Cell Signalling

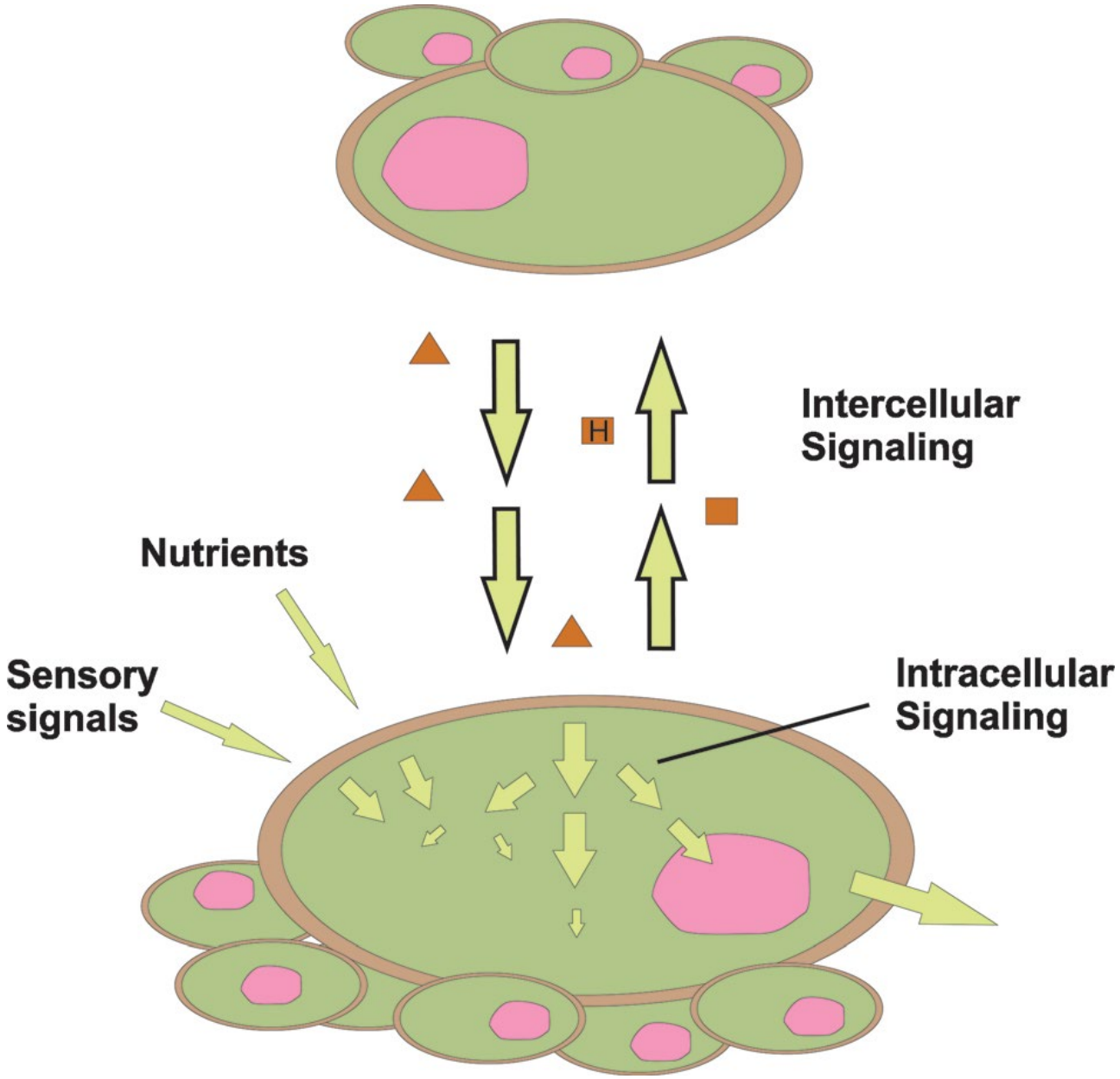
The higher organisms have to coordinate a large number of physiological activities such as:

- Intermediary metabolism
- Response to external signals
- Cell growth
- Cell division activity
- Differentiation and development: coordination of expression programs
- Cell motility
- Cell morphology

- **Intercellular signaling:**
  - Communication between cells.
- **Intracellular signaling:**
  - Signaling chains within the cell, responding to extracellular and intracellular stimuli.

Intercellular and Intracellular Signaling

The major method of intercellular communication employs messenger substances (hormones) that are secreted by signal-producing cells and registered by target cells. All cells produce and receive multiple, diverse signals. The extracellular signals are transduced into intracellular signaling chains that control many of the biochemical activities of a cell and can also trigger the formation of further extracellular signals.



In higher organisms, intercellular signaling pathways have the important task of coordinating and regulating cell division. The pathways ensure that cells divide synchronously and, if necessary, arrest cell division and enter a resting state.

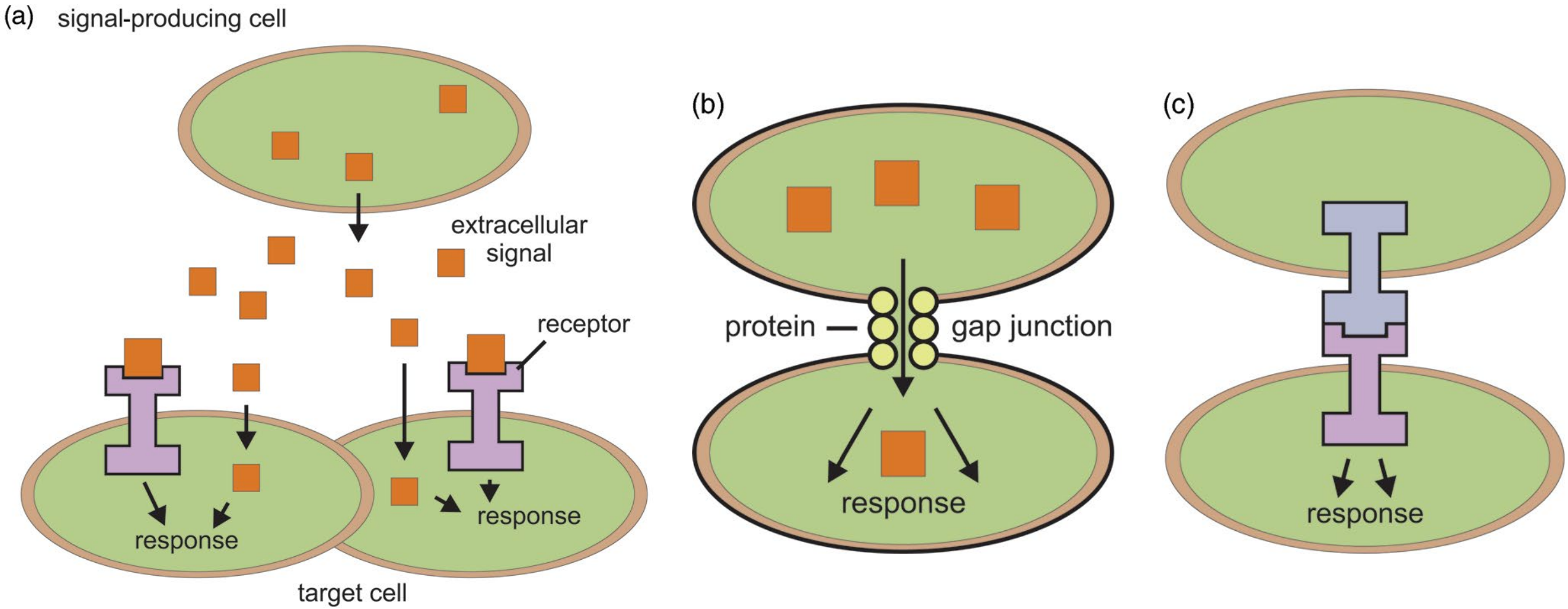
- Intercellular signaling:
  - **Processes**
    - sensory information
  - **Controls**
    - Metabolic fluxes
    - Cell division
    - Growth
    - Differentiation
    - Development

Tools for Intercellular Signaling

Various forms of communication between cells are currently known:

- **Extracellular messengers:** Cells send out signals in the form of specific messenger molecules that the target cell transmits into a biochemical reaction. Signaling cells can simultaneously influence many cells by messenger molecules so as to enable a temporally coordinated reaction in an organism.

- **Gap junctions:** Communication between bordering cells is possible via direct contact in the form of “gap junctions.” Gap junctions are channels that connect two neighboring cells to allow a direct exchange of metabolites and signaling molecules between the cells.



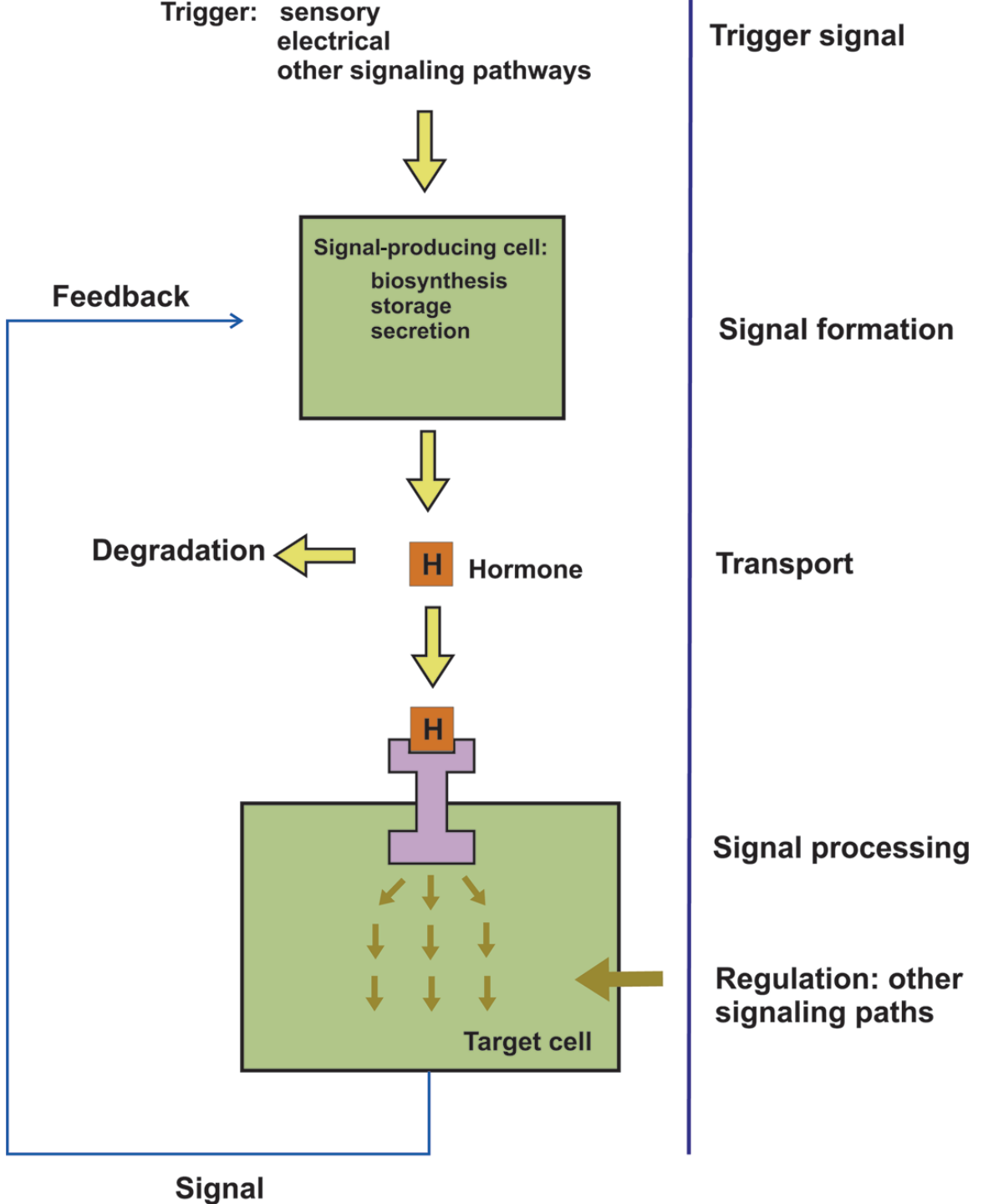
The principal mechanisms of intercellular communication. (a) Communication via intercellular messengers; (b) Communication via gap junctions, which provide direct connections between cells. Gap junctions are coated by proteins (shown as circles in the figure) that can have a regulatory influence on the transport; (c) Communication via surface proteins.

- Cells communicate via:

— Messenger substances
— Gap junctions
— Surface proteins
— Electrical signals

Steps of intercellular signaling:

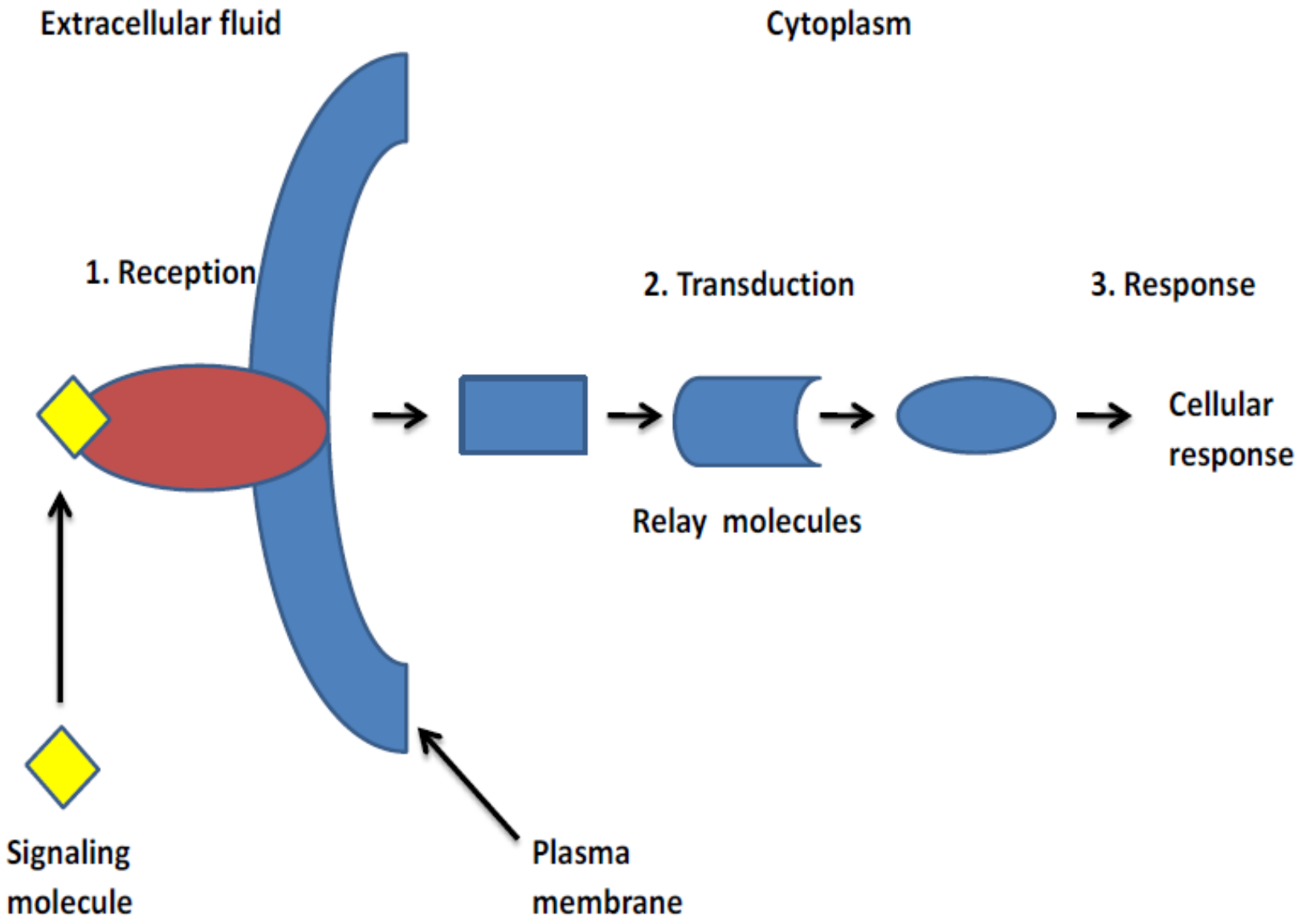
1) Trigger signal induces release of stored messenger or stimulates its biosynthesis
2) Transport to target cell
3) Receipt of signal by the target cell
4) Conversion of signal into intracellular signal chain in the target cell.



Cell signaling can be divided into 3 stages:

1. Reception: A cell detects a signaling molecule from the outside of the cell. A signal is detected when the ligand binds to a receptor protein on the surface of the cell or inside the cell.

2. Transduction: When the signaling molecule binds to the receptor, it changes the receptor protein. This change initiates the process of transduction. Each relay molecule in the signal transduction pathway changes the next molecule in the pathway.



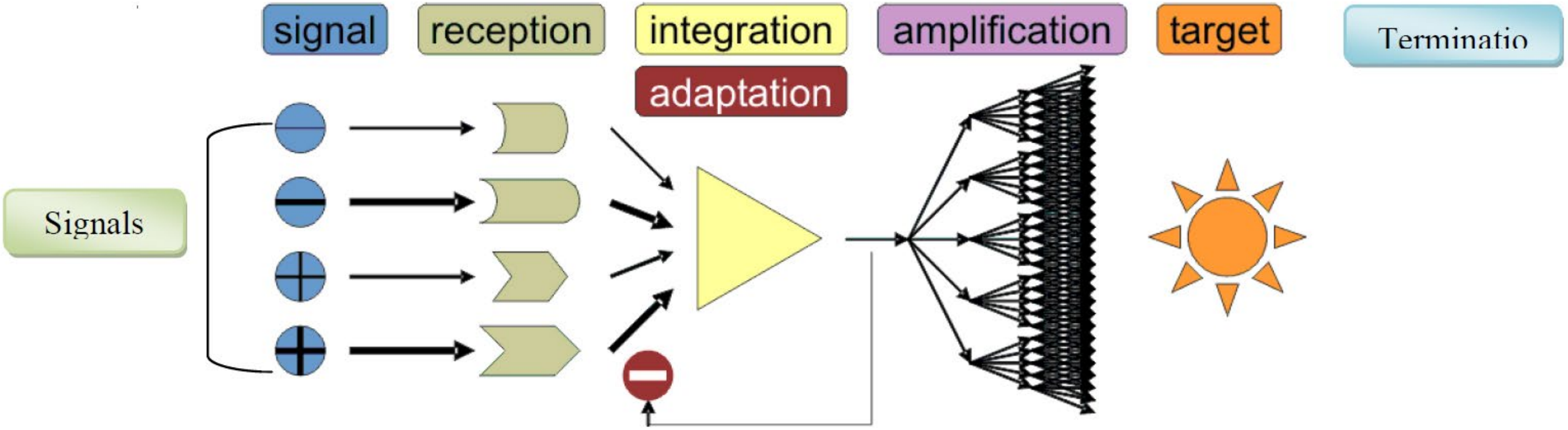
3. Response: Finally, the signal triggers a specific cellular response as shown in Figure.

Signal Transduction:

Signal transduction is phenomenon which involves in the transfer of signal from extracellular to intracellular environment through the cell surface receptor protein that stimulate intracellular target enzymes, which may be either directly linked or indirectly coupled to receptors by G proteins. These intracellular enzymes serve as downstream signalling elements that propagate and amplify the signal initiated by ligand binding. Thus, signal transduction pathway allows cells to respond to extracellular environmental signals. These signals can be physical and chemical such as light, oxygen, nutrient, hormones. Figure 3 represents the signal transduction pathway.

Signal transduction is the combination of following phenomenon:

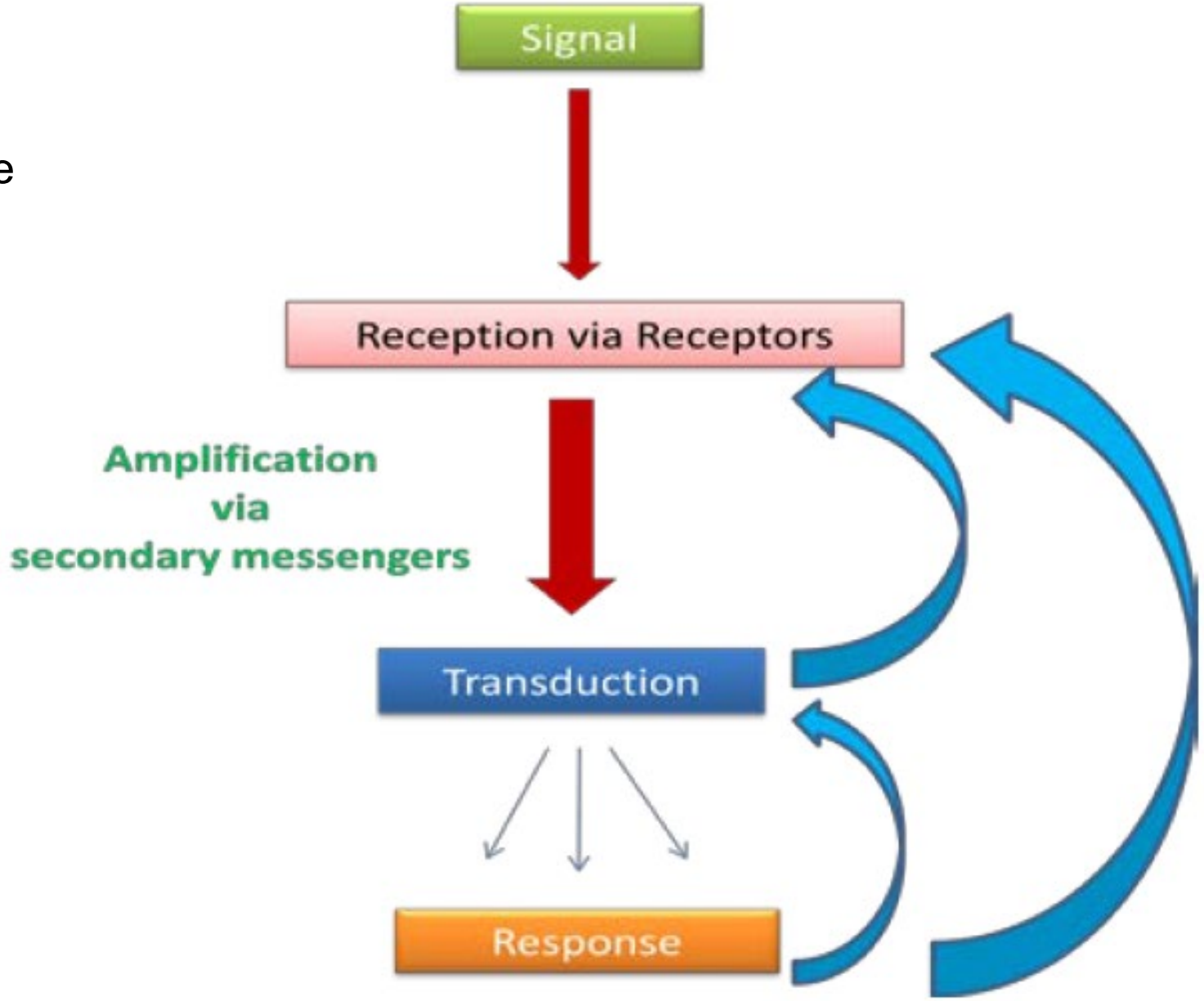
1. Signal reception
2. Integration
3. Amplification
4. A target that is affected
5. Termination



The signal transduction begins with receiving signal to the cell receptor and end with a change in cellular function. The cell receptor can be of various types- G-protein coupled receptor, tyrosin kinase receptor etc. The transduction process is typically mediated via a cascade of some important second messengers including cAMP, cGMP, calcium ion, inositol 1, 4, 5-trisphosphate, (IP_3), and diacylglycerol (DAG). Second messengers are intracellular molecules that change in concentration in response to environmental signals and involve in conveying information inside the cell.

Signal amplification

Signal amplification is phenomenon in which when receptor proteins interact with the signal molecules at the surface of the cell, in most cases signals are relayed to the cytoplasm or the nucleus by second messengers which influences the activity of one or more enzymes or genes inside the cell. However, most signalling molecules are found in such a low concentration that their effect in cytoplasm would be minimal unless the signal was amplified. Therefore, most enzymes linked and G-protein linked receptor use a chain of other protein messenger to amplify the signal as it is being relayed. Thus in case of protein kinase one cell surface receptor activates many G protein molecules. Each G protein activates many adenylyl cyclases. Each cyclic AMP in turn will activate protein kinase which then activates several molecules of a specific enzyme.



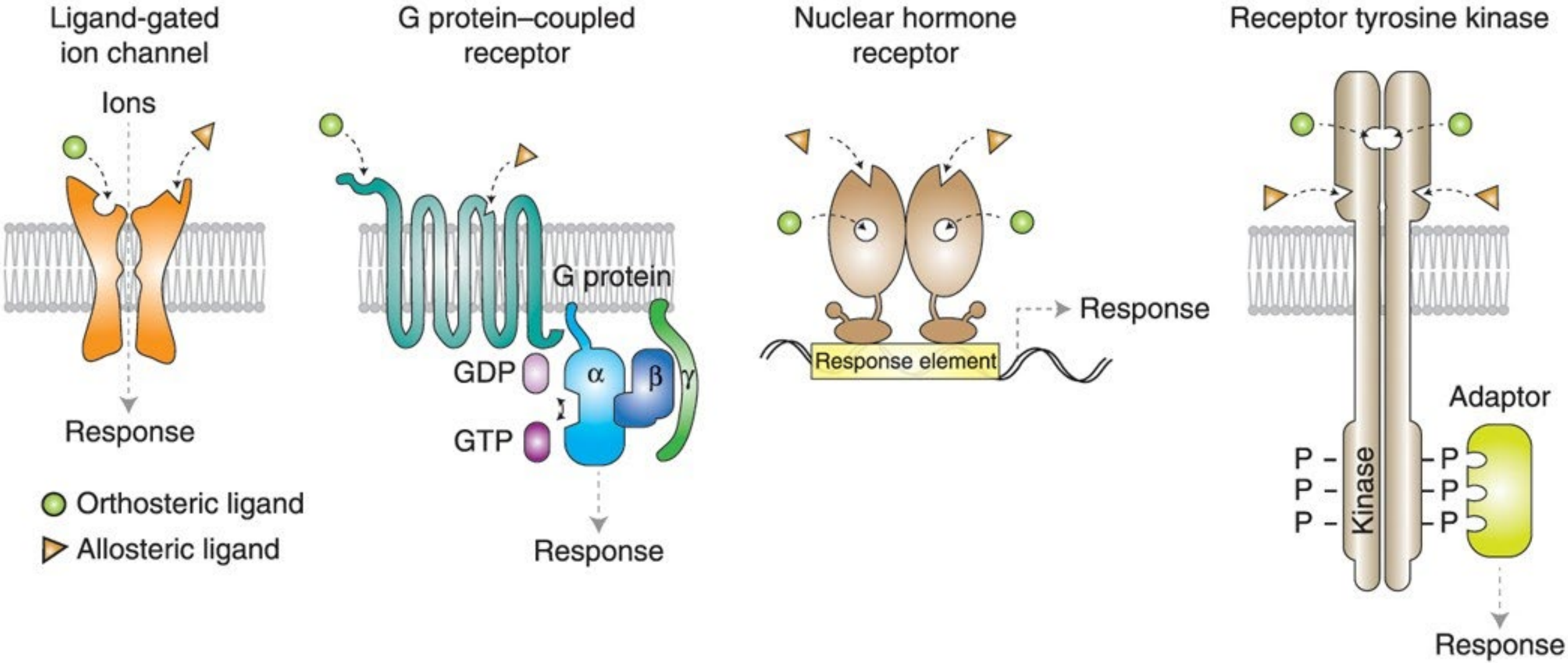
Cell Surface Receptors

Cell surface receptors play an essential role in the biological systems of single- and multi-cellular organisms and malfunction or damage to these proteins is associated with cancer, heart disease, and asthma. These trans-membrane receptors are able to transmit information from outside the cell to the inside because they change conformation when a specific ligand binds to it. There are three major types: Ion channel linked receptors, G protein–coupled receptors, and enzyme-linked receptors.

Classification of Cell Surface Receptors

1. **G Protein coupled receptors epinephrine, serotonine, glucagon**
2. **Ion channel receptors acetylcholine receptor**
3. **Tyrosine kinase-linked receptors cytokine-receptor family**
4. **Receptors with intrinsic enzymatic activity the receptor has intrinsic catalytic activity receptor tyrosine kinases**

Types of Cell Surface Receptors

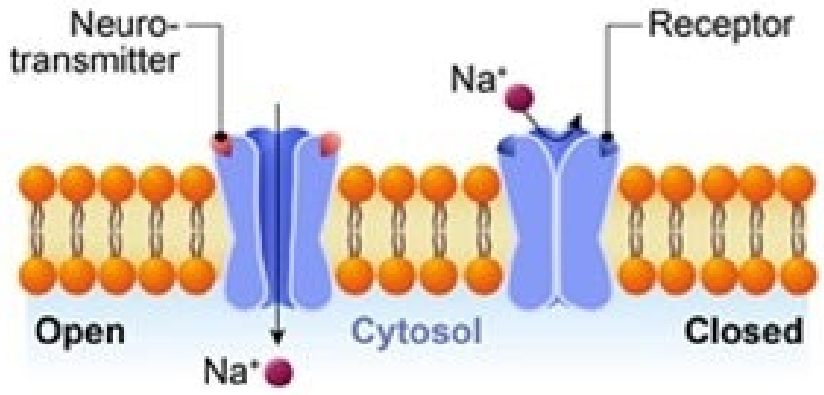


Ion channel linked receptors

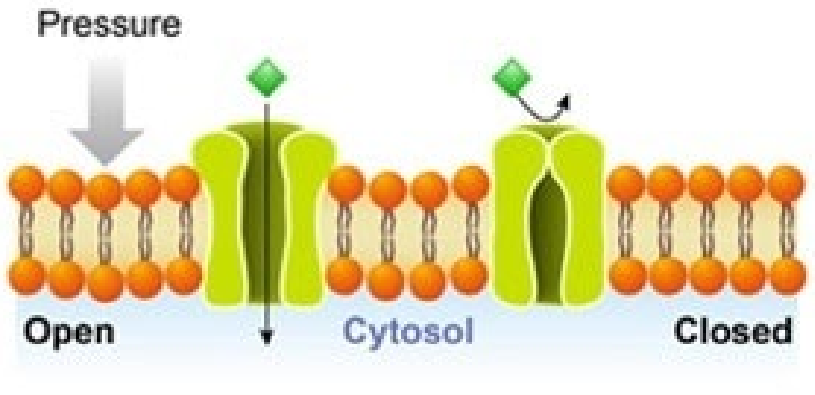
- Ion channel linked receptors are a group of transmembrane ion-channel proteins which open to allow ions such as Na^+, K^+, Ca^{2+}, and/or Cl^- to pass through the membrane in response to the binding of a chemical messenger (i.e. a ligand), such as a neurotransmitter.
- When a presynaptic neuron is excited, it releases a neurotransmitter from vesicles into the synaptic cleft. The neurotransmitter then binds to receptors located on the postsynaptic neuron. If these receptors are ligand-gated ion channels, a resulting conformational change opens the ion channels, which leads to a flow of ions across the cell membrane. This, in turn, results in either a depolarization, for an excitatory receptor response, or a hyperpolarization, for an inhibitory response.
- These receptor proteins are typically composed of at least two different domains: a transmembrane domain which includes the ion pore, and an extracellular domain which includes the ligand binding location (an allosteric binding site). This modularity has enabled a 'divide and conquer' approach to finding the structure of the proteins (crystallising each domain separately). The function of such receptors located at synapses is to convert the chemical signal of presynaptically released neurotransmitter directly and very quickly into a postsynaptic electrical signal. Many LICs are additionally modulated by allosteric ligands, by channel blockers, ions, or the membrane potential.
- LICs are classified into three superfamilies which lack evolutionary relationship: cys-loop receptors, ionotropic glutamate receptors and ATP-gated channels.

ION CHANNEL

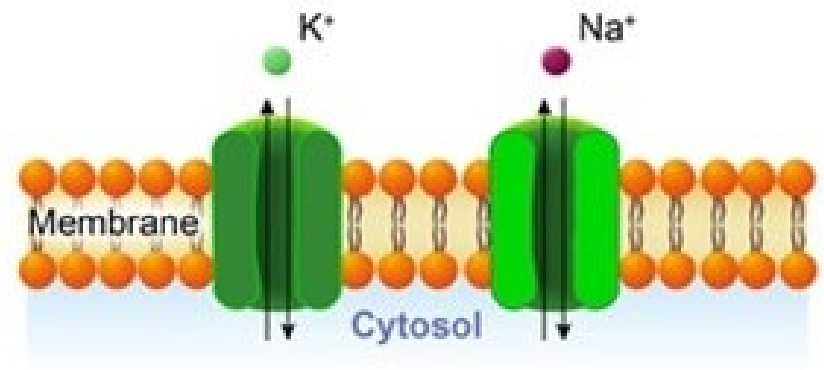
Ligand-gated



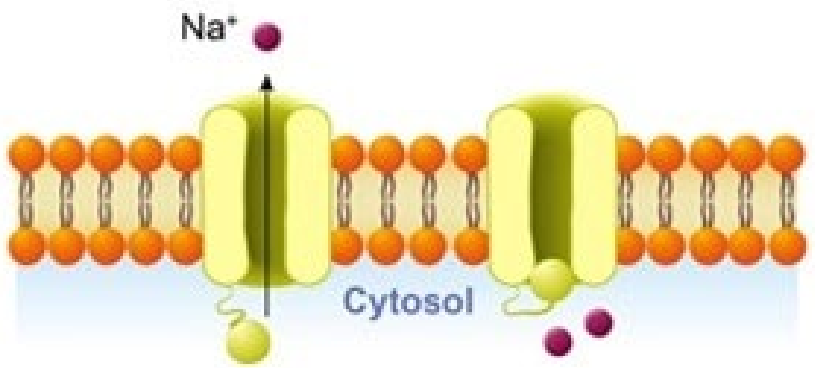
Mechanically-gated

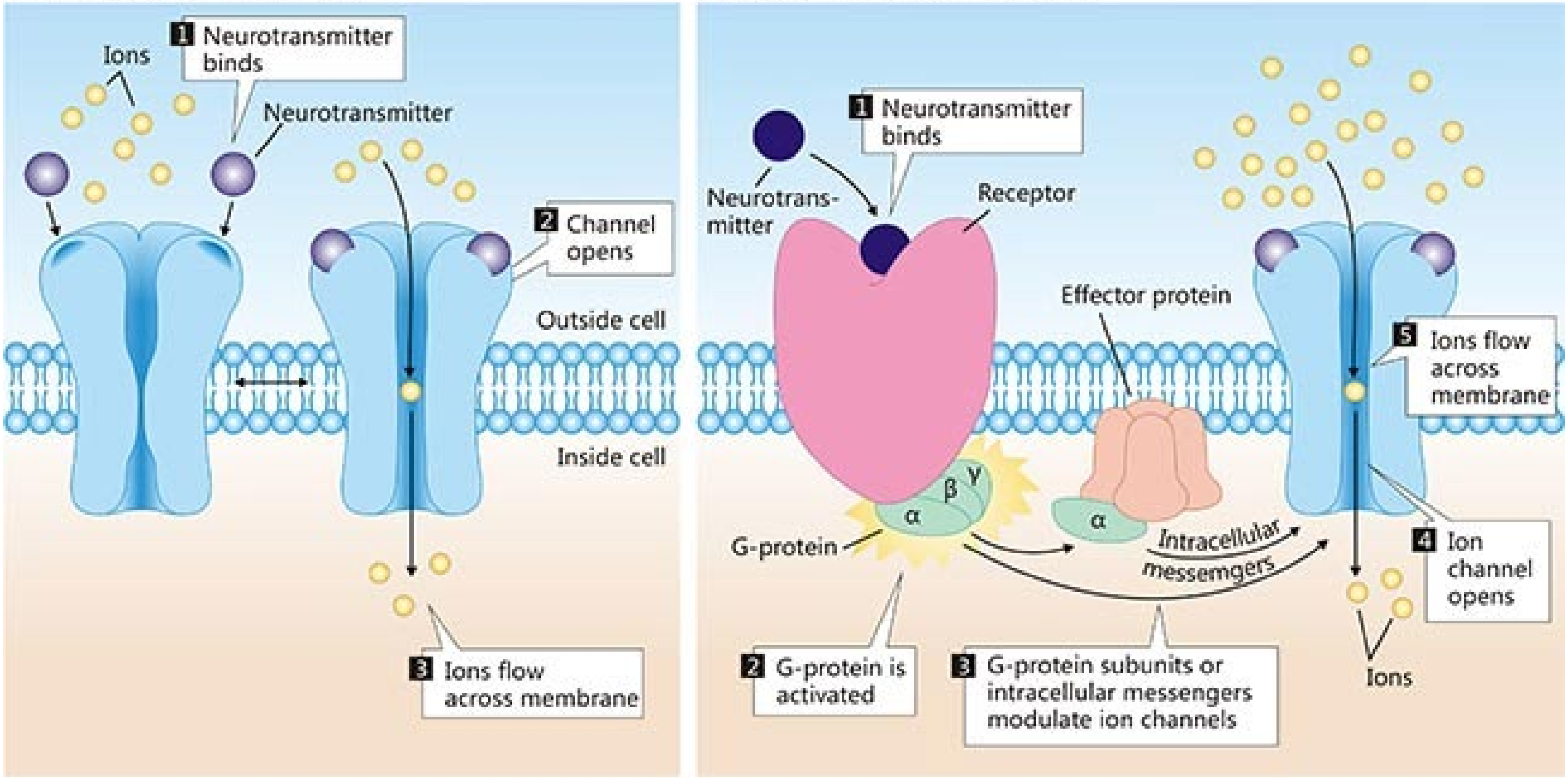


Always open



Voltage-gated




(A) Ligand-gated ion channels
Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane
(B) G-protein-coupled receptors
1 Neurotransmitter binds
Neurotrans-mitter
Receptor
Effector protein
5 Ions flow across membrane
α
β
γ
G-protein
α
Intracellular messengers
4 Ion channel opens
Ions
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels

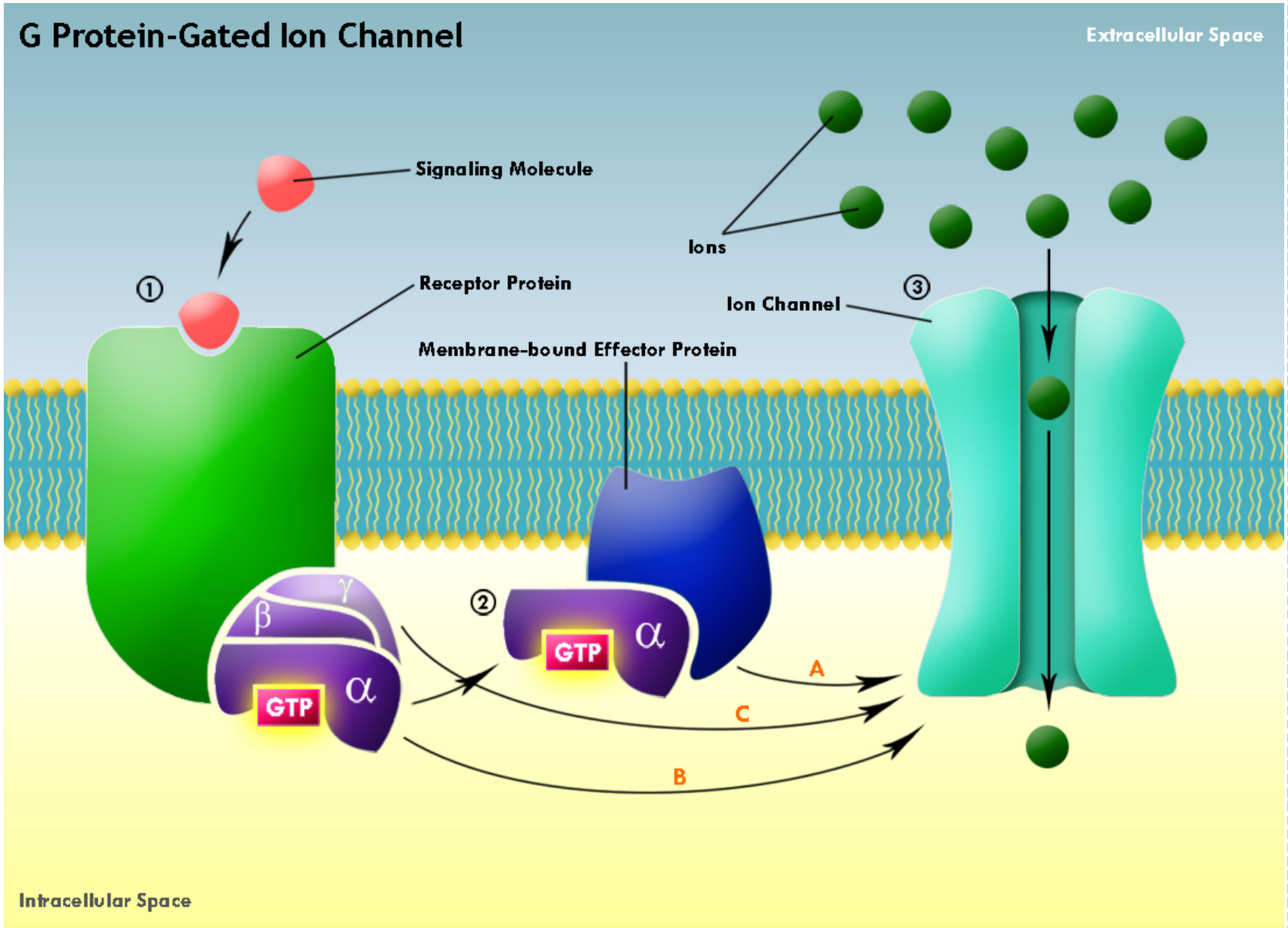
G Protein-Coupled Receptors (GPCR)

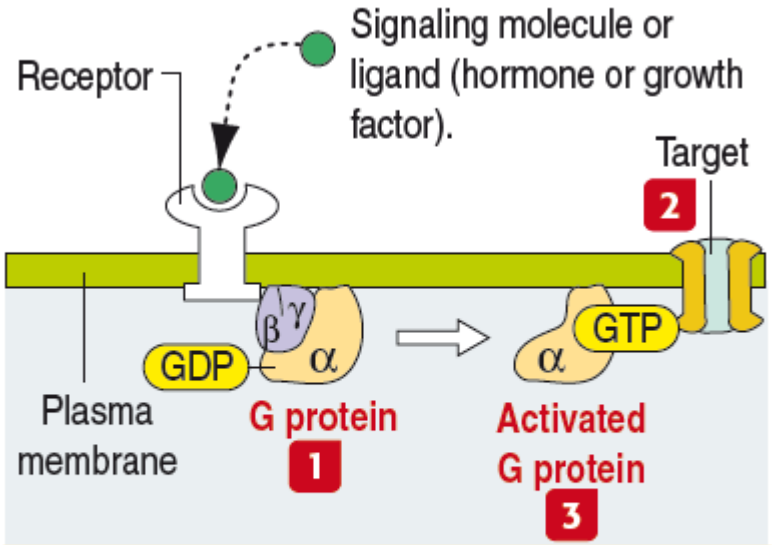
G protein-coupled receptors are a large group of evolutionarily-related proteins that are cell surface receptors that detect molecules outside the cell and activate cellular responses. Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times. Ligands can bind either to extracellular N-terminus and loops (e.g. glutamate receptors) or to the binding site within transmembrane helices (Rhodopsin-like family). They are all activated by agonists although a spontaneous auto-activation of an empty receptor can also be observed. GPCRs are found only in eukaryotes, including yeast, choanoflagellates, and animals. The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to peptides to large proteins.

There are two principal signal transduction pathways involving the GPCRs:

- **cAMP signal pathway and**
- **phosphatidylinositol signal pathway**

When a ligand binds to the GPCR it causes a conformational change in the GPCR, which allows it to act as a guanine nucleotide exchange factor (GEF). The GPCR can then activate an associated G protein by exchanging the GDP bound to the G protein for a GTP. The G protein's α subunit, together with the bound GTP, can then dissociate from the β and γ subunits to further affect intracellular signaling proteins or target functional proteins directly depending on the α subunit type.





G protein

1 **G protein consists of three subunits** (α, β, and γ). The α subunit regulates G protein activity. In the resting state, guanosine diphosphate (GDP) is bound to the α subunit in a complex with β and γ subunits.

2 G protein transmits a cell surface signal to an adjacent **target molecule (adenylyl cyclase or ion channel)**.

3 Hormone binding stimulates the release of GDP and its exchange for guanosine triphosphate (GTP).

The activated GTP-bound α subunit dissociates from β and γ and interacts with a target to induce a response.

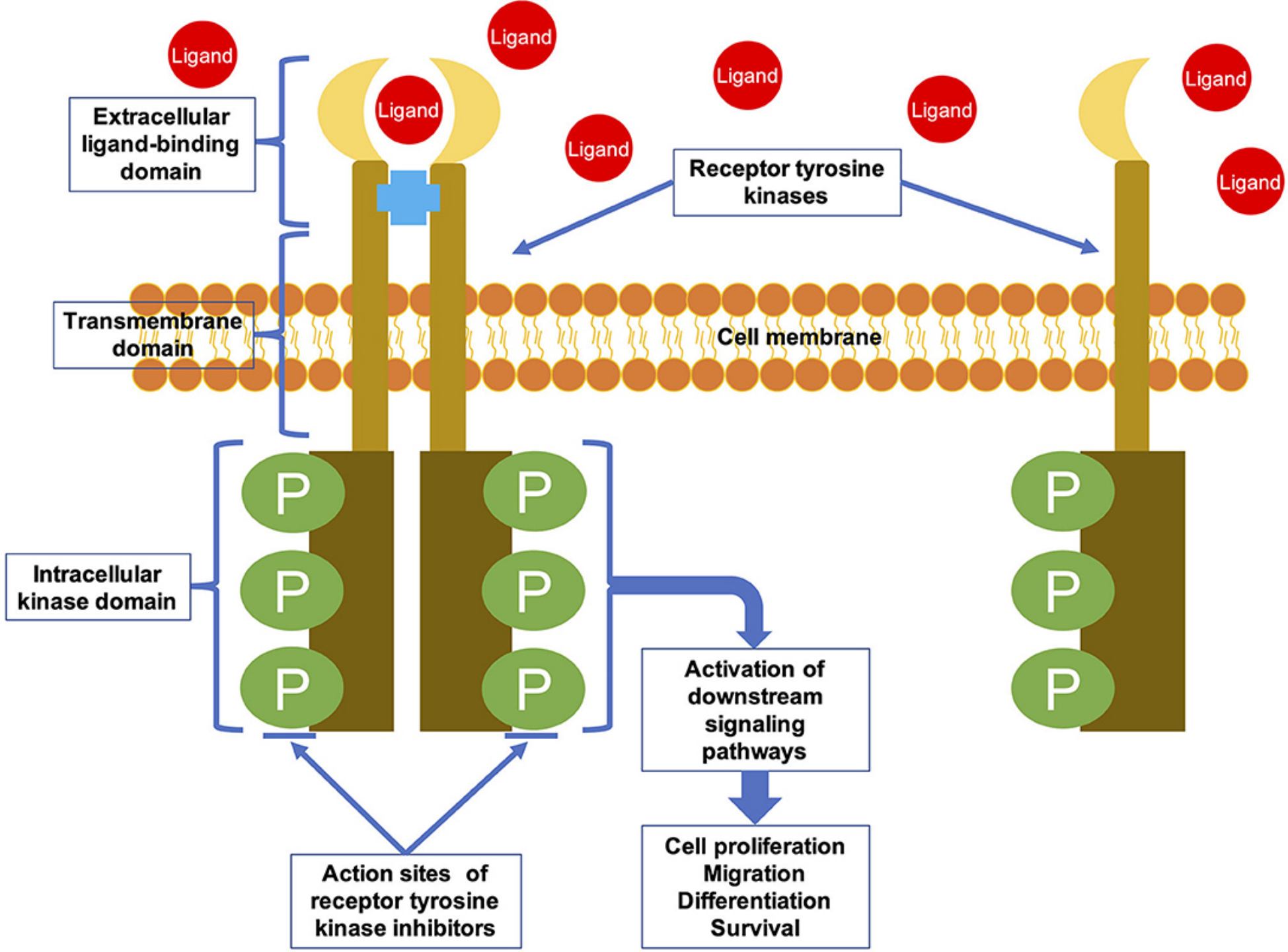
Enzyme-linked Receptors (or Catalytic Receptors)

Enzyme-linked receptors (or catalytic receptors) are transmembrane receptors that, upon activation by an extracellular ligand, causes enzymatic activity on the intracellular side. Hence a catalytic receptor is an integral membrane protein possessing both enzymatic, catalytic, and receptor functions.

They have two important domains, an extra-cellular ligand binding domain and an intracellular domain, which has a catalytic function; and a single transmembrane helix. The signaling molecule binds to the receptor on the outside of the cell and causes a conformational change on the catalytic function located on the receptor inside the cell.

Types of receptors:

- **Receptor tyrosine kinase, as in fibroblast growth factor receptor**
- **Serine/threonine-specific protein kinase**
- **Guanylate cyclase**


Ligand
Ligand
Ligand
Ligand
Ligand
Ligand
Ligand
Extracellular ligand-binding domain
Receptor tyrosine kinases
Transmembrane domain
Cell membrane
Intracellular kinase domain
P
P
P
P
P
P
P
P
P
Activation of downstream signaling pathways
Cell proliferation
Migration
Differentiation
Survival
Action sites of receptor tyrosine kinase inhibitors

Serine/Threonine Protein Kinase

A **serine/threonine protein kinase** (EC 2.7.11.-) is a kinase enzyme that phosphorylates the OH group of serine or threonine (which have similar sidechains). At least 125 of the 500+ human protein kinases are serine/threonine kinases (STK).

In enzymology, the term *serine/threonine protein kinase* describes a class of enzymes in the family of transferases, that transfer phosphates to the oxygen atom of a serine or threonine sidechain in proteins. This process is called phosphorylation. Protein phosphorylation in particular plays a significant role in a wide range of cellular processes and is a very important posttranslational modification.

The chemical reaction performed by these enzymes can be written as

ATP + a protein ADP + a phosphoprotein

Thus, the two substrates of this enzyme are ATP and a protein, whereas its two products are ADP and phosphoprotein. The systematic name of this enzyme class is *ATP:protein phosphotransferase (non-specific)*.

Serine/Threonine Kinase receptors play a role in the regulation of cell proliferation, programmed cell death (apoptosis), cell differentiation, and embryonic development.