





REPAIR

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Types of signals

- Pathogens and neighbor cells .
- Cell to cell signal
(gap junction signaling)
- Cell to ECM signals (Integrines)
- Secretory molecules (cytokines and hormones)



Autocrine signaling,

which a soluble mediator acts predominantly (or even exclusively) on the cell that secretes it.

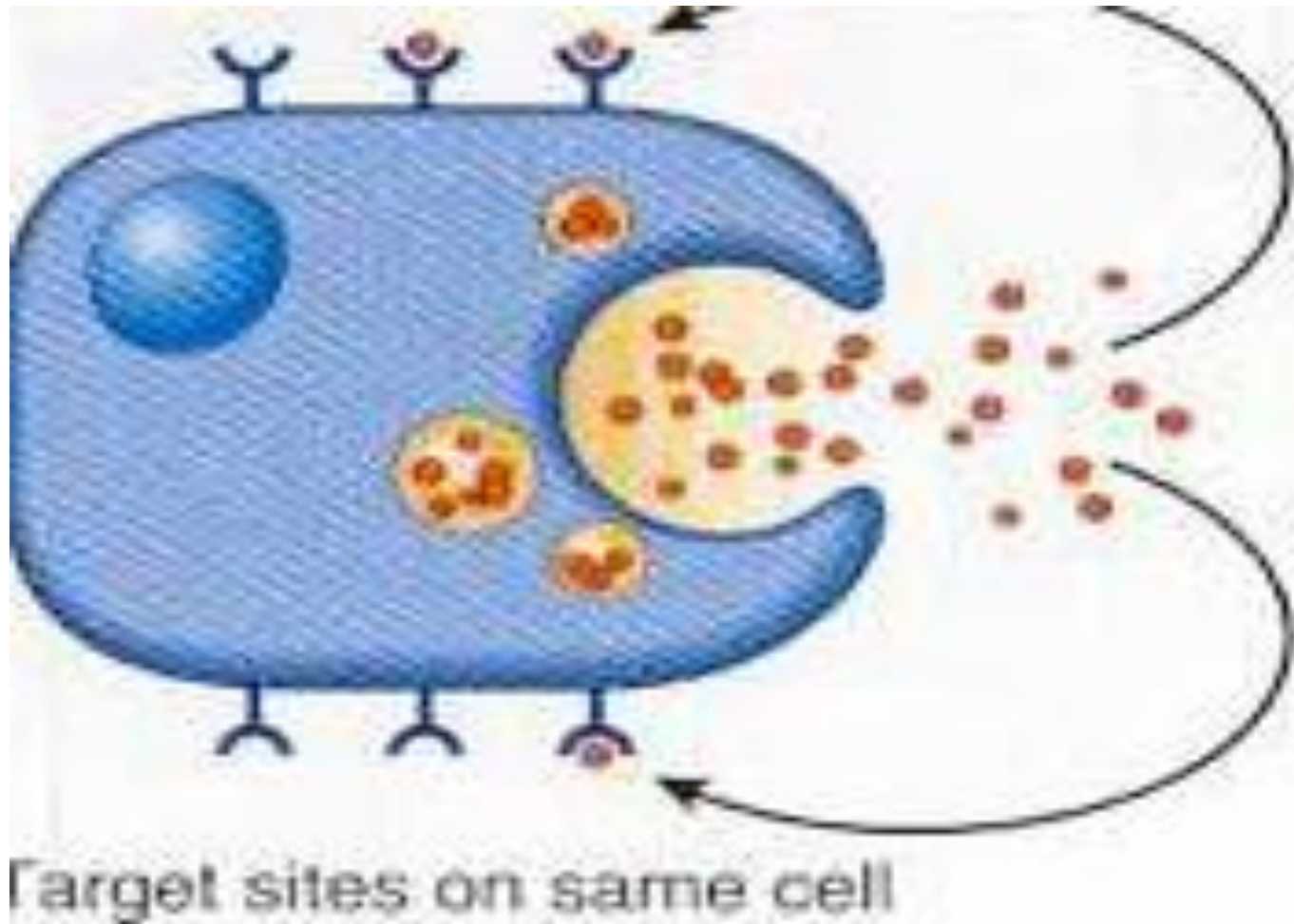
Differentiation of a cell group during evolution.

Positive and negative **feed back**.

This pathway is important in the **immuneresponse (cytokines)** and in **compensatory epithelial hyperplasia(liver regeneration)**



Autocrine signaling



Paracrine signal

Affect cells only in the **immediate vicinity**.

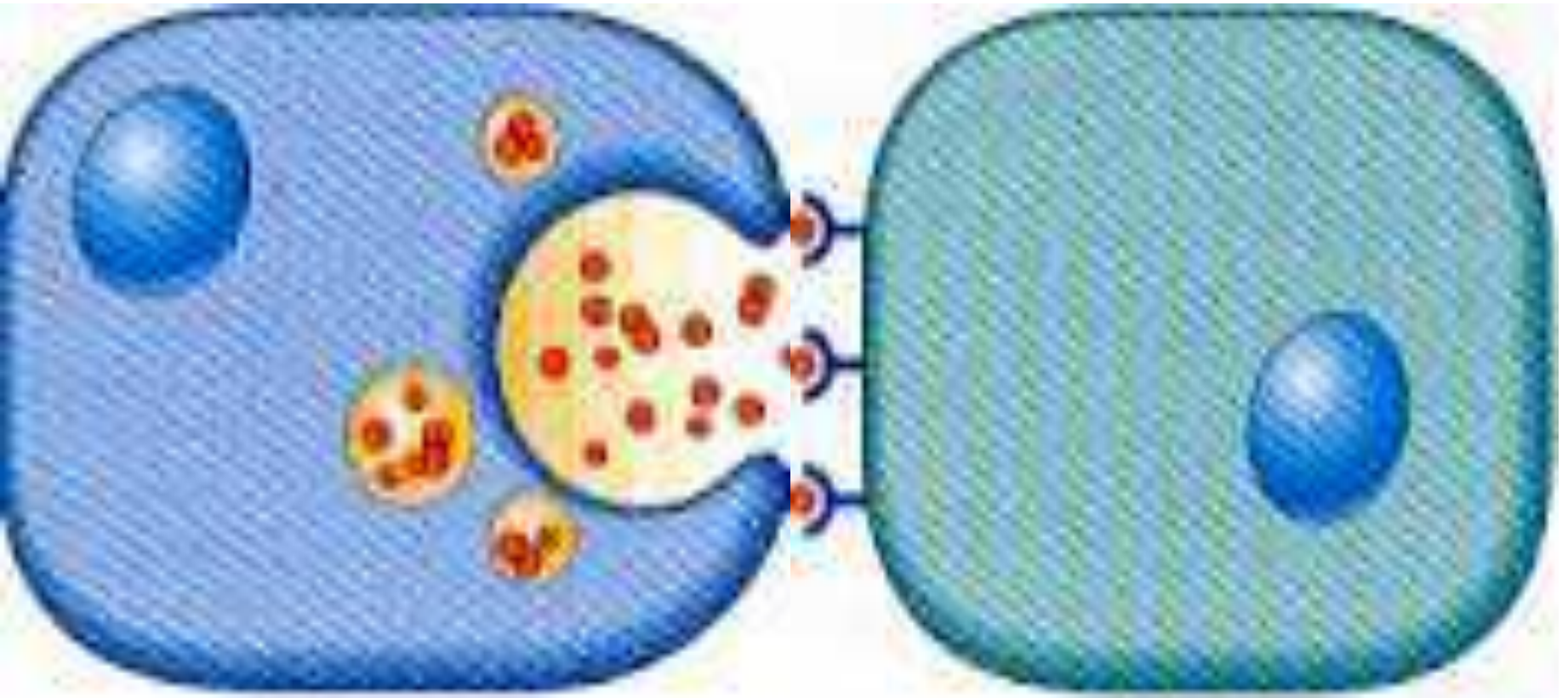
To accomplish this, there can be only minimal **diffusion**, with the signal rapidly degraded up by other cells,
or **trapped in the ECM**.

Transmembrane signals activate receptors
Attachment to ECM.

This pathway is important for **recruiting inflammatory cells** to the site of infection and for the **controlled process of wound healing**.



Paracrine signaling

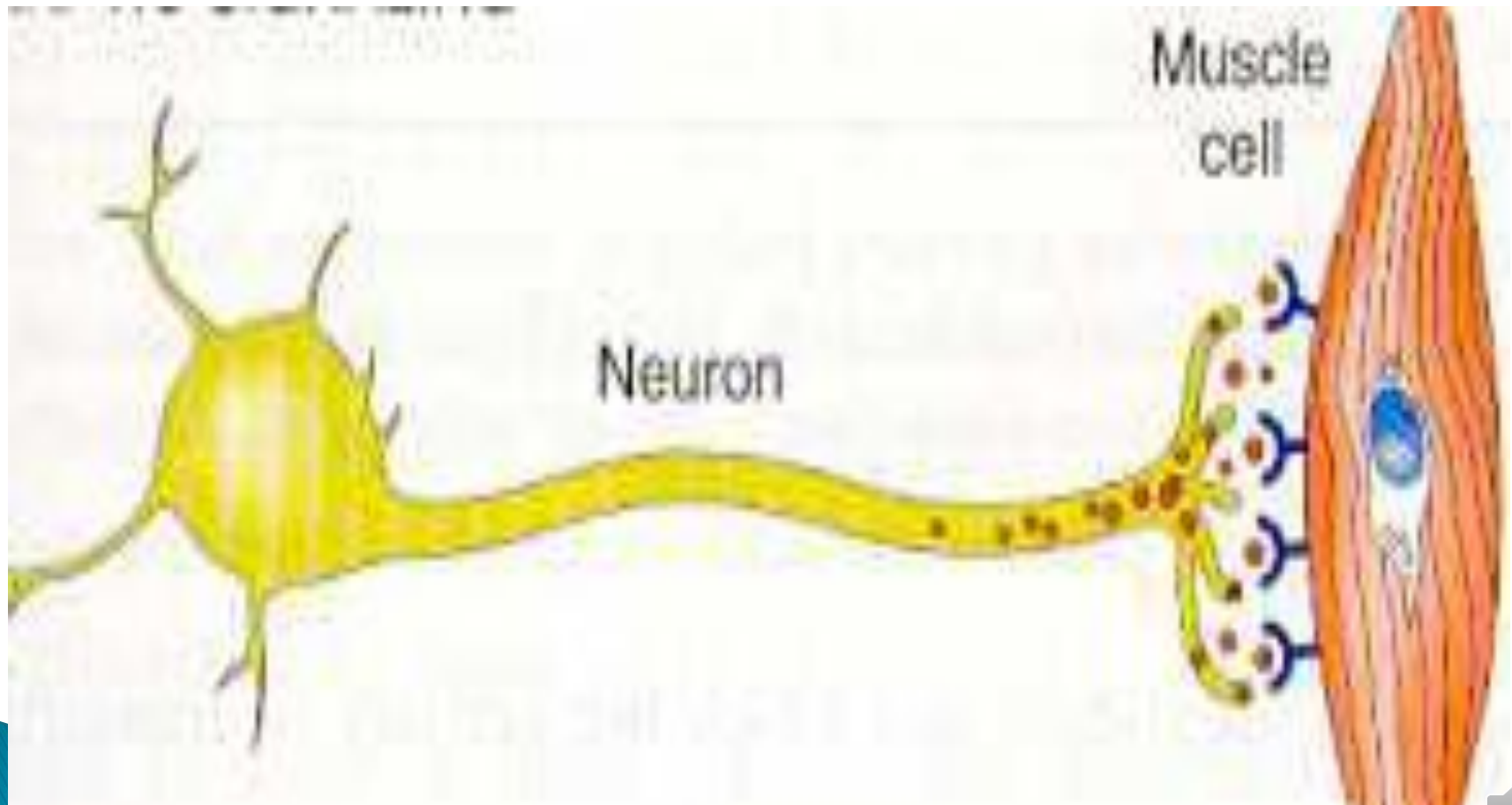


Synaptic

in which activated neural tissue secretes **neurotransmitters** at a specialized cell junction (synapse) on to target cells such as other nerves or muscles.



Synaptic signaling

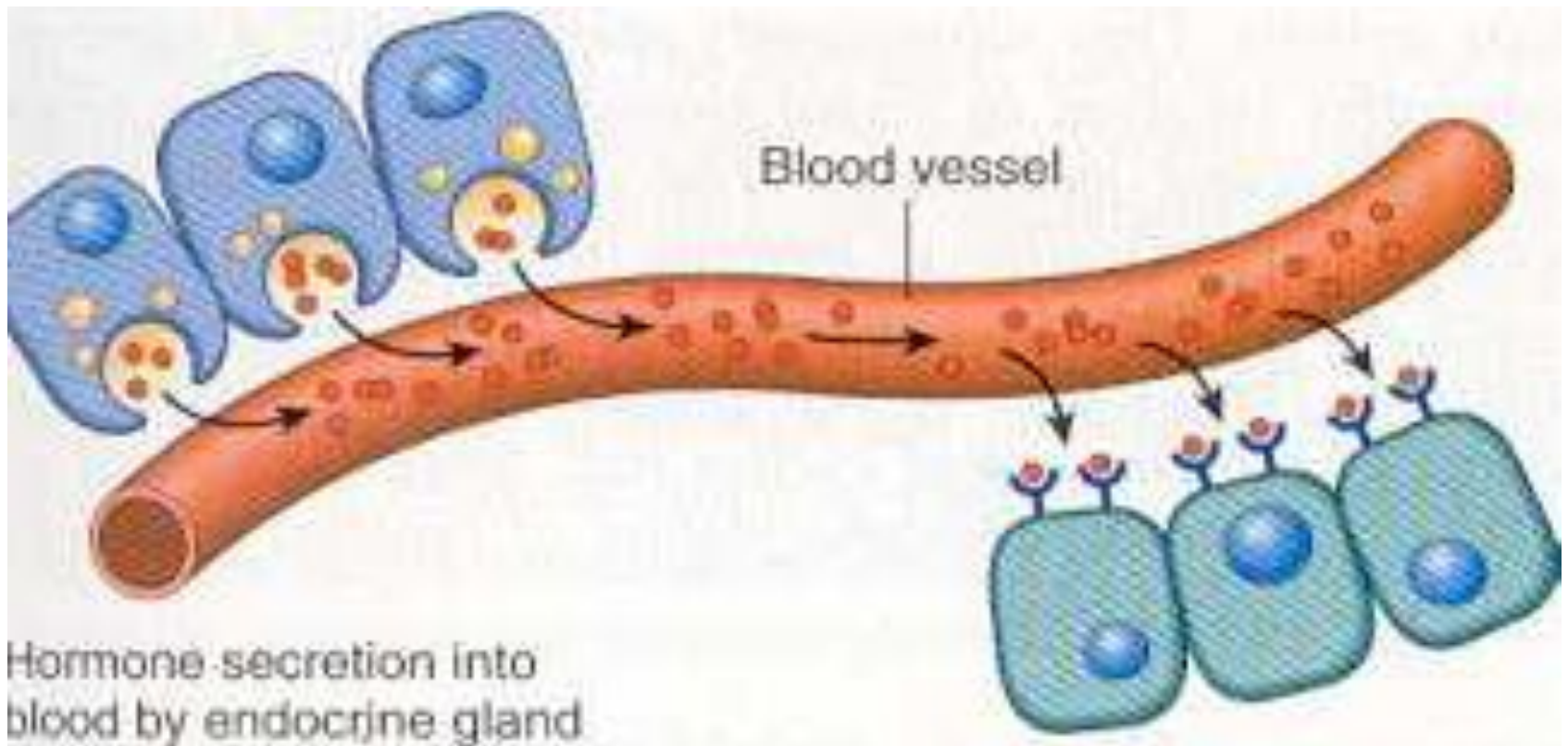


Endocrine

which a regulatory substance, such as a hormone, is released into the bloodstream and acts on target cells at a distance.



Endocrine signaling



Types of receptors

- Intra cellular receptors
- Cell surface receptors.



For intracellular receptors,

- Activate by **Lipid Soluble ligands** such as Vit d and steroids.

- Diffusion** to adjacent cells.(NO)

Form CGMP ligand binding leads to the formation of receptor–ligandcomplexes that **directly** associate with nuclear DNA and subsequently either activate or turn off gene transcription.





Cell surface receptors

- Receptores with instrinsis kinase activity
- Receptores coupled with Pr G
- other types of receptores (notch and wnt)
- Receptores with out instrinsic ensymatic activity



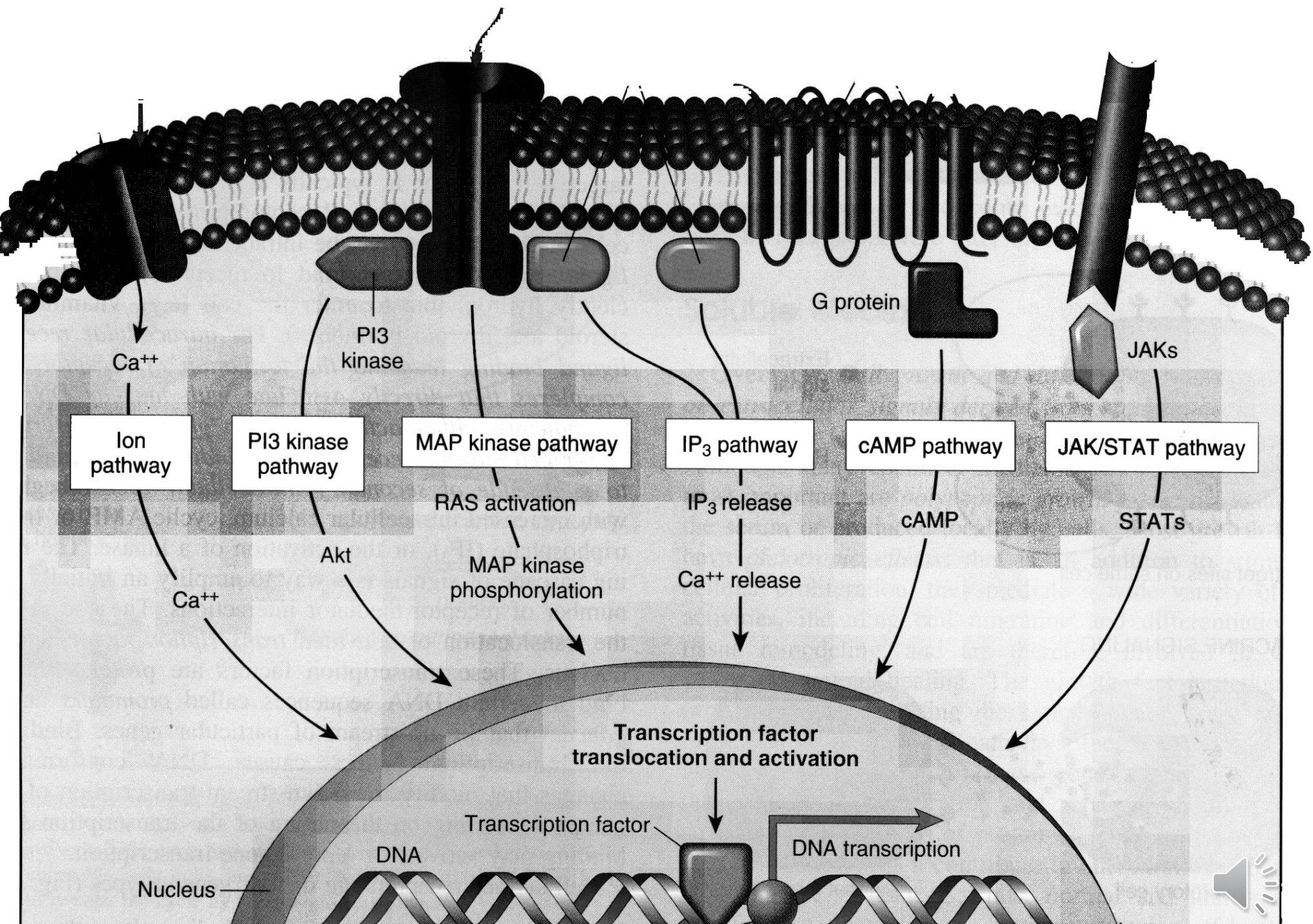
Receptors associated with kinase activity

1–Throsin kinase receptores. ▶

2–Non receptor thyrosin kinase ▶
(serin ,treonin ,lipid kinase) ▶

Phosphatase are inhibitory ▶





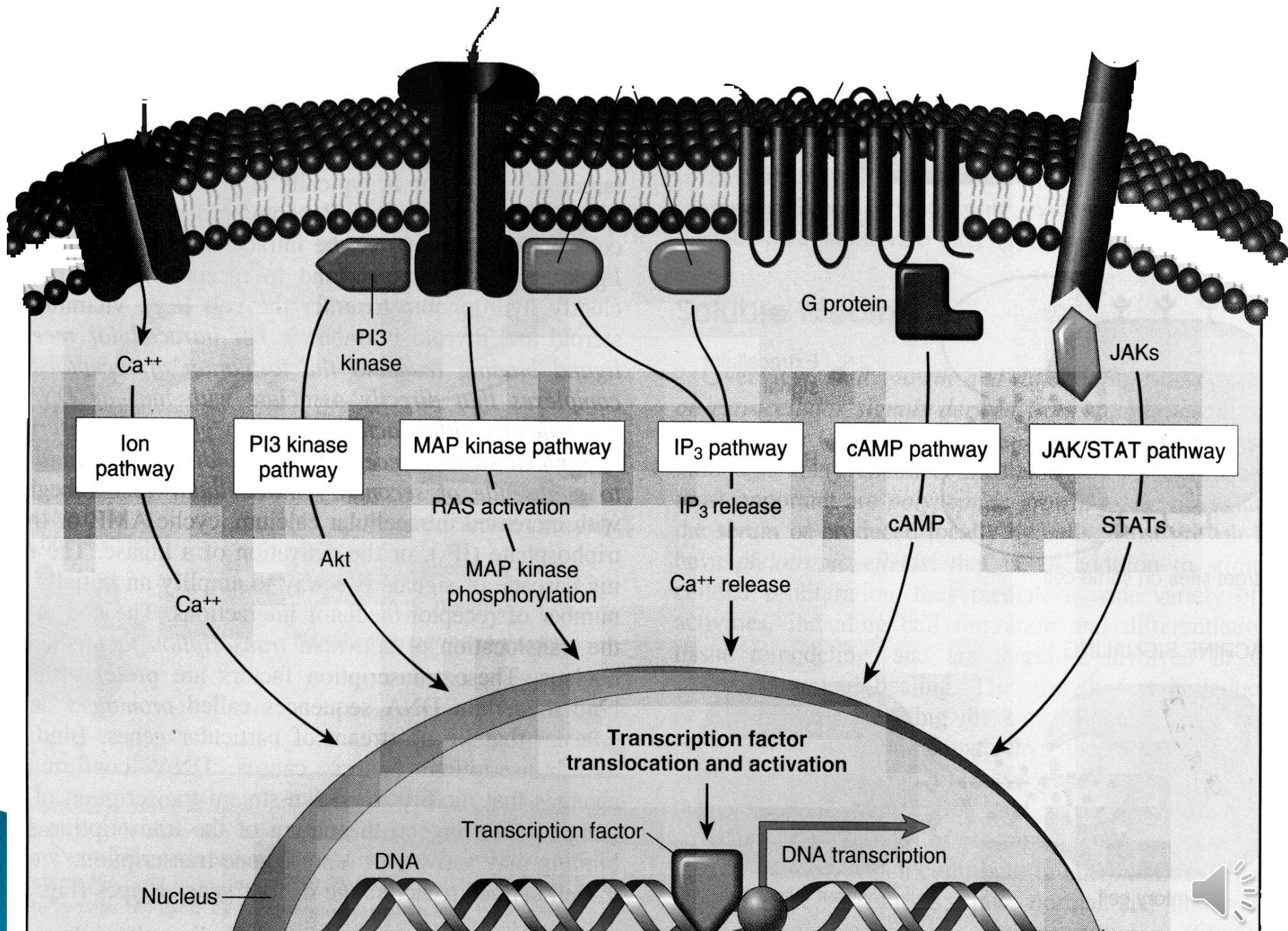
Receptors with intrinsic kinase activity.

. These are usually **dimeric** transmembranem or extracellular ligand-binding domain; ligand binding causes stable **dimerization** with subsequent **phosphorylation** of the receptor subunits.



Once phosphorylated, these receptors can bind to other intracellular proteins (e.g., RAS, GDP to GTP then RAS activated . **phosphatidylinositol3-kinase**, phospholipase C (PLC) and stimulate a cascade of events leading to entrance into S phase or induction of other transcriptional programs. An especially important pathway stimulated by RAS activation is the **mitogen-activated protein (MAP) kinase** cascade, which is involved in the intracellular signaling of multiple growth factors, including **epidermal growth factor (EGF)** and **fibroblast growth factor (FGF)**. Then GTP hydrolyze to GDP and RAS inactivated.





G-protein-coupled receptors

seven transmembrane segments; after binding the their specific ligand, the receptors associate with intracellular **GTP-hydrolyzing proteins** (hence the name G protein-coupled receptors). results in their activation, where upon they dissociate and can stimulate a variety of other proteins, including adenylate cyclase (to make cyclic AMP.)

Induce release of Ca from ER.



Other receptores

Roles in immune system ▶

ACT WITH Pr –PR INTERACTION ▶
(NOTenzymes)

–**Notch** fammily receptore Pr ▶

Ligand attach to receptor ,induce proteolitic ▶
brikage of receptor and transfer to
cytoplasm–

Wnt pr ligands process

Act throuw trnsmembrane **Frizzled** family ▶
make stable and **protect B catenin** ▶





Groth factors

Increase cell papulation is due to
Groth ,devision,apoptpsis supresion.

- Groth factors and mitogens.
- Stimulaion or supresion of proliferation.
- EGF,HGF,VEGF,PDGF,FGF...



- Ligand to receptor attachment start s serial events to tranducing extra cellular signals.
- Induce stimulation or supresion of gen expresion.

Growth factors

They induce activity of pr for life ,growth and division.

–Induce gens for :

Entrance to cell cycle

–Destroy barriers

–Inhibite apoptosis

–Enhancment of production of cell materials.

–



EGF and TGF α

Attached to a receptors common biologic activity. ▶

Produce by macrophages and epithelial cells ▶

There are mitogen for hepatocytes ,fibroblast and epithelial cells . ▶

There are 4 receptors ▶

Mutation in EGFR1 associated with cancers of lung ,head and neck ,brain and breast. ▶

–Ab and antagonist of receptor ▶



HGF

Distraction factor ▶

Produce by fibroblasts, mesenchymal and epithelial cells .

It is mitogen for hepatocytes and epithelial cells. ▶

It is a **morphogen factor** in tissue differentiation in embryogenesis ▶

Inactivated form ,is proteolyzed by serine protease for activation . ▶

Receptor (MET) is overexpressed in papillary carcinoma of thyroid and kidney ▶



PDGF

- Have two chain,5 isoformMultiple dimeric pr
Storage in PL granules also macrophages
,endothelial and smooth muscle .
- Release from plateletes during activation also
from endothelial,macrophages and tumor cells.
- Migration and proliferation of
fibroblaslts,muscle (matrix production)
and,macrophages
- Induce chemotaxis of inflammatory cells.



VEGF

They are dimeric glycoproteins, present in most tissues mostly in myocard and renal podocytes.

- Type VEGF a is the **most important angiogenesis factor in tumor or repair.**

Type b in embryogenesis

type C; in angiogenesis and lymphangiogenesis

- Attached to tyrosin kinase receptors.



The most important receptor for angiogenesis is **VEGFR2** ,restricted to endothelial cells High level in fenestrate arteries
(renal pdoucytes,retinal arteries,and choroid vesseles)

