Cellular information and signaling

Principles and components

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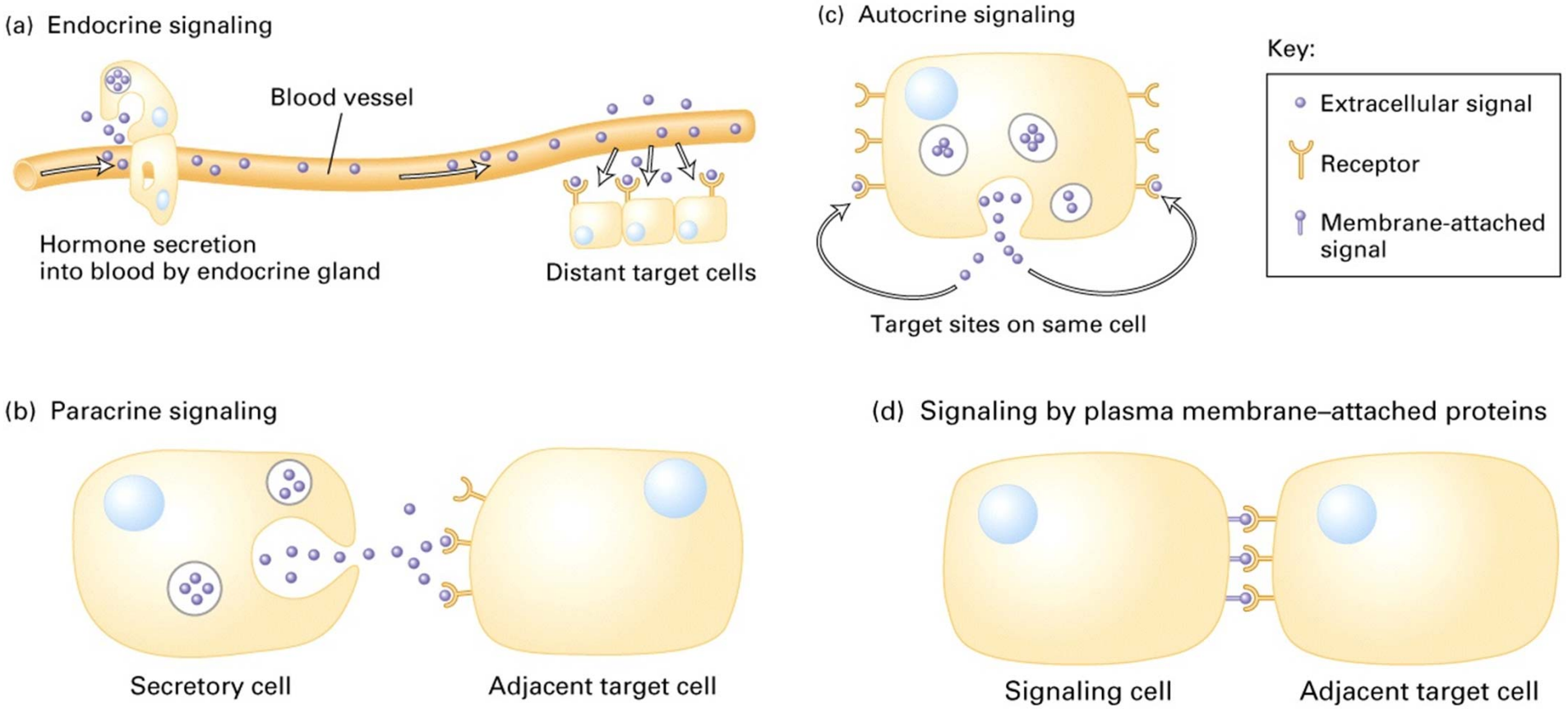
Information in cells

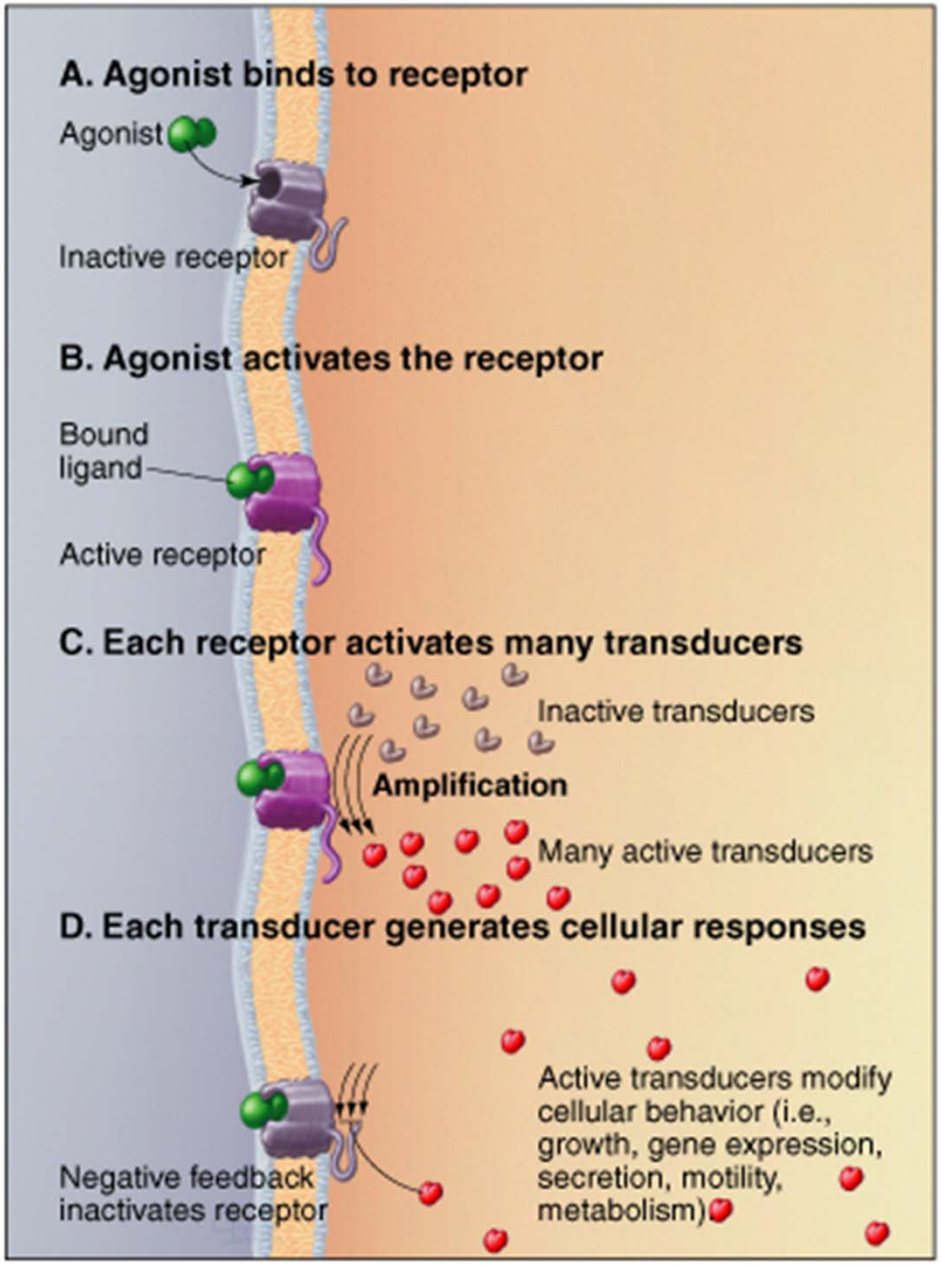
- Potential information is held in the genome (DNA) of the cell.
  - Less than 5% of the human genome codes for proteins (structural genes)
  - The ENCODE project reveals that most of the remaining 95% of genomic DNA is regulatory!
- Not all genes are active in all cells or at all times.
- Gene regulation is therefore central to utilization of information. How is this accomplished?

Cell signaling

- Cells must be able to respond to changes in external conditions (external “information”) in order to survive.
- The ability to respond to an external signal is dependent on the expression of its receptor.
- Signal transduction mechanisms act to amplify a signal and effect a change in the cell’s behavior.
- This behavioral change can involve altered gene expression, or other responses.

Signaling may be distant or local





Signal transduction is a cascade of events

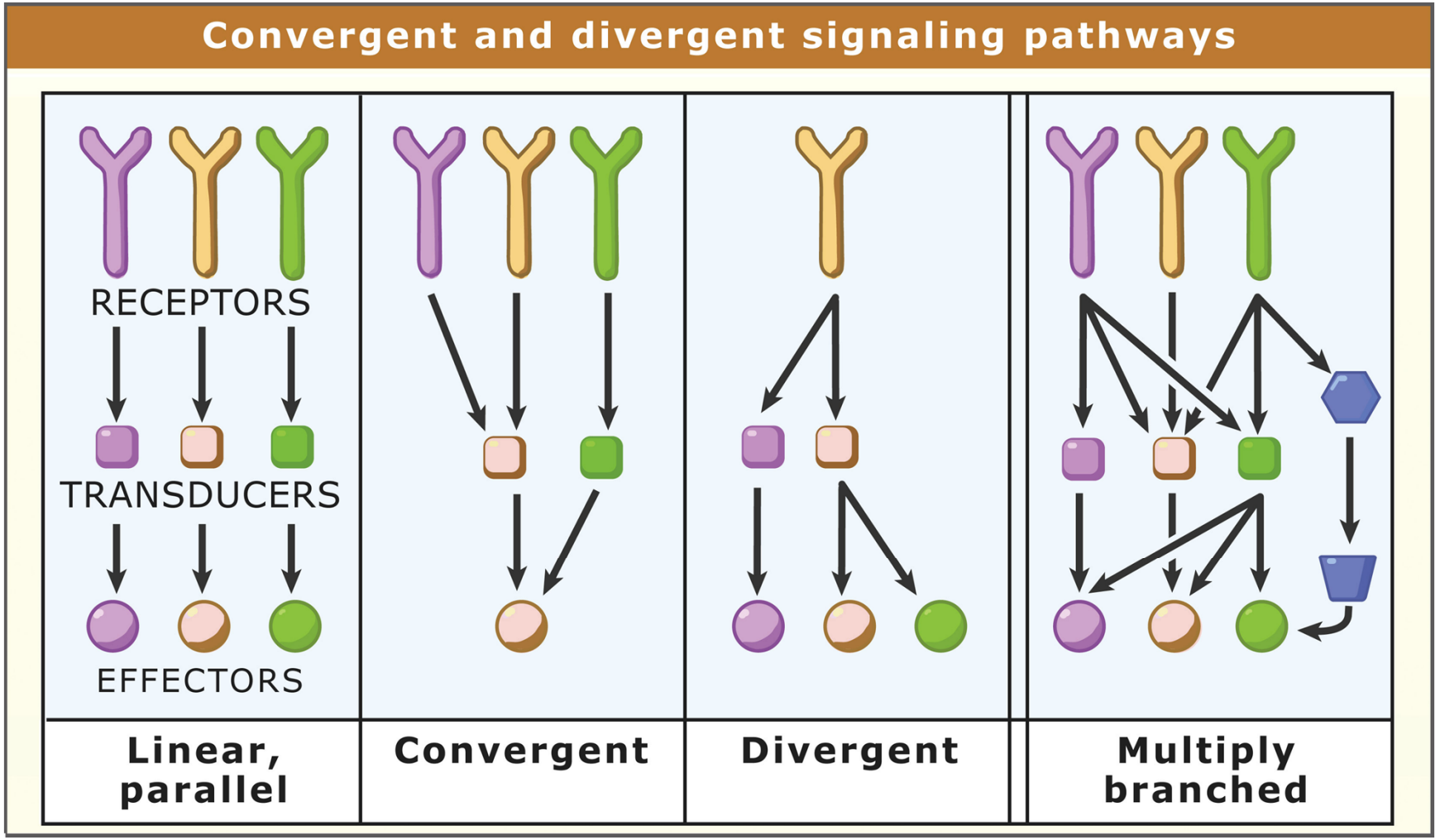
A weak external signal may produce a large effect through Amplification.

Signaling pathways are highly regulated; many feedback mechanisms!

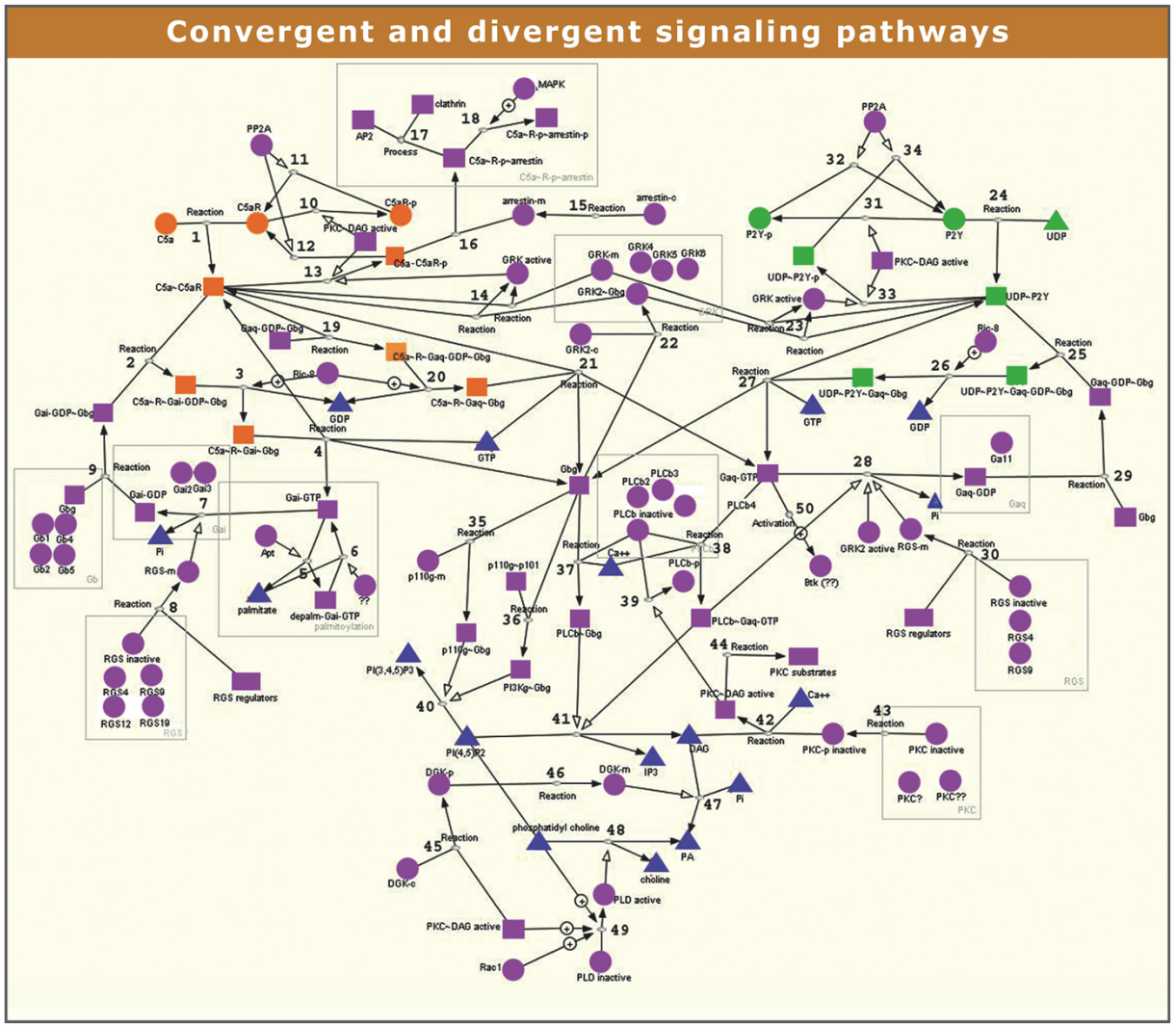
Features of signaling cascades

- Ligand binding triggers changes in receptors.
- This R-L binding is transduced into an intracellular signal by a variety of methods.
- The signal is amplified through a cascade involving second messengers.
- Virtually all cellular functions are influenced by these cascades.

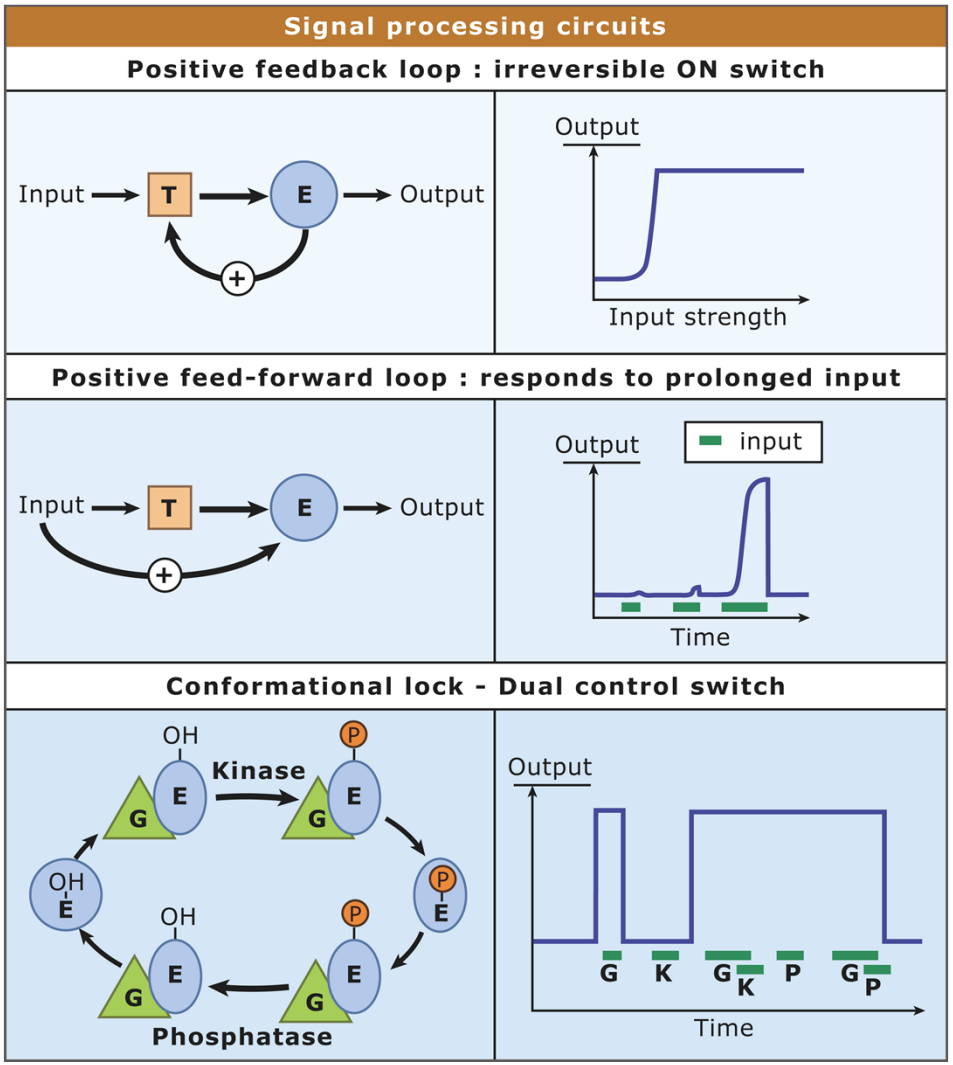
Signaling pathways may be branched



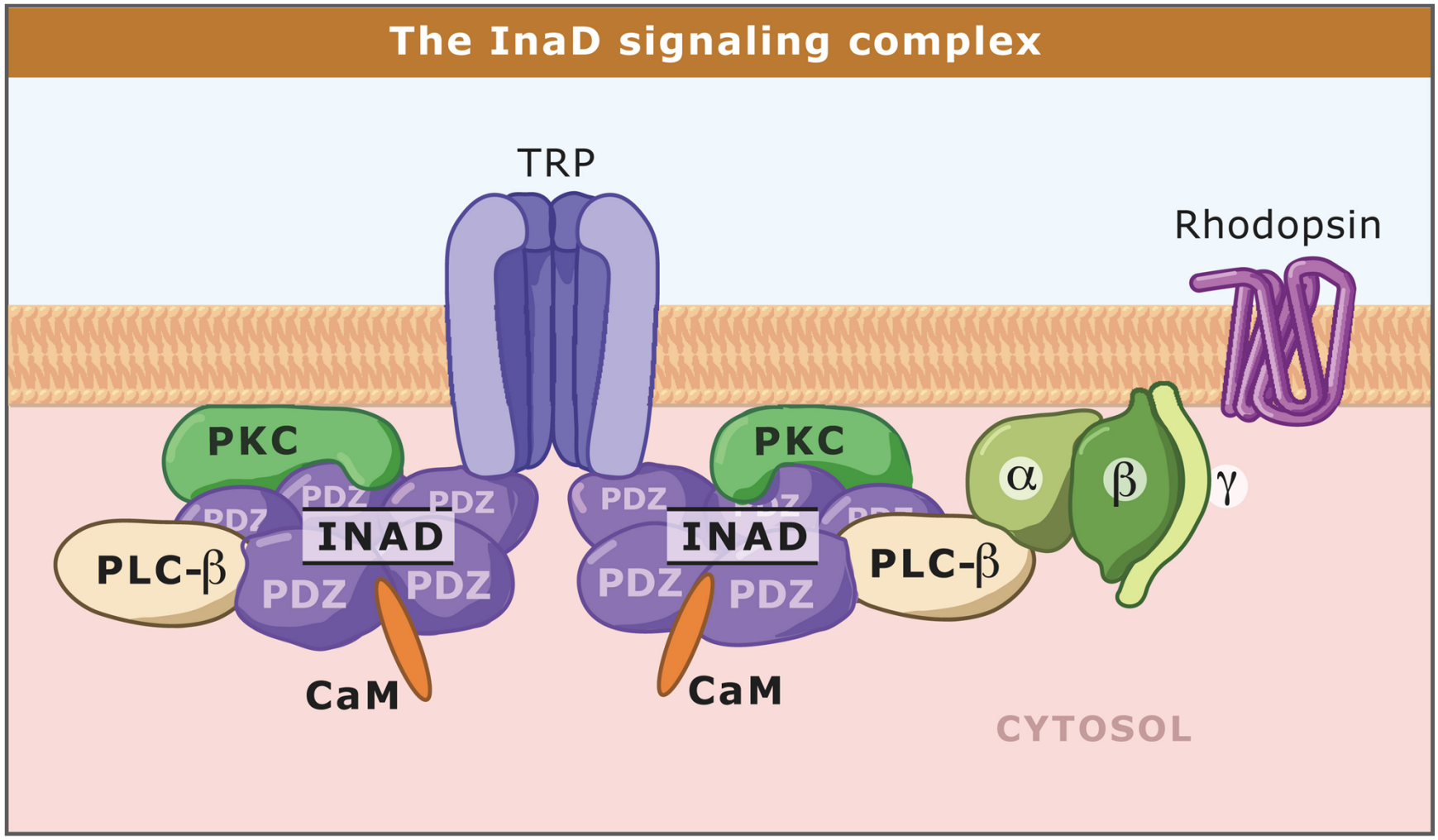
Cross-talk between pathways creates a complex network



Signaling pathways are regulated



Signaling complexes allow spatial organization and increase signaling efficiency



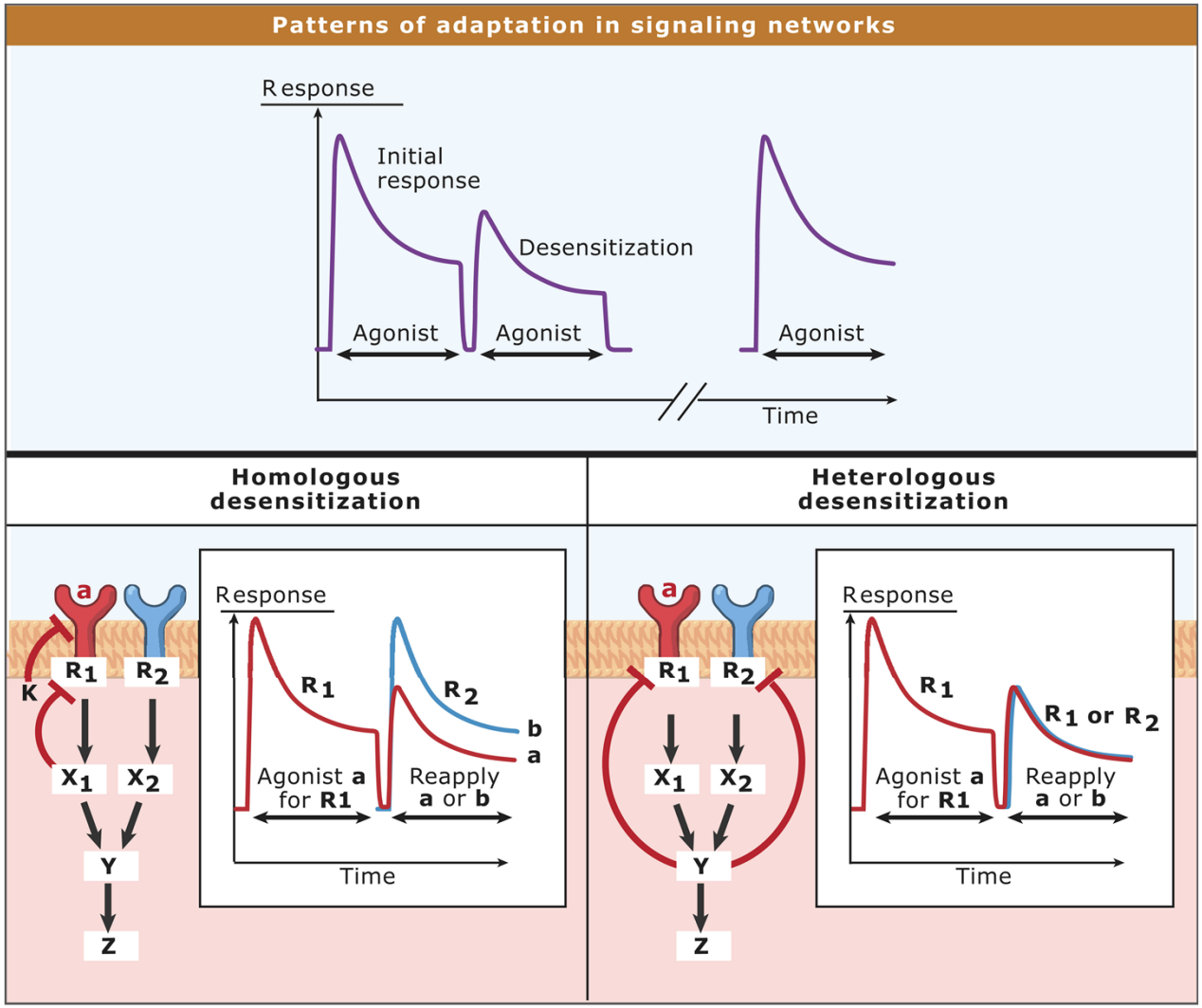
Modular organization of signaling proteins

- Modular domains occur in many signaling proteins.
- Domains mediate binding of upstream or downstream targets, carry enzymatic activity and/or provide regulation.
- Signaling cascades include both adapter proteins (signaling only, no enzymatic activity) and those with enzymatic activity.
- The most frequent enzymes are kinases (add phosphate groups to amino acids on proteins) and phosphatases (remove phosphate groups).

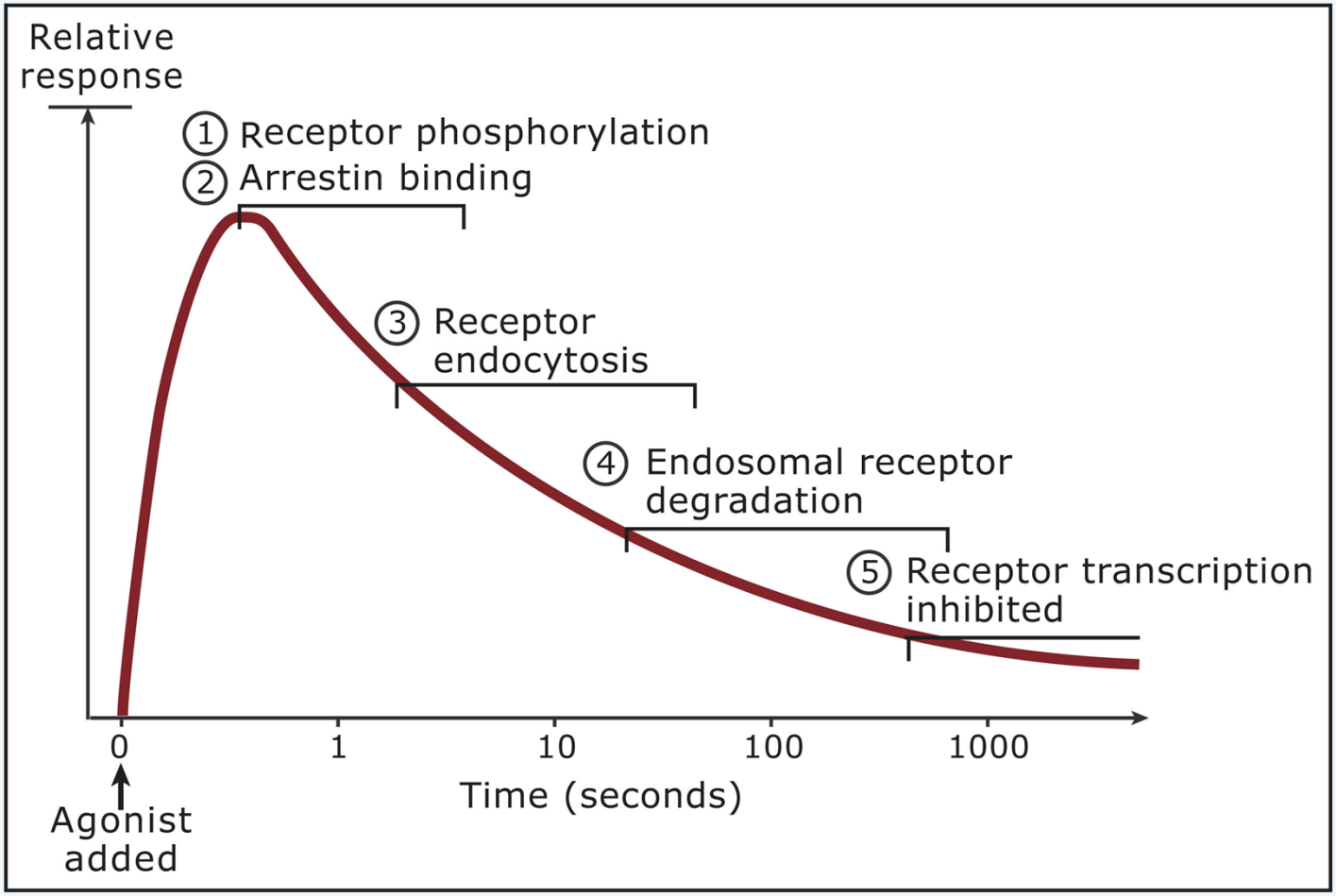
Altering cellular sensitivity to signals

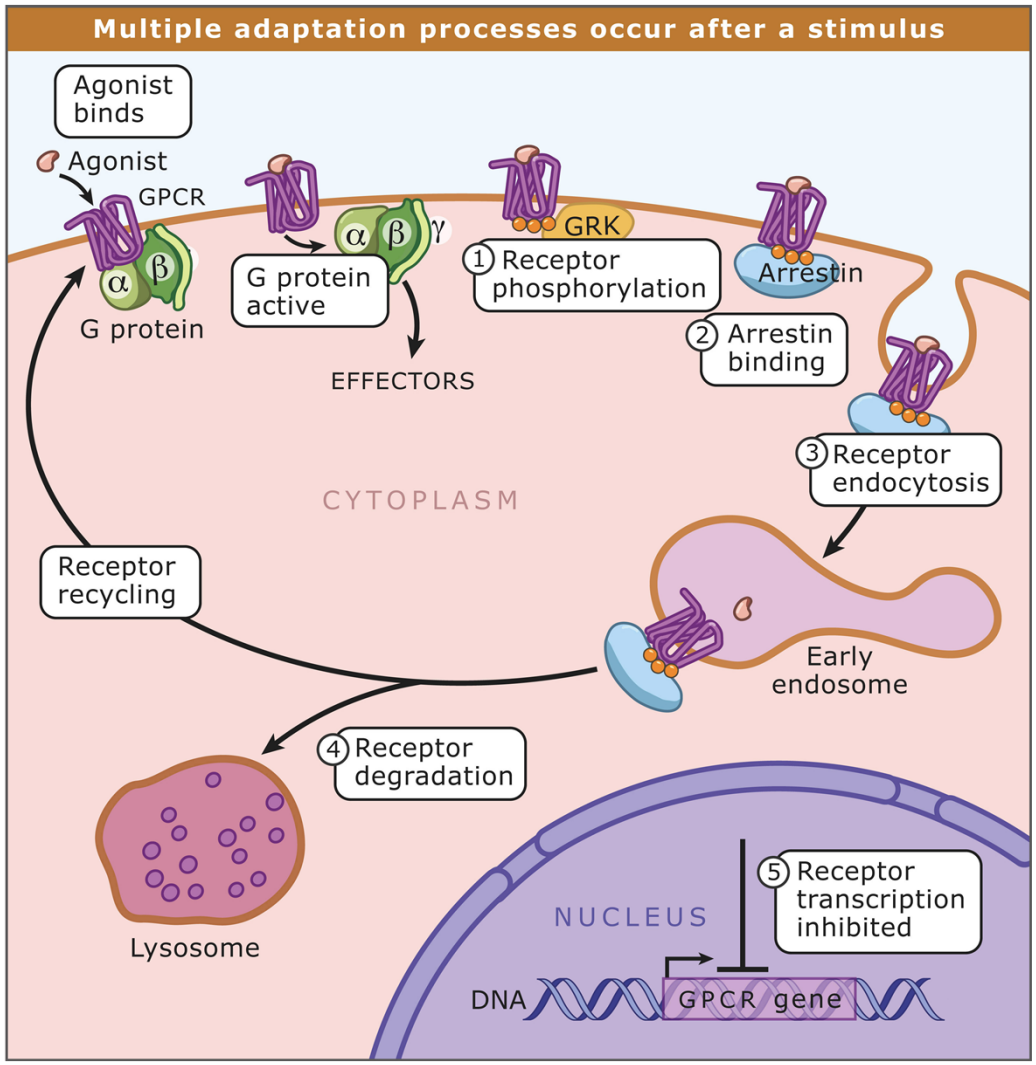
- Cells adapt after receiving signals.
- Cells may reduce their response (desensitization) in a variety of ways.
- Cells may increase their response (hyper-sensitization) in a variety of ways.
- Most common strategy is modification and/or removal or addition of receptors.

Signaling networks are flexible

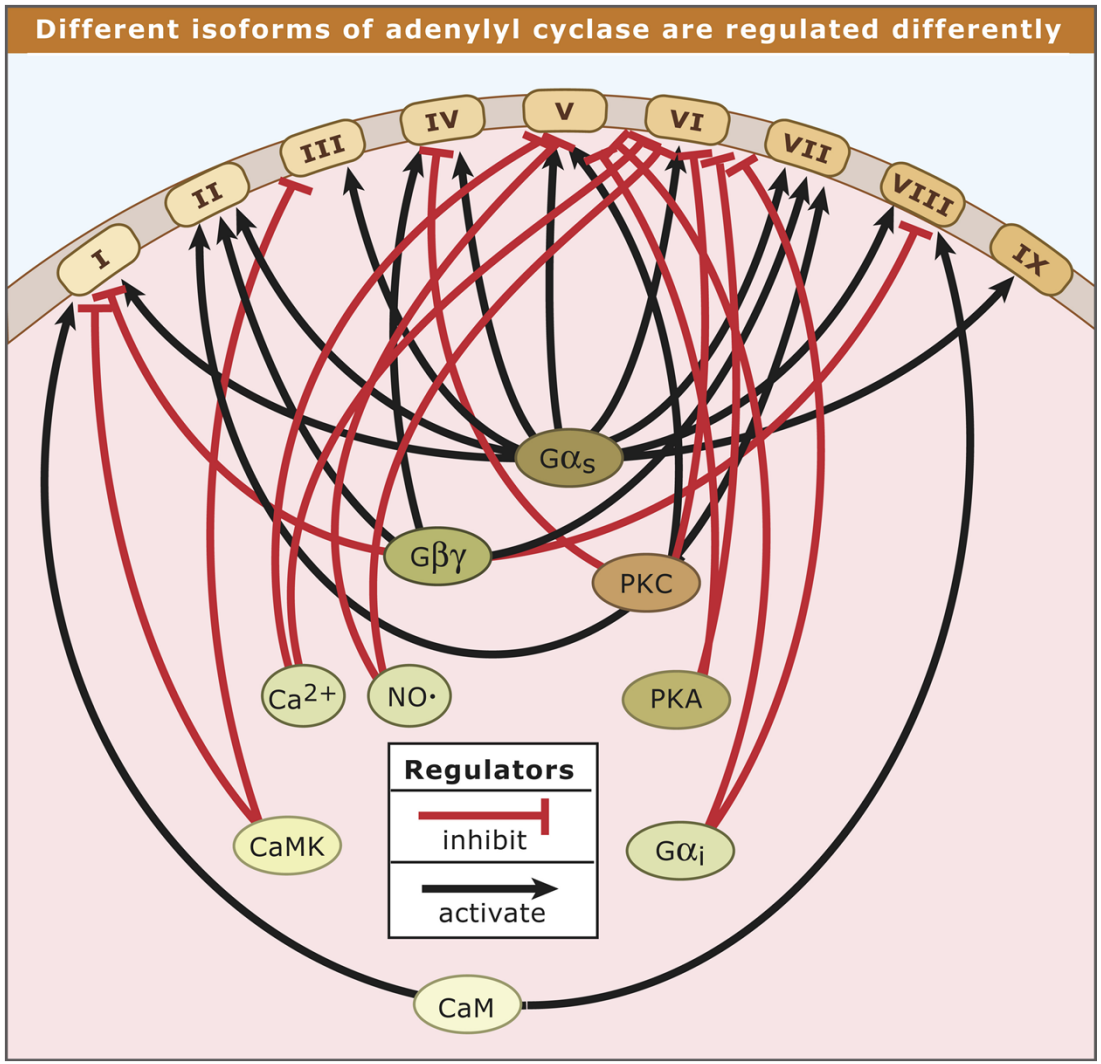


Multiple adaptation processes occur after a stimulus

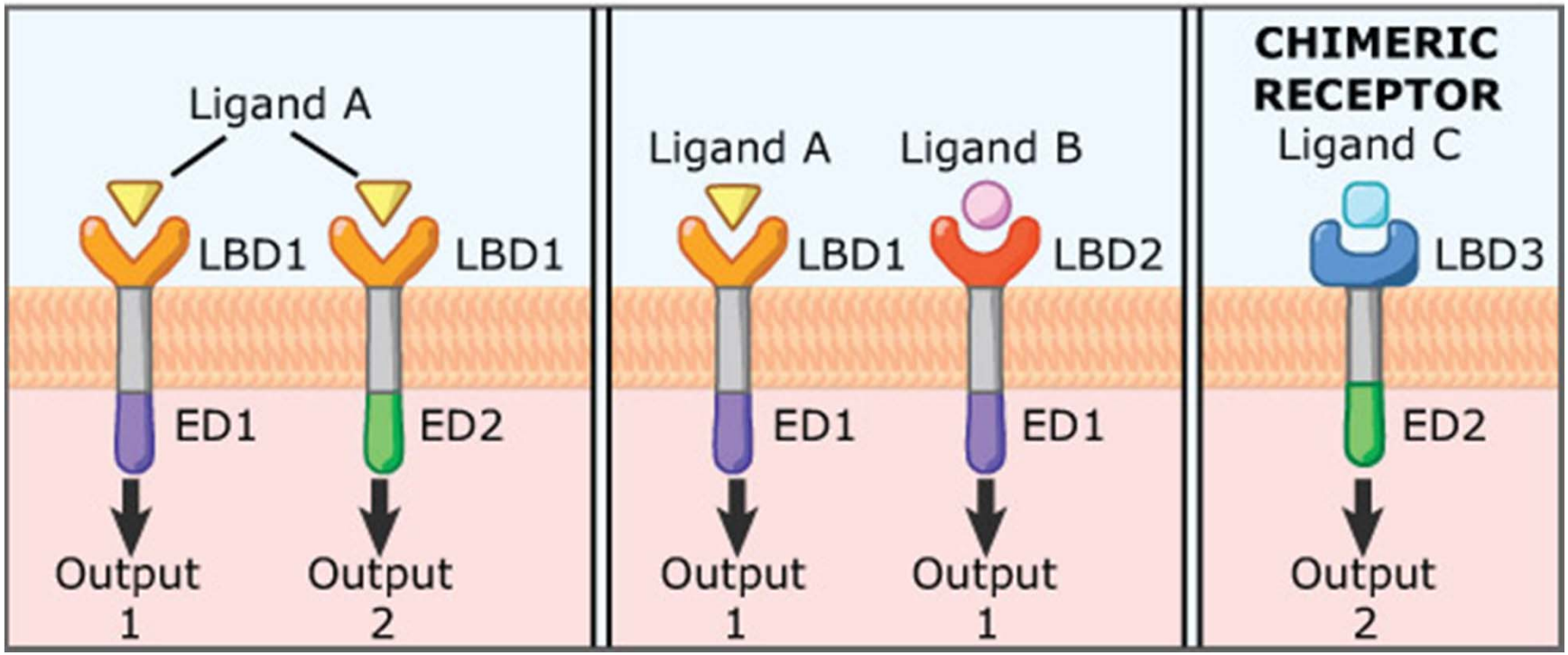



Multiple adaptation processes occur after a stimulus
Agonist binds
Agonist
GPCR
α
β
G protein
G protein active
α
β
γ
EFFECTORS
GRK
1 Receptor phosphorylation
Arrestin
2 Arrestin binding
3 Receptor endocytosis
CYTOPLASM
Receptor recycling
Early endosome
4 Receptor degradation
Lysosome
NUCLEUS
5 Receptor transcription inhibited
DNA
GPCR gene

Closely related proteins are regulated separately



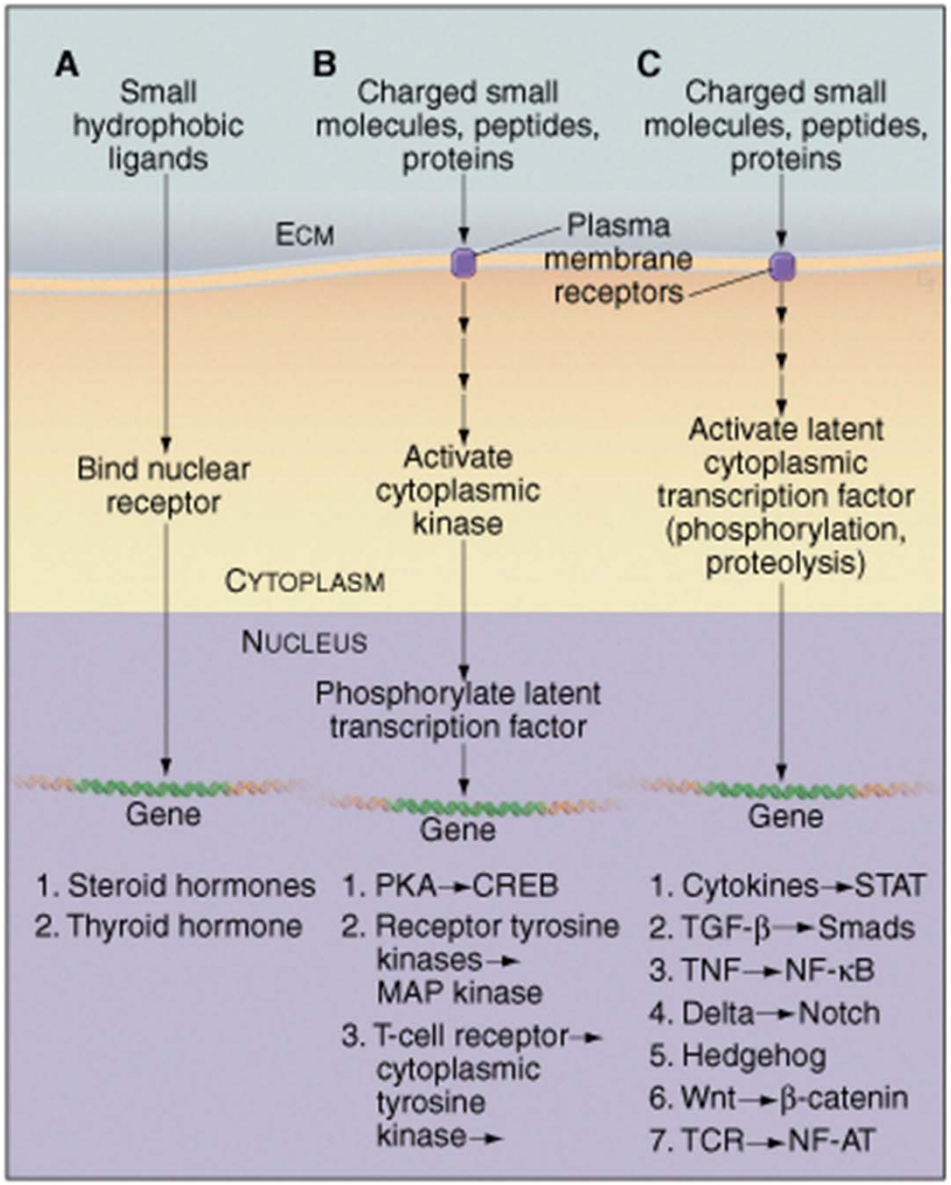
.Receptor family members can generate different responses



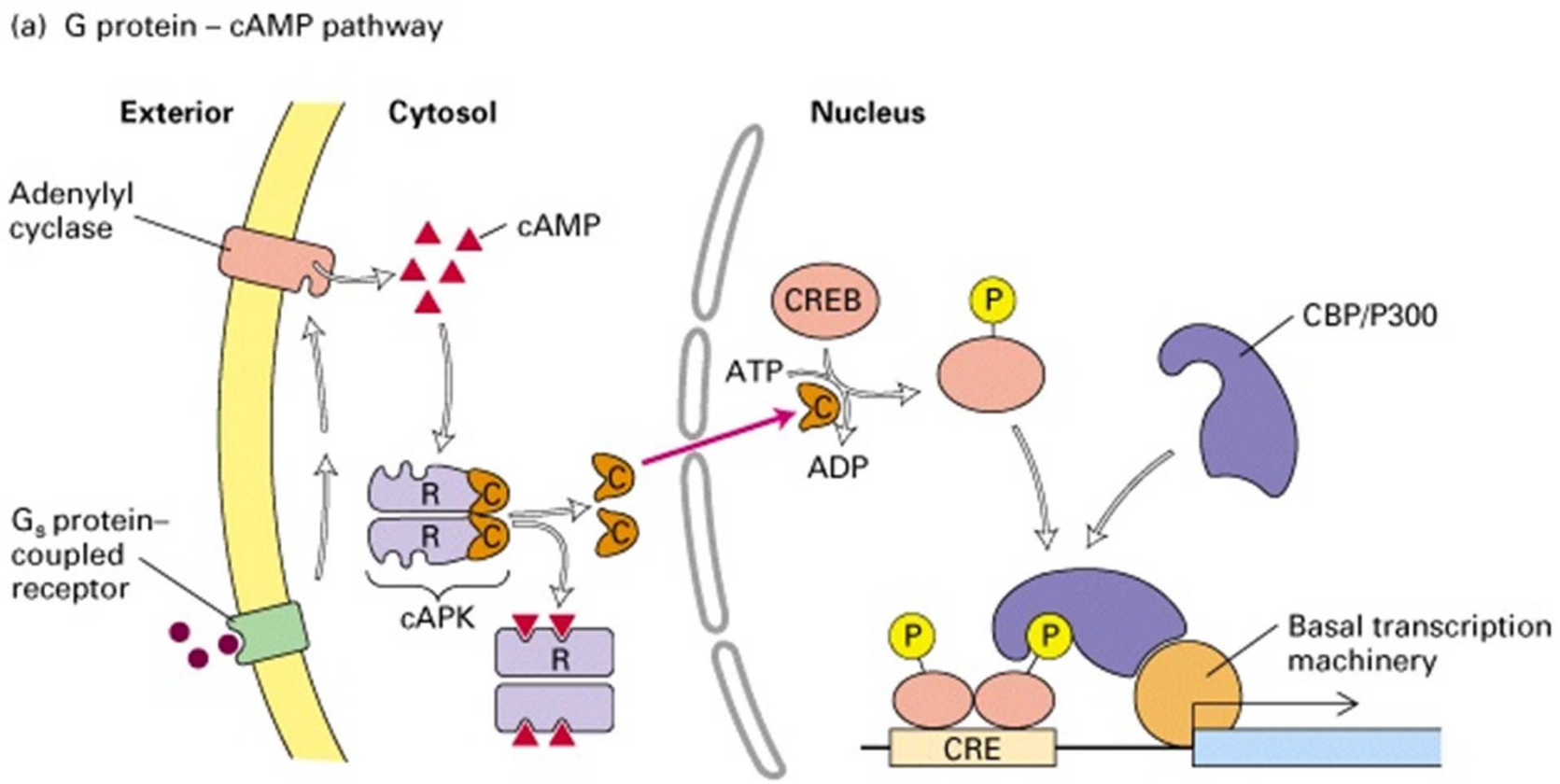
Receptor families

- Family members arose from gene duplication and divergence.
- Family members share structurally homologous domains.
- However, downstream events are not predictable from the type of receptor or its ligand.

Several paths lead to changes in transcription

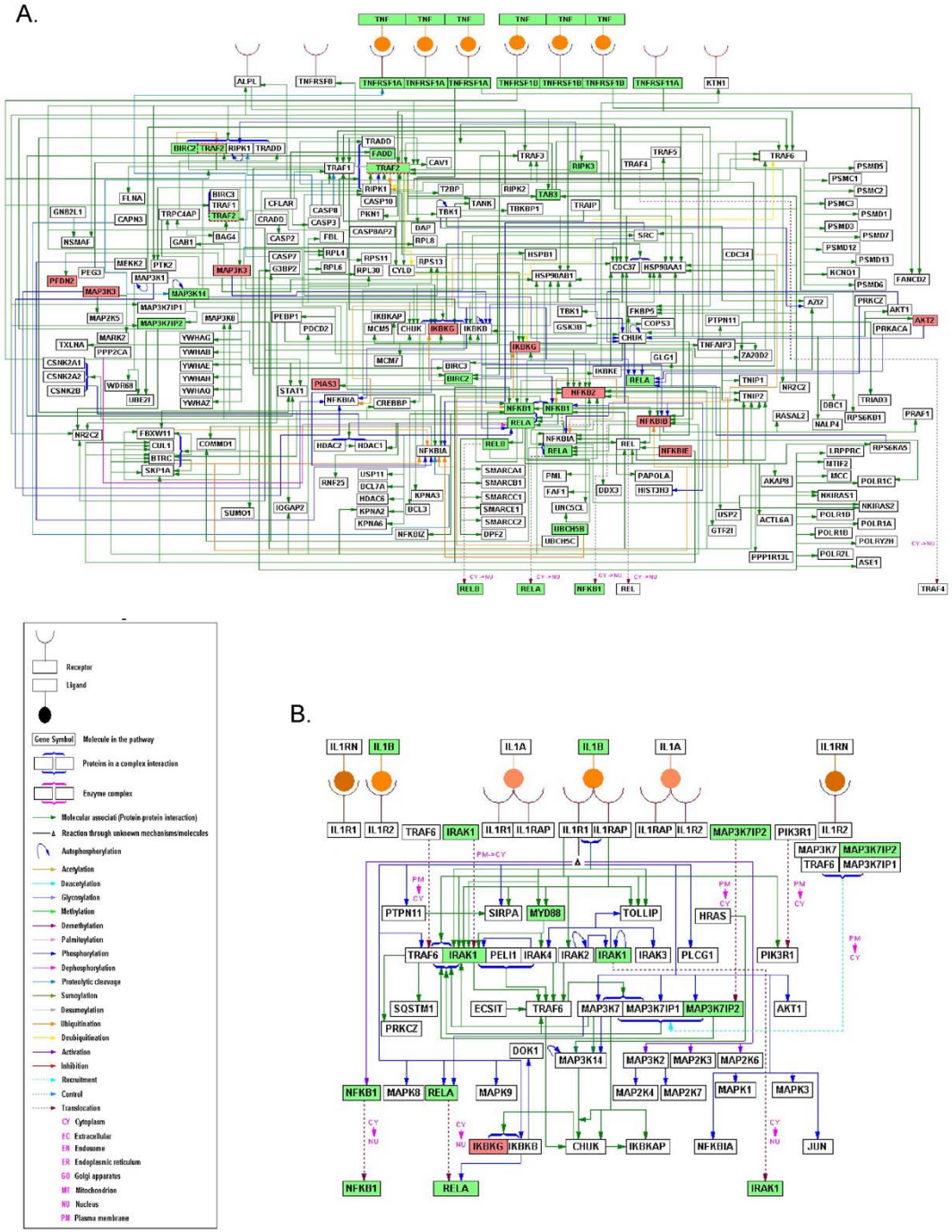


cAMP influences gene expression via CREB



Phosphorylation of CREB allows binding to DNA, activating gene transcription

Regulation of the transcription factor NF-kB



genomebiology.com/2007/8/6/R104

Questions to ponder

- Given the complexity of cell signaling pathways, will it be possible to fully understand information processing in cells?
- How can models, such as synthetic circuits, help us understand cell function?

Relevant readings

- Scott, JD and T Pawson. (2000) Cell communication: The inside story. Sci. Am., June 2000: 72-79.
- Slusarczyk, AL, A Lin and R Weiss. (2012) Foundations for the design and implementation of synthetic genetic circuits. Nature Rev. Genetics, 13: 406-420.
- Greif, KF. (2007) Can we model a cell? Emergent approaches to biological research. Soundings, XC: 91-101.