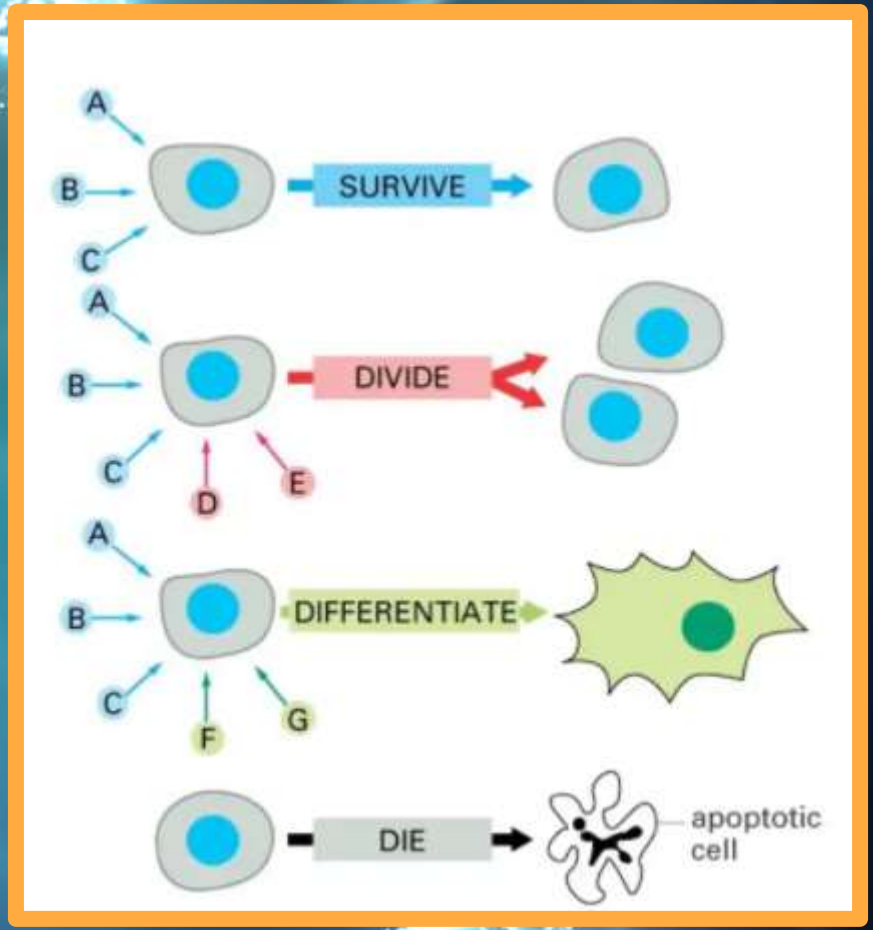
Cell signaling



Receptor Enzyme

- An enzyme-linked receptor, also known as a catalytic receptor, is a transmembrane receptor, where the binding of 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.
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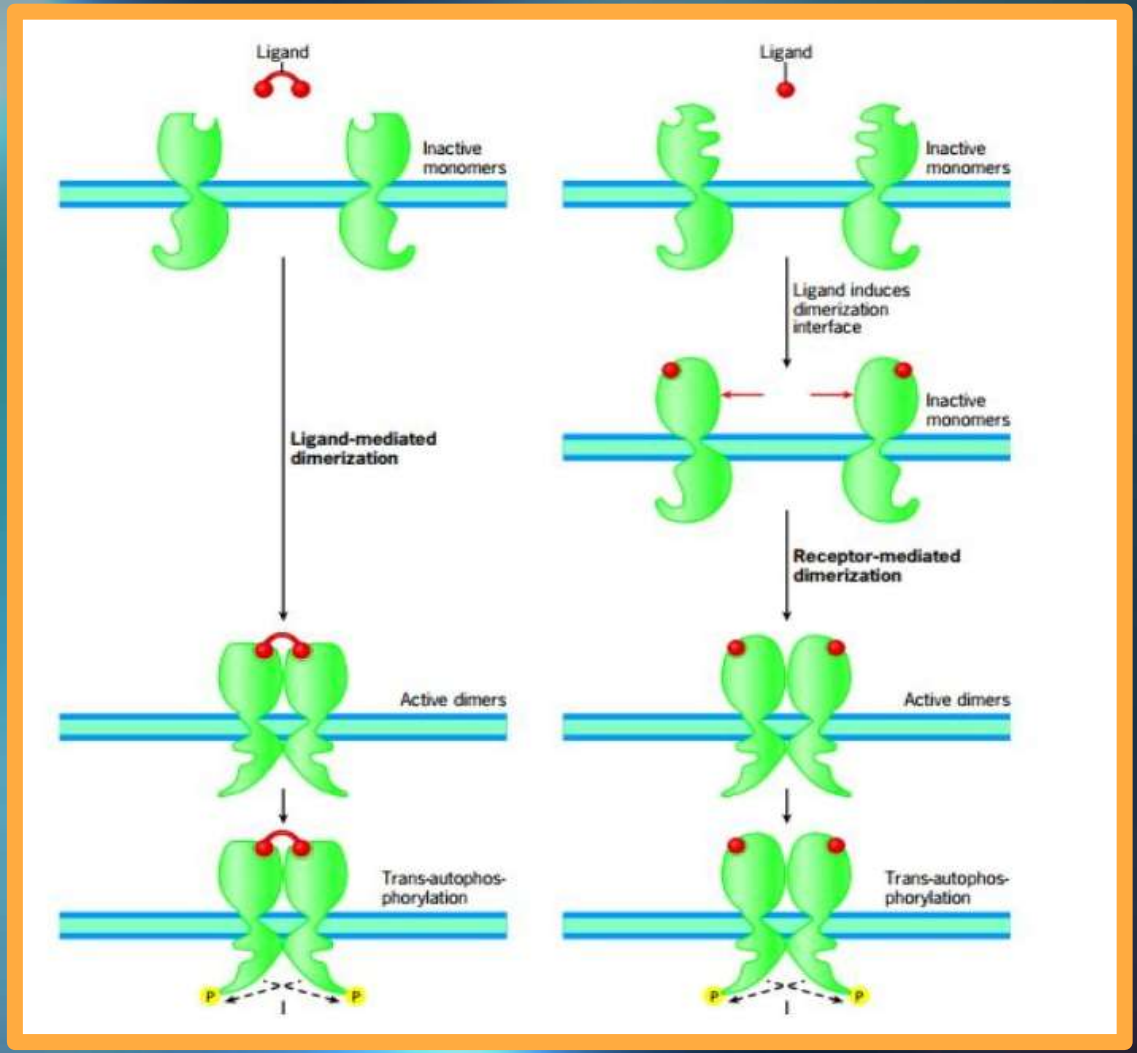
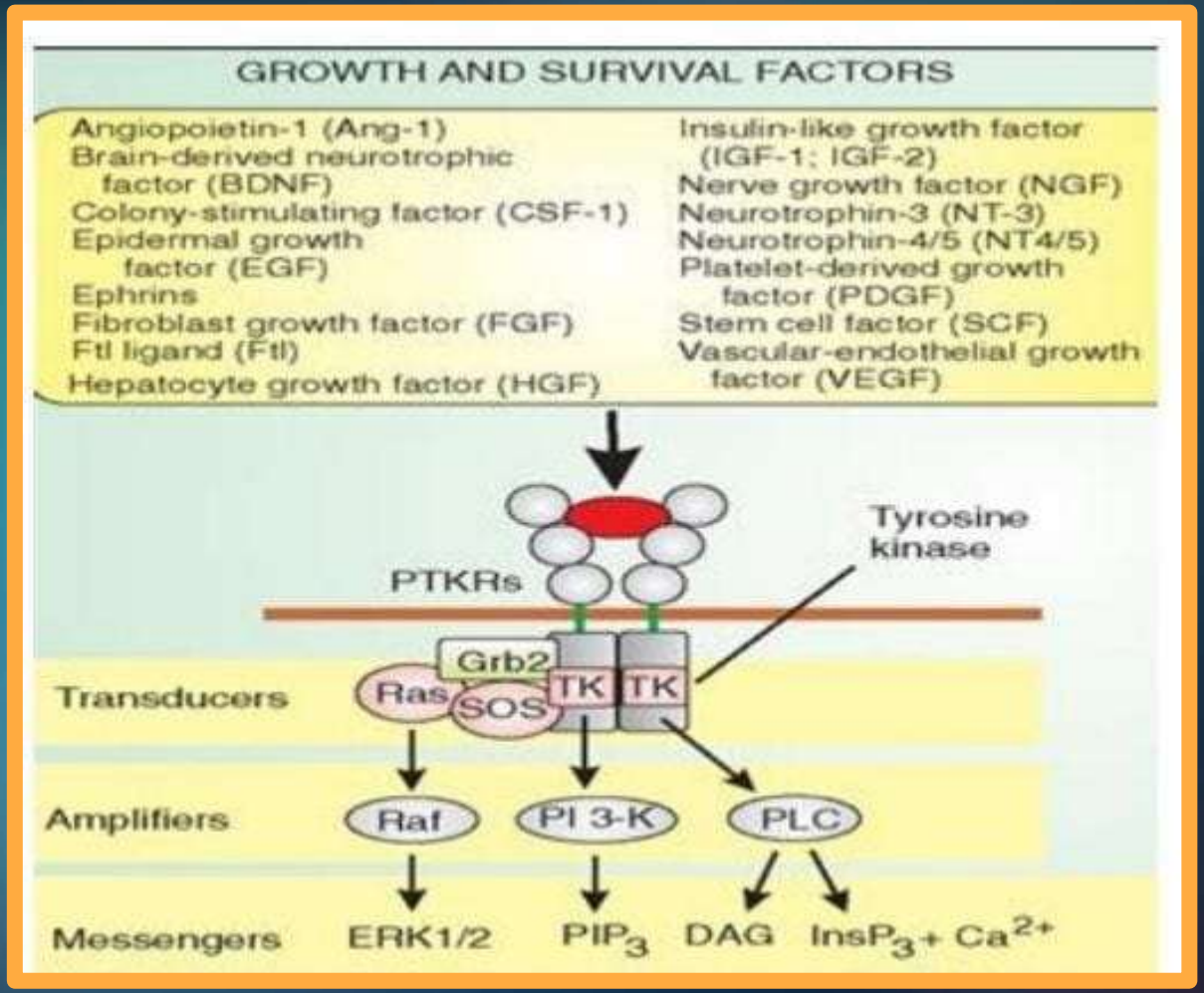
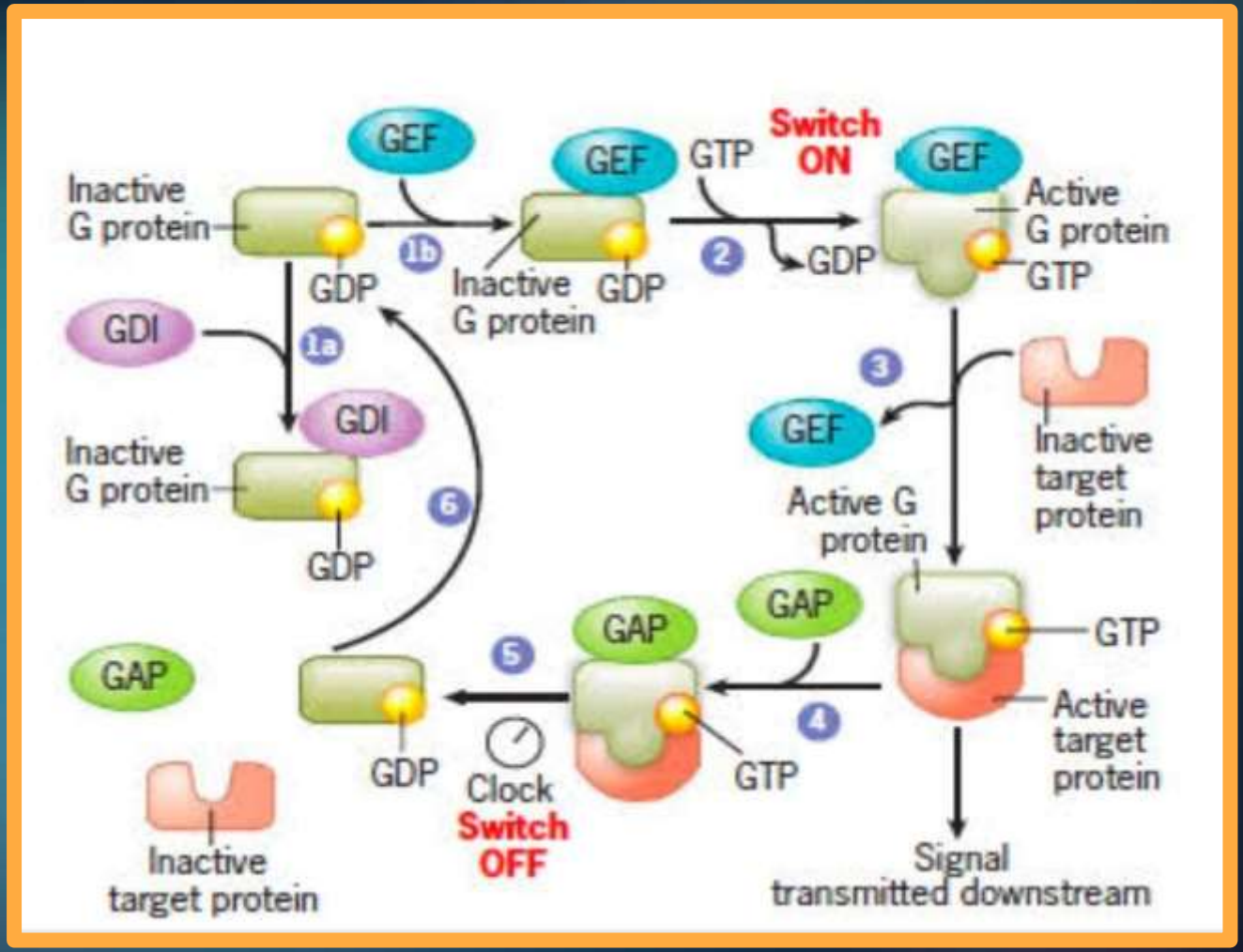
- Examples of the enzymatic activity include: Receptor tyrosine kinase, as in fibroblast growth factor receptor.

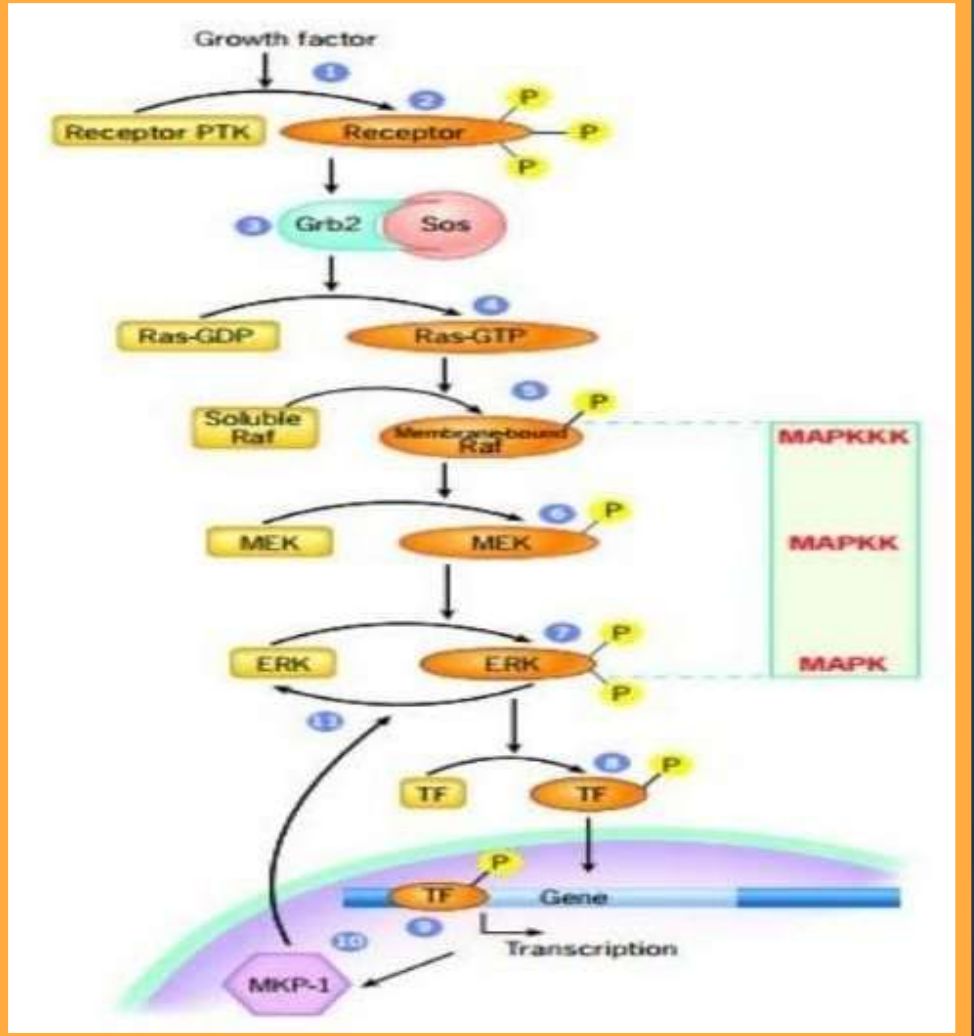

Ligand
Inactive monomers
Ligand-mediated dimerization
Active dimers
Trans-autophos-phorylation
P
P
Ligand
Inactive monomers
Ligand induces dimerization interface
Inactive monomers
Receptor-mediated dimerization
Active dimers
Trans-autophos-phorylation
P
P


GROWTH AND SURVIVAL FACTORS
Angiopoietin-1 (Ang-1)
Brain-derived neurotrophic factor (BDNF)
Colony-stimulating factor (CSF-1)
Epidermal growth factor (EGF)
Ephrins
Fibroblast growth factor (FGF)
Ftl ligand (Ftl)
Hepatocyte growth factor (HGF)
Insulin-like growth factor (IGF-1; IGF-2)
Nerve growth factor (NGF)
Neurotrophin-3 (NT-3)
Neurotrophin-4/5 (NT4/5)
Platelet-derived growth factor (PDGF)
Stem cell factor (SCF)
Vascular-endothelial growth factor (VEGF)
PTKRs
Tyrosine kinase
Transducers
Grb2
Ras
SOS
TK
TK
Amplifiers
Raf
PI 3-K
PLC
Messengers
ERK1/2
PIP3
DAG
InsP3 + Ca2+

Ras-MAP Kinase Pathway

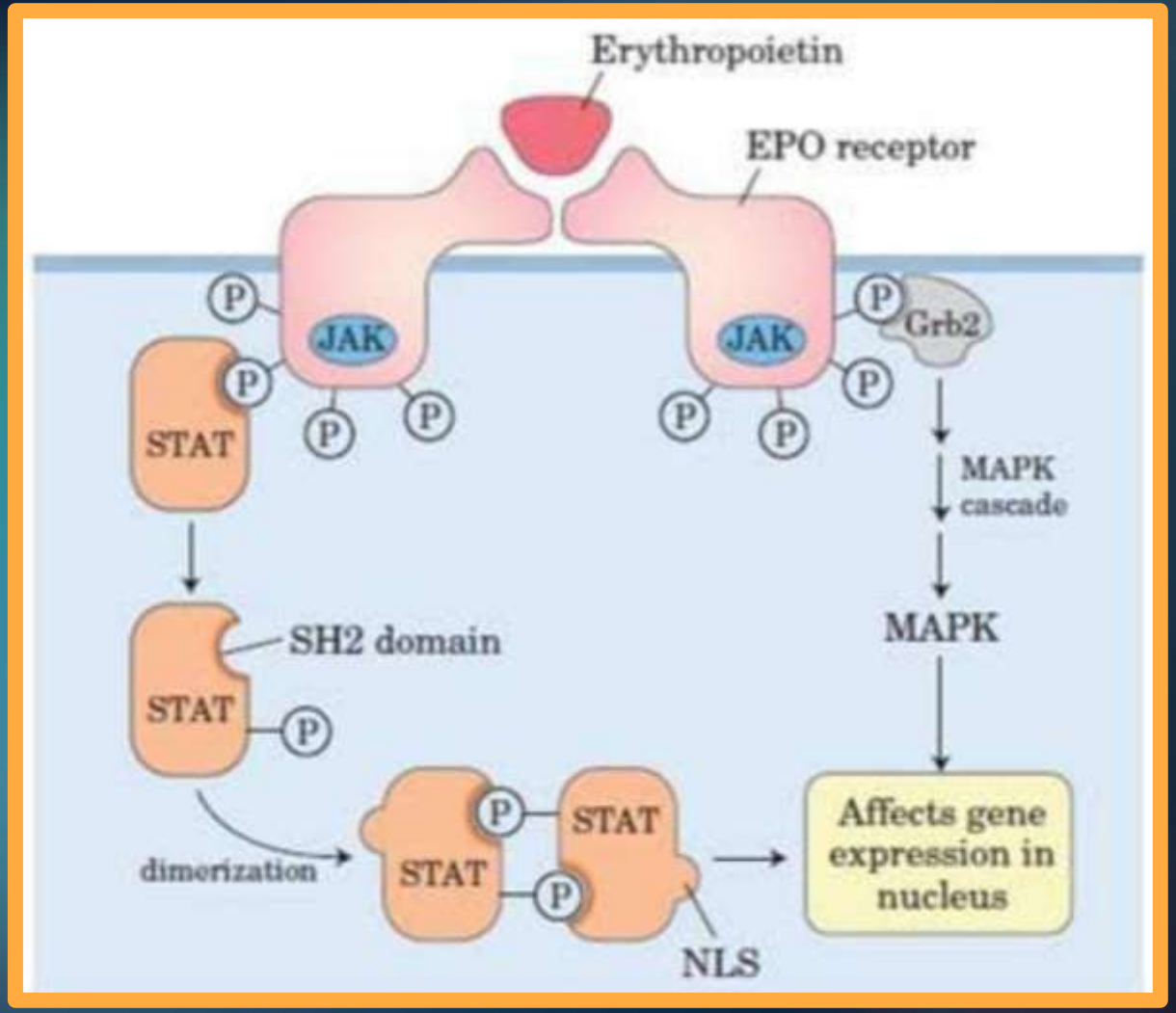
- Ras is a small GTPase that is anchored at the inner surface of the plasma membrane by a covalently attached lipid group that is embedded in the inner leaflet of the bilayer
- Ras proteins are present in two different forms: an active GTP bound form and an inactive GDP bound form
- Ras-GTP binds and activates downstream signaling proteins
- Ras is turned off by hydrolysis of its bound GTP to GDP
- Accessory proteins : GTPase-activating proteins (GAPs)Guanine nucleotide-exchange factors (GEFs) Guanine nucleotide-dissociation inhibitors (GDIS)

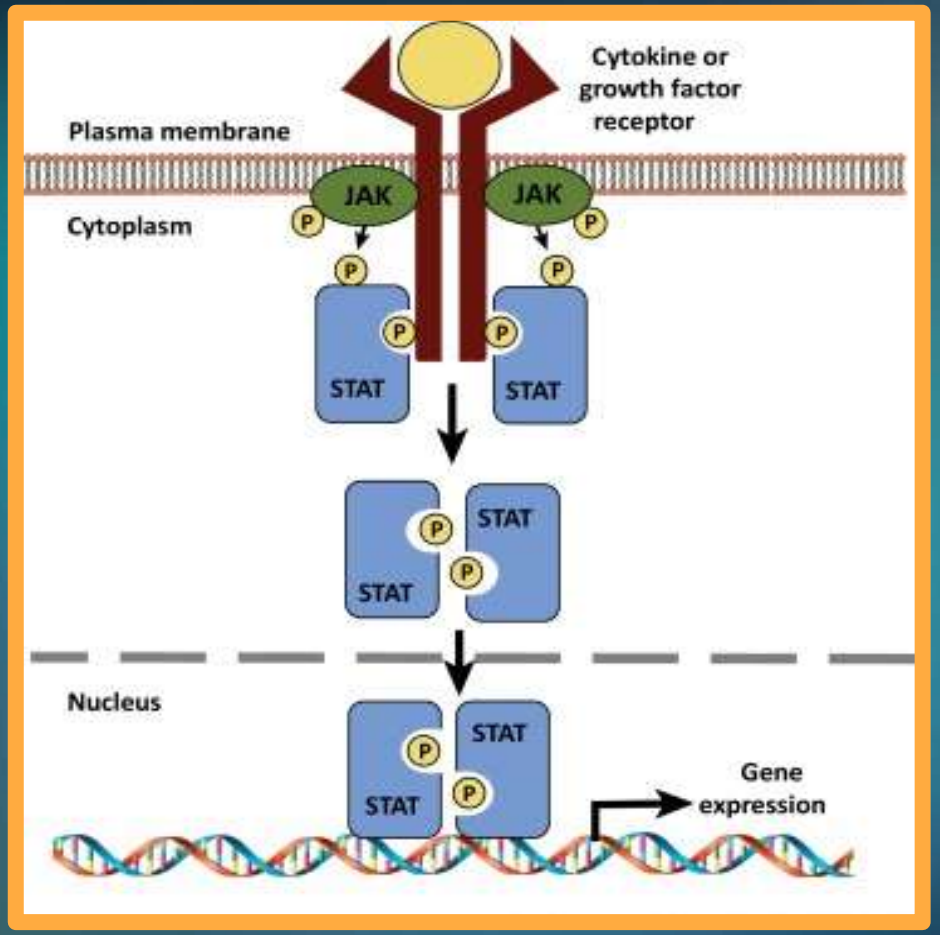

GEF
GEF
GTP
Switch
ON
GEF
Inactive
G protein
1b
Inactive
G protein
GDP
GDP
2
GDP
Active
G protein
GTP
GDI
1a
3
GDI
GEF
Inactive
target
protein
Inactive
G protein
GDP
6
Active G
protein
GAP
GAP
GTP
5
GAP
4
GDP
Clock
Switch
OFF
GTP
Active
target
protein
Inactive
target protein
Signal
transmitted downstream

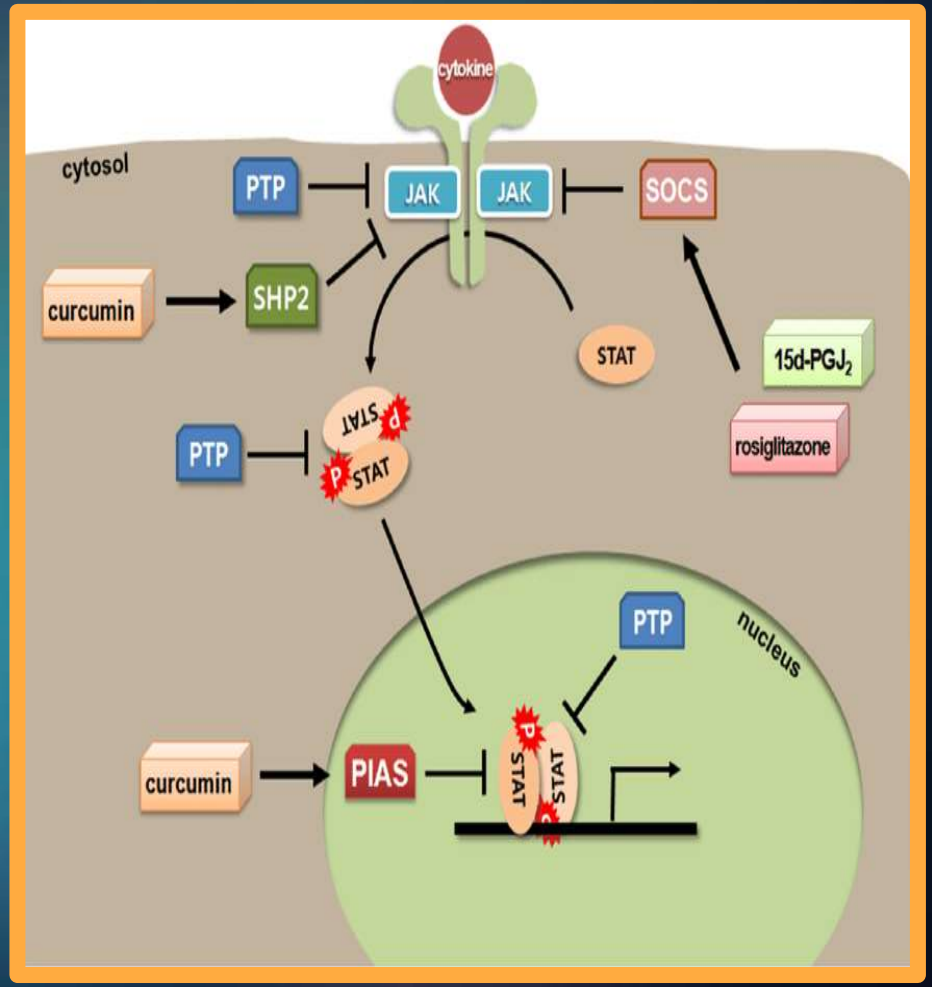

Growth factor
1
Receptor PTK
2
Receptor
P
P
P
3
Grb2
Sos
4
Ras-GDP
Ras-GTP
5
Soluble Raf
Membrane-bound Raf
P
MAPKKK
6
MEK
MEK
P
MAPKK
7
ERK
ERK
P
P
MAPK
11
8
TF
TF
P
P
TF
Gene
9
Transcription
10
MKP-1

JAK STAT PATHWAY

- The JAK-STAT signaling pathway is a chain of interactions between proteins in a cell, and is involved in processes such as immunity, cell division, cell death and tumour formation.
- The pathway communicates information from chemical signals outside of a cell to the cell nucleus, resulting in the activation of genes through a process called transcription.
- There are three key parts of JAK-STAT signalling: Janus kinases (JAKs), signal transducer and activator of transcription proteins (STATs), and receptors (which bind the chemical signals).
- Disrupted JAK-STAT signaling may lead to a variety of diseases, such as skin conditions, cancers, and disorders affecting the immune system


Erythropoietin
EPO receptor
JAK
JAK
Grb2
P
STAT
MAPK
cascade
SH2 domain
MAPK
STAT
dimerization
STAT
STAT
Affects gene
expression in
nucleus
NLS


Cytokine or
growth factor
receptor
Plasma membrane
Cytoplasm
JAK
JAK
P
STAT
STAT
Nucleus
Gene
expression


cytokine
cytosol
PTP
JAK
JAK
SOCS
curcumin
SHP2
STAT
15d-PGJ2
rosiglitazone
PTP
STAT
STAT
nucleus
PTP
curcumin
PIAS
STAT
STAT

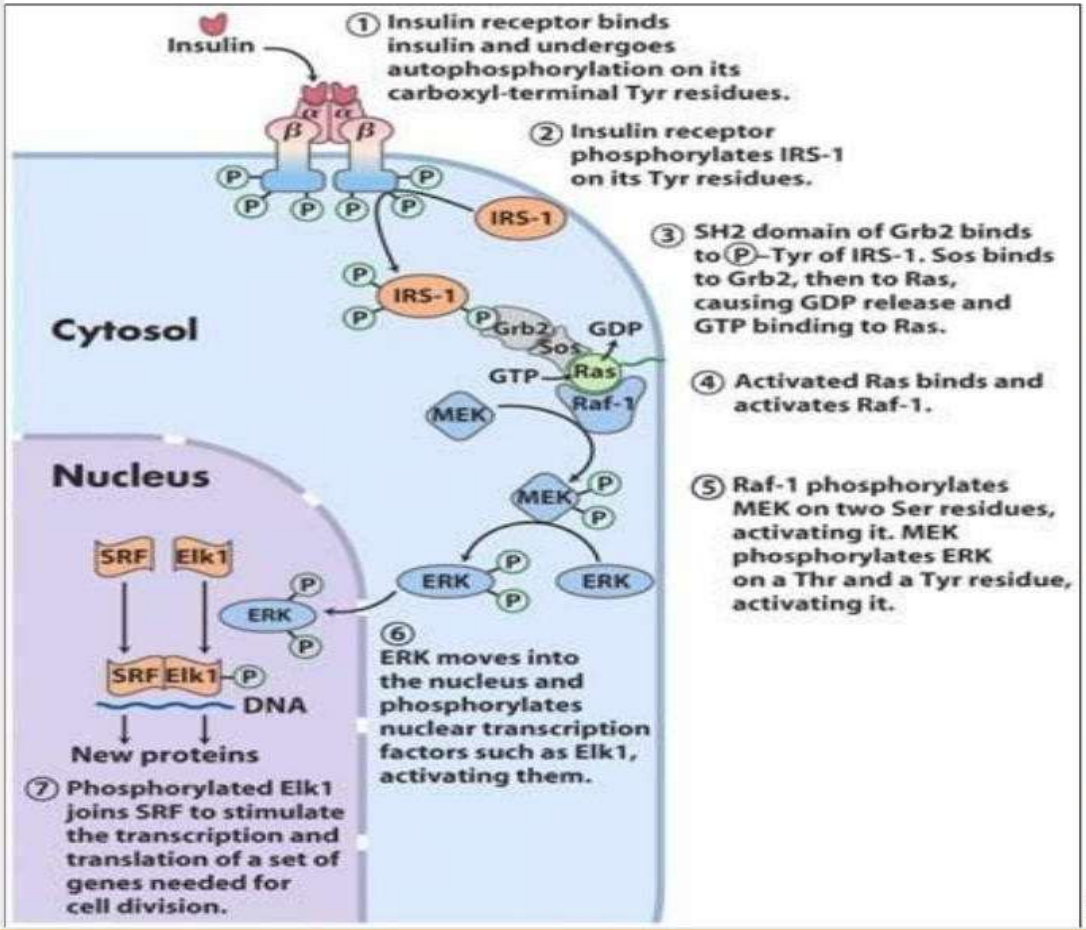
INSULIN SIGNALING PATHWAY

- The insulin transduction pathway is a biochemical pathway by which insulin increases the uptake of glucose into fat and muscle cells and reduces the synthesis of glucose in the liver and hence is involved in maintaining glucose homeostasis. This pathway is also influenced by fed versus fasting states, stress levels, and a variety of other hormones.

- When carbohydrates are consumed, digested, and absorbed the pancreas senses the subsequent rise in blood glucose concentration and releases insulin to promote uptake of glucose from the bloodstream. When insulin binds to the insulin receptor, it leads to a cascade of cellular processes that promote the usage or, in some cases, the storage of glucose in the cell. The effects of insulin vary depending on the tissue involved, e.g., insulin is most important in the uptake of glucose by muscle and adipose tissue.

- This insulin signal transduction pathway is composed of trigger mechanisms (e.g., autophosphorylation mechanisms) that serve as signals throughout the cell. There is also a counter mechanism in the body to stop the secretion of insulin beyond a certain limit. Namely, those counter-regulatory mechanisms are glucagon and epinephrine. The process of the regulation of blood glucose (also known as glucose homeostasis) also exhibits oscillatory behavior.

REGULATION OF GENE EXPRESSION BY INSULIN

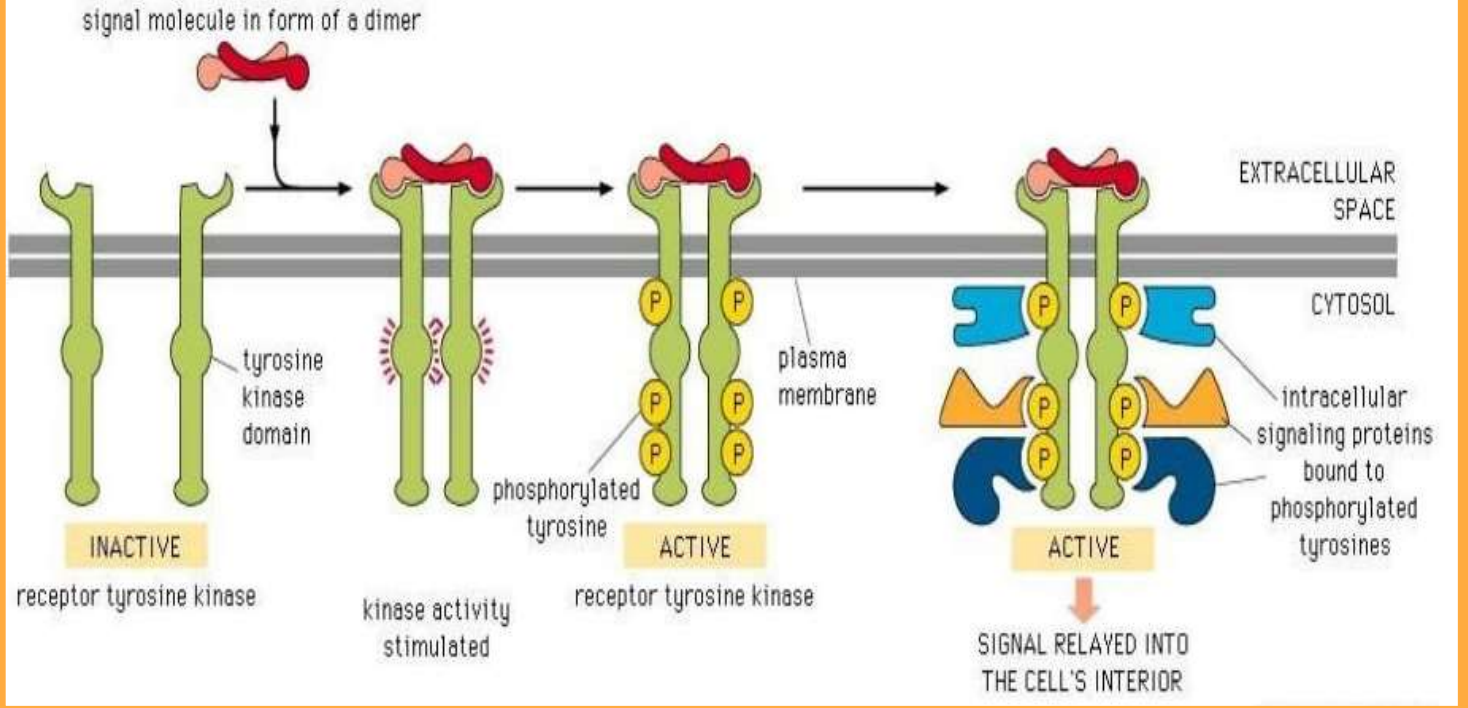


- Unlike the other RTKs Insulin Receptor is tetrameric.
- Binding of insulin to the receptor (*a*-chains) triggers conformational changes in the *b*-subunits starting the signal transduction process.
- Also, the majority of the docking sites for phosphotyrosine binding proteins are not the pY sites on the receptor itself, but on a specialized docking protein called Insulin Receptor Substrate (IRS-1) which is phosphorylated at multiple tyrosine residues by the receptor kinase.

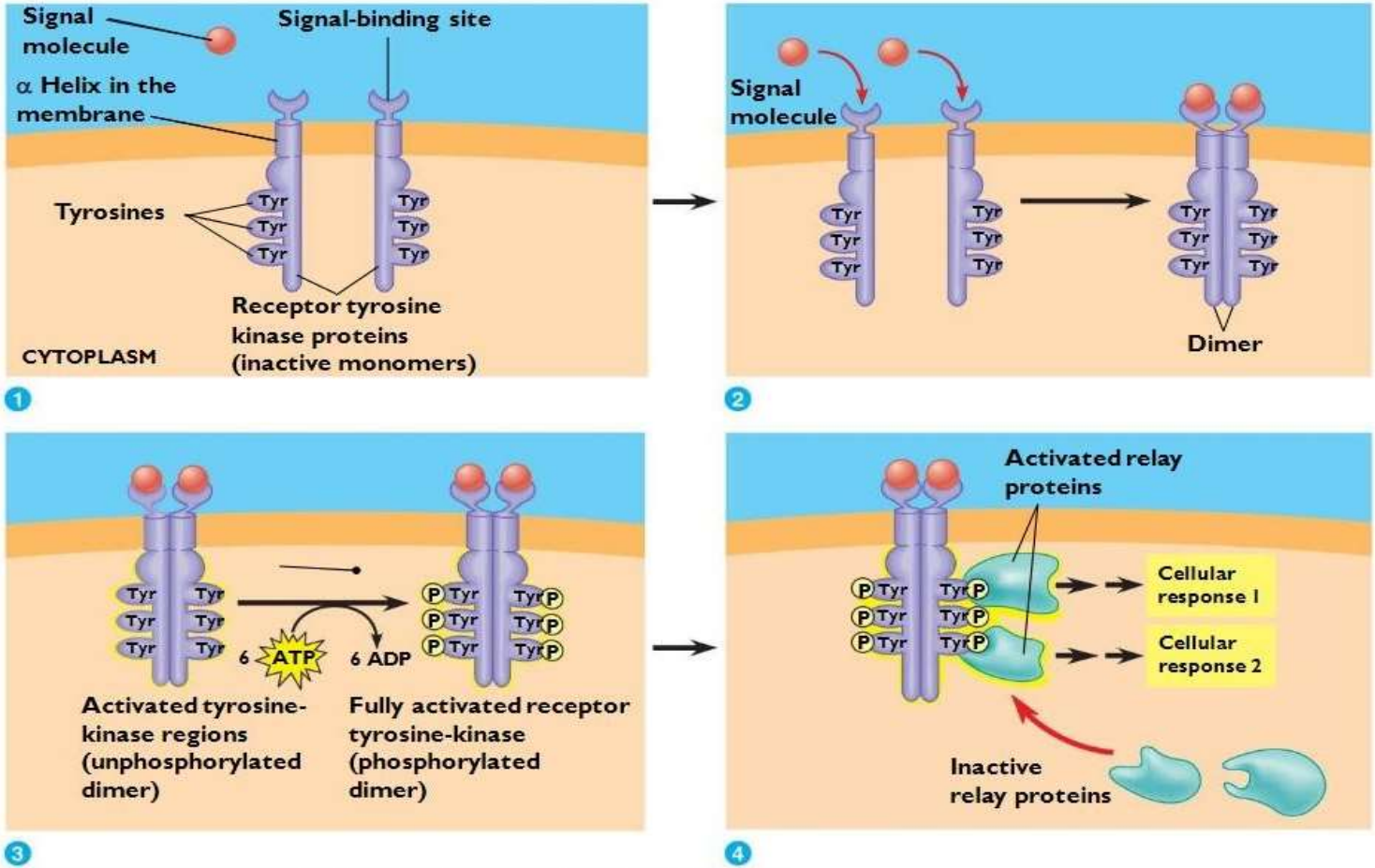
Glucose transporters:

GLUT1 is present in most tissues;
GLUT2 is found primarily in intestine, pancreatic β-cells, kidney and liver;
GLUT3 is found primarily in neurons but also found in the intestine;
GLUT4 is found in insulin-responsive tissues such as heart, adipose tissue and skeletal muscle; and
GLUT5 is expressed in intestine, kidney, testes, skeletal muscle, adipose tissue and brain.

TYROSINE KINASE PATHWAY



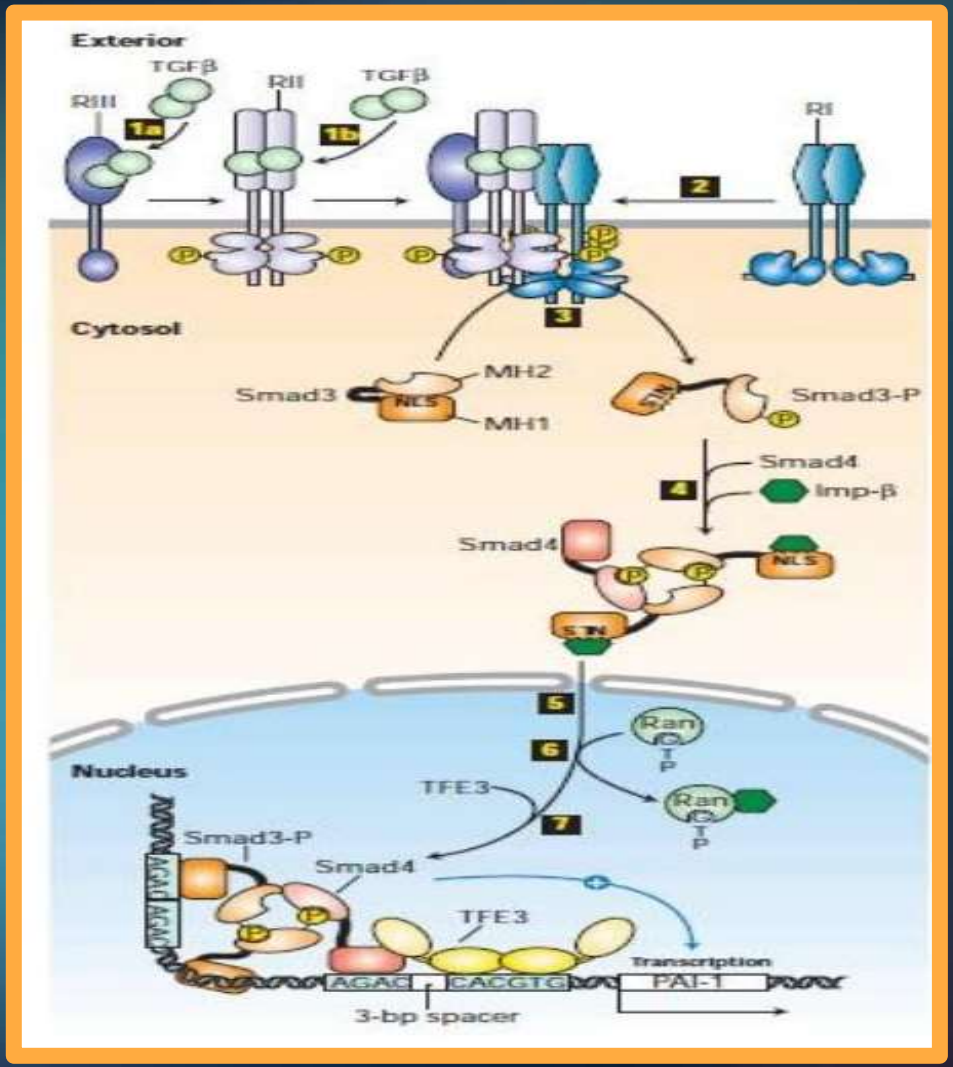
RECEPTOR TYROSINE KINASE



SIGNALING LIGAND	RECEPTOR-ASSOCIATED JAKS	STATS ACTIVATED	SOME RESPONSES
γ-interferon	Jak1 and Jak2	STAT1	activates macrophages; increases MHC protein expression
α-interferon	Tyk2 and Jak2	STAT1 and STAT2	increases cell resistance to viral infection
Erythropoietin	Jak2	STAT5	stimulates production of erythrocytes
Prolactin	Jak1 and Jak2	STAT5	stimulates milk production
Growth hormone	Jak2	STAT1 and STAT5	stimulates growth by inducing IGF-1 production
GM-CSF	Jak2	STAT5	stimulates production of granulocytes and macrophages
IL-3	Jak2	STAT5	stimulates early blood cell production

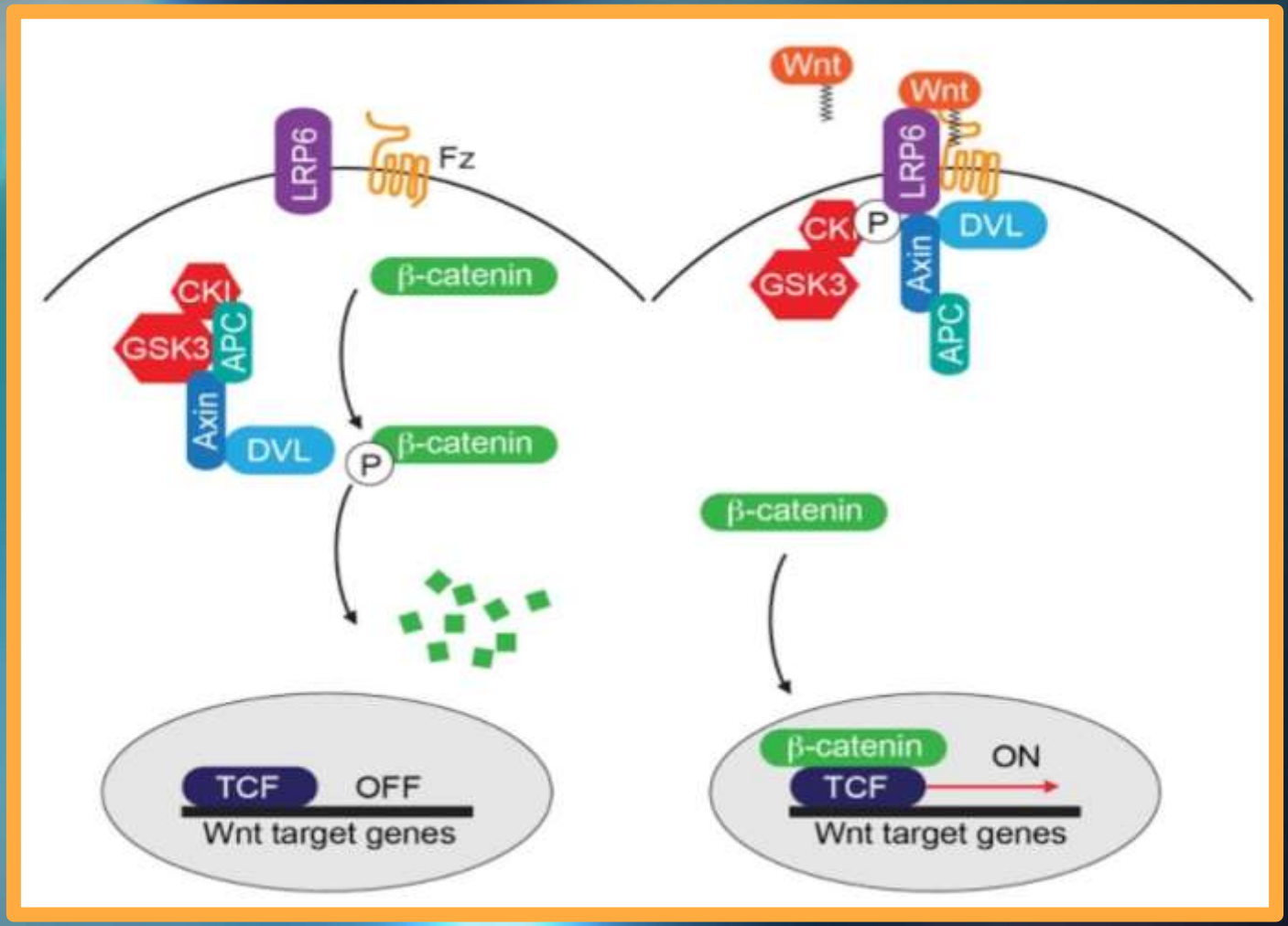
TGF Receptors

- TGF superfamily-regulating development in both invertebrates and vertebrates
- promote expression of cell-adhesion molecules and extracellular-matrix molecules
- In humans TGF consists of three protein isoforms. TGF-1.TGF-2, and TGF-3
- Virtually all mammalian cells secrete at least one TGF isoform, and most have TGF receptors on their surface.
- The cell-surface TGF receptors are three different polypeptides with apparent molecular weights of 55, 85, and 280 kDa, referred to as types RI, RII, and RIII TGF receptors, respectively
- Three types of Smad proteins function in the TGF signaling pathway: receptor-regulated Smads (R-Smads), co-Smads, and inhibitory or antagonistic Smads (I-Smads).


Exterior
TGFβ
RIII
1a
RII
TGFβ
1b
RI
2
Cytosol
3
MH2
Smad3
NLS
MH1
Smad3-P
Smad4
4
Imp-β
Smad4
NLS
5
6
Ran
GTP
TFE3
7
Ran
GTP
Nucleus
Smad3-P
Smad4
TFE3
Transcription
AGAC
CACGTG
PAI-1
3-bp spacer

Wnt Signaling

- The Wnt signaling pathways are a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors. The name Wnt is a portmanteau created from the names Wingless and Int-1.
- Wnt signaling pathways use either nearby cell-cell communication (paracrine) or same-cell communication (autocrine). They are highly evolutionarily conserved in animals, which means they are similar across animal species from fruit flies to humans.
- Three Wnt signaling pathways have been characterized: the canonical Wnt pathway, the noncanonical planar cell polarity pathway, and the noncanonical Wnt/calcium pathway.
- All three pathways are activated by the binding of a Wnt-protein ligand to a Frizzled family receptor, which passes the biological signal to the Dishevelled protein inside the cell.
- The canonical Wnt pathway leads to regulation of gene transcription, and is thought to be negatively regulated in part by the SPATS1 gene.
- The noncanonical planar cell polarity pathway regulates the cytoskeleton that is responsible for the shape of the cell. The noncanonical Wnt/calcium pathway regulates calcium inside the cell.


LRP6
Fz
CKI
GSK3
APC
Axin
DVL
β-catenin
P
β-catenin
TCF
OFF
Wnt target genes
Wnt
Wnt
LRP6
CKI
P
DVL
GSK3
Axin
APC
β-catenin
β-catenin
ON
TCF
Wnt target genes

SONIC HEDGEHOG

- Hedgehog Family (Mammalian)
- Desert hedgehog (DHH)
- Indian hedgehog (IHH)
- Sonic hedgehog (SHH)

- Hedgehog gene (hh) was first identified in the fruit-fly Drosophila melanogaster
- Assumes various roles in patterning the central nervous system (CNS) during vertebrate development.
- Induction of the floor plate and diverse ventral cell types within the neural tube
- Metastasis and cancer
- Brain, lung, skeleton, gastrointestinal tract development and polarity

Hedge hog

multipass transmembrane protein
Patched (PTC)