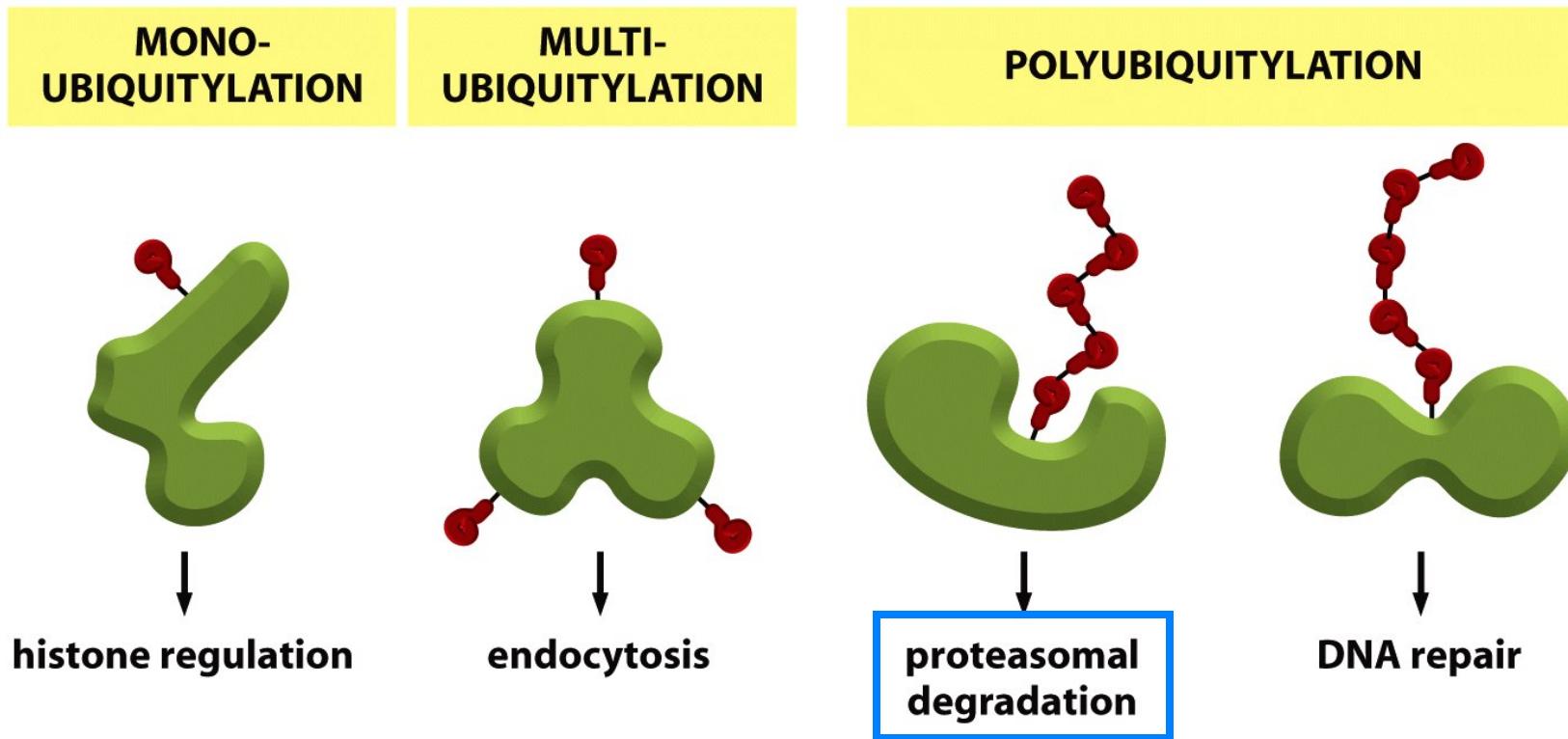
Several ubiquitin-like modifications (Sumoylation, Neddylation, and ISGylation) have also been identified.

Protein Ubiquitination - A Mechanism to Induce Protein Degradation

Ubiquitin:
76 aa protein

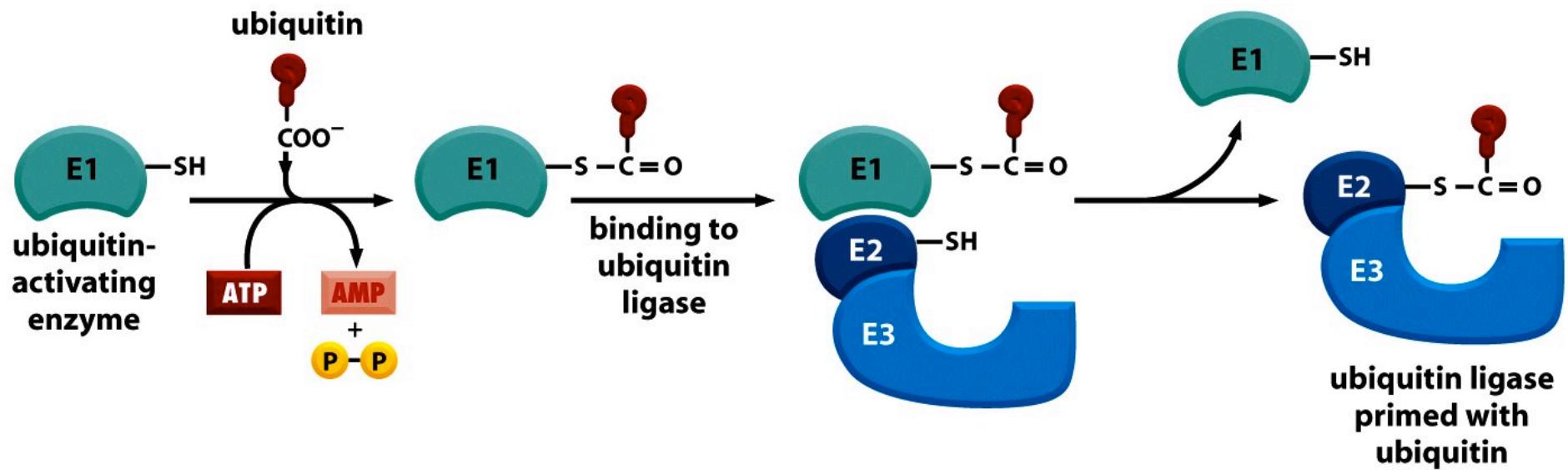


**There are multiple types of ubiquitination with distinct functions
some examples below**



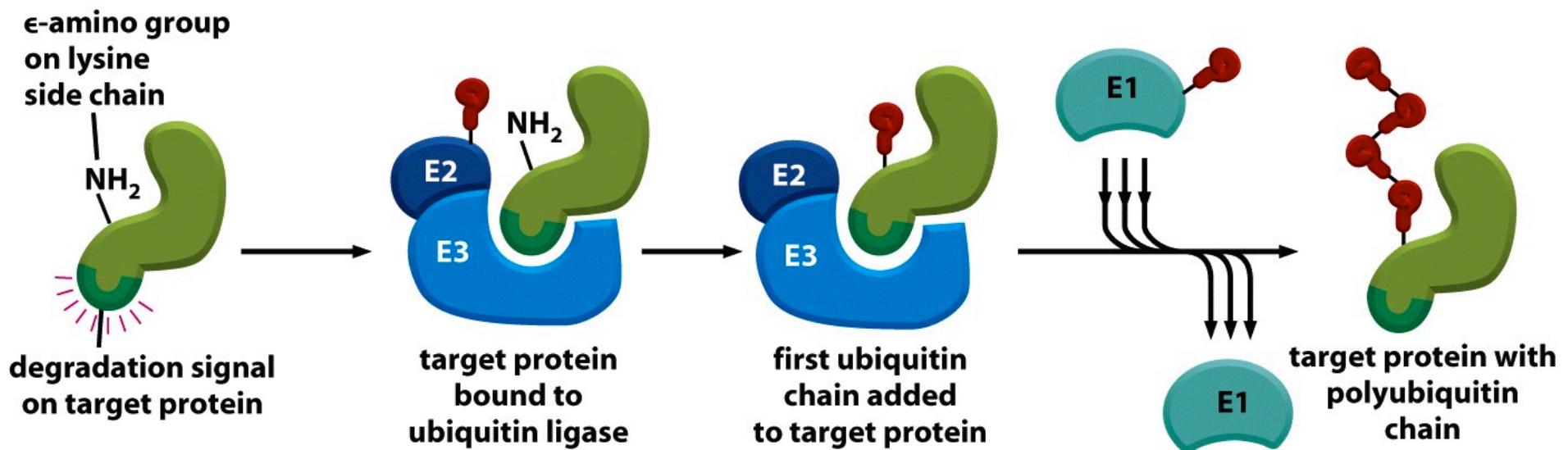
Ubiquitin signals within the endocytic pathway are primarily in the form of multi-ubiquitination but possibly include mono-ubiquitination as well.

Protein Ubiquitination Pathway



then...

Protein Ubiquitination Pathway: Including Polyubiquitination

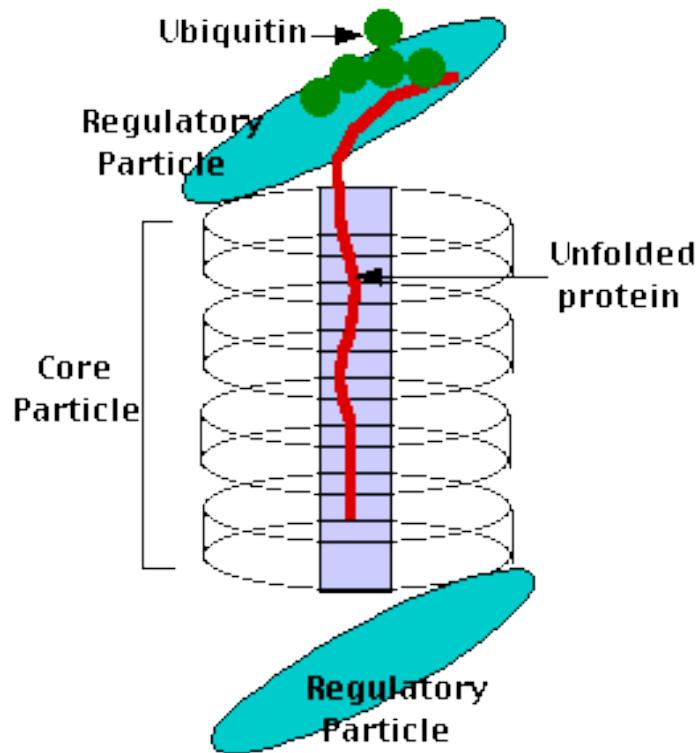


Ubiquitination requires a cascade of three enzymatic activities for activating (E1), conjugating (E2) and ligating (E3) ubiquitin covalently to a substrate. The E3 ubiquitin ligases provide two distinct functions: catalysing isopeptide bond formation and targeting of the substrate

the number of genes: E1(a few), E2 (30 or so) and E3 (hundreds) – why?

Ubiquitination Targets Cytoplasmic Proteins for Degradation by the Proteosome

The 20S proteosome is conserved in evolution, although its complexity has increased

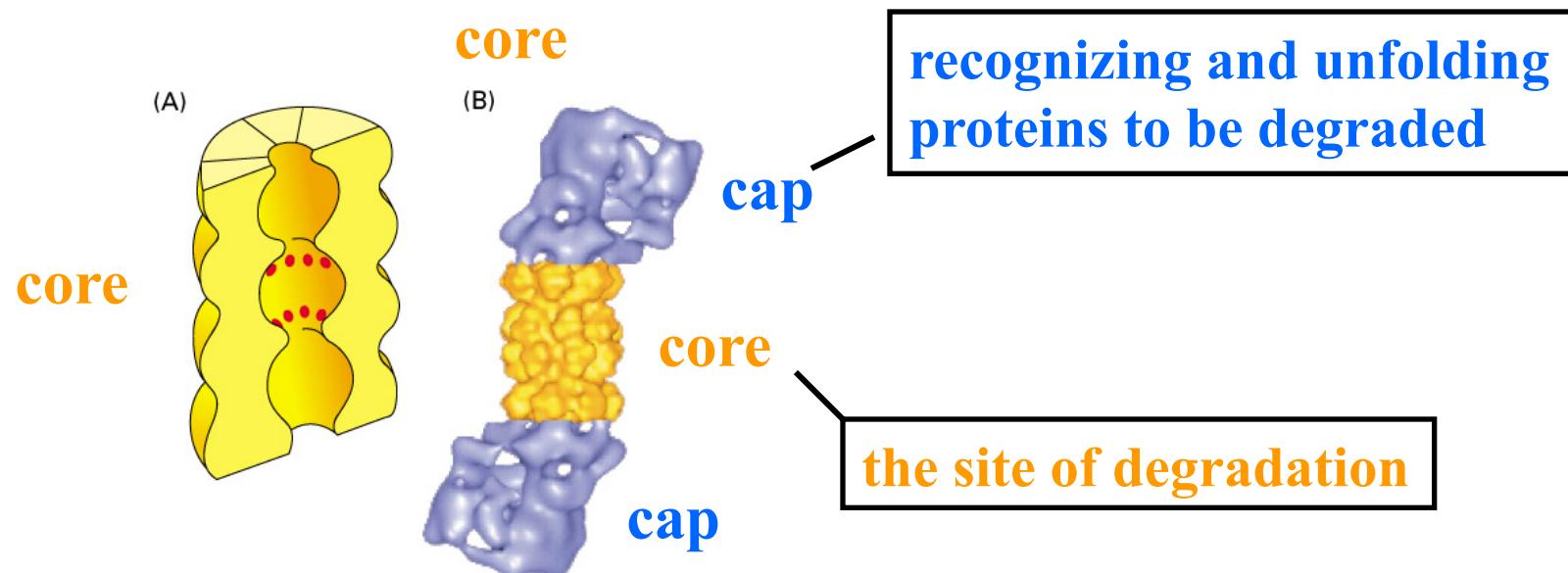


- * The complex binds to ubiquitin-recognition site(s) on the regulatory particle.
- * The protein is unfolded by the ATPases using the energy of ATP
- * The unfolded protein is translocated into the central cavity of the core particle.
- * Several active sites on the inner surface of the two middle "donuts" break various specific peptide bonds of the chain.
- * This produces a set of peptides averaging about 8 amino acids long.
- * These leave the core particle by an unknown route where they may be further broken down into individual amino acids by peptidases in the cytosol or in mammals, they may be incorporated in a class I histocompatibility molecule to be presented to the immune system as a potential antigen [see below].
- * The regulatory particle releases the ubiquitins for reuse.

The Core particle is made of 2 copies each of 14 different proteins, assembled in groups of 7 forming 4 stacked rings. Two identical regulatory particles exist at each end of the core Particle. Each is made of 14 different proteins (none the same as in the Core particle). Six are ATPases, some have ubiquitin recognition sites.

Misfolded integral membrane proteins are also degraded in the proteasomes

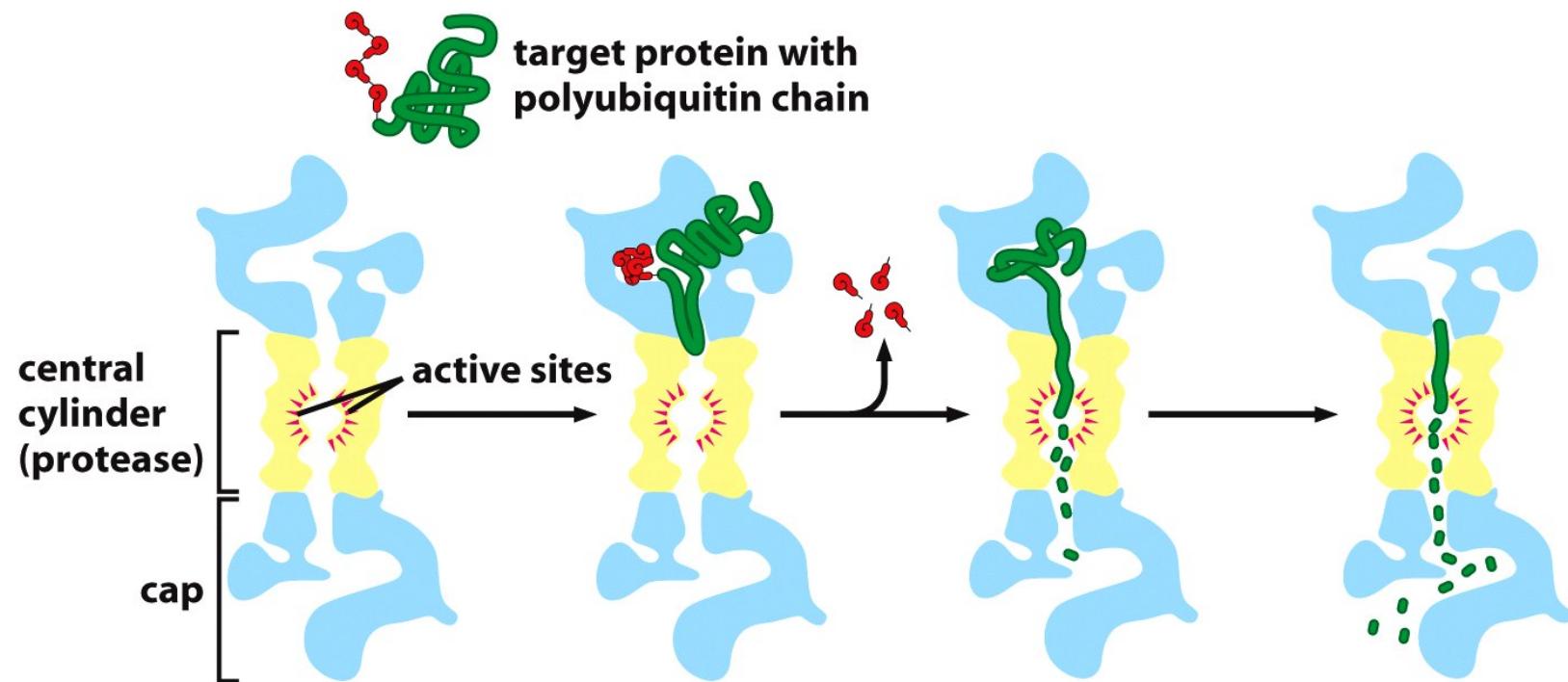
Proteasome: an ATP-dependent protease complex in the cytosol and nucleus
It is composed of three parts: two side caps and one central core, with each part containing multiple subunits.



How does a proteasome recognize misfolded membrane proteins?

Proteasomes recognize misfolded membrane proteins via a ubiquitin tag

Ubiquitin is a small protein of 76 a.a. Multiple ubiquitins are added to a misfolded membrane protein to form a poly-ubiquitin chain which can be recognized by proteasomes



At least 5-7 ubiquitins are needed to tag a protein for proteasomal recognition and degradation.

The Following are also Degraded by Proteasomes

Misfolded cytosolic proteins: Almost all cellular misfolded proteins are degraded by proteasomes.

Folded cytosolic proteins: for a regulatory purpose (e.g. degradation of proteins involved in mitosis).

As a general rule, proteasomes can degrade folded cytosolic proteins, whereas lysosomes degrade folded integral and luminal proteins.

Proteasome defects are associated with many human diseases including neurodegenerative syndromes (but so far these appear as secondary effects).