Cell membranes

Principles of cell transport and cell signaling

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Plasma membrane

*** biological structure that separates the inside of the cell from the outside**

*** lipid bilayer, total thickness 6-10 nm**

*** dynamic**

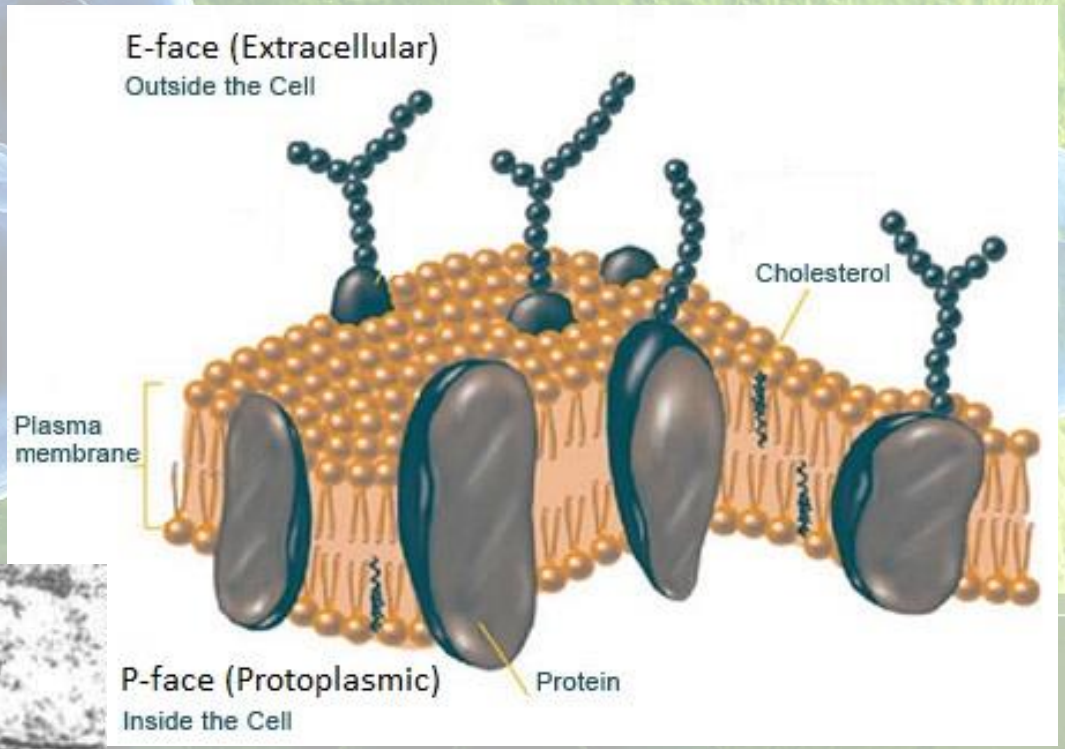
*** semipermeable**

*** primarily consists of:**

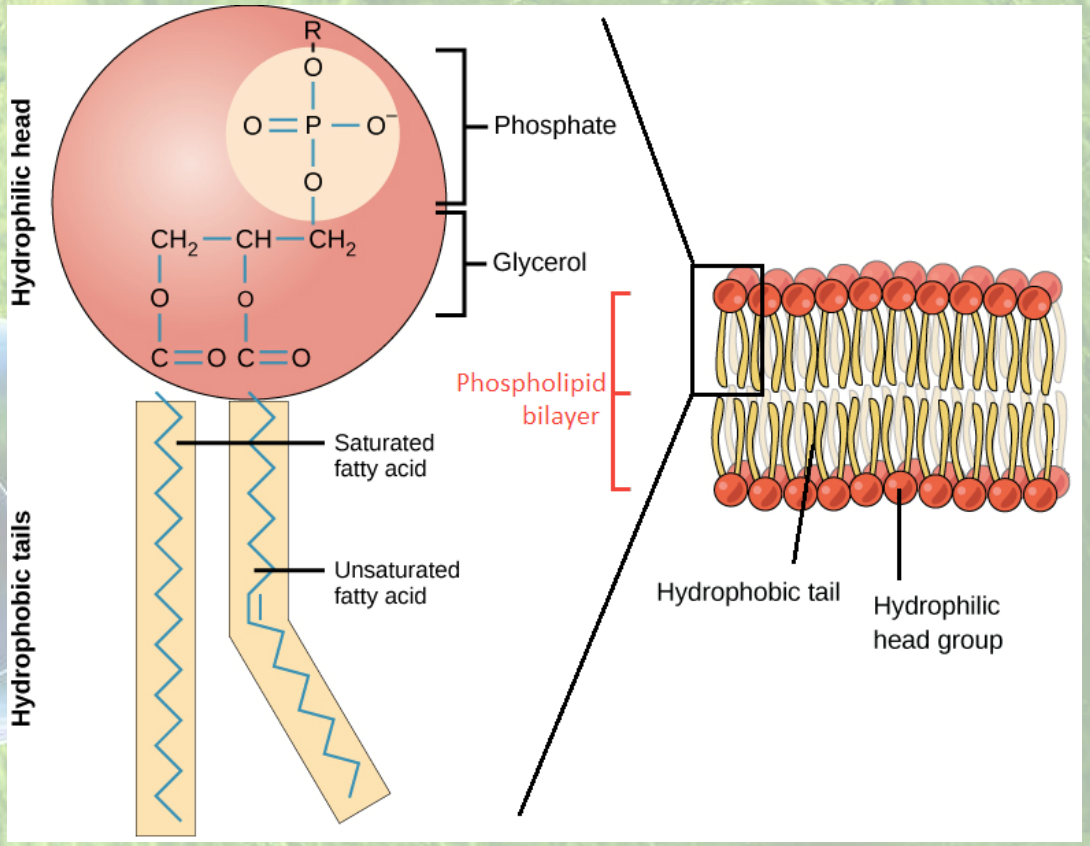
1. phospholipids

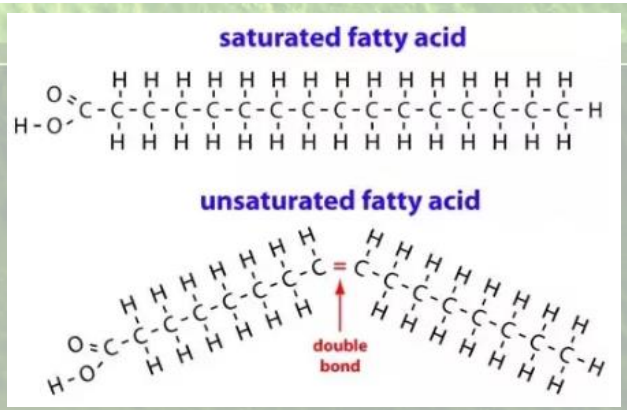
2. cholesterol

3. protein molecules



Phospholipids





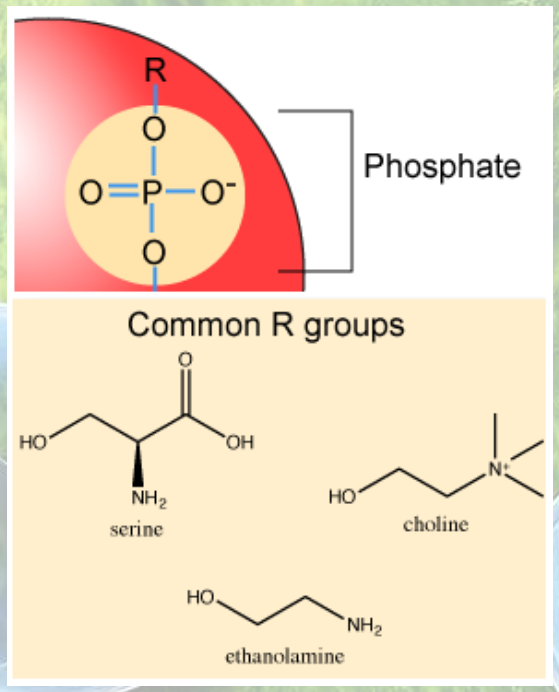
HYDROPHILIC
= with affinity for water / polar

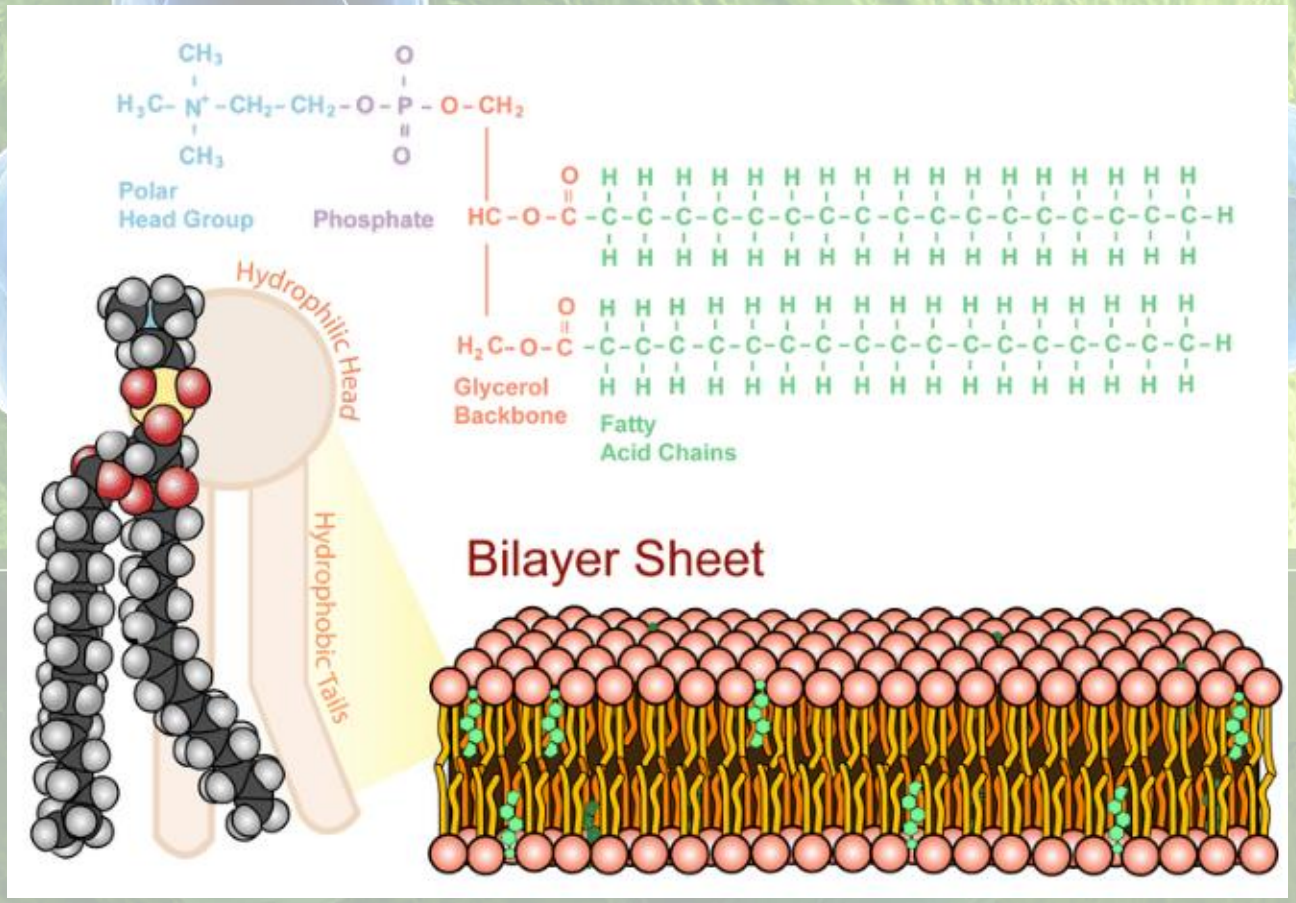
HYDROPHOBIC
= no affinity for water / non-polar

* the fatty acid chains of the lipid molecules face each other (inner portion of the membrane)
* the surfaces of the membrane are formed by the polar head groups of the lipid molecules

Most membranes are **AMPHIPATHIC** (both polar and non-polar properties).

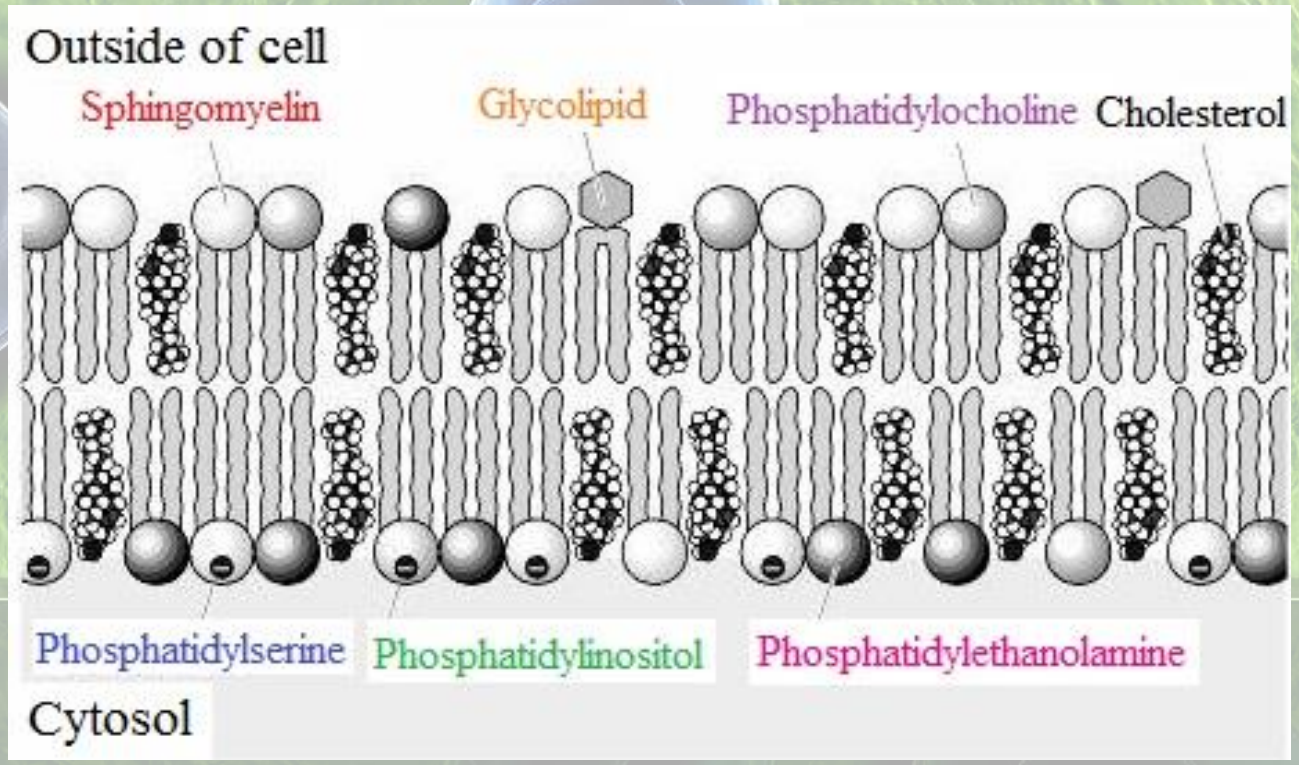
Phospholipids





Plasma membrane

* **asymmetrical distribution** of specific phospholipids in the bilayer



Phospholipids

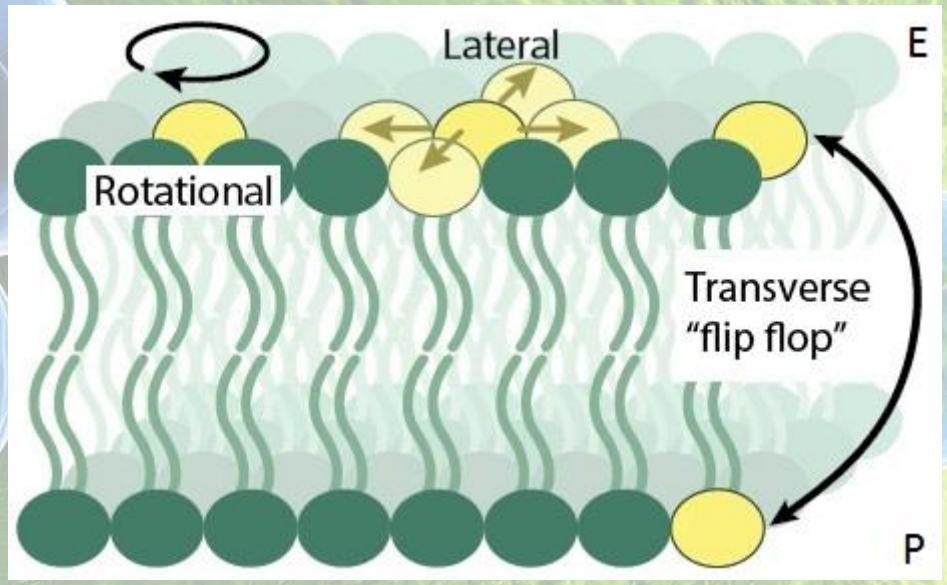
Phospholipids' movement:

Rotational movement
occurs ~ 10^9/sec,
phospholipids rotate on its axis to interact with its immediate neighbours

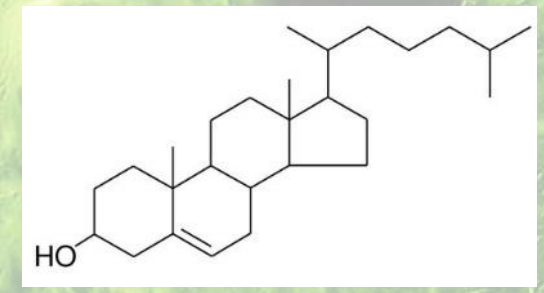
Lateral movement
occurs ~10^7 times/sec

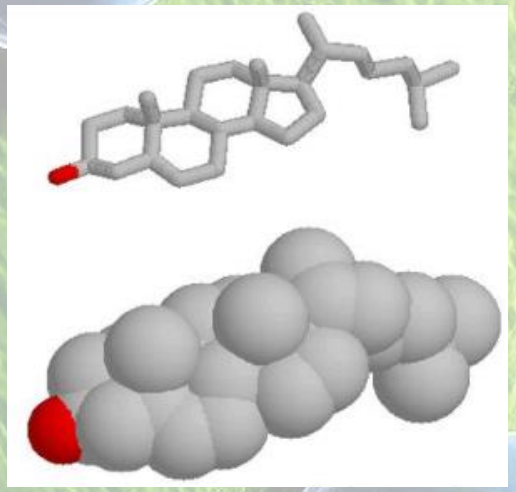
Transverse diffusion = flip-flop
from one half of the bilayer to the other, catalyzed by:
flippase (E->P), more often
floppase [**scramblase**] (P->E),

very **slow** and **rare**: once/month



Cholesterol



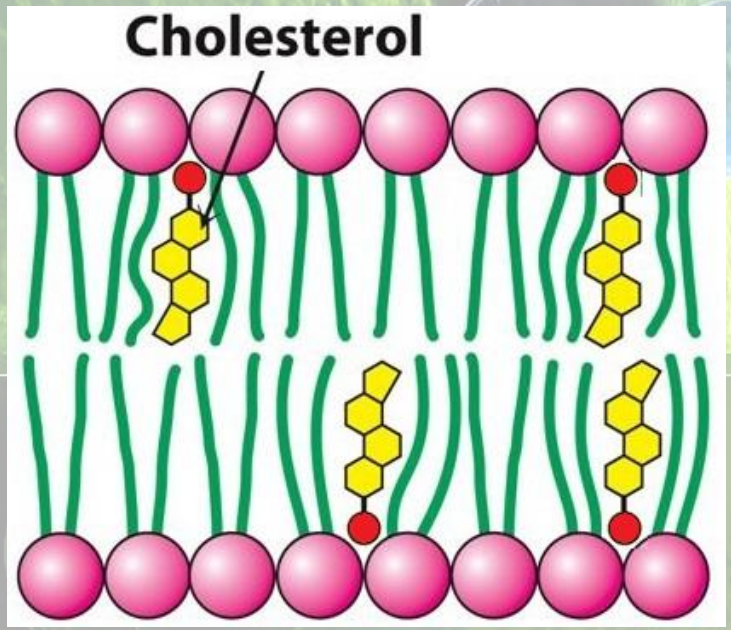


***** has a rigid ring system and a short-branched hydrocarbon tail

* largely hydrophobic but one polar hydroxyl group makes it amphipathic

* incorporated within the gaps between phospholipids

equally on both sides of the membrane, with its hydroxyl group oriented towards the aquaeous phase

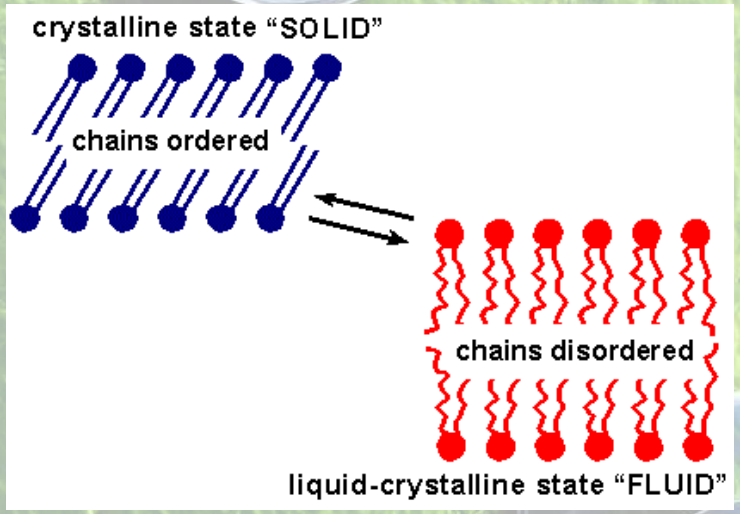


Plasma membrane with a high concentration of cholesterol have a fluidity intermediate between the

liquid crystalline and crystalline state.

Membrane fluidity

In the crystalline state (solid ordered) fatty acid tails are fully extended, packing is highly ordered, van der Waals intercations between adjacent chains are max.



In the liquid crystalline state (liquid disordered) chains of phospholipids are disordered and in constant motion.

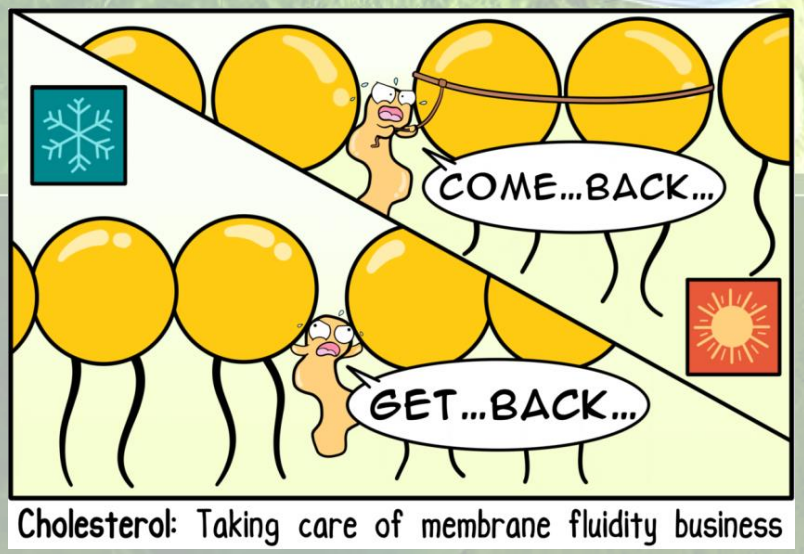
Influenced by several factors:

Saturation of fatty acids – more unsaturated C=C bonds increase fluidity
– kinks prevent tight packing

Lipid packing – lipids with shorter fatty acid tails are less stiff

Temperature – lipids move around more with incresed T

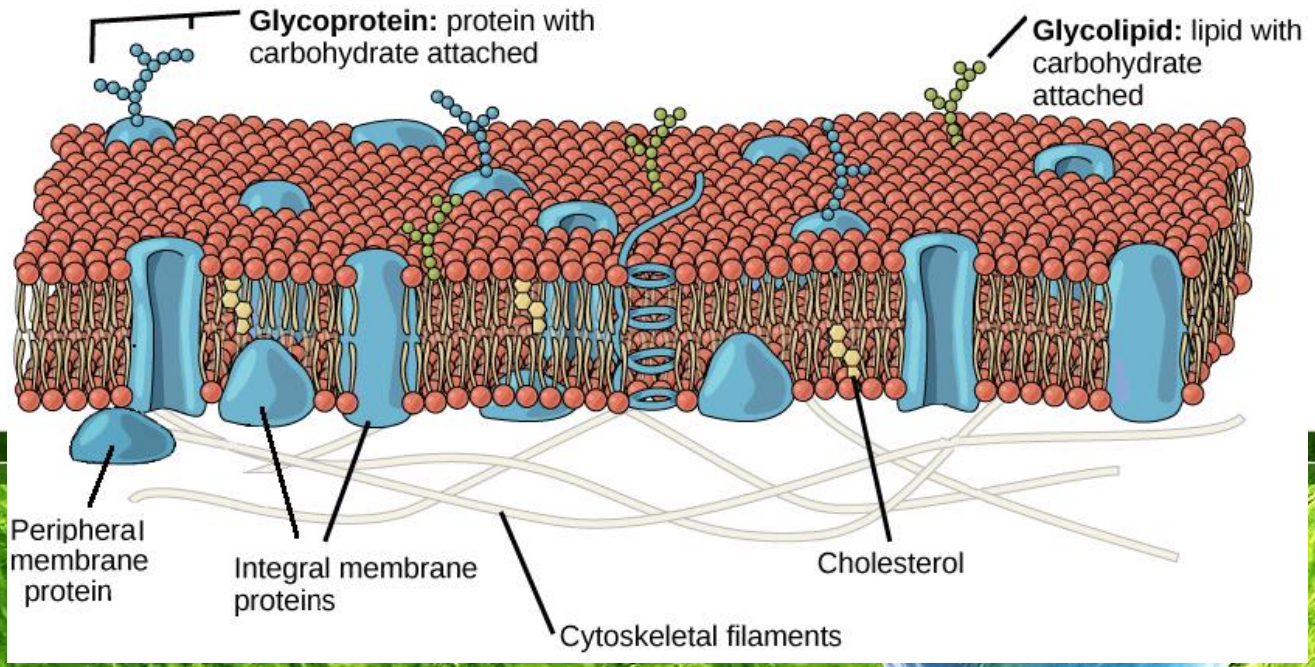
Cholesterol – decreseas fluidity at warmer T, increases at lower T



Membrane proteins

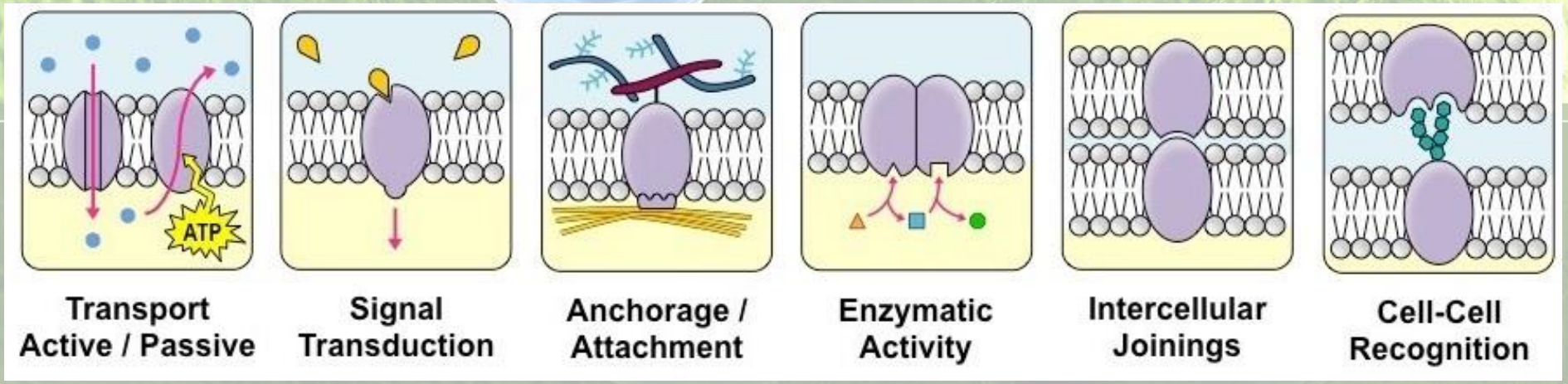
In most plasma membranes proteins constitute approximately **half of the total membrane mass**.

1. **Integral membrane proteins** – embedded within the bilayer or pass through it completely, can move – like an iceberg floating in the ocean
2. **Peripheral membrane proteins** – not embedded, but associated with the plasma membrane by strong ionic interactions, on both the extra- and intra-cellular surfaces of the membrane
3. **Peripheral**, having a **lipid anchor**



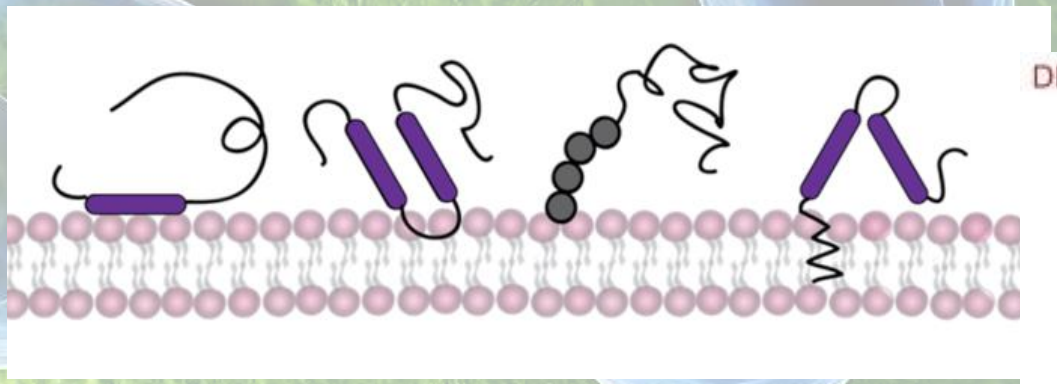
Functions of membrane proteins

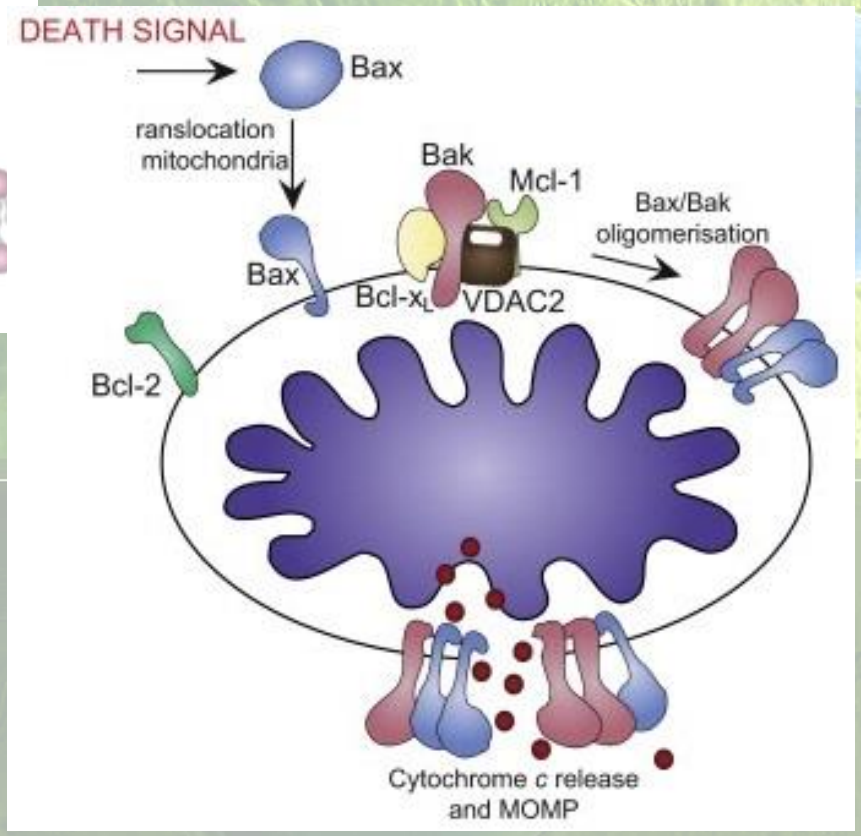
- **Pumps** – to transport certain ions and macromolecules (aa, sugars) actively across the membrane
- **Channels** – allow the passage of small ions and molecules across the plasma membrane in either direction through passive diffusion e.g. gap junctions
- **Receptor proteins** – allow recognition and localized binding of ligands
- **Linker proteins** – anchor the intercellular cytoskeleton to the extracellular matrix e.g. integrins in focal adhesions
- **Enzymes** – e.g. ATP synthase at the inner mitochondrial membrane
- **Structural proteins** – form junctions with neighbouring cells *e.g.* claudins and occludins in tight junctions / cell recognition



Peripheral membrane proteins (PMP)

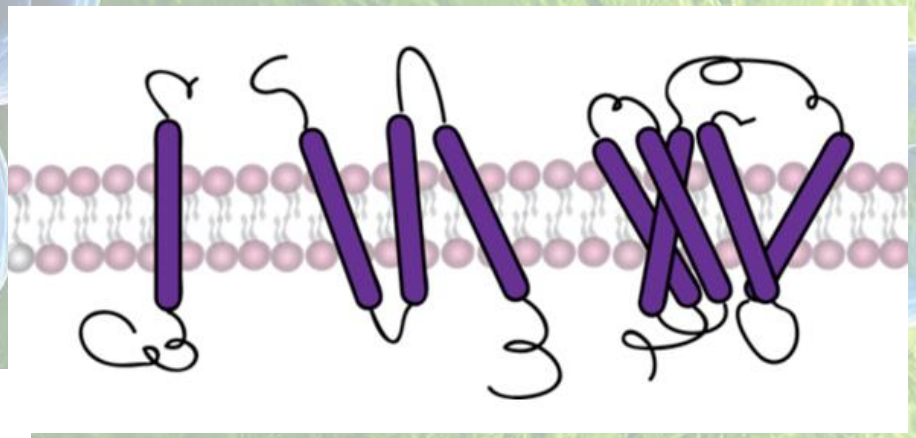
* attached to integral membrane proteins or penetrate the peripheral regions of the lipid bilayer, water soluble *e.g.* Bcl-2
* attachment is **reversible**, some associate irreversibly and can form transmembrane channels during *e.g.* Bax



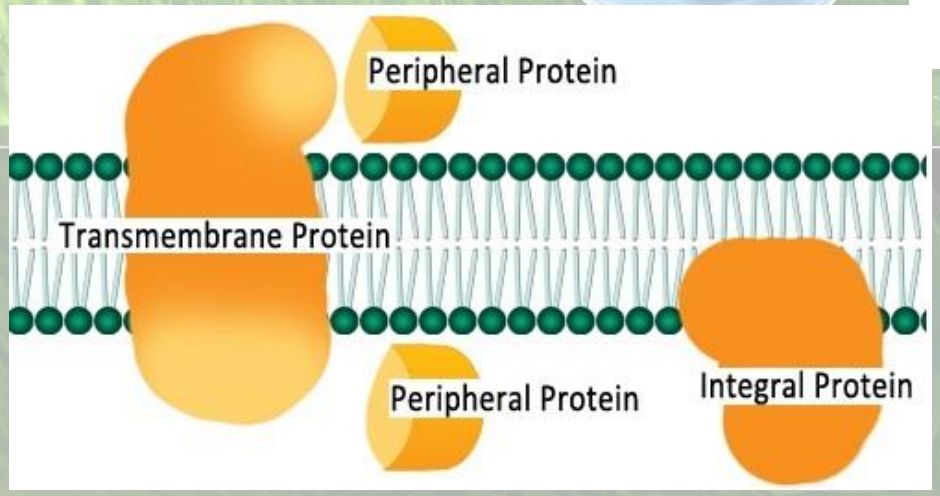


Integral membrane proteins (IMP)

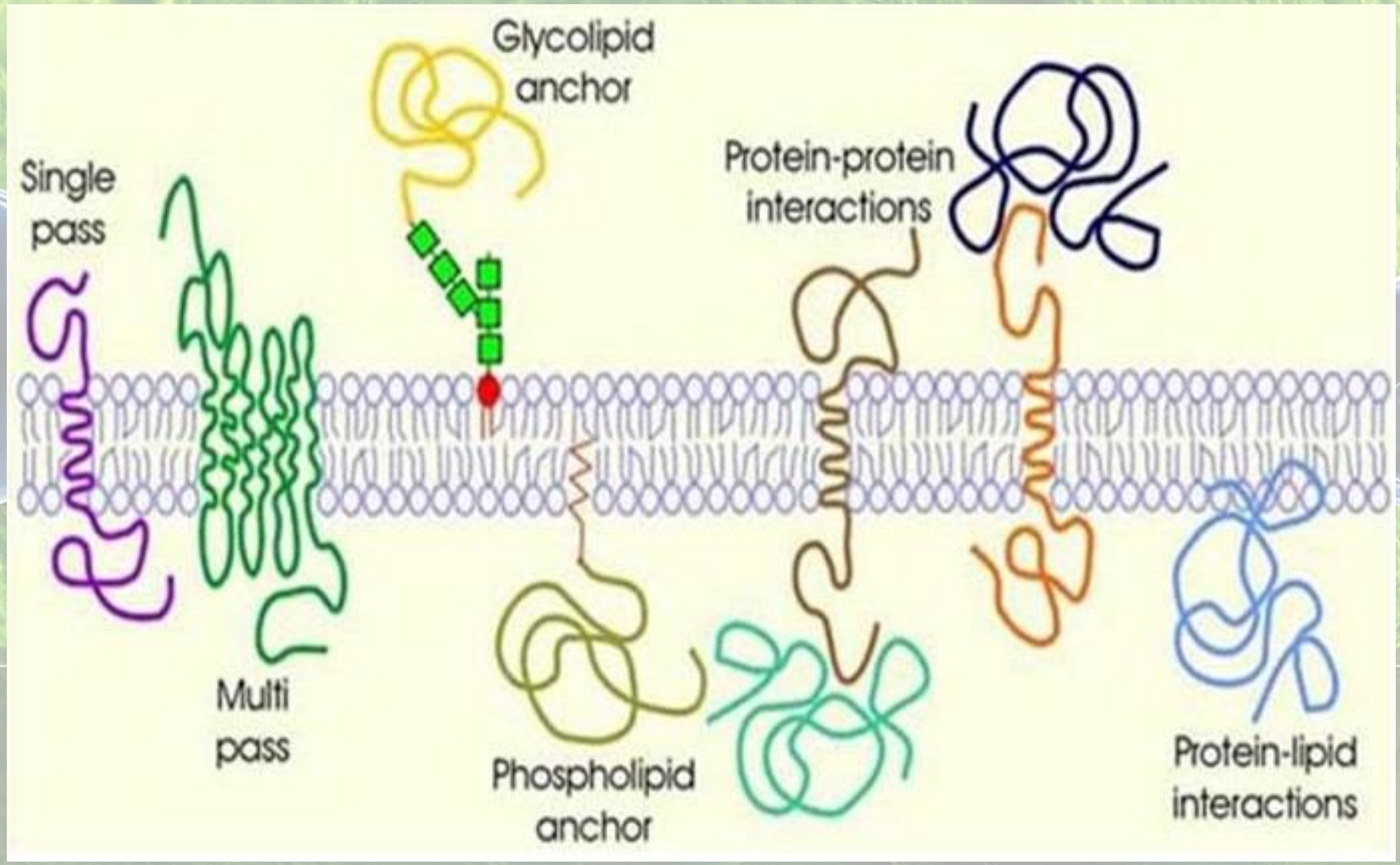
* have **intra**membrane domain(s) that extend into the core of the membrane, often span the whole bilayer
* the intramembrane domains have largely hydrophobic surfaces that interact with membrane lipids' tails
* permanently attached to the membrane
* have **the same orientation** relative to the membrane = flip-flop movement does not occur



Integral ≠ transmembrane



Association of proteins with the plasma membrane



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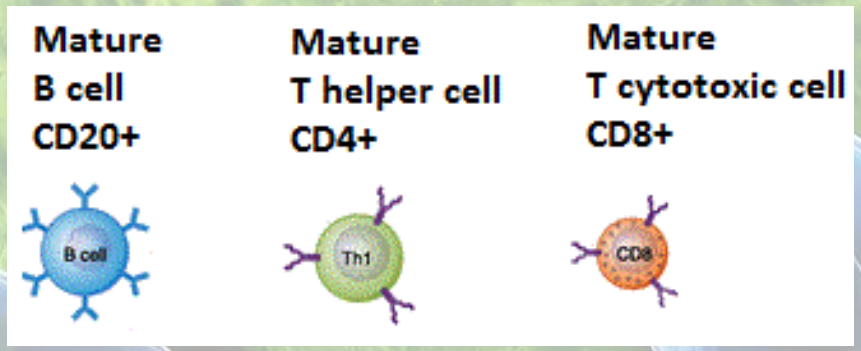
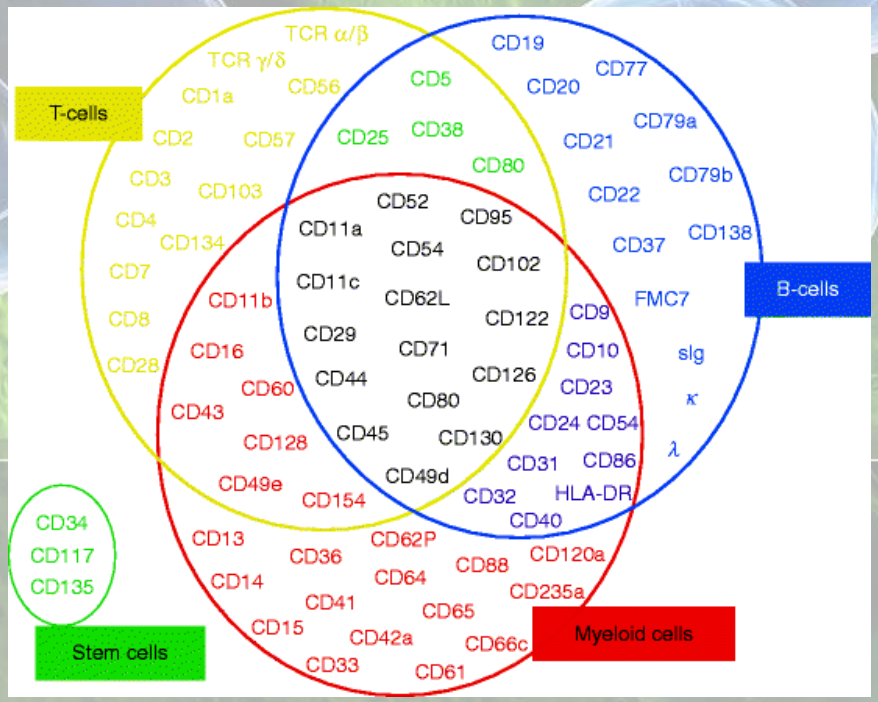


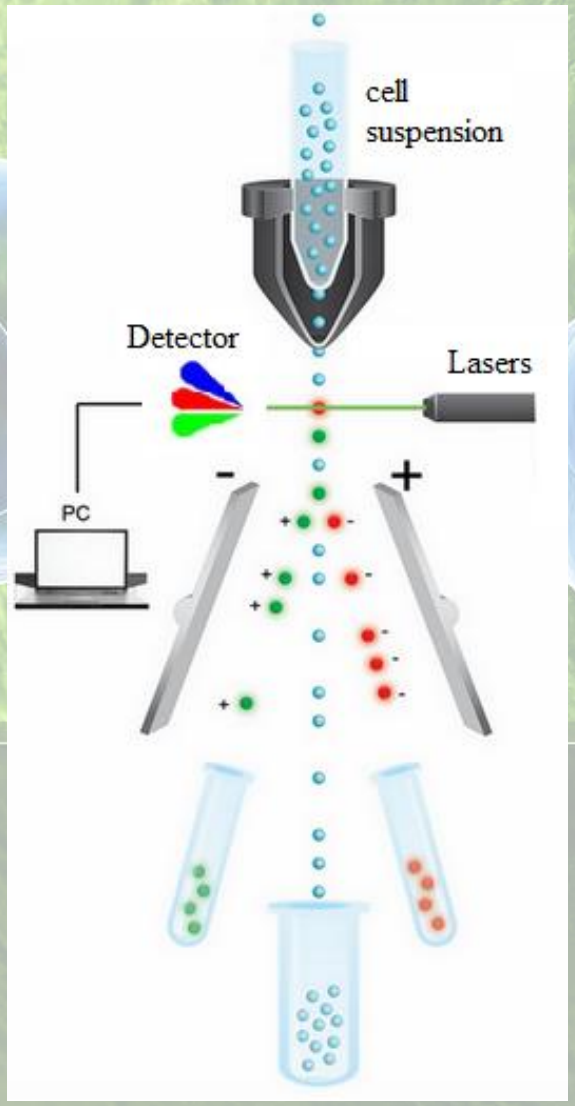
CD-molecules
CD-antigens
cluster of differentiation/ classification determinant glycoprotein

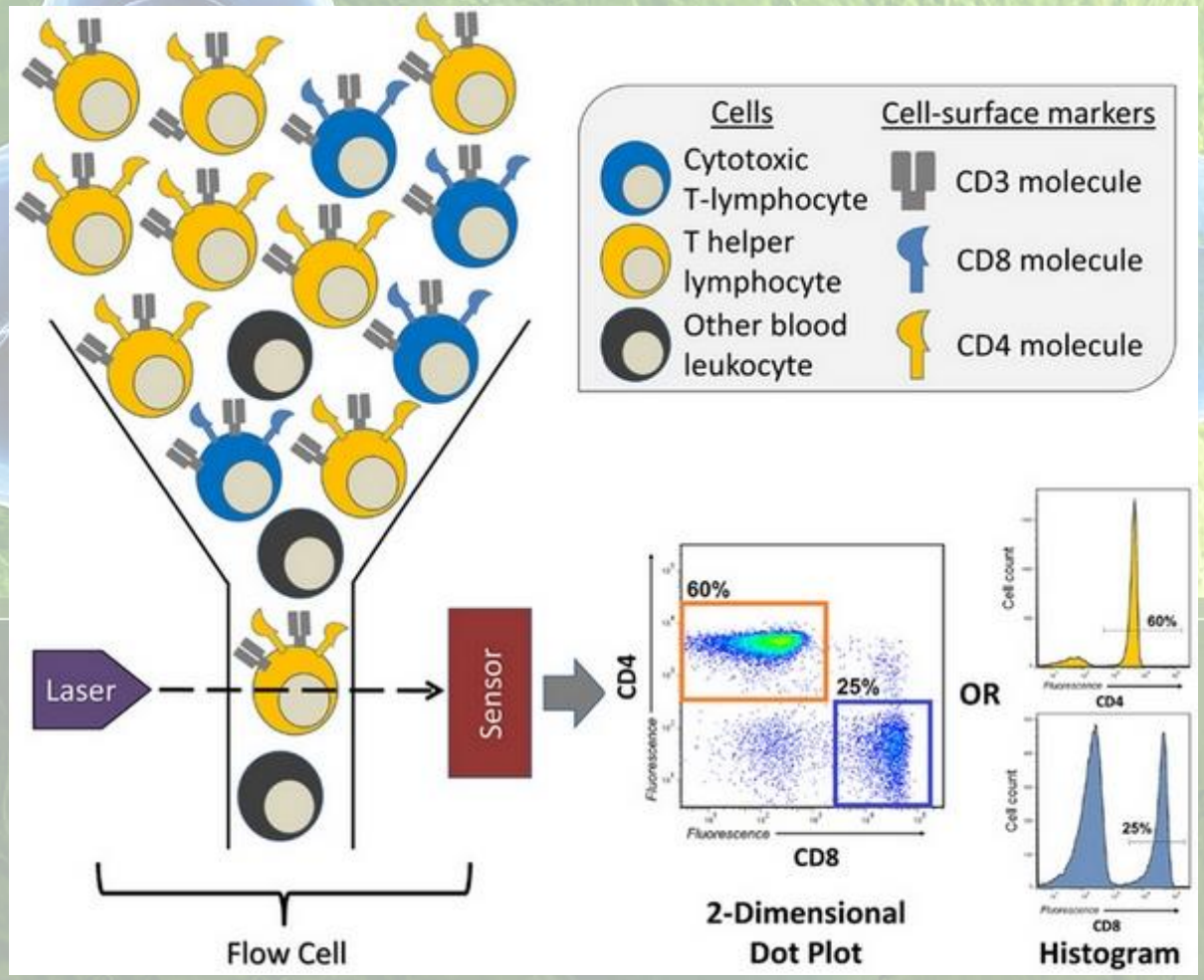


CD328 (siglec-7, AIRM1/p75)	V-set Ig-like CRD ➤ C2-set Ig-like modules (2) ➤ Transmembrane sequence ➤ Cytoplasmic tail ➤ (with 1 ITIM and 1 ITIM-like motif)		V-set Ig-like domain PDB code:2HRL
CD337 ((activating) natural cytotoxicity (triggering) receptor-3, NKp30)	V-set Ig-like domain ➤ Transmembrane sequence ➤ Cytoplasmic tail ➤ (shown in complex with CD3ζ and its 3 ITAM motifs)	CD3ζ (with assumed ionic interaction in the transmembrane regions)	V-set Ig-like domain PDB code:3NOI

Association of proteins with the plasma membrane

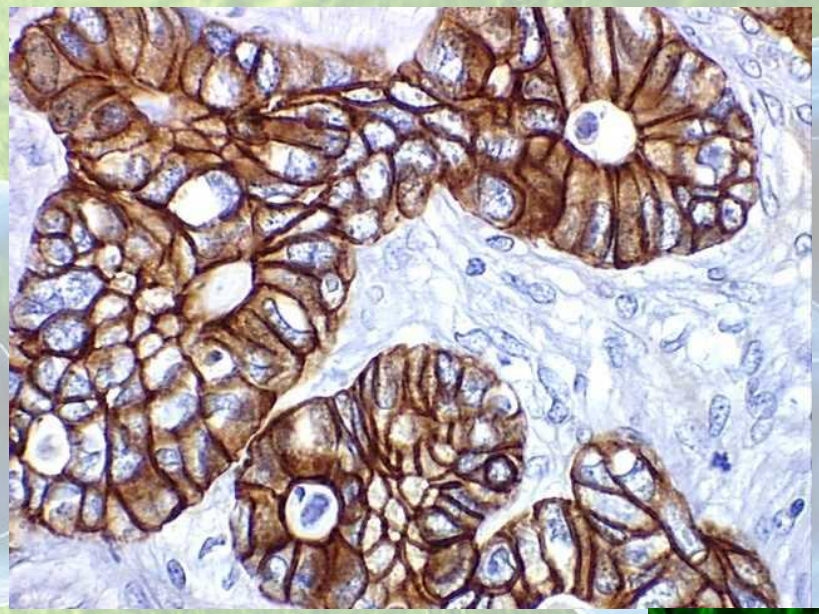
High throughput flow cytometry





Association of proteins with the plasma membrane

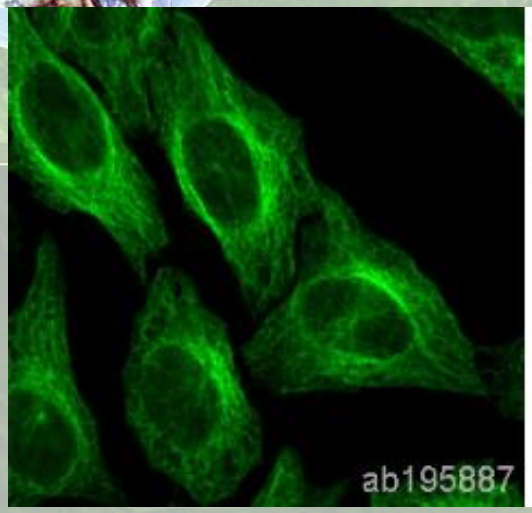
Immunochemistry

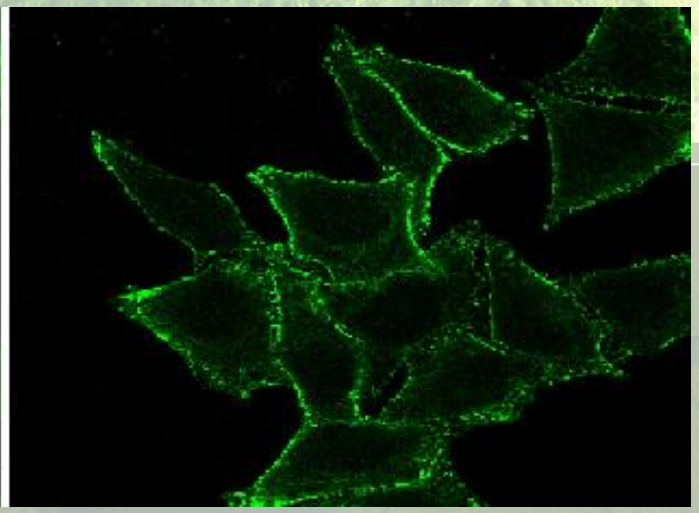


E-cadherin

Immunofluorescent staining

Cytoplasmic *vs.* Membraine protein

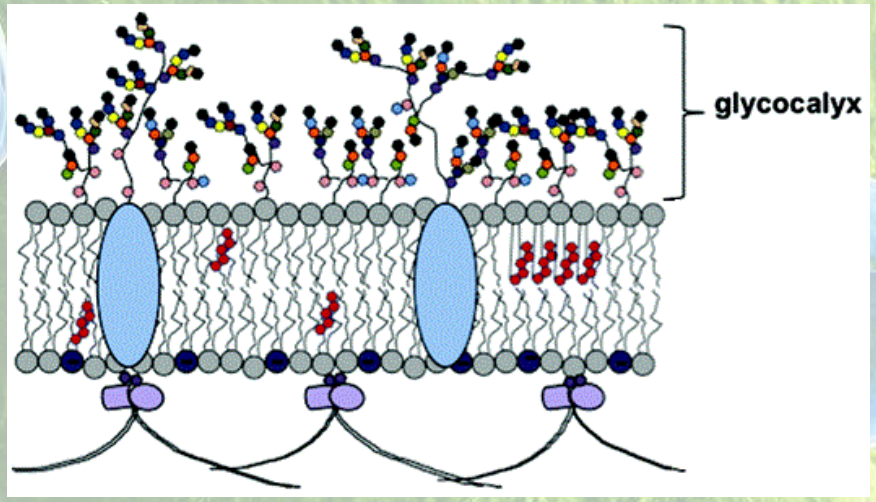




Glycocalyx

* carbohydrate moieties attached to both integral and peripheral membrane proteins: **GLYCOPROTEINS**

and to polar phospholipid heads: **GLYCOLIPIDS**



Function:

-cell protection

- cell recognition (e.g. inflammation)

- cell-to-cell adhesion

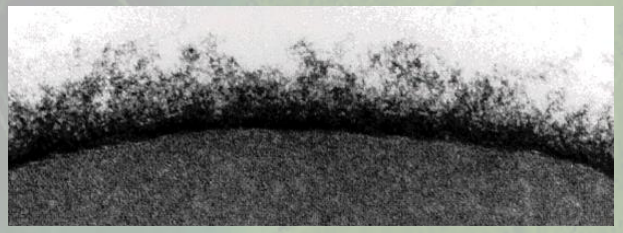
- receptor sites for hormones

- defense against cancer

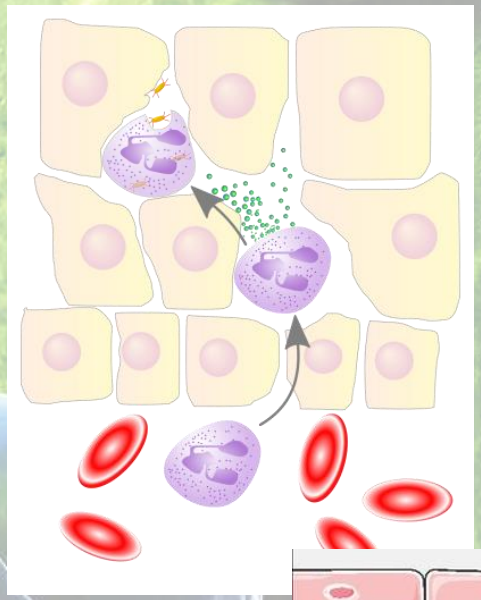
- fertilization and embryonic precesses

- helps establish extracellular microenvironment (cell-to-cell / cell-to-EXM adhesion)

- red blood cells group antigens

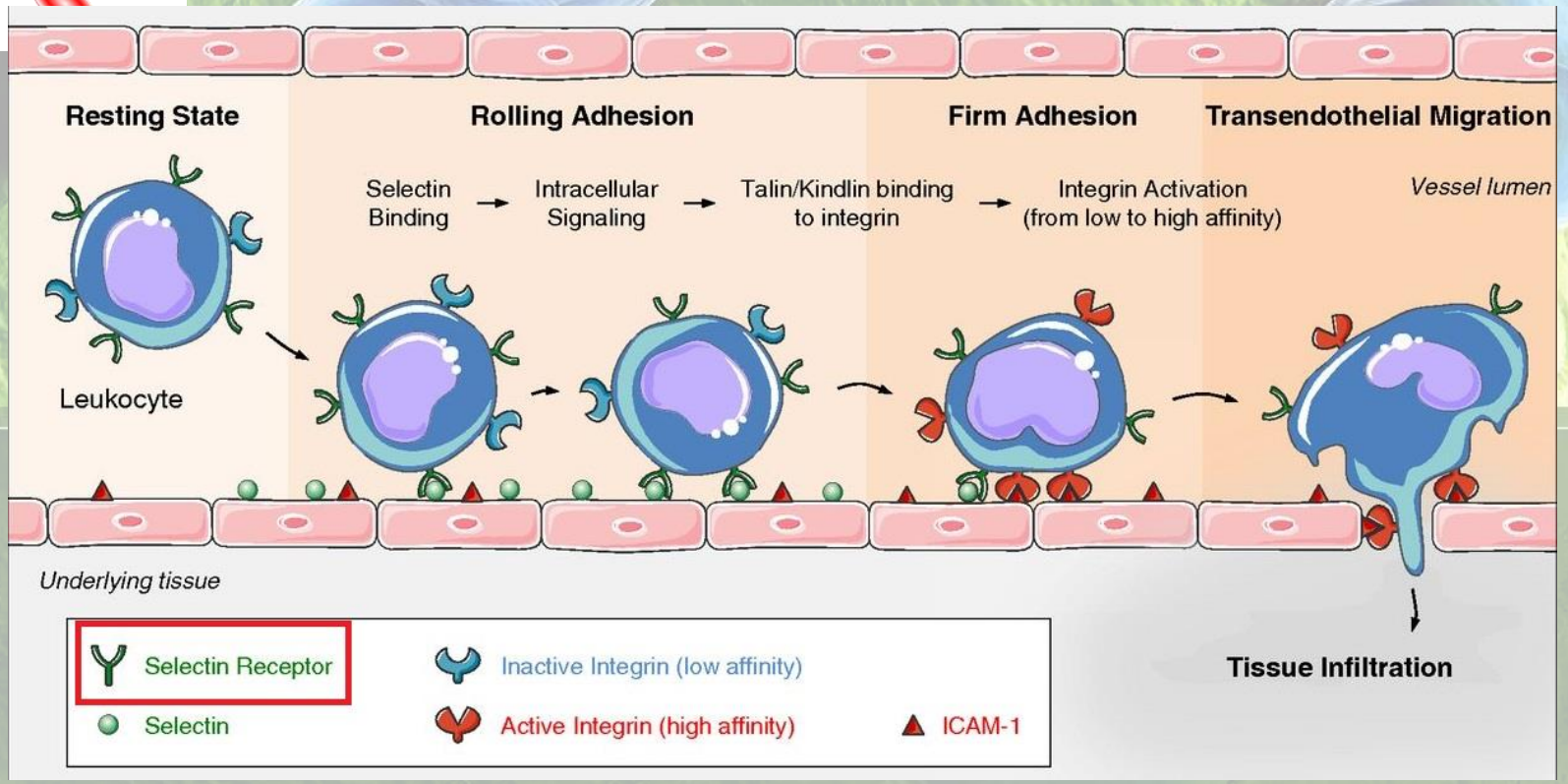


Glycocalyx

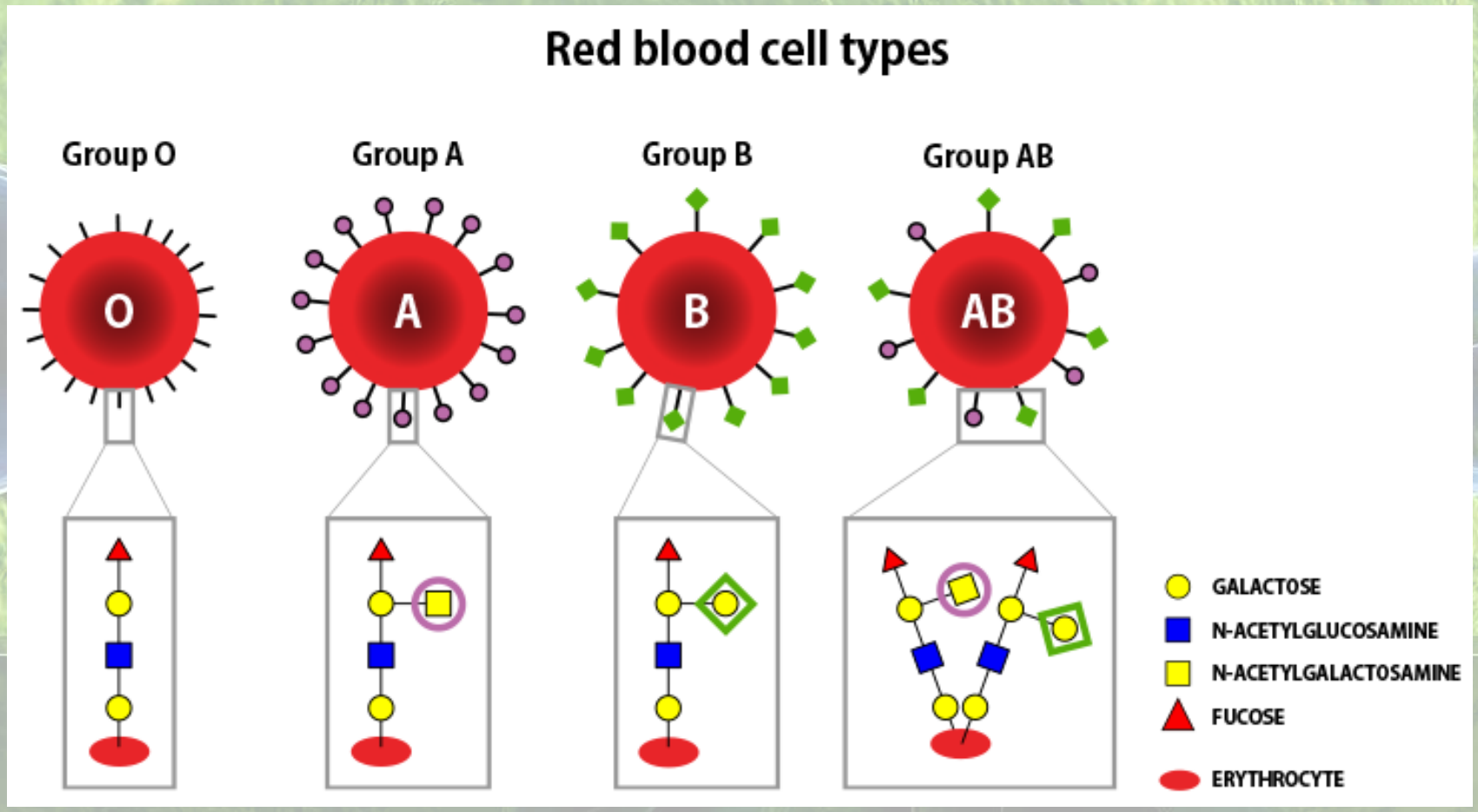


Leukocyte extravasation

Movement of leukocytes out of the circulatory system towards the site of infection/damage (inside the tissue).

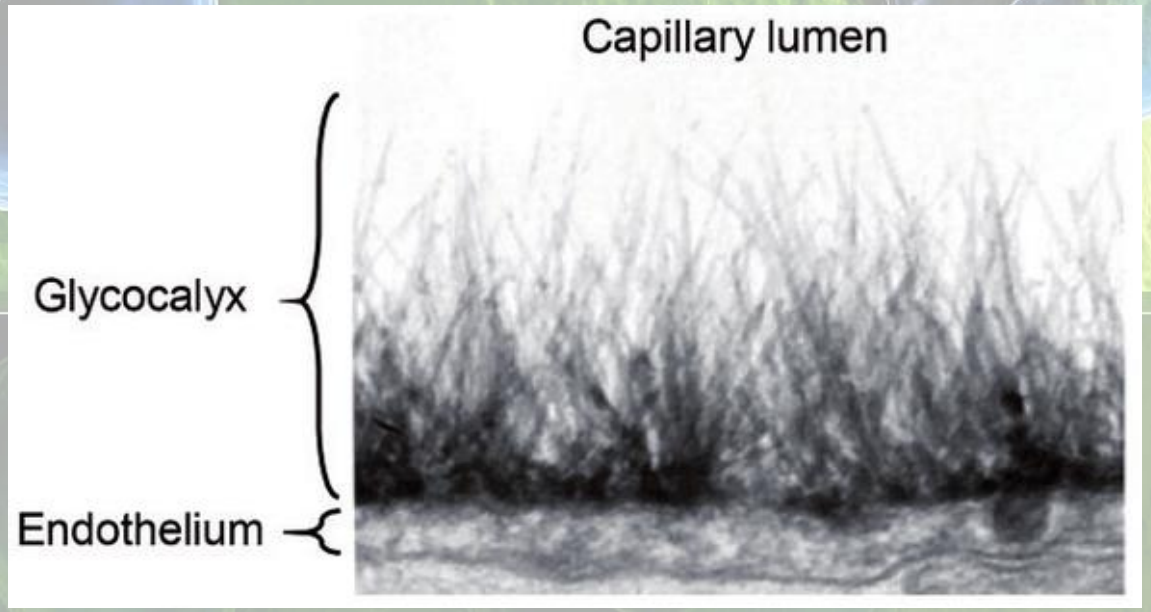


Glycocalyx

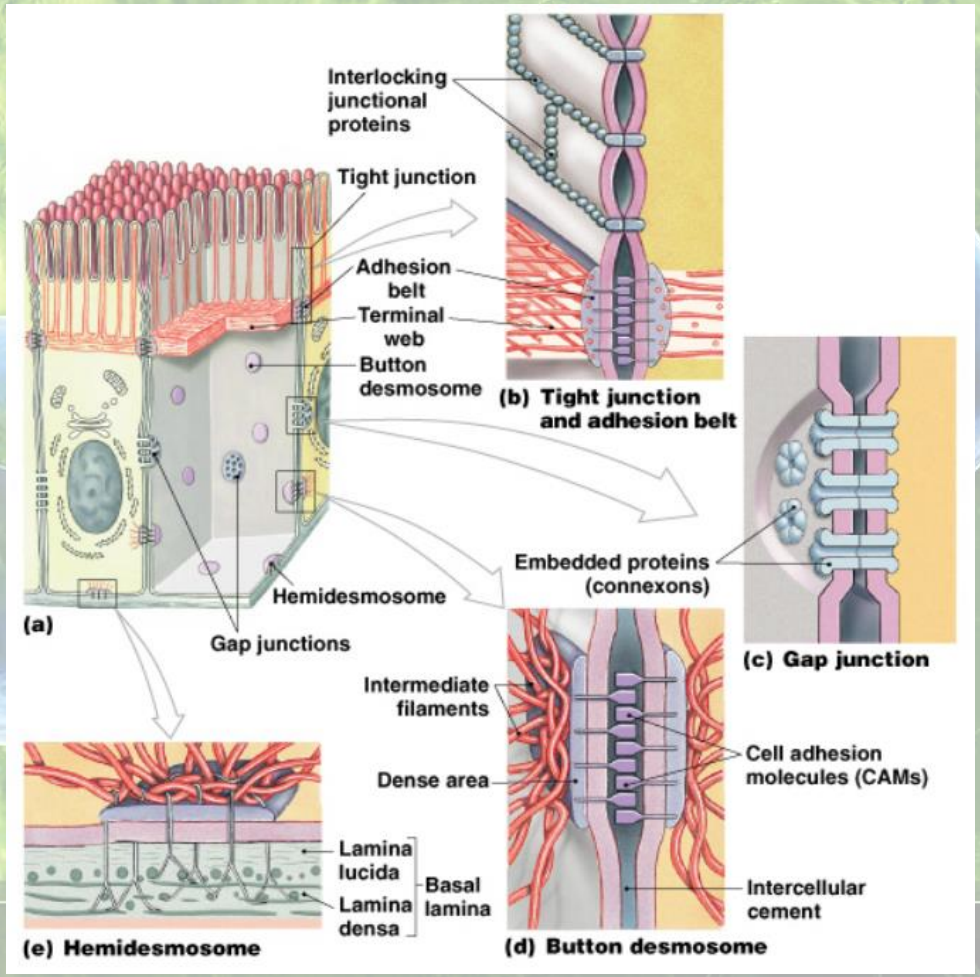

Red blood cell types
Group O
Group A
Group B
Group AB
O
A
B
AB
GALACTOSE
N-ACETYLGLUCOSAMINE
N-ACETYLGALACTOSAMINE
FUCOSE
ERYTHROCYTE

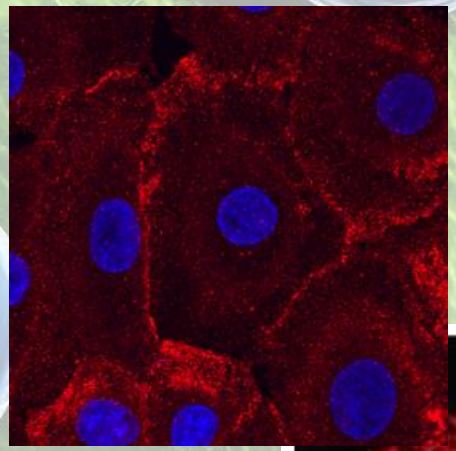
Glycocalyx

the apical surface of enodthelial cells in small intestine –
carbohydrates + proteoglycans + enzymes
thick meshwork (0,3 μm)

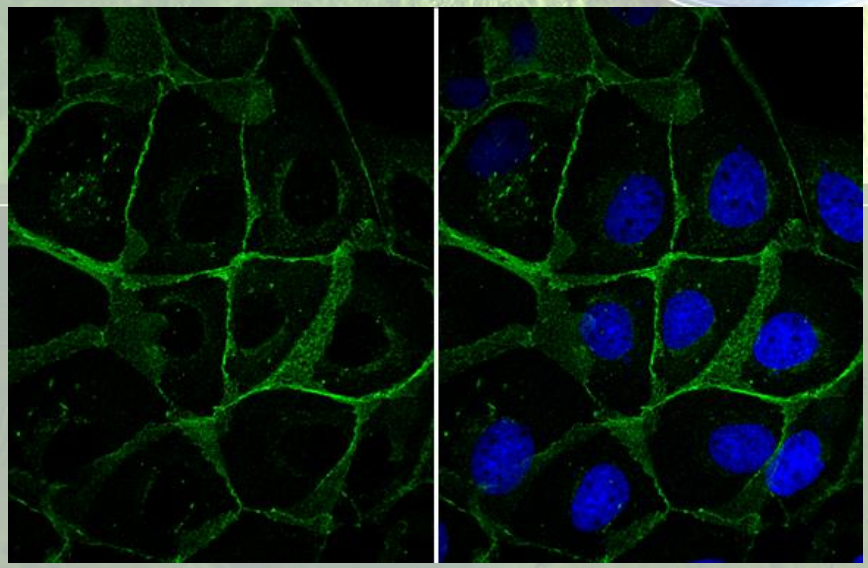


Glycocalyx





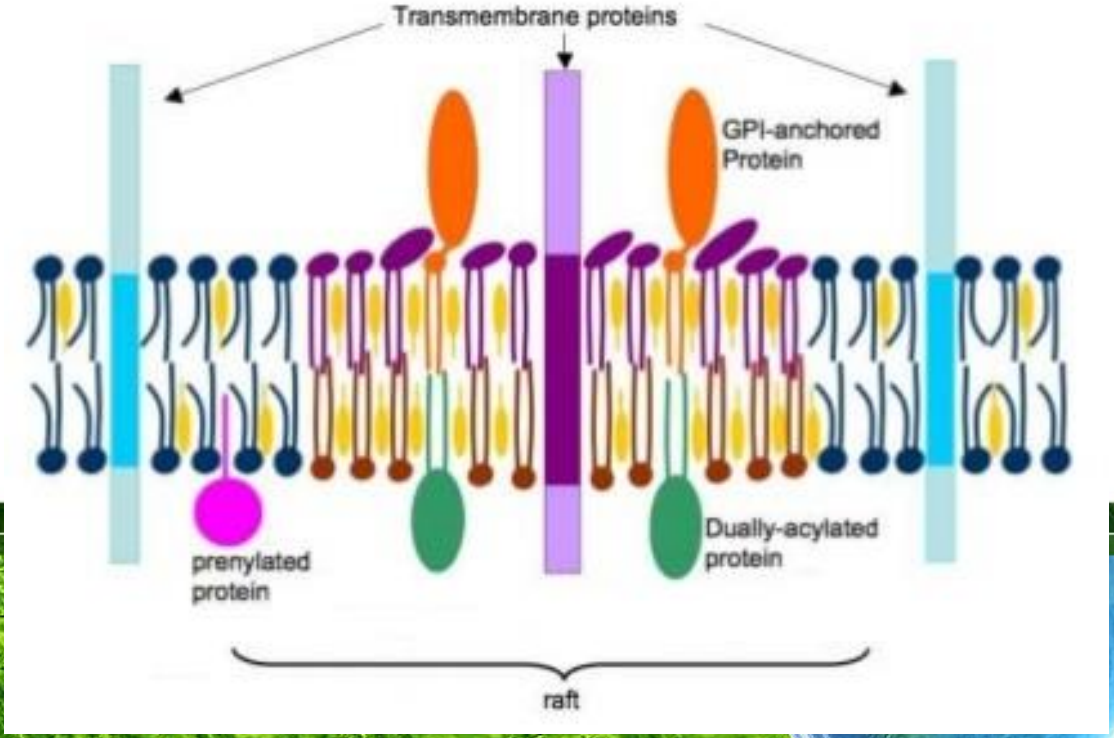
Desmoglein 1



Beta catenin

Lipid rafts

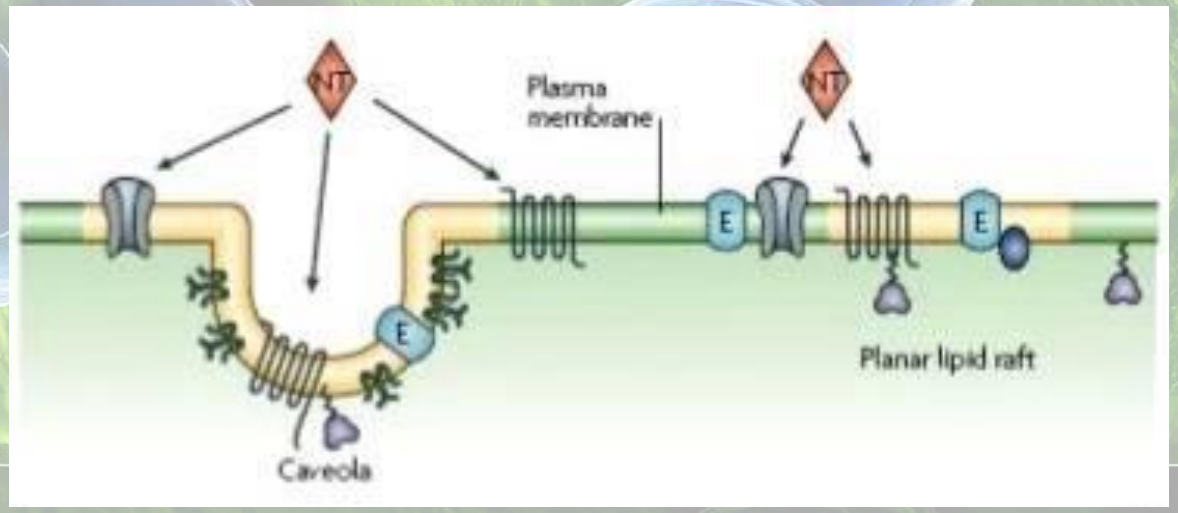
* complex fragments of the lipid membrane
* **sphingolipids** that co-localize with **cholesterol** in the membrane microdomains
* proteins can be induced
* tightly packed – tighter than the surrounding bilayer but float freely
* resistant to detergent solubilization
* very common structure in the plasma membrane but present also in GA and lysosomes



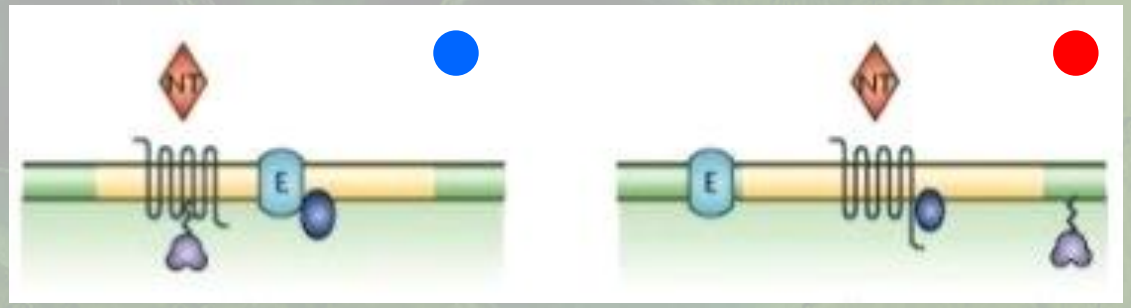
Lipid rafts

CAVEOLAE – small flask-shaped invagination, contain **caveolin** proteins,
* signal transduction (*e.g.* EGF, IgE, T and B cell antigen receptor signaling)
* membrane internalization

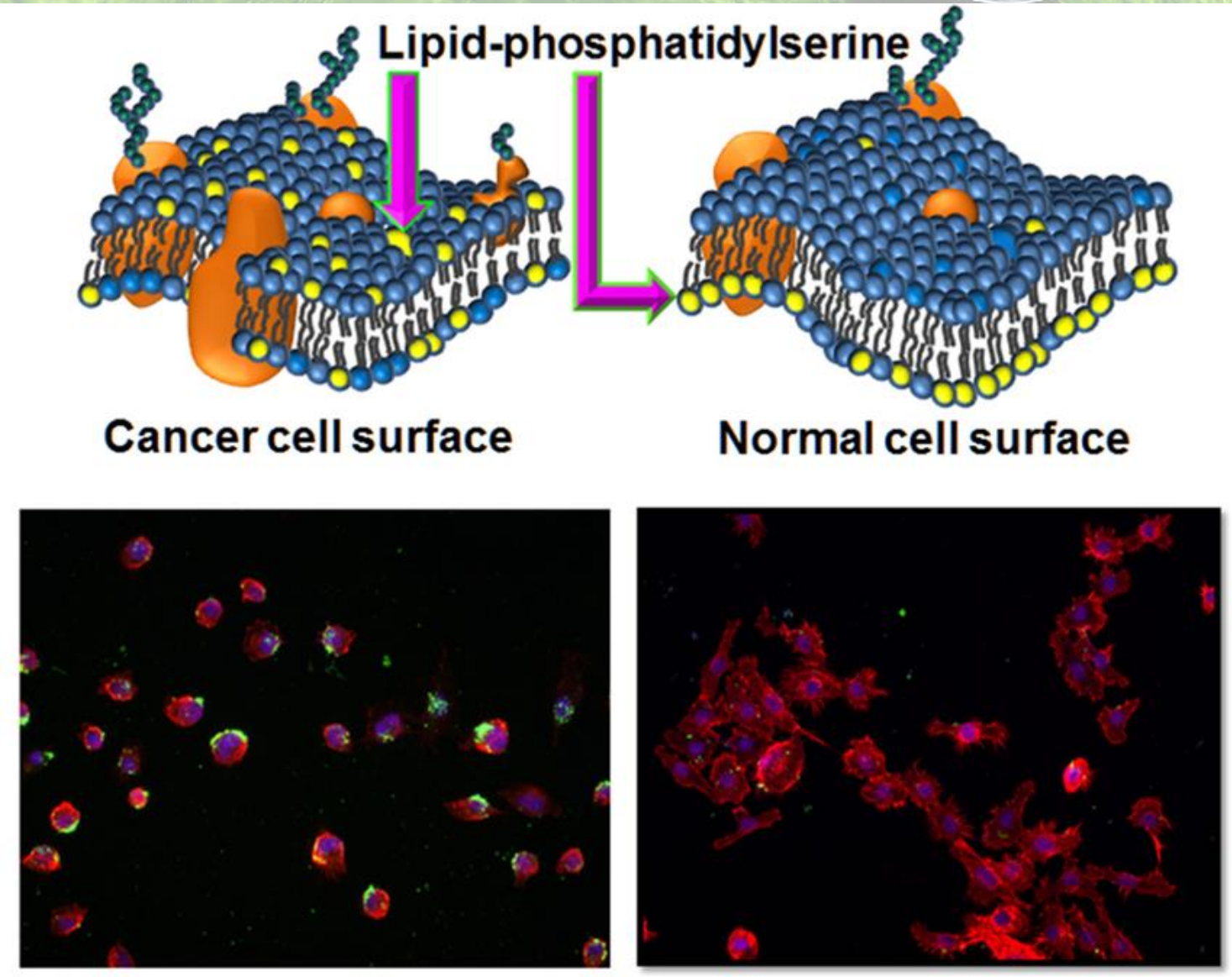
PLANAR (non-caveolar, glycolipid rafts) – not invaginated, contain **flotillin** protein, found in nerve tissue cells where caveolaes are absent

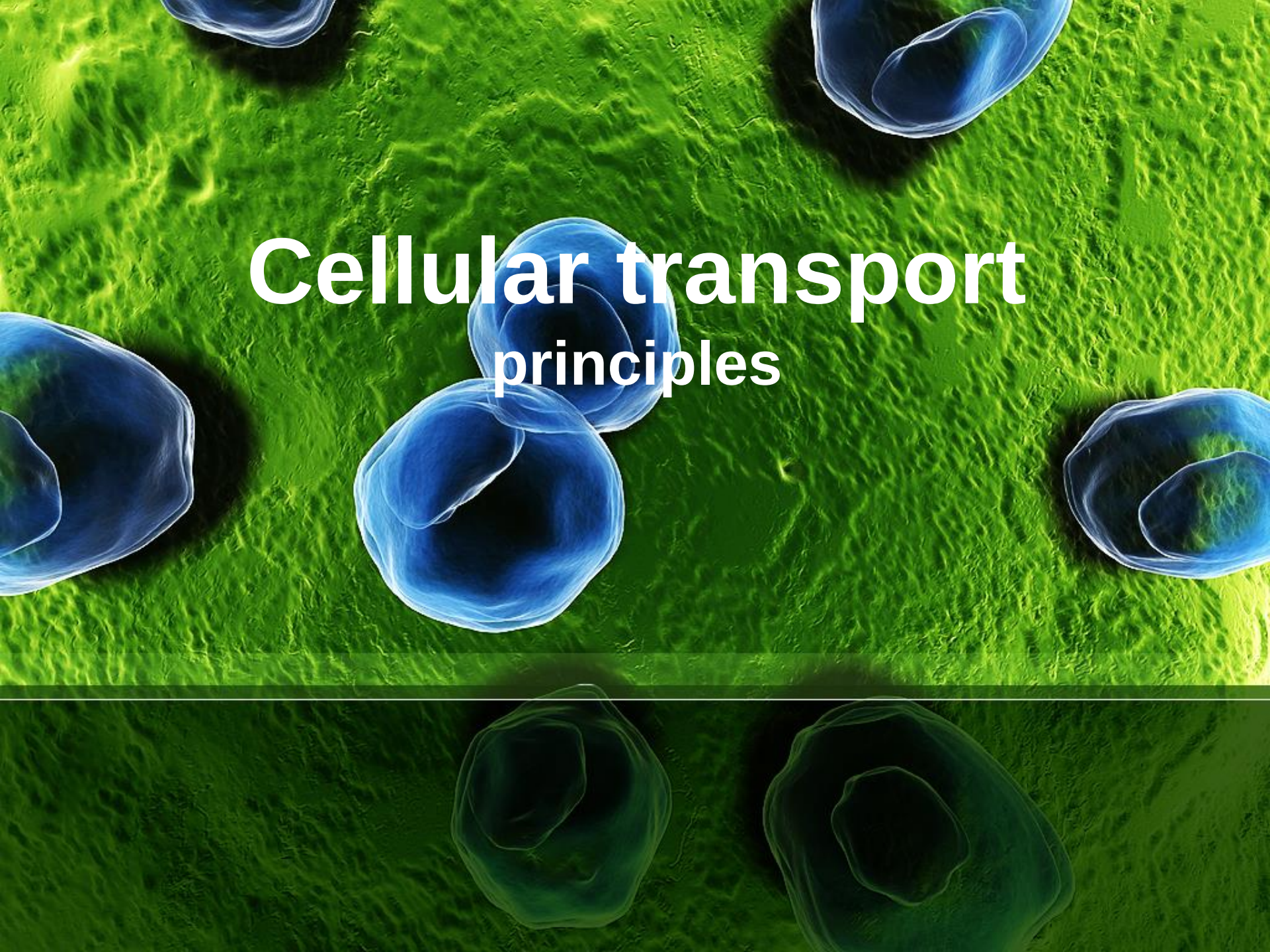


Receptors and effectors can be organized into rafts to **promote** signaling
or be separated by the raft to **prevent** signaling.



Lipid rafts


Lipid-phosphatidylserine
Cancer cell surface
Normal cell surface

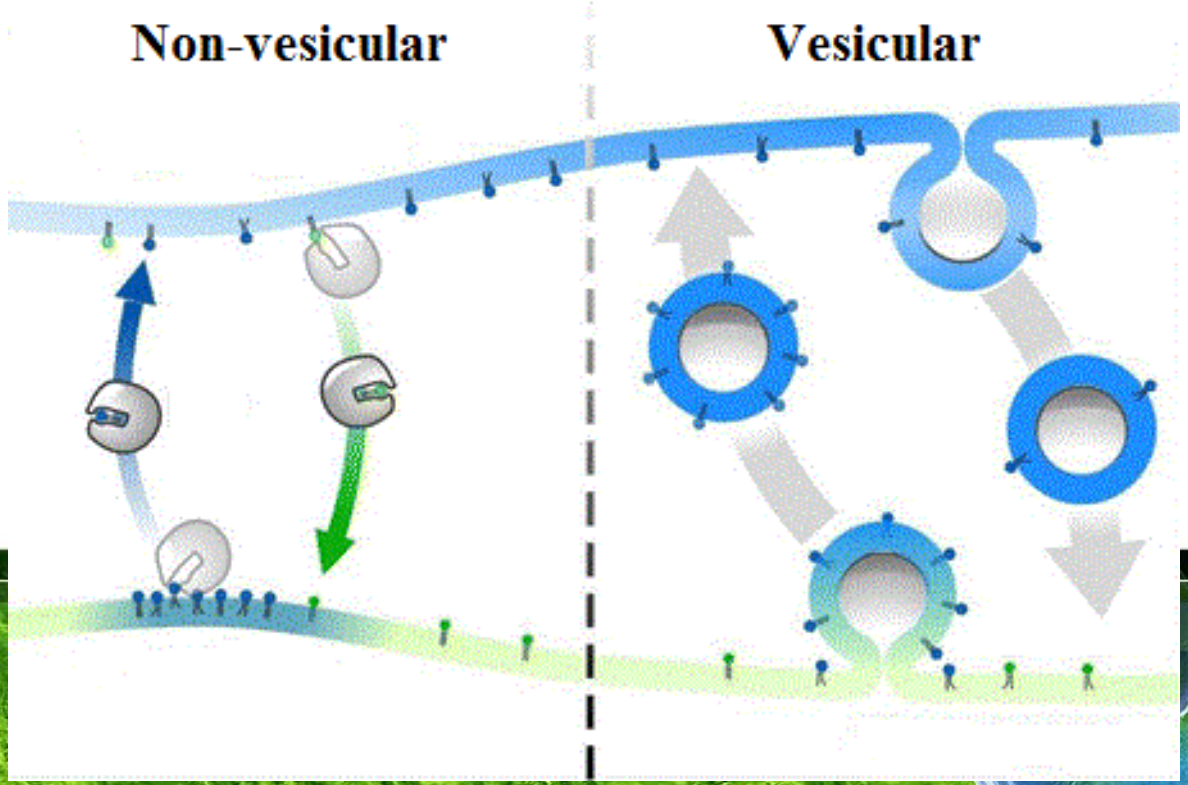

Cellular transport
principles

Cellular transport

2 types:
MEMBRANE & **VESICULAR**

MEMBRANE
(Non-vesicular)
through the membrane, membrane is **untouched**

VESICULAR
uses the membrane but maintains its integrity, involves configurational changes, formation of vesicles from the membrane, fusion of the vesicles with the membrane



MEMBRANE transport

PASSIVE

SIMPLE DIFFUSION
(no additive proteins)

PASSIVE

FACILITATED DIFFUSION
(with additive proteins, e.g. channels, carrier proteins)

ACTIVE!

ATP

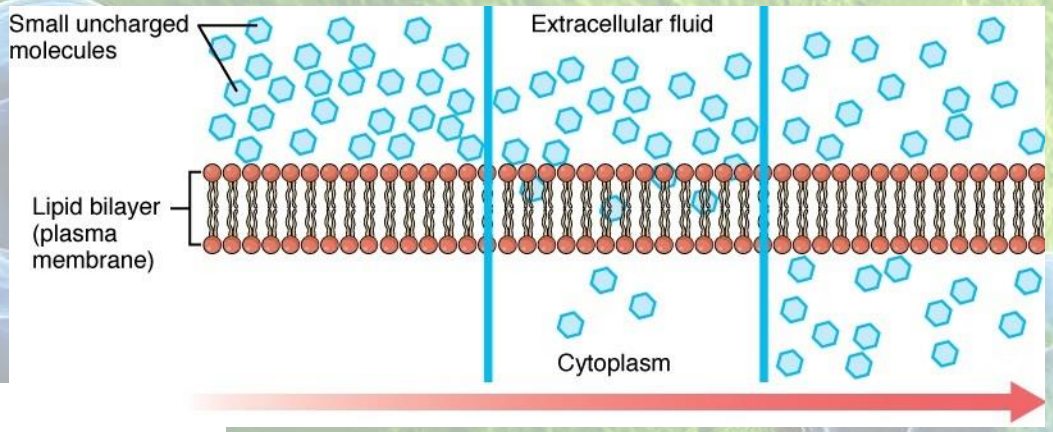
FACILITATED DIFFUSION (active transport)
(with additive proteins, e.g. channels, carrier proteins)

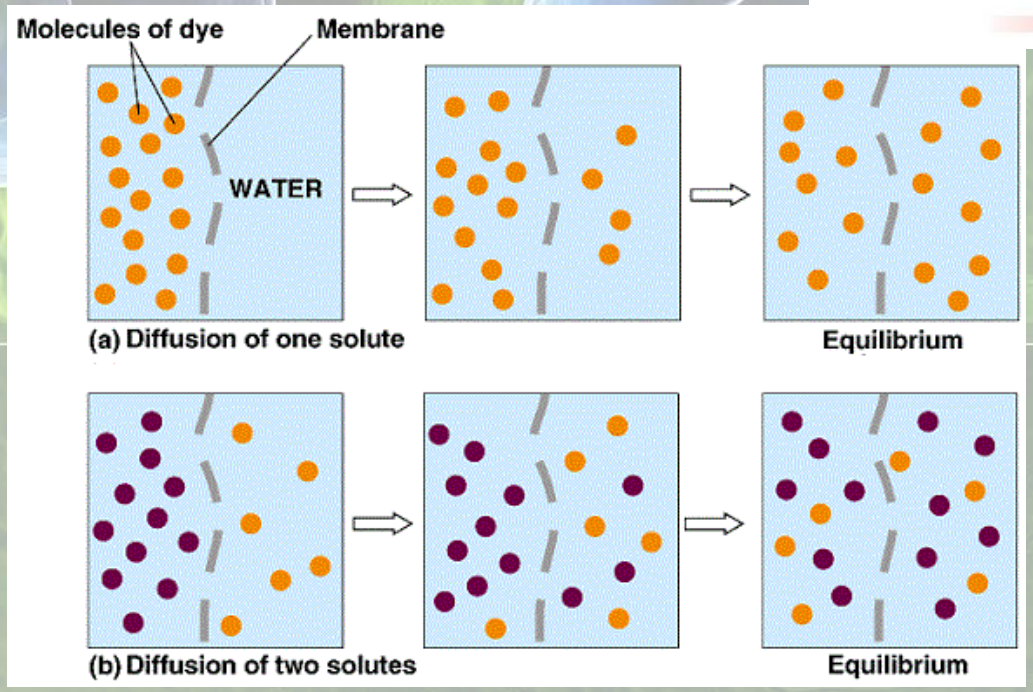
MEMBRANE transport

SIMPLE DIFFUSION

* substances cross spontaneously the plasma membrane down their concentration gradient
* non-selective

gases (CO_2, O_2, N_2),
fat-soluble (steorids),
small, uncharged molecules
(ethanol, urea)





PASSIVE

MEMBRANE transport

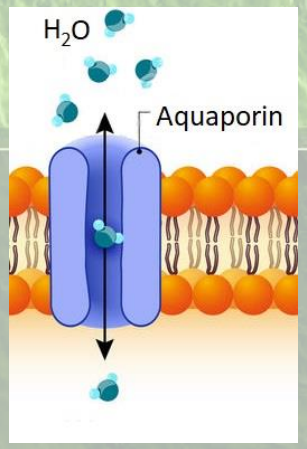
FACILITATED DIFFUSION

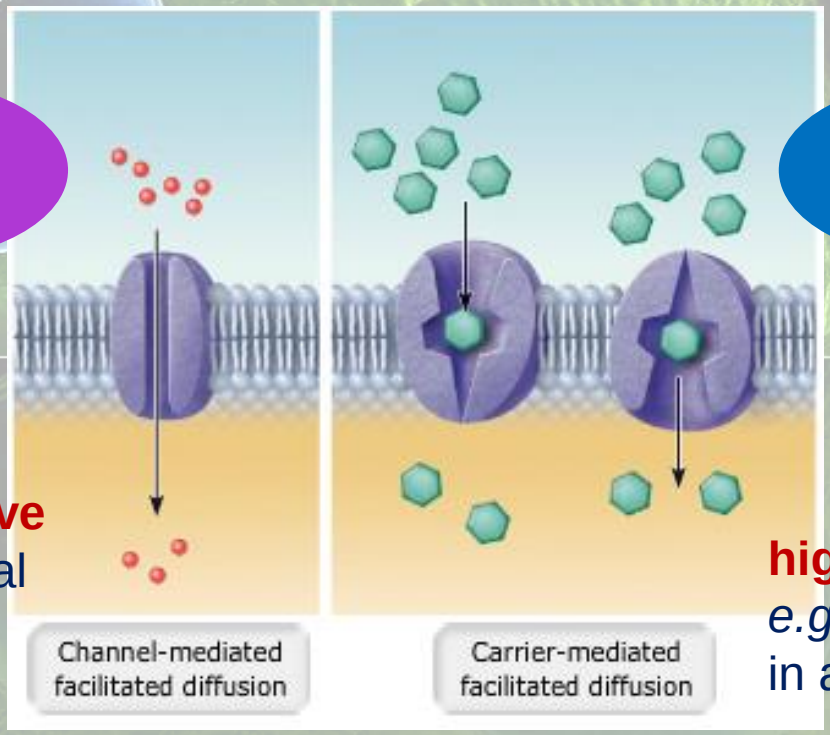
PASSIVE

* small, water-soluble molecules
  (ions and small polar molecules)
* regulated on the basis of cell's needs:
- by **membrane potentials**
  (voltage-gated ion channels in neurons),
- **mechanically-gated**
  (mechanical stress in the internal ear)
- by ligands (ligand-gated receptors)
  (neurotransmitters)

Channel proteins

Carrier proteins



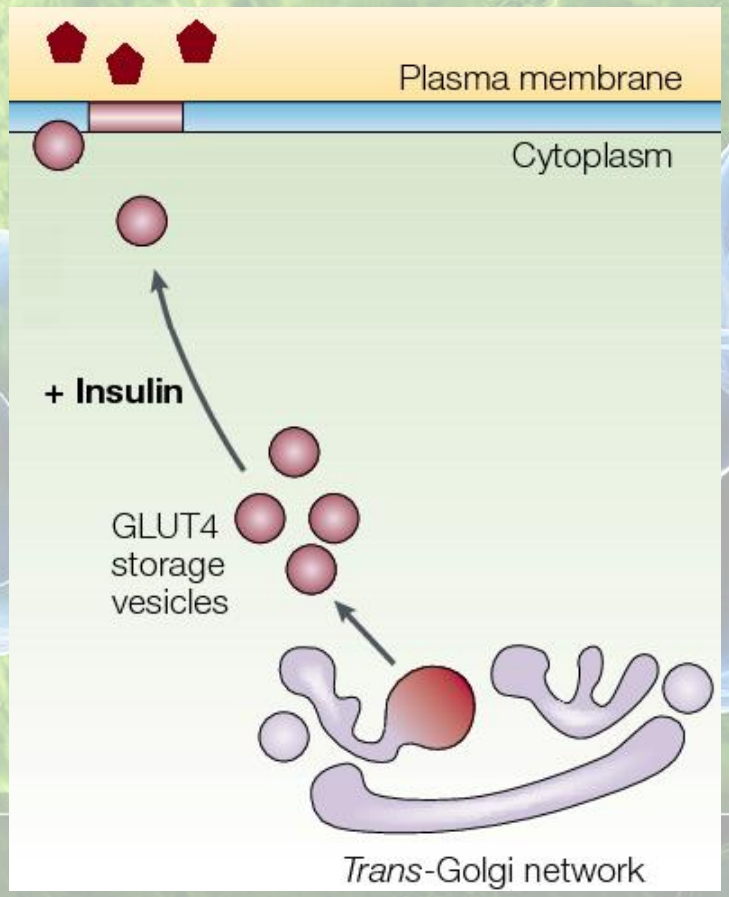


non-selective
water- cannal

highly selective
e.g. glucose
in adipocytes

e.g. glucose transporter

PASSIVE

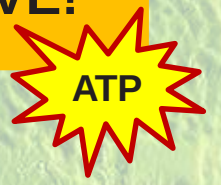


Transporter	Tissues	Function
GLUT1	All tissues, especially red cells and blood-brain barrier	Basal uptake of glucose
GLUT2	Liver, kidney, gut, beta cells of pancreas	Regulation of insulin release, glucose homeostasis, low affinity
GLUT3	Brain, kidney, placenta, neurons, sperm	Uptake into neurons, high affinity
GLUT4	Skeletal muscle, heart, adipose	Insulin-mediated uptake of glucose
GLUT5	Kidney, gut Epithelium	Absorption of fructose

MEMBRANE transport

FACILITATED DIFFUSION

ACTIVE!



* transport with **carrier proteins**
* water-soluble molecules
* **highly selective**
* requires energy for **ACTIVE TRANSPORT** of molecules

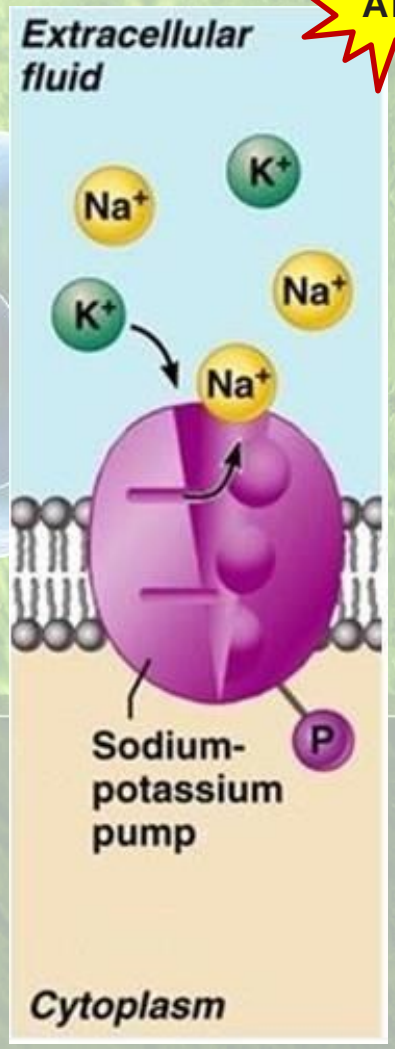
against their concentration!

Facilitated diffusion

ACTIVE!

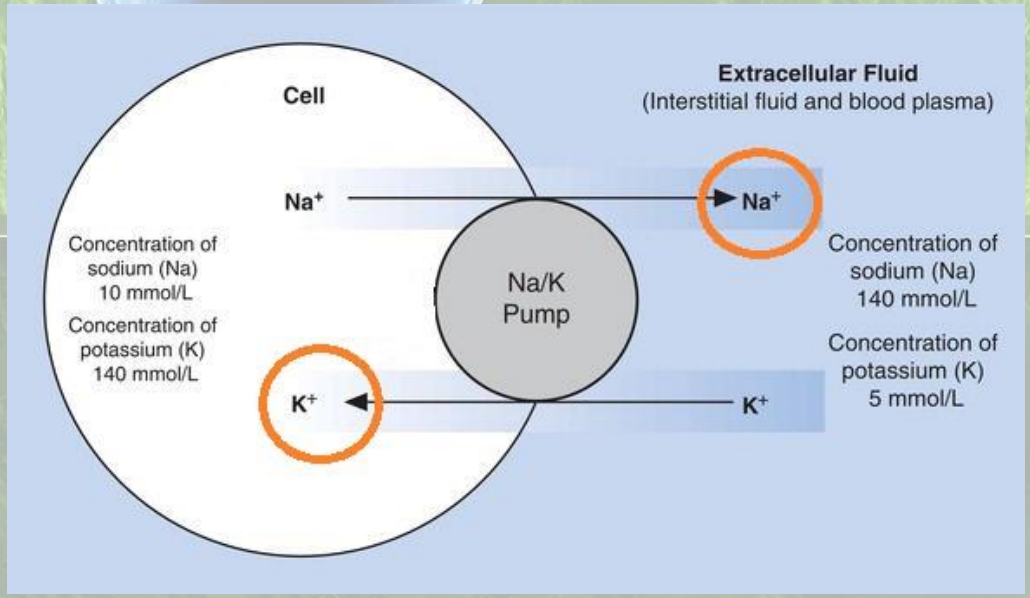
ATP

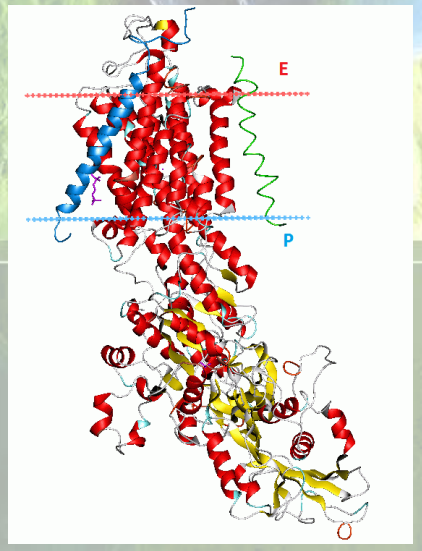
e.g. Na^+/K^+ pump
sodium-potassium pump



Actively pumps potassium INTO cell (2 ions) while pumping sodium OUT of cell (3 ions), both **against their concentration gradients**.

e.g. nerve cells, muscle cells, renal tubular cells

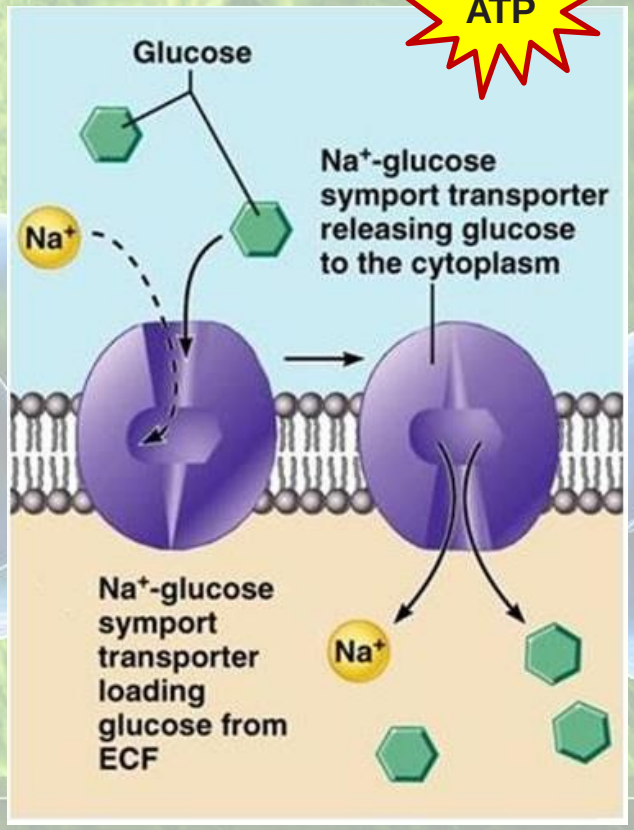




Facilitated diffusion

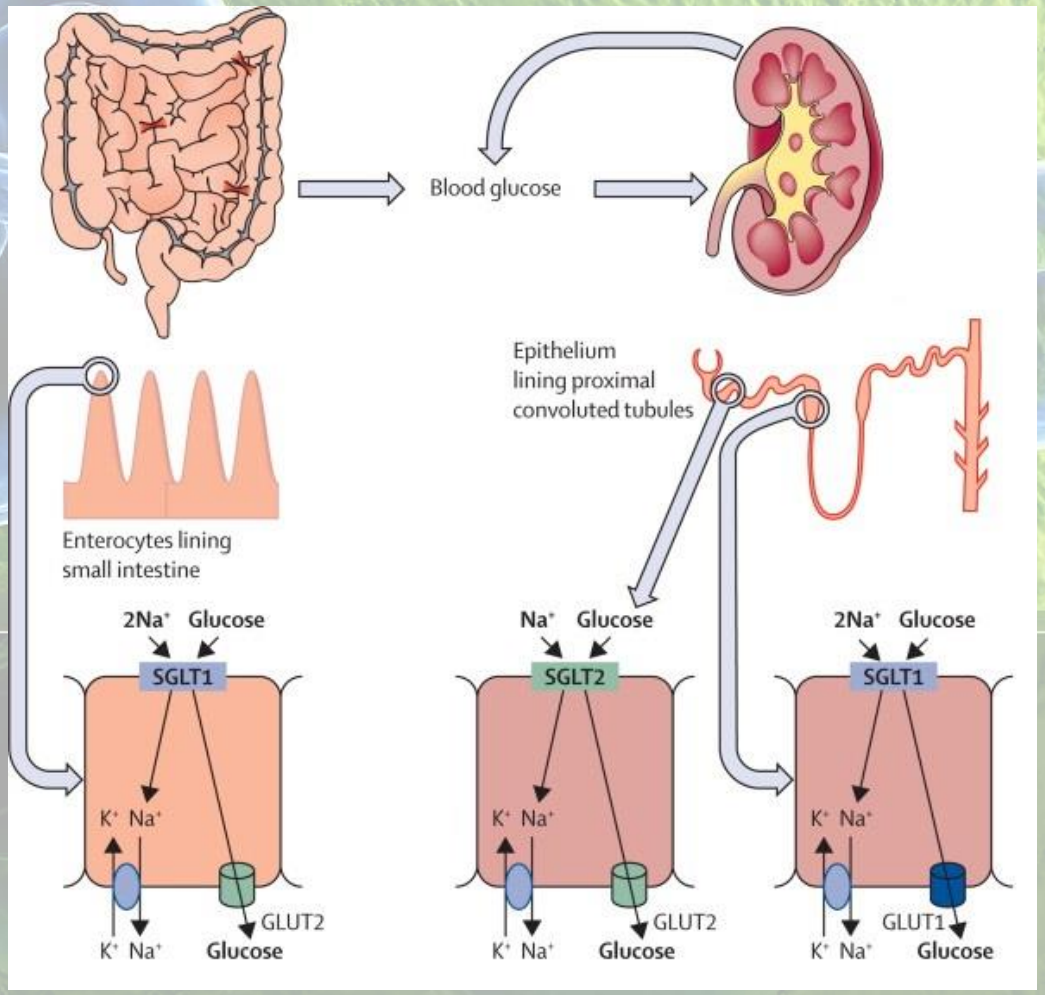
ACTIVE!

ATP

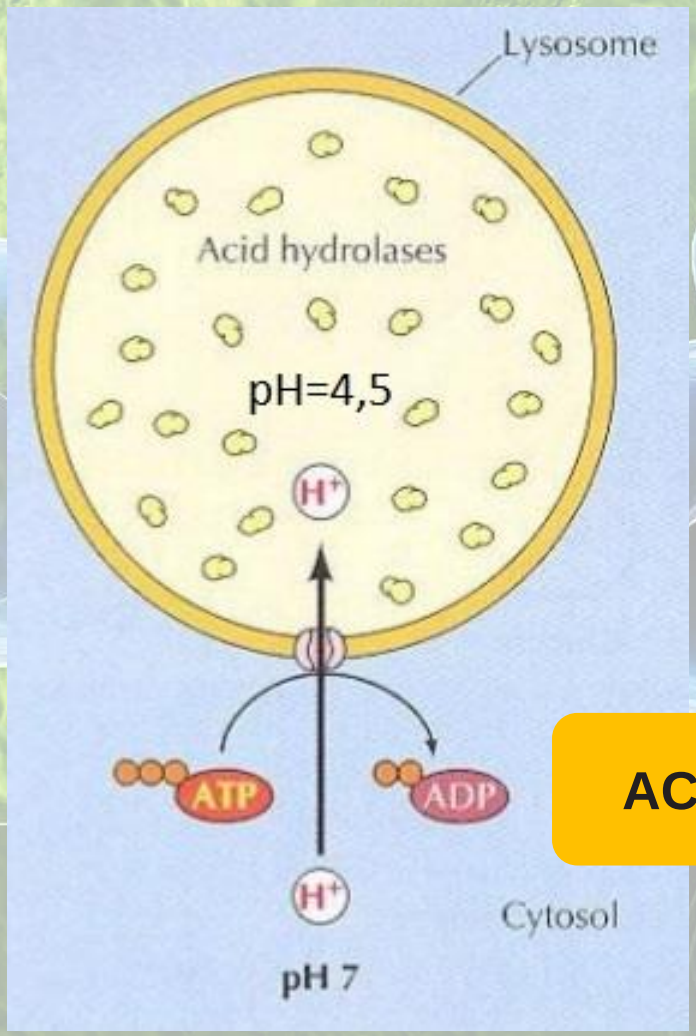


e.g. **Co-transporter of Na^+ -glucose**

SGLT (Sodium-dependent glucose co-transporter)



Facilitated diffusion



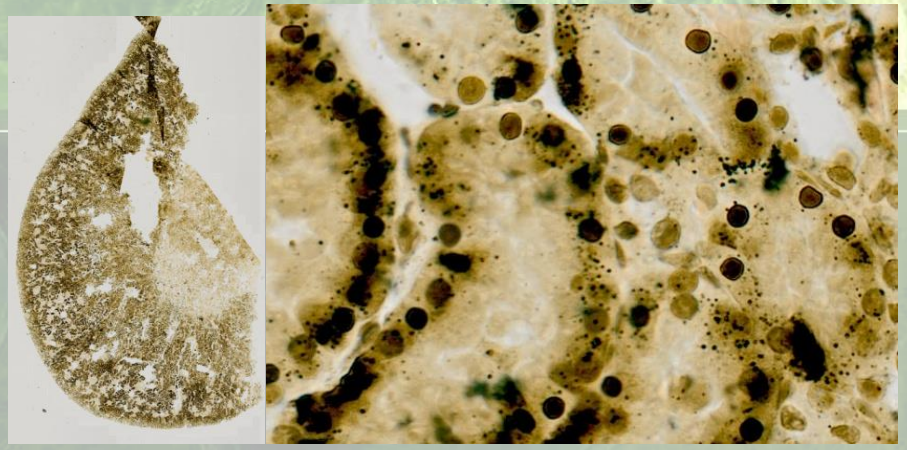
e.g. Proton pump

Most digestive enzymes are **acid hydrolases**.

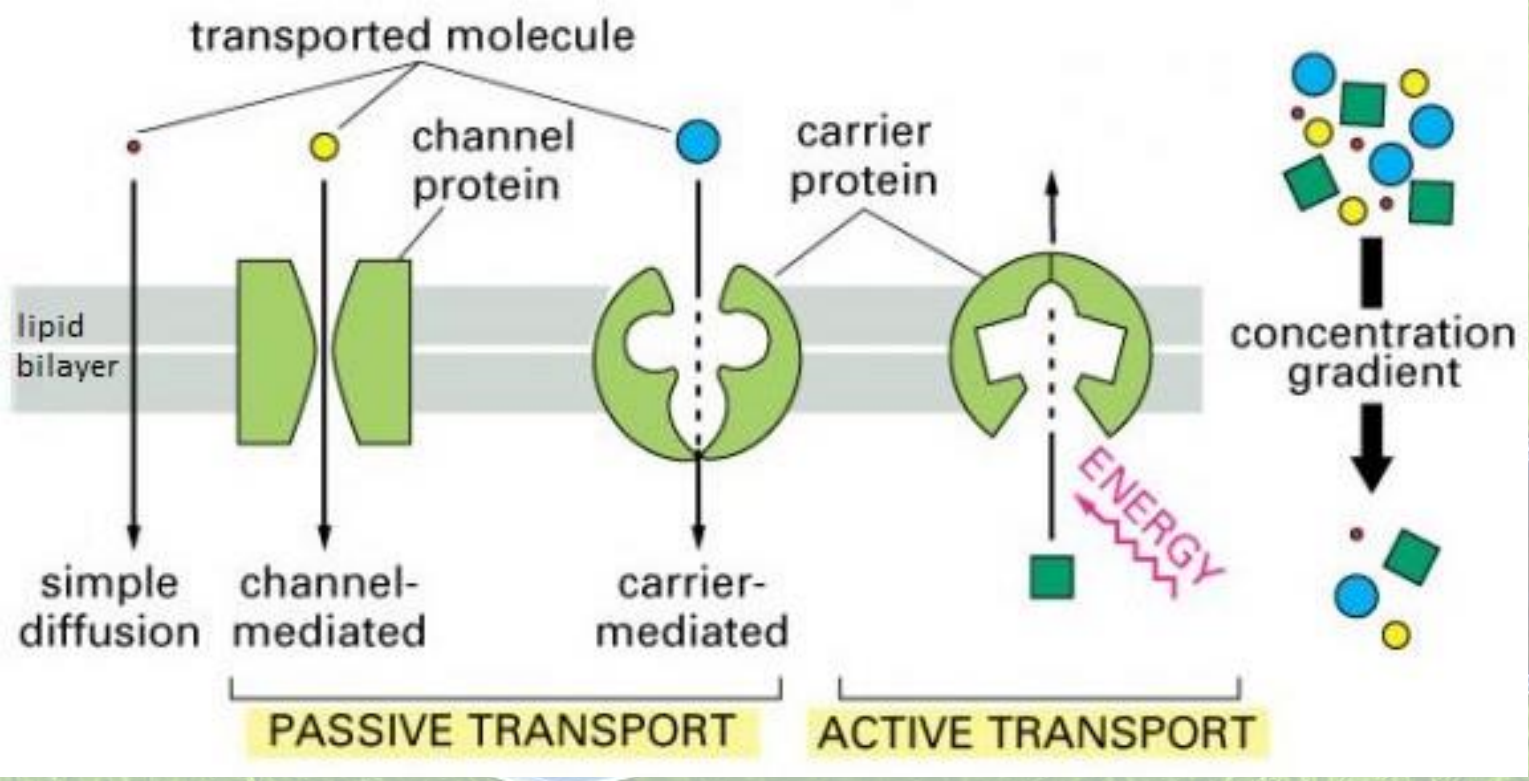
The acidic internal pH is is a result of an action of proton pump, which imports protons from the cytosol into the vesicle.

ACTIVE!

ATP



MEMBRANE transport - summary



PASSIVE **PASSIVE** **PASSIVE** **ACTIVE!** ATP

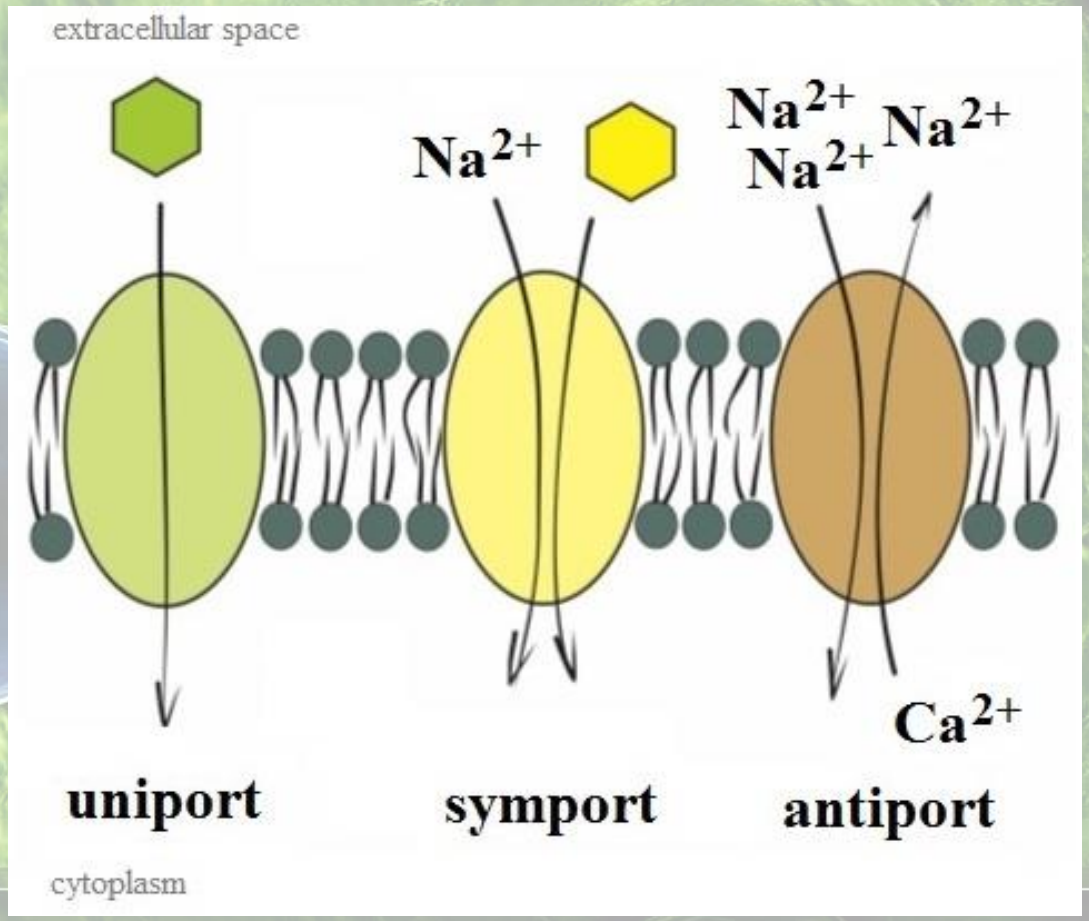
Channel proteins

Carrier proteins

Carrier proteins

Channel proteins

Transport



*e.g. p*assive glucose transport

e.g. Na^+/glucose (in gut)

exchange, counter-transport
e.g. Na^+/Ca^{2+} exchanger (in cardiac muscle)

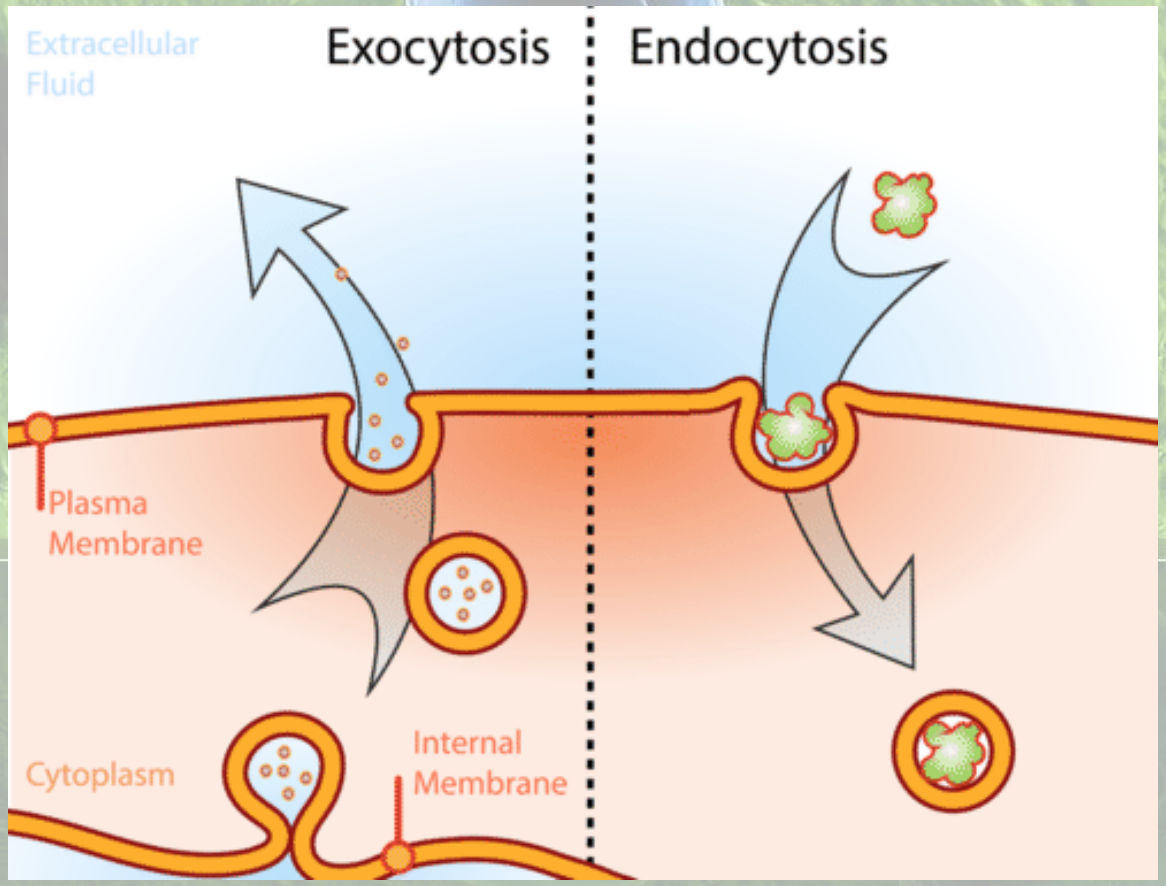
VESICULAR transport

ACTIVE!

ATP

EXOCYTOSIS
when substances leave the cell

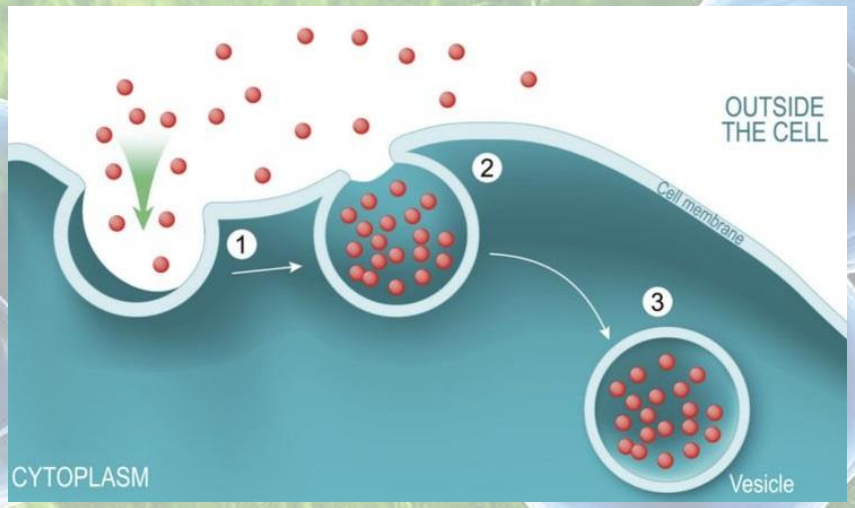
ENDOCYTOSIS
when substances enter the cell

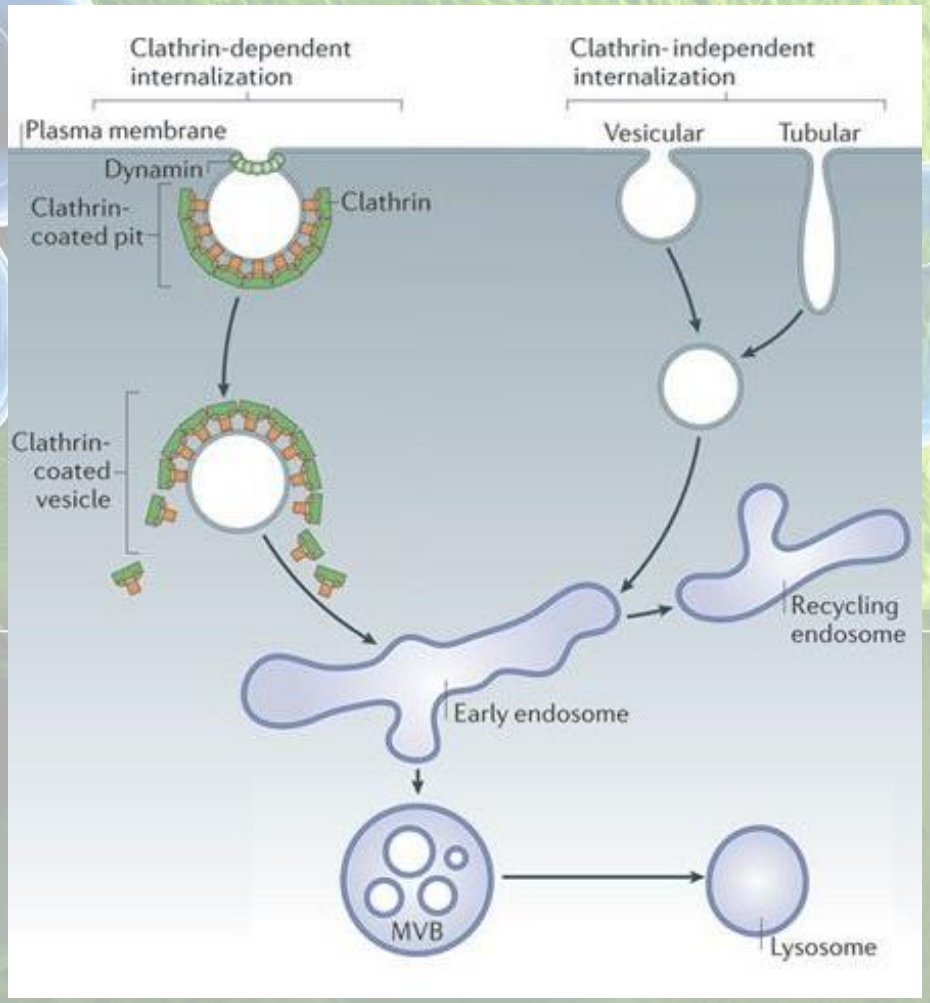


ENDOCYTOSIS

* may require **CLATHRIN** protein that interacts with the plasma membrane during vesicle formation:

→ clathrin-independent & clathrin-dependent (receptor-mediated endocytosis)

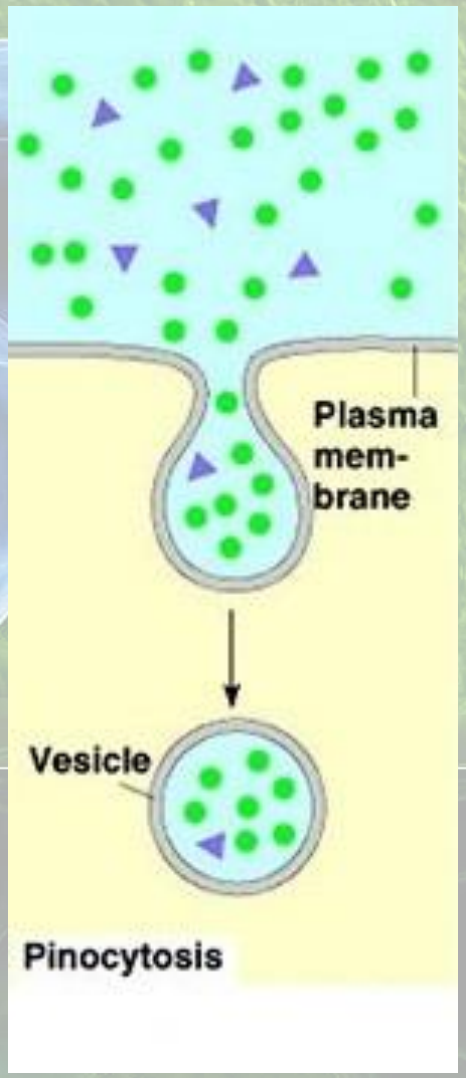


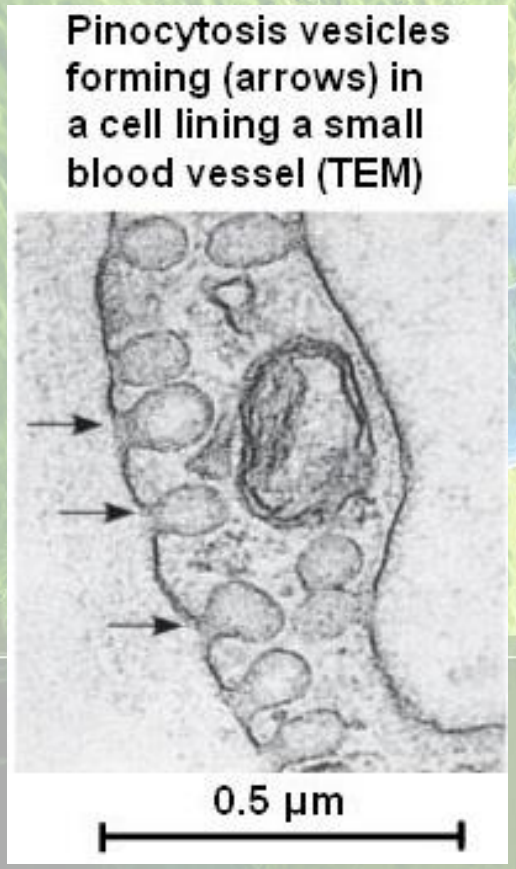


ENDOCYTOSIS

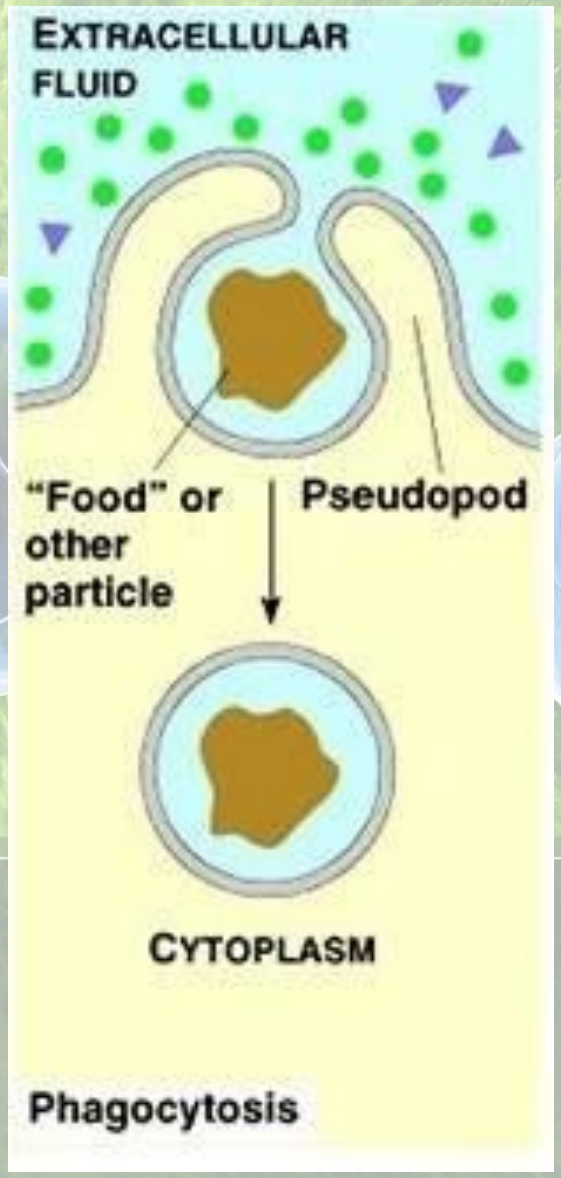
PINOCYTOSIS
(„cell-drinking”)

* intake of fluids or small proteins (<150 nm)
* **CLATHRIN-independent**
* performed by all the cells in the body





ENDOCYTOSIS



PHAGOCYTOSIS („cell-eating")

* ingestion of large particles, cell can send pseudopodia to engulf particle to form large vesicle (~250 nm)
=phagosome

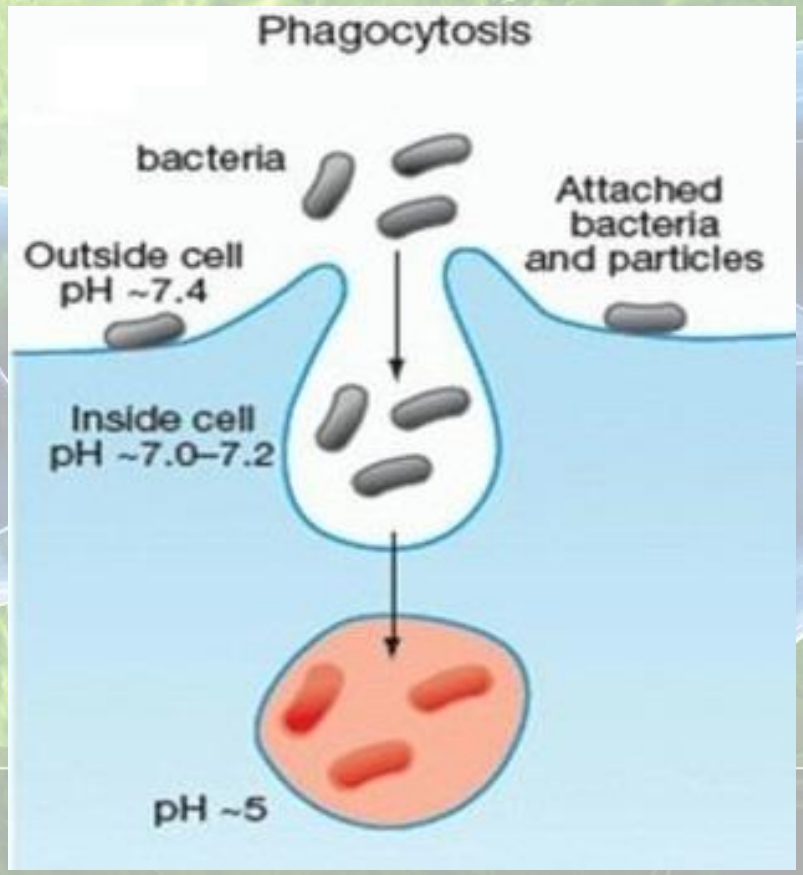
* performed by specialized group of cells:

Mononuclear Phagocytotic System (MPS):

Macrophages (adipose tissue m., Kuppfer cells, sinus histiocytes, osteoclasts, peritoneal m., red pulp = sinusoidal m., etc.)
Langerhans cells
Microglia
Intraglomerular mesangial cell

ENDOCYTOSIS

PHAGOCYTOSIS („cell-eating”)



1. <u>Without involvement of receptors</u>

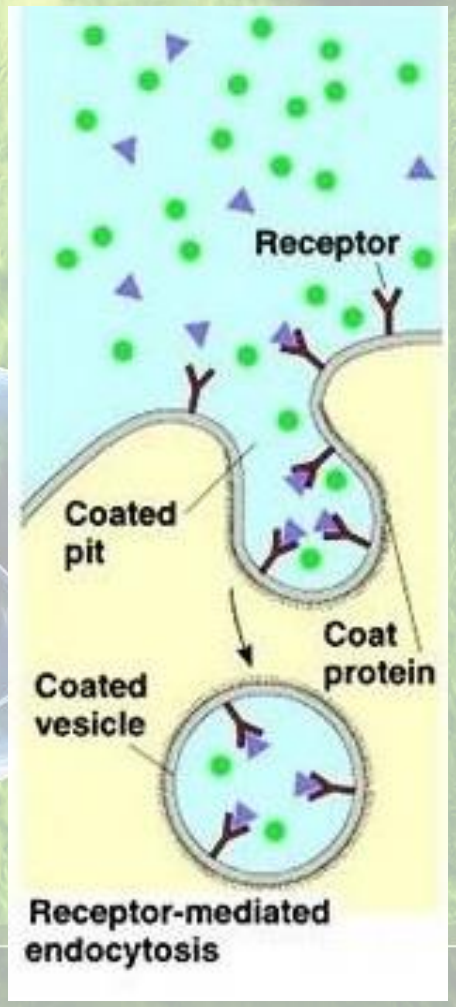
* **CLATHRIN-independent**

* non-selective
* less often

* dead cells’ fragments, biological debris, inhaled carbon particles

ENDOCYTOSIS

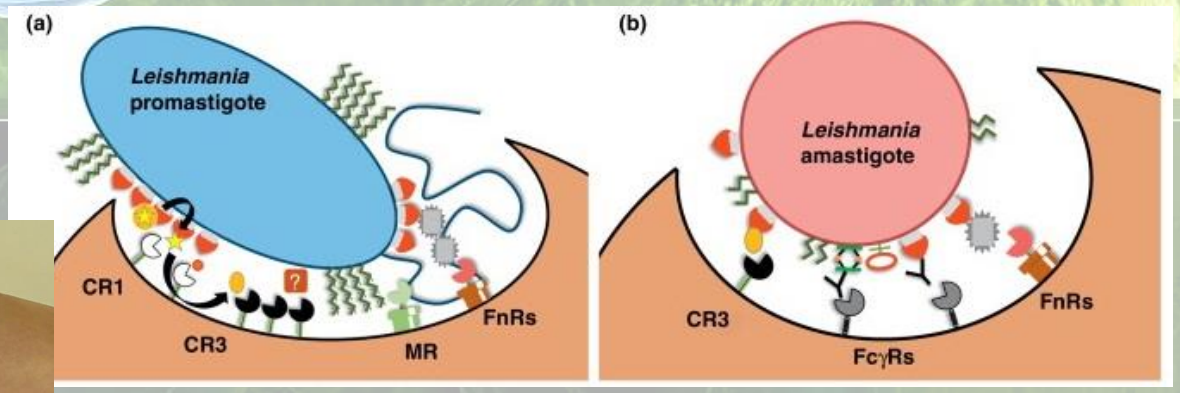
PHAGOCYTOSIS („cell-eating”)



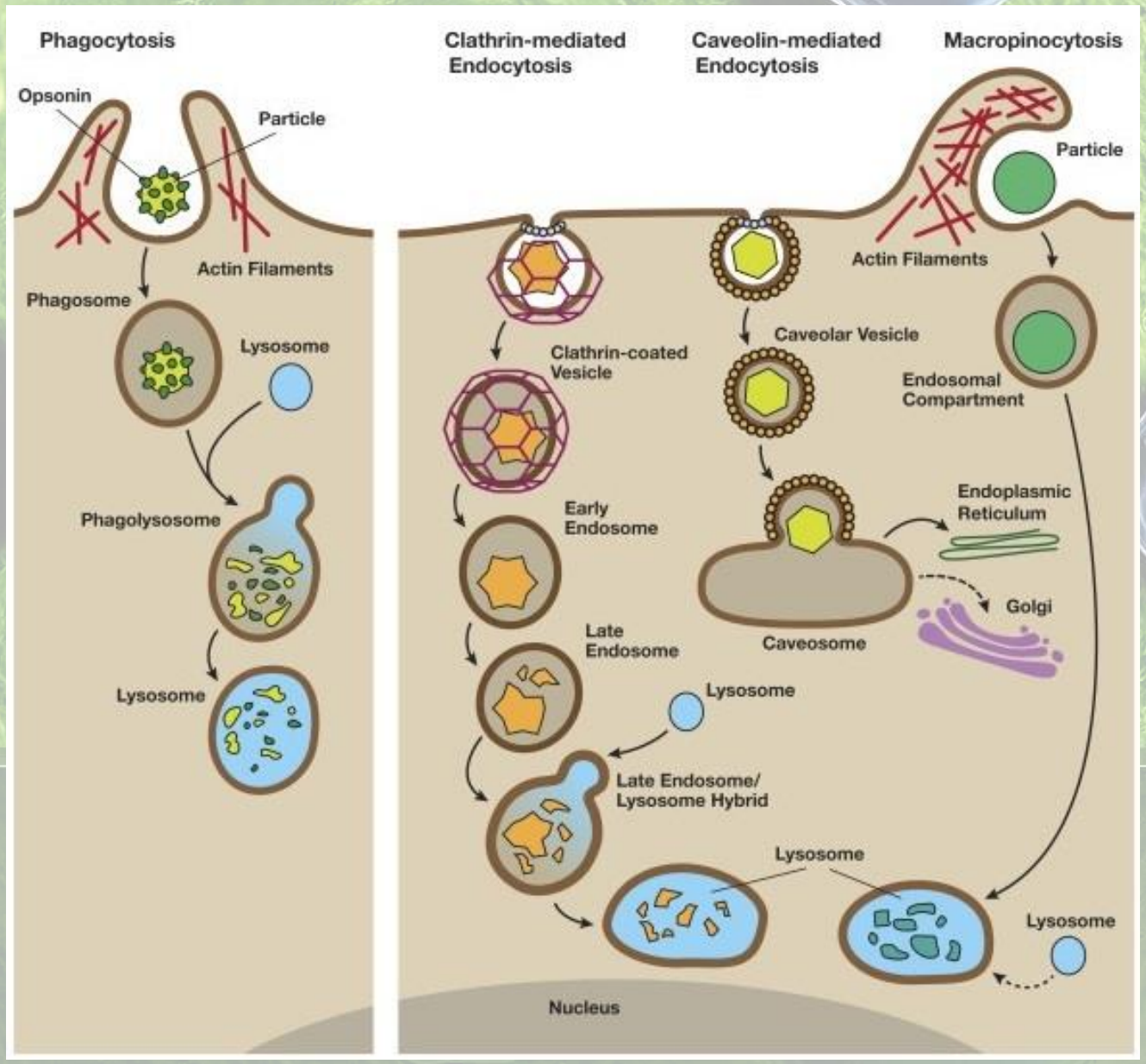
2. Receptor-mediated

* **most often**
* selective – specific molecules enter the cell, receptors accumulate in well-defined regions of the plasma membrane, on the internal surface side of the PM **coated pit** is formed, accumulation of **clathrin** molecules (via adaptor proteins **adaptin)**
* **CLATHRIN-dependent**

e.g. pathogens, surrounded by the Ab – APCs; some drugs



ENDOCYTOSIS



EXOCYTOSIS

Expelling molecules (waste & products) through the active process using secretory vesicles that move from cytoplasm to the PM where they fuse and discharge its content to the extracellular space.

1. Constitutive pathway
2. Regulated secretory pathway

EXOCYTOSIS

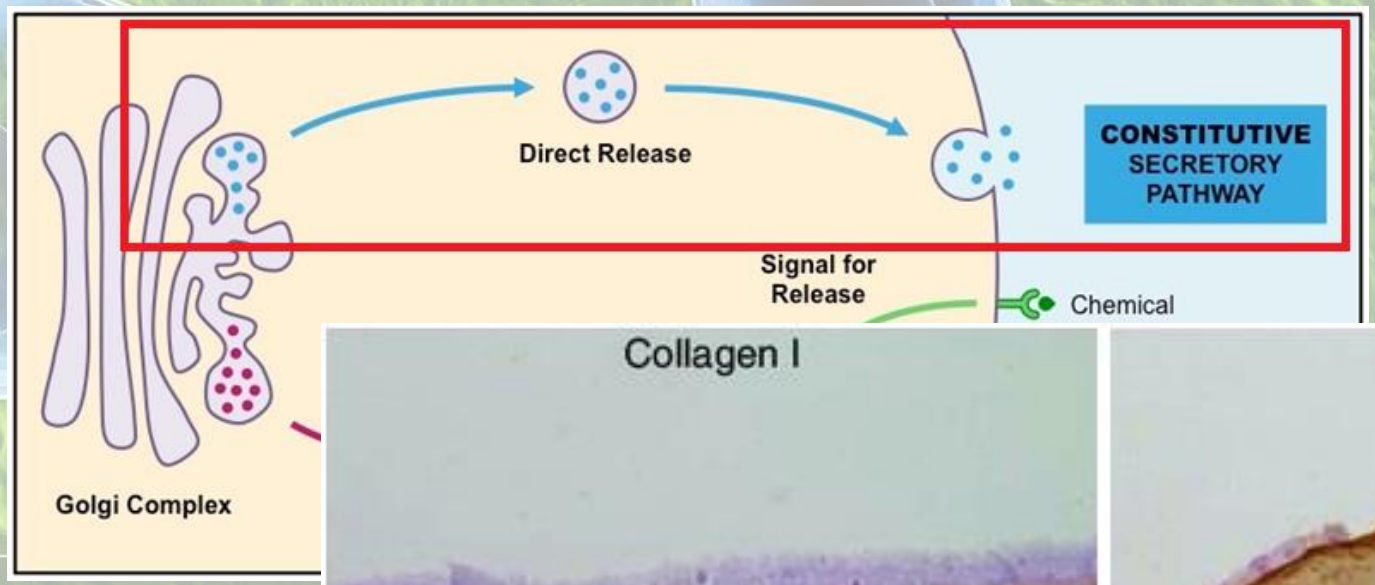
1. Constitutive pathway:

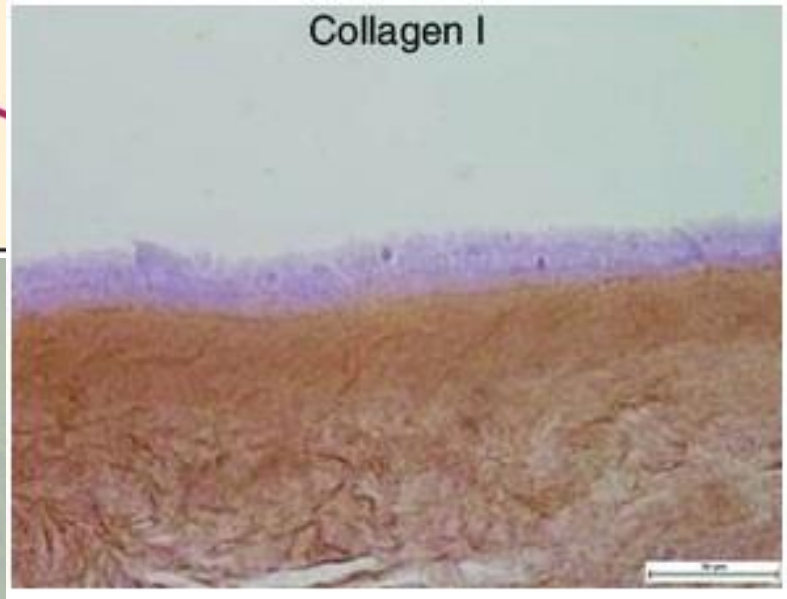
substances for export are continuously delivered to the PM

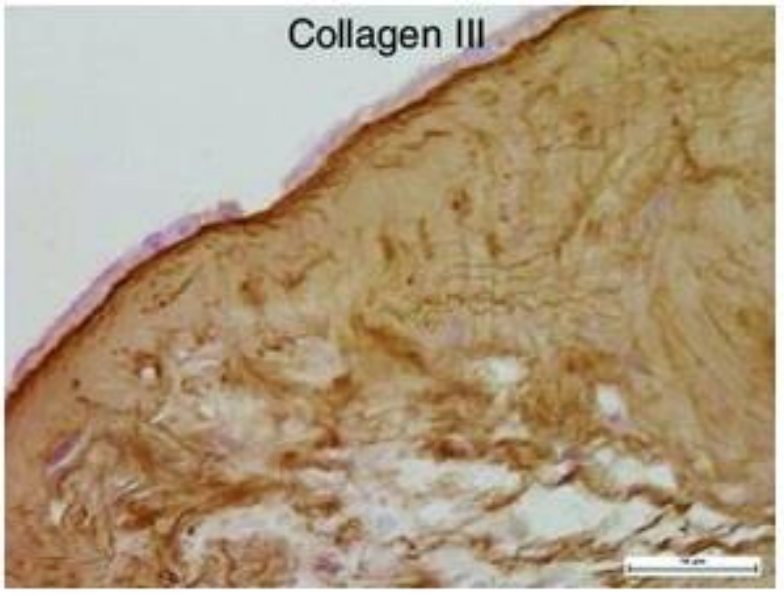
proteins from GA secreted immediately after their synthesis

(*e.g.* Ig by plasma cells, procollagens by fibroblasts, TNF)

lack of storage vesicles







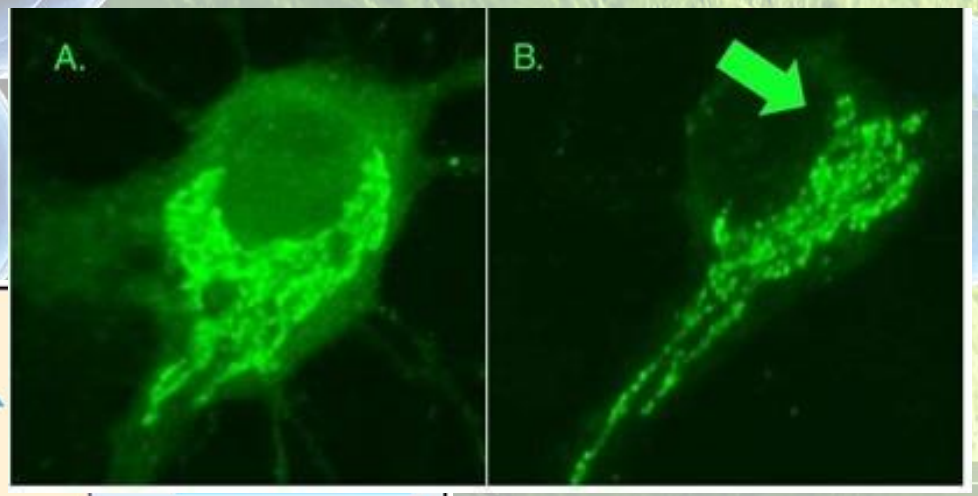
EXOCYTOSIS

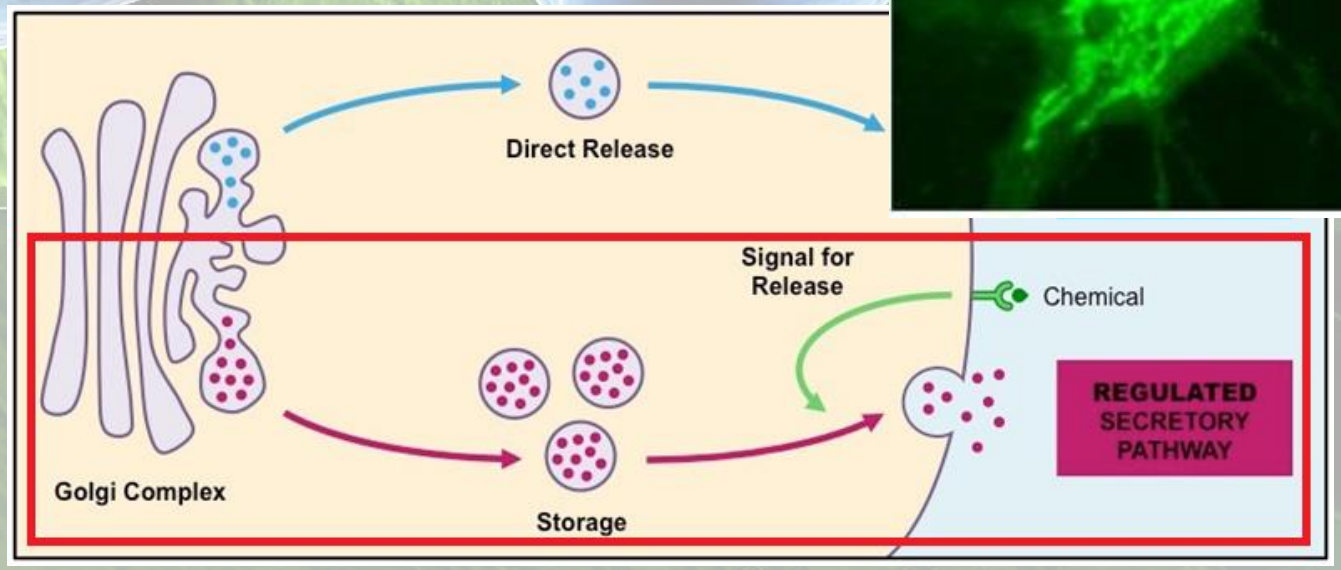
2. Regulated secretory pathway:

needs activation signal/stimulus (hormonal/neural) to release the molecules

the stimulus causes influx of Ca^{2+} into the cytoplasm which stimulates secretory vesicles to fuse with the PM and discharge its content

by specialized cells – *e.g.* exocrine cells, neurons



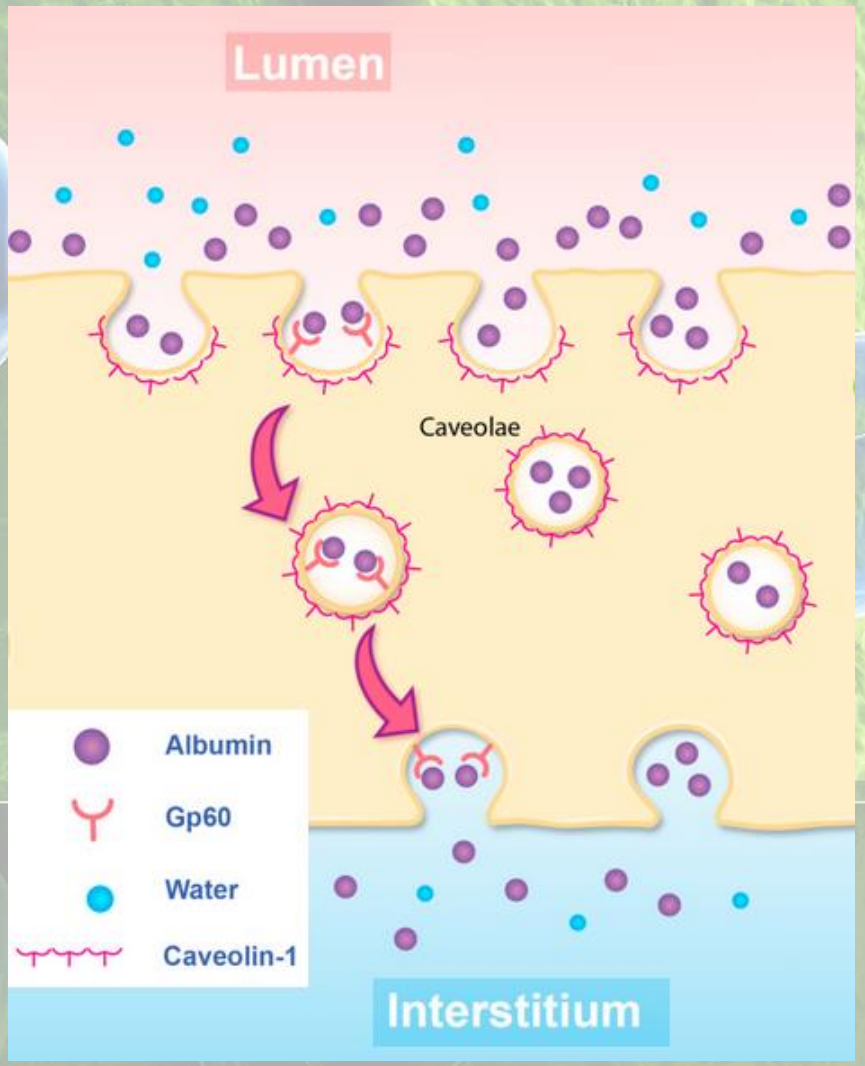


TRANSCYTOSIS

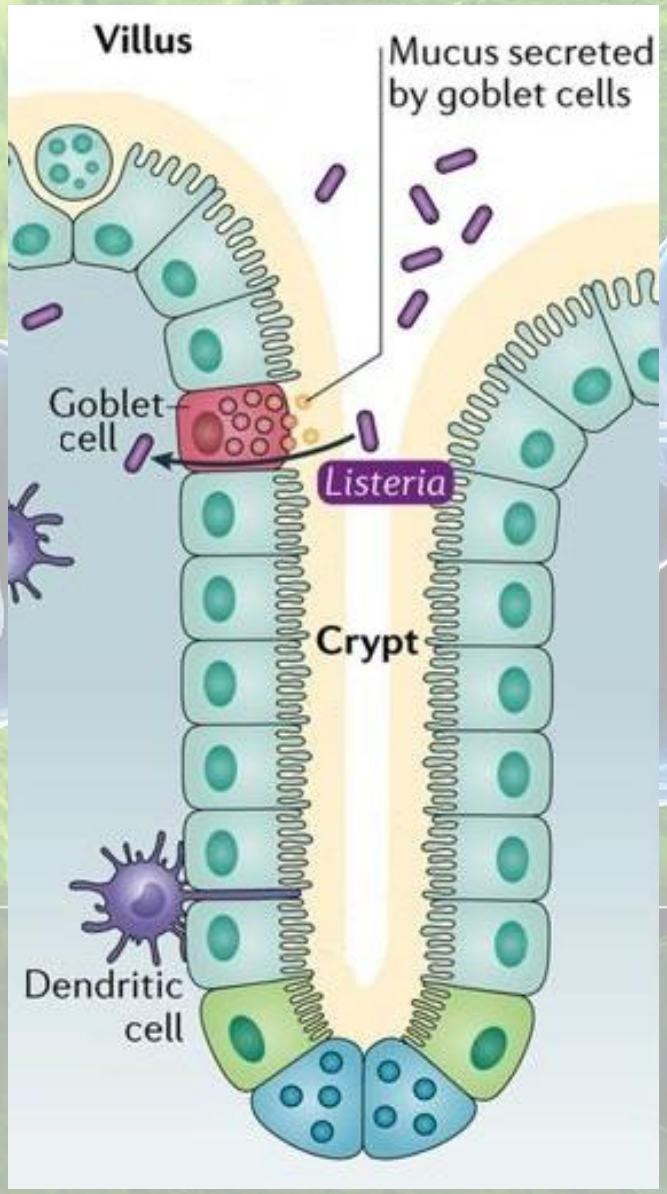
transport of molecules **across the interior** of a cell –
molecules are captured in vesicles on one side of the cell,
drawn across the cell and ejected on the other side

= endocytosis followed by exocytosis

e.g. in enterocytes in the gut,
in stratified epithelia



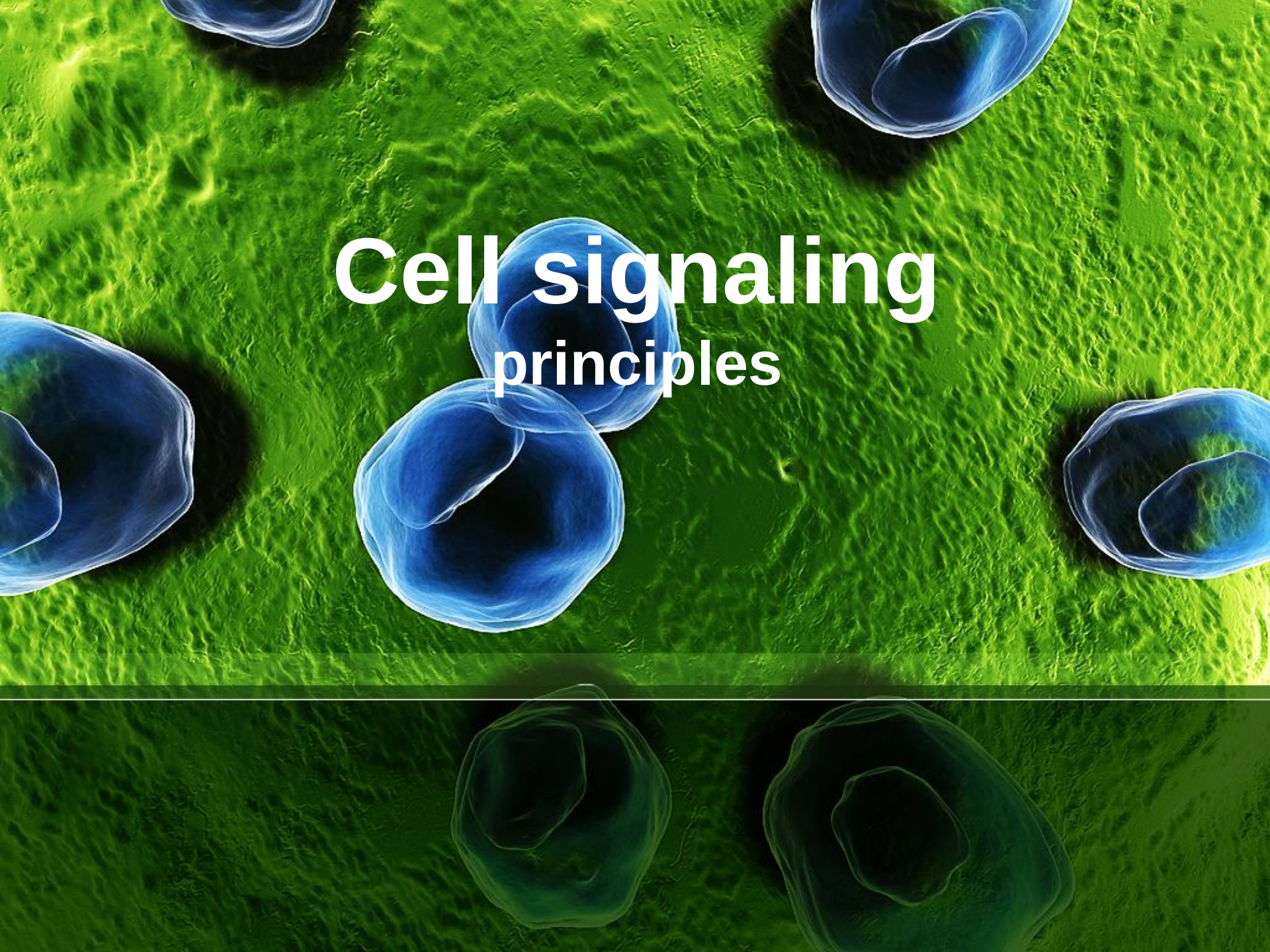
TRANSCYTOSIS



most commonly in epithelial cells,
insulin, transferrin

used to transport therapeutic drugs
across the blood-brain barrier

also used by pathogens to enter the body
(Listeria monocytogenes enters
the intestitial lumen via transport across
the goblet cells)


Cell signaling
principles

TYPES OF SIGNALING

Local signaling:

Autocrine

Paracrine

(Synaptic signaling)

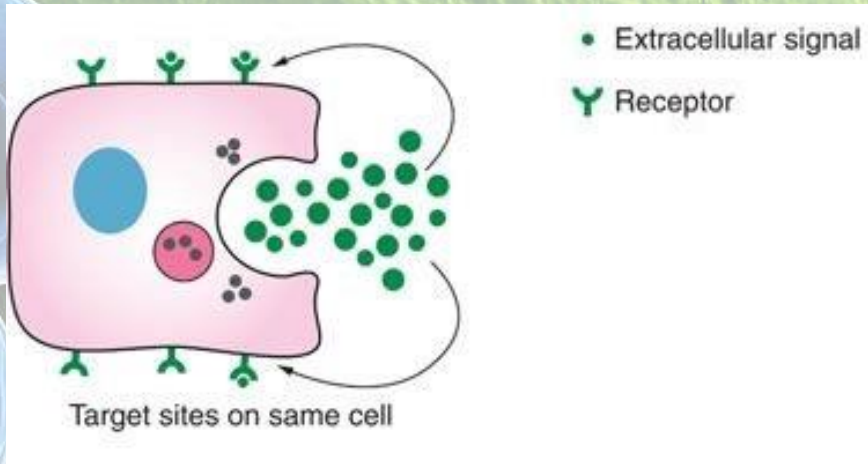
Juxtacrine

Long-distance signaling:

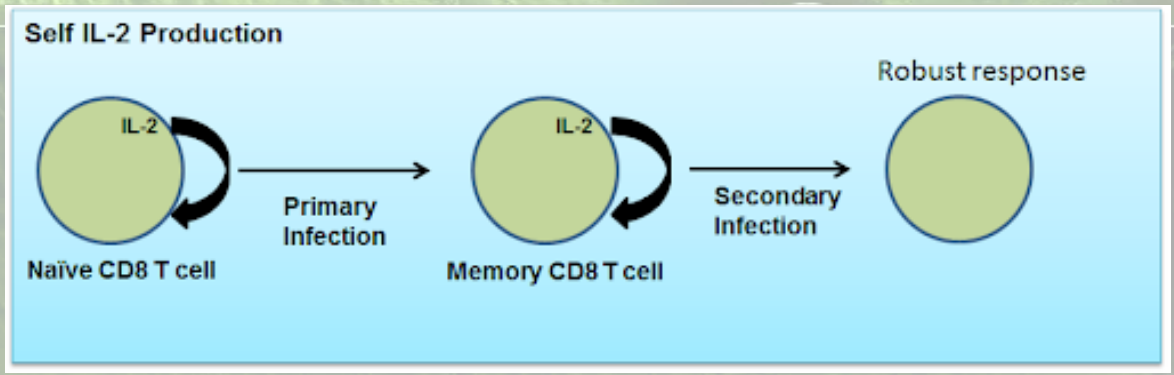
Endocrine

TYPES OF SIGNALING

Autocrine (self-signaling)
cell produces and secretes a molecule that binds to autocrine receptors on the same cell



e.g. IL-2 productiona & self activation of T cells



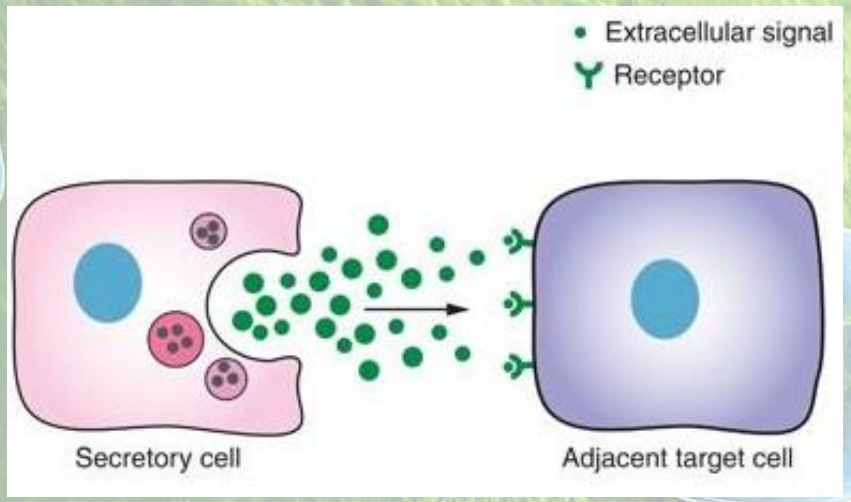
most cytokines
and growth factors

TYPES OF SIGNALING

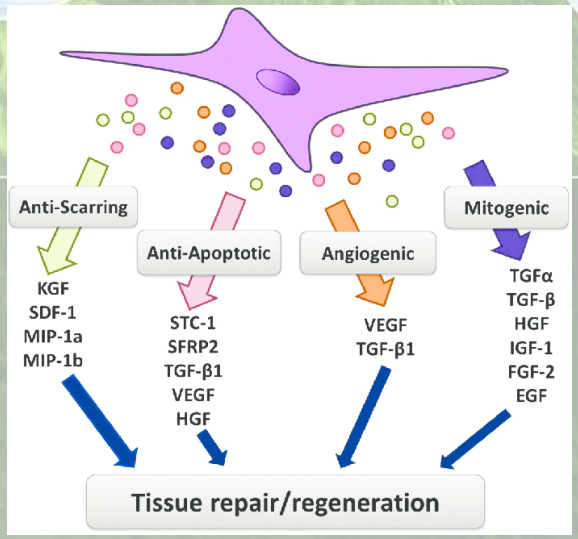
Paracrine (adjacent-signaling)

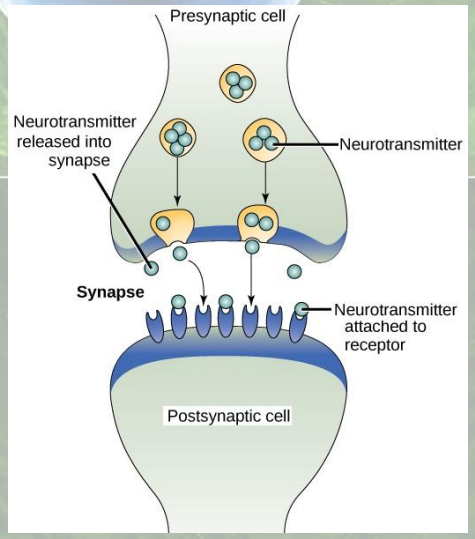
cell-to-cell communication on short distance

one cell produces signal to induce changes in nearby cells, molecules are secreted into extracellular environment



e.g. fibroblasts, neurosignaling





neurotransmitters and hormones

TYPES OF SIGNALING

Juxtacrine (contact-dependent-signaling)

cell-to-cell or cell-to EXM signaling

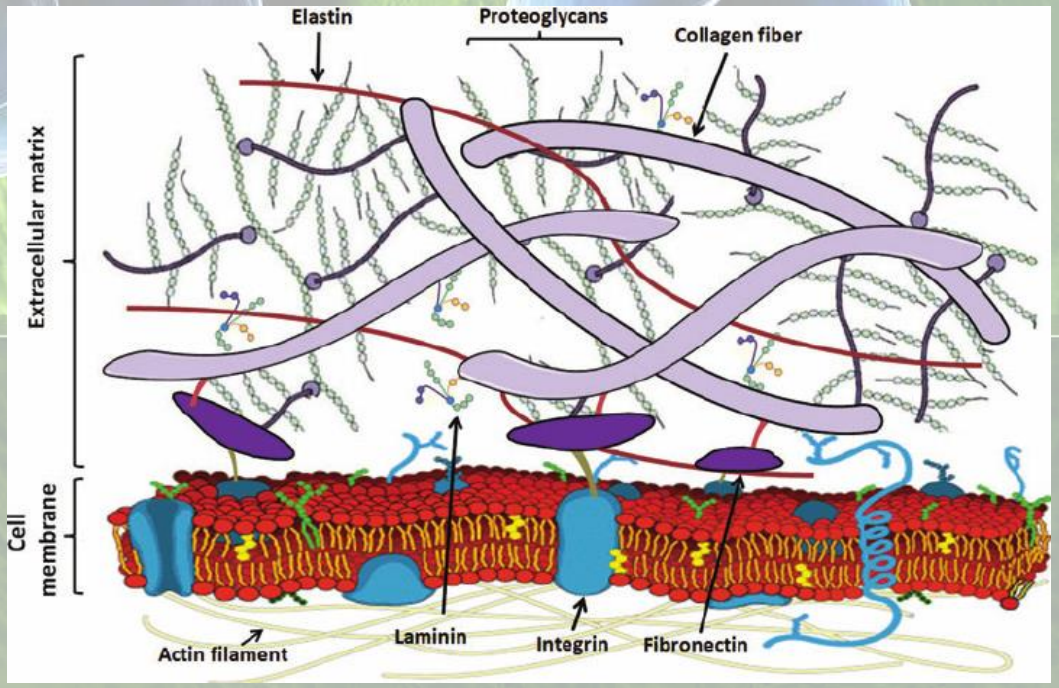
„touching”

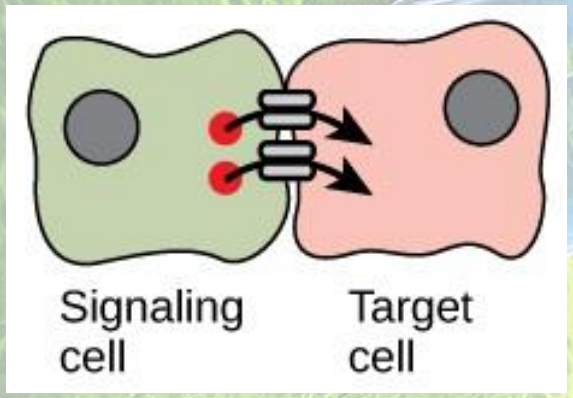
requires close contact and molecular „bridge”

secreted molecule is connected

to the membrane of the cell that produces it

e.g. adhesion molecules (cell-to-cell, cell-to-ECM)



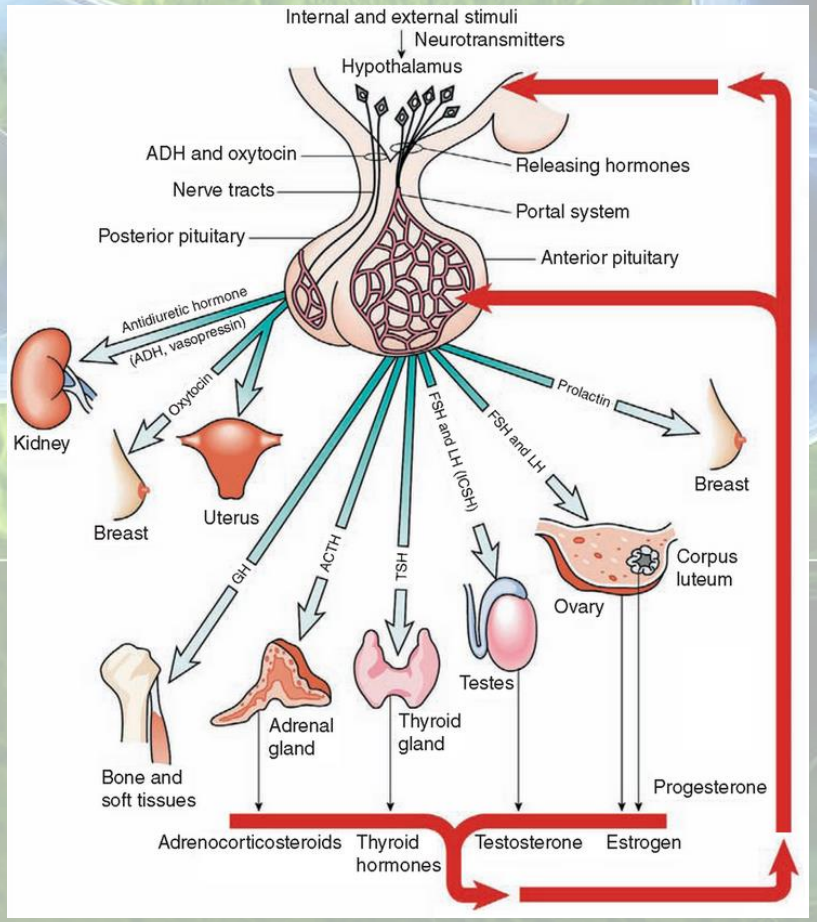


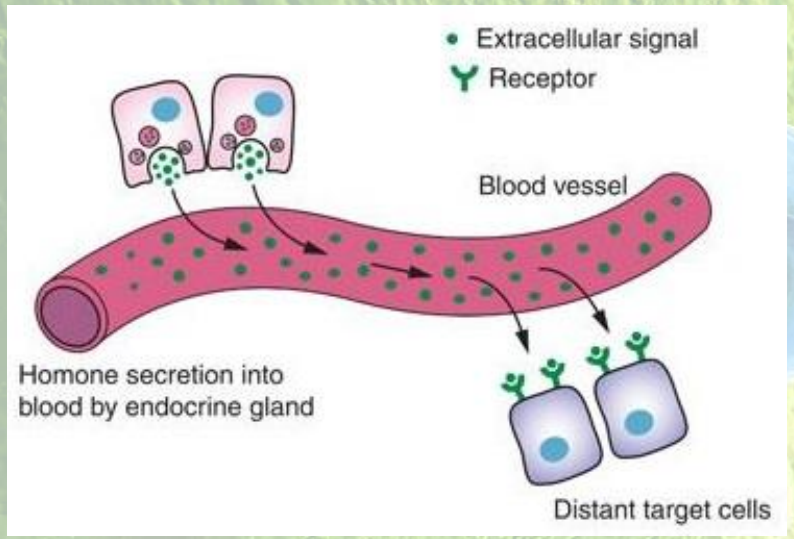
TYPES OF SIGNALING

Endocrine (distant-signaling)

cells act on distant target cells

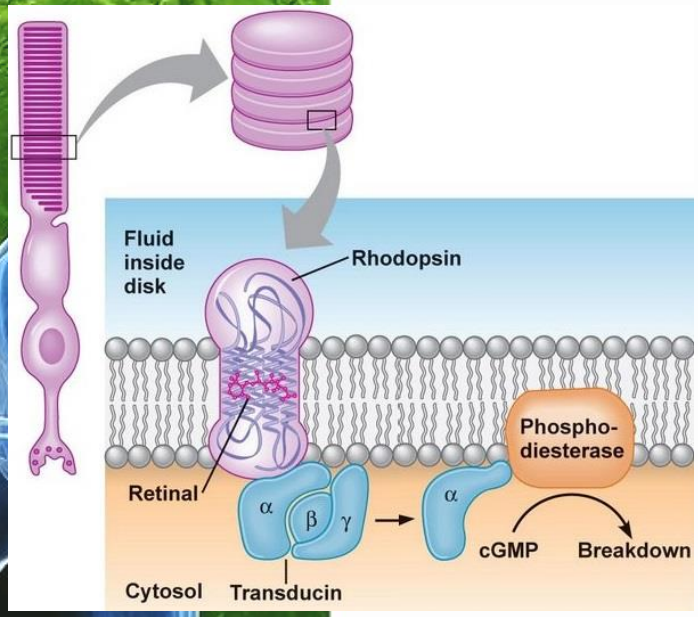
cell releases molecules **into the bloodstream** that requires **transporter molecules** (albumins, globulins)

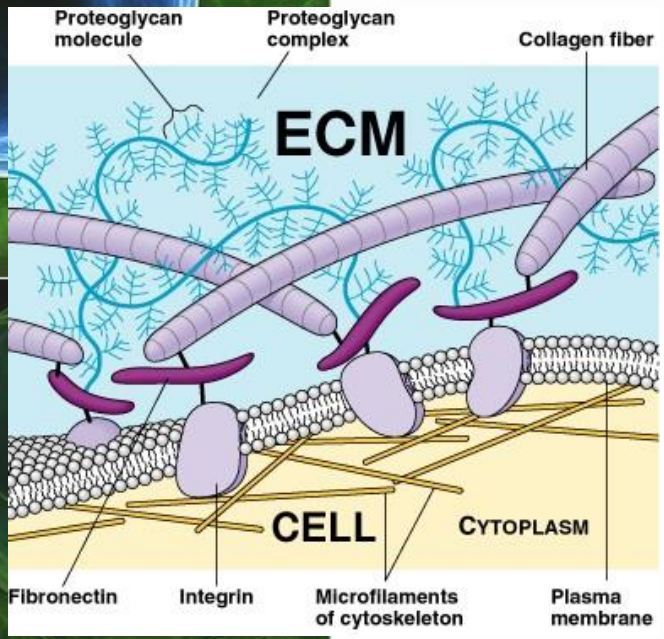




hormones of endocrine organs and neurotransmitters

CELL RECEPTORS





RECEPTOR (R) - specialized protein molecule that receives signals from outside of the cell

structure closely related to reception of different signals/information (Rs have fragments/domains capable of conformational changes)

- **Physical signals**

e.g. protein receptor RHODOPSIN light-sensitive, in photoreceptor cells of the retina, that accepts the photon of light and convers it into a chemical signals

- **Mechanical signals**

e.g. cytoskeleton elements of the cells distort under mechanical stress

- **Chemical signals**

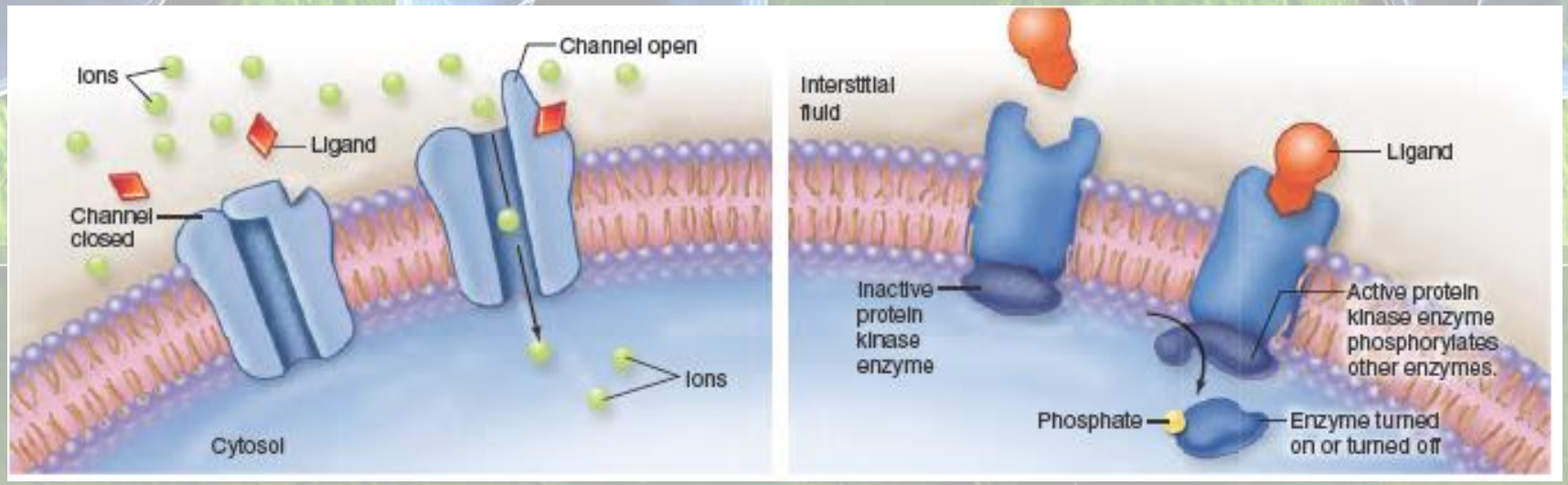
e.g. conected to **ligand-receptor** binding

LIGAND-RECEPTOR INTERACTION

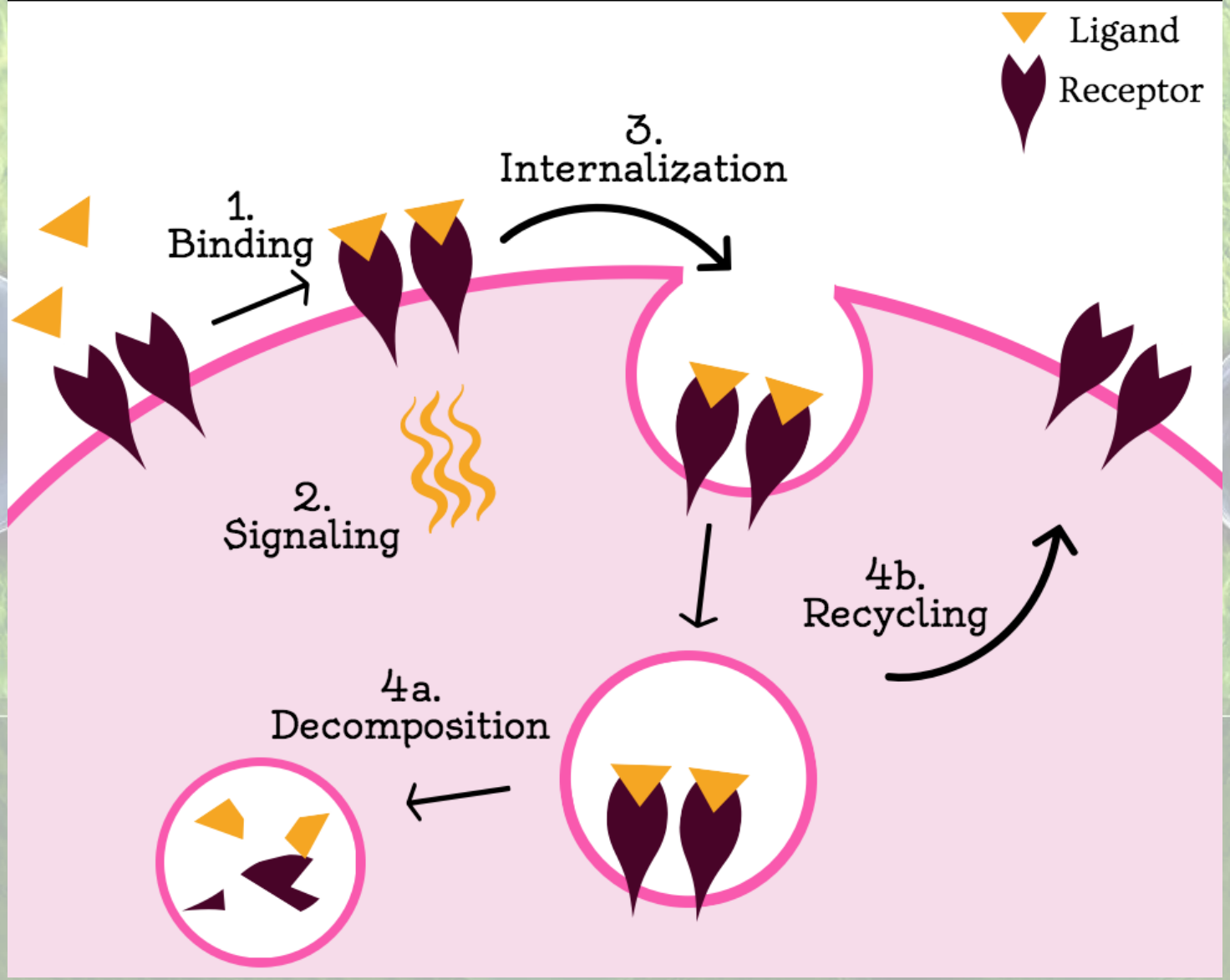
Ligand (L) – any substance/factor/molecule that is capable of specific binding to specific receptor (R); signal molecule, first messenger

binding occurs by electrostatic forces, ionic bonds, hydrogen bonds or van der Waals forces

the association is reversible and is based mainly on the conformational spatial fit on both molecules



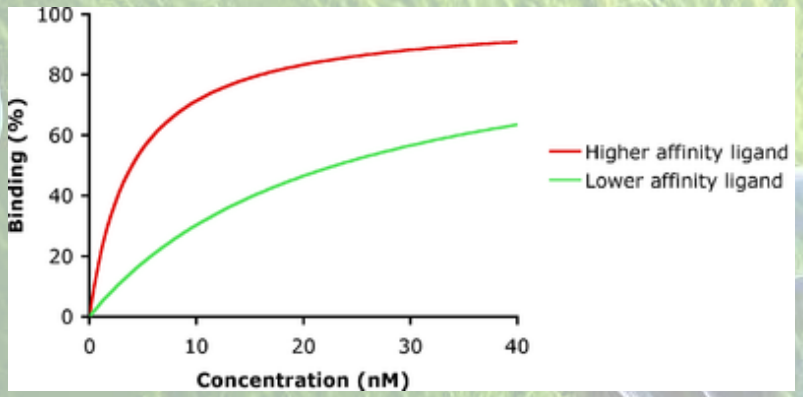
What happens to a receptor?

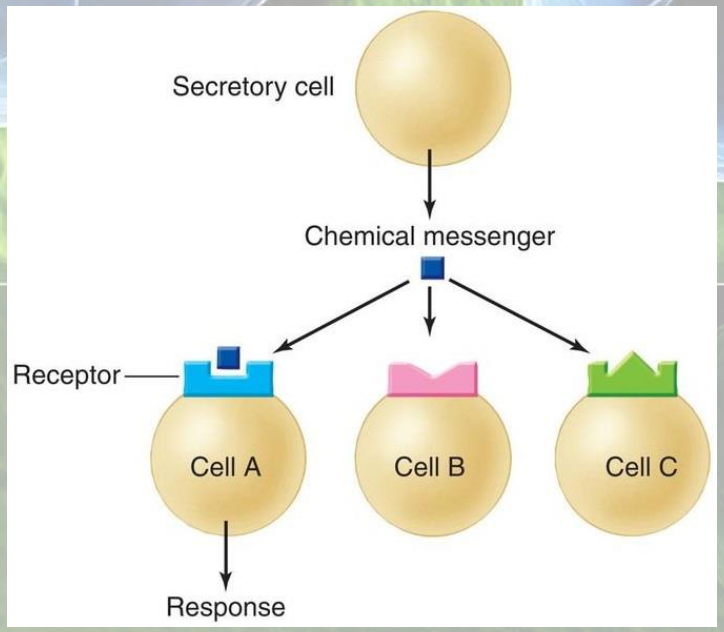


LIGAND-RECEPTOR INTERACTION

Affinity – rate of binding (tendency or strength of the binding) and **stability** of the complex
depends on pH, T, ionic forces, conformation of R and L, quantitative ratio R:L

→ **high-affinity** – great intermolecular force between R and L
→ **low-affinity** – low intermolecular force between R and L





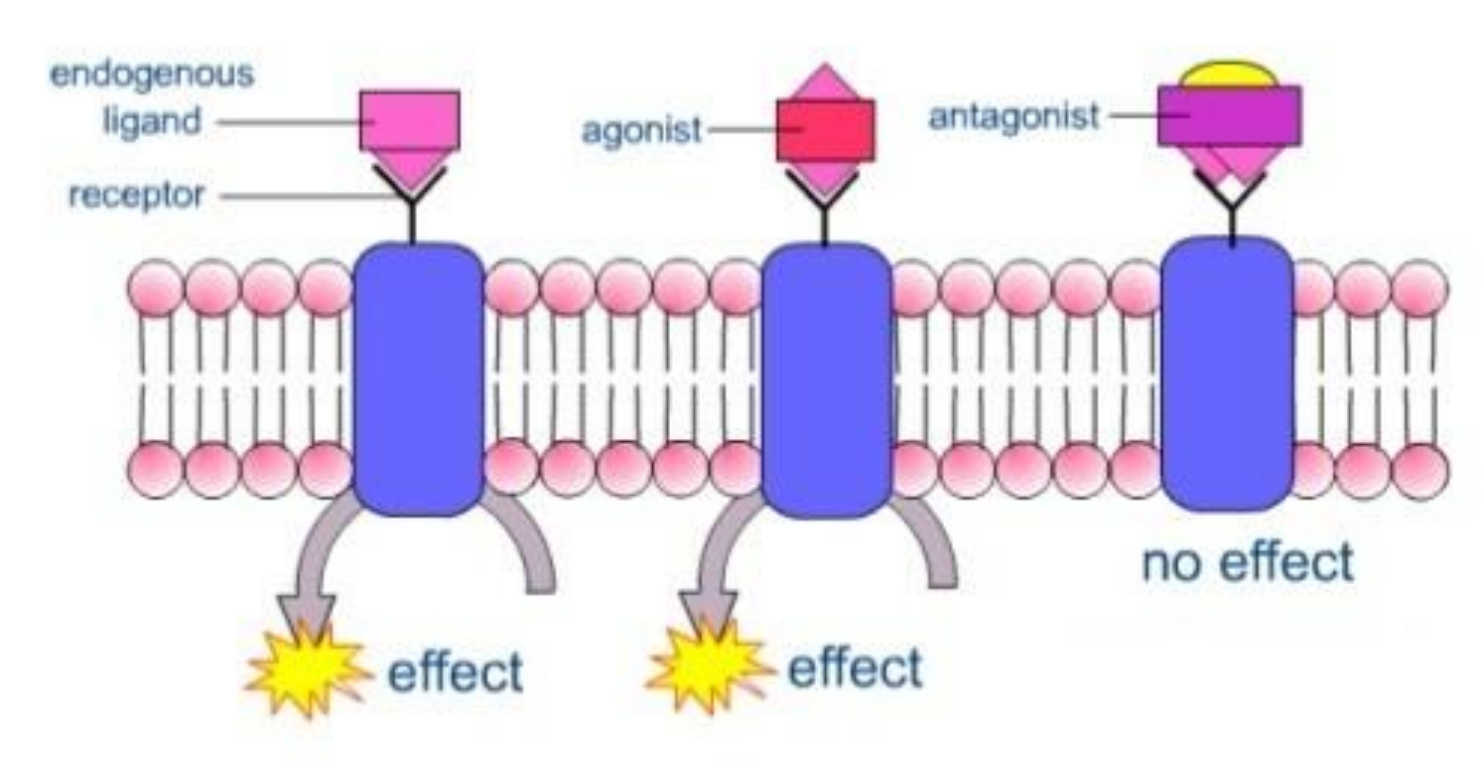
Specificity

not all the cells express the same receptors

Selectivity

in pharmacology, drugs that are non-selective may have more adverse effects, as they bind to several Rs, generating both the desired effect and additional effect

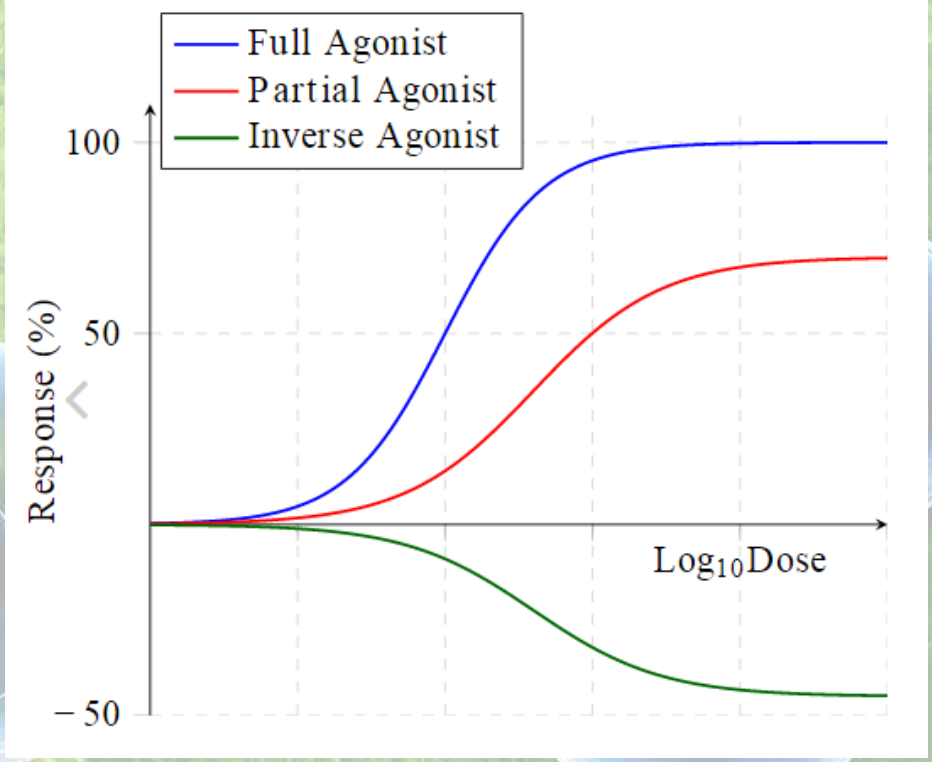
LIGAND TYPES

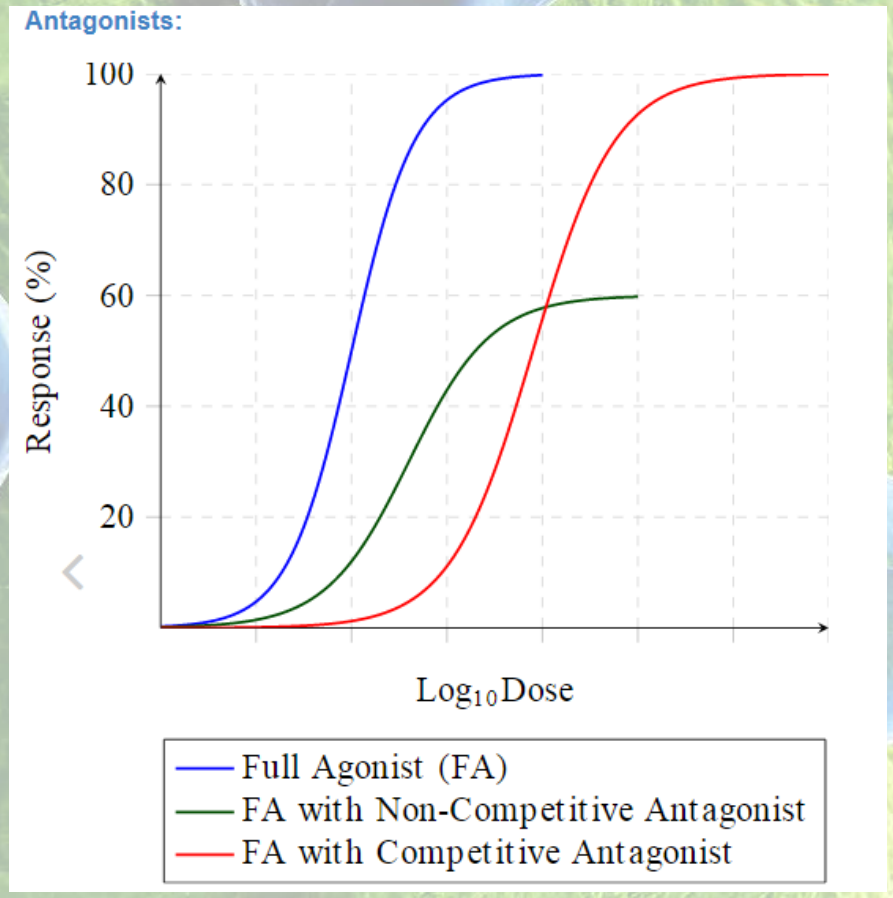


Endogeneous L
binds to a R and produces an effect

AGONIST
a ligand (drug) that has an active site of similar shape to the endogeneous L and that binds to a R and produces the effect
e.g. Nicotine

ANTAGONIST
a ligand (drug) which shape is close enough to the endogeneous L to bind to a R, it takes up R space so it prevents the endogeneous L from binding, no effect itself!
e.g. Atropine





Partial Agonists do not reach 100% response, *e.g.* Opoids

Inverse Agonists have a negative response, *e.g.* Benzodiazepine (GABA system)

Non-Competitive Antagonists prevent maximal response being reached

Competitive Agonists right shift the curve, as they can be overcome with increasing dose of agonist

RECEPTOR TYPES

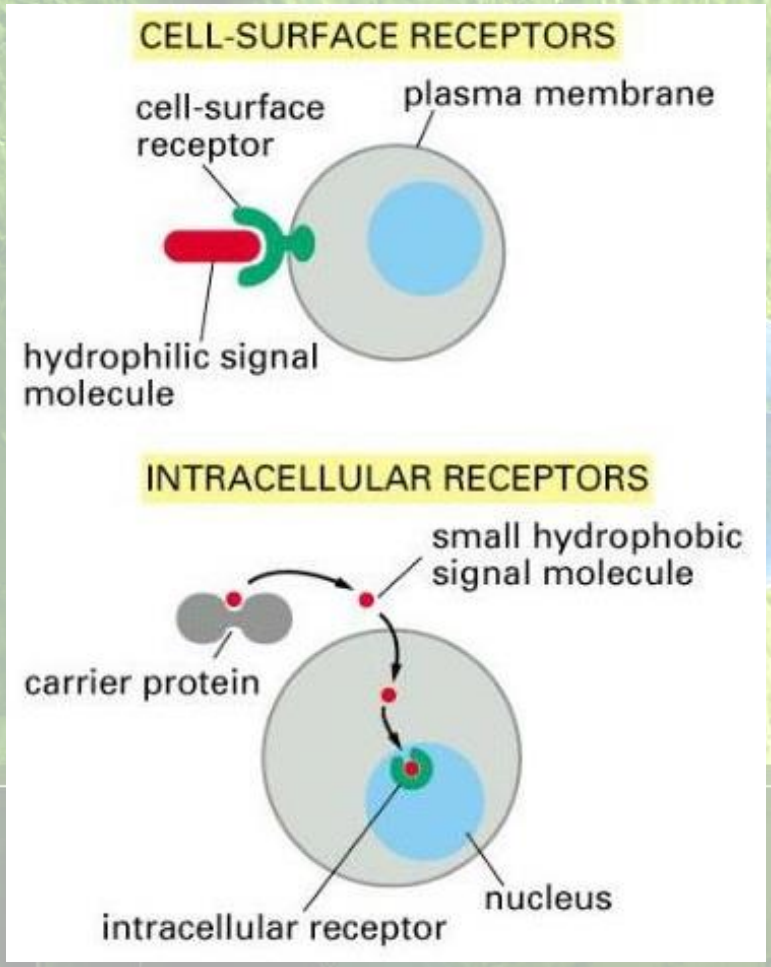
→LOCATION:

membrane receptors

located in the cell membrane

transduces signal from larger hydrophobic molecules

protein is covalently attached to the lipids of the bilayer or is a transmembrane protein/domain



intracellular receptors

bind L that can directly go through the plasma membrane

cytoplasmic *e.g.* steroid hormones

& nuclear receptors *e.g.* thyroid hormones

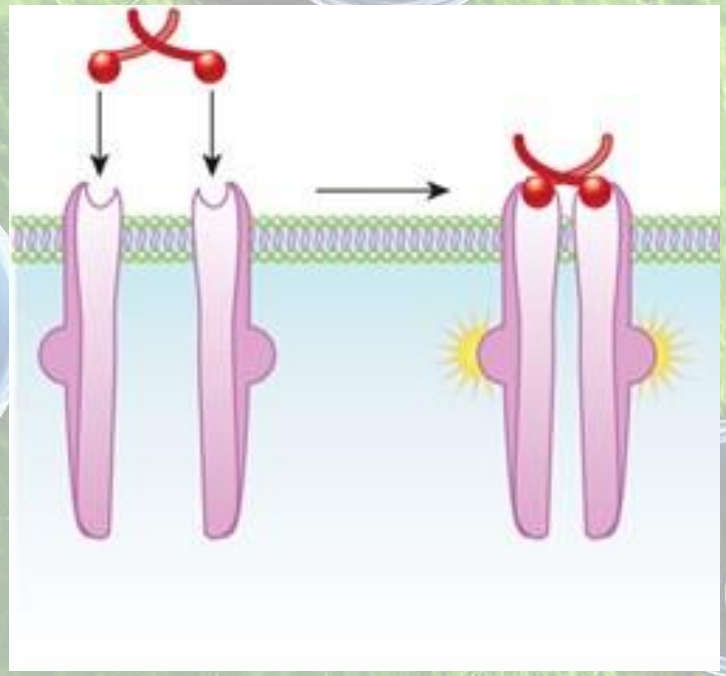
in membranes of vesicles and other cell organelles, used in the intracellular signaling between cytoplasm compartments and organelles

RECEPTOR TYPES

2 modes of action:

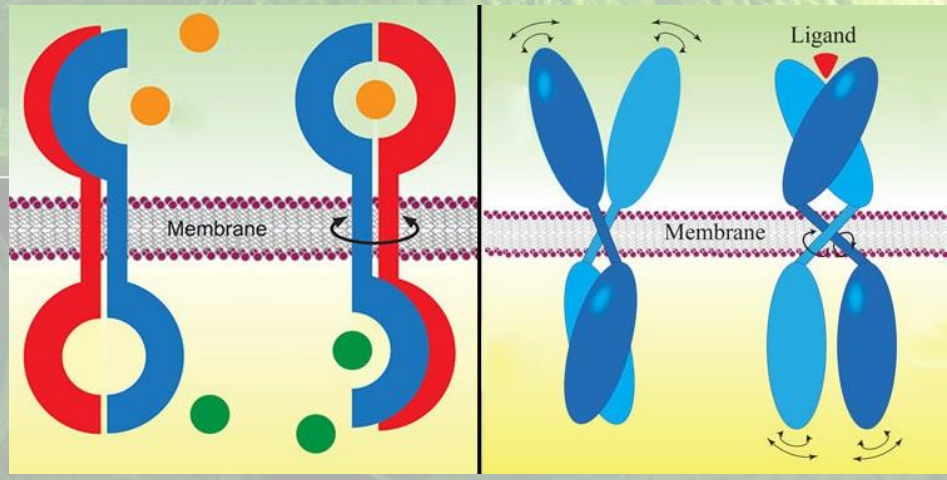
1. Dimerization

   R exists in inactive monomeric forms, after L binding the monomers combine to form an active dimer



2. Rotation

   L binding occurs to the extracellular part of the R and induces conformational change which alters the intracellular part and exerts signaling



RECEPTOR TYPES

→ STRUCTURE and SIGNAL TRANSDUCTION:

Ionotropic receptors

ion channels, upon L binding can „open” or „close” and let ions travel through the membrane

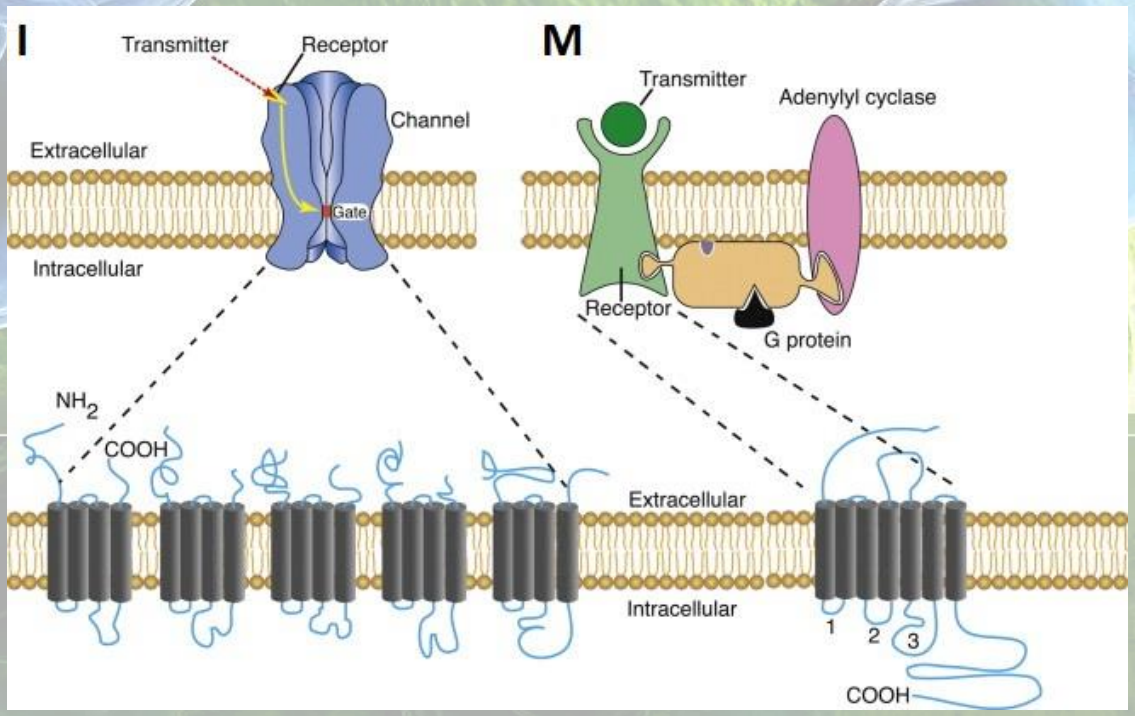
very fast (ms):

good target for drugs

limited to K^+, Na^+, Cl^-, Ca^{2+}, neurotransmitters

Metabotropic receptors

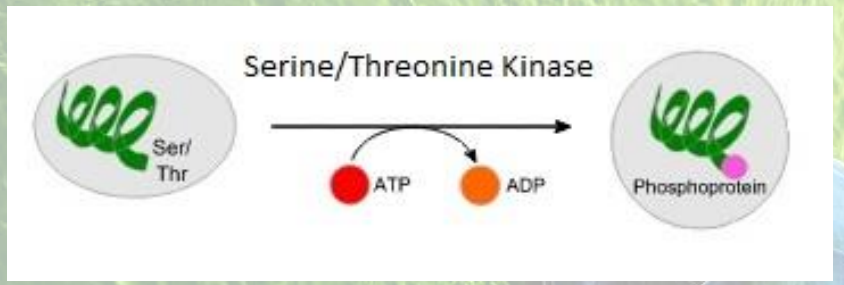
cascade signaling, ultimately activate or inactivate target proteins



METABOTROPIC RECEPTORS

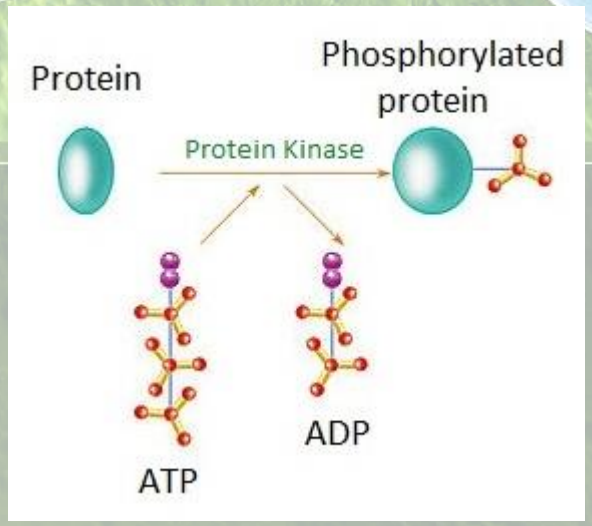
PHOSPHORYLATION
Activation (mostly)
KINASES

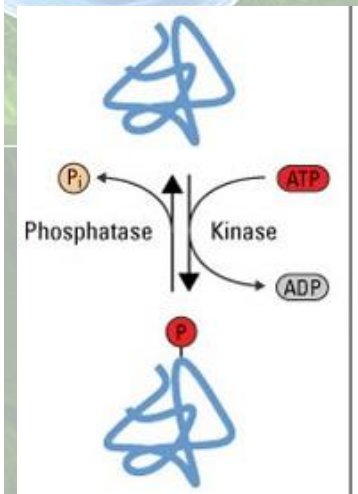
DEPHOSPHORYLATION
Deactivation (mostly)
PHOSPHATASES



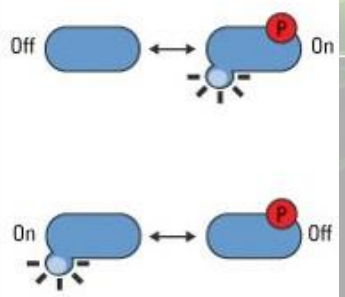
transfer of a phosphoryl group
from a nucleoside triphosphate donor
(ATP) to an acceptor molecule (protein)

Serine/Threonine
&
Tyrosine





more common



METABOTROPIC RECEPTORS

(a) Signaling using heterotrimeric G proteins and G protein-coupled receptors (GPCR)

(b) Direct activation of protein kinases/phosphatases

(a) **G PROTEIN-COUPLED RECEPTORS**

GPCR

7 transmembrane domains, the C-domain (cytoplasmic) is a place where the G protein is attached

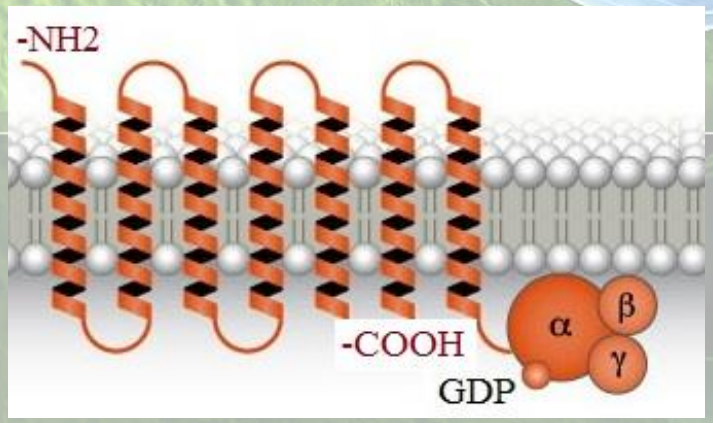
G protein

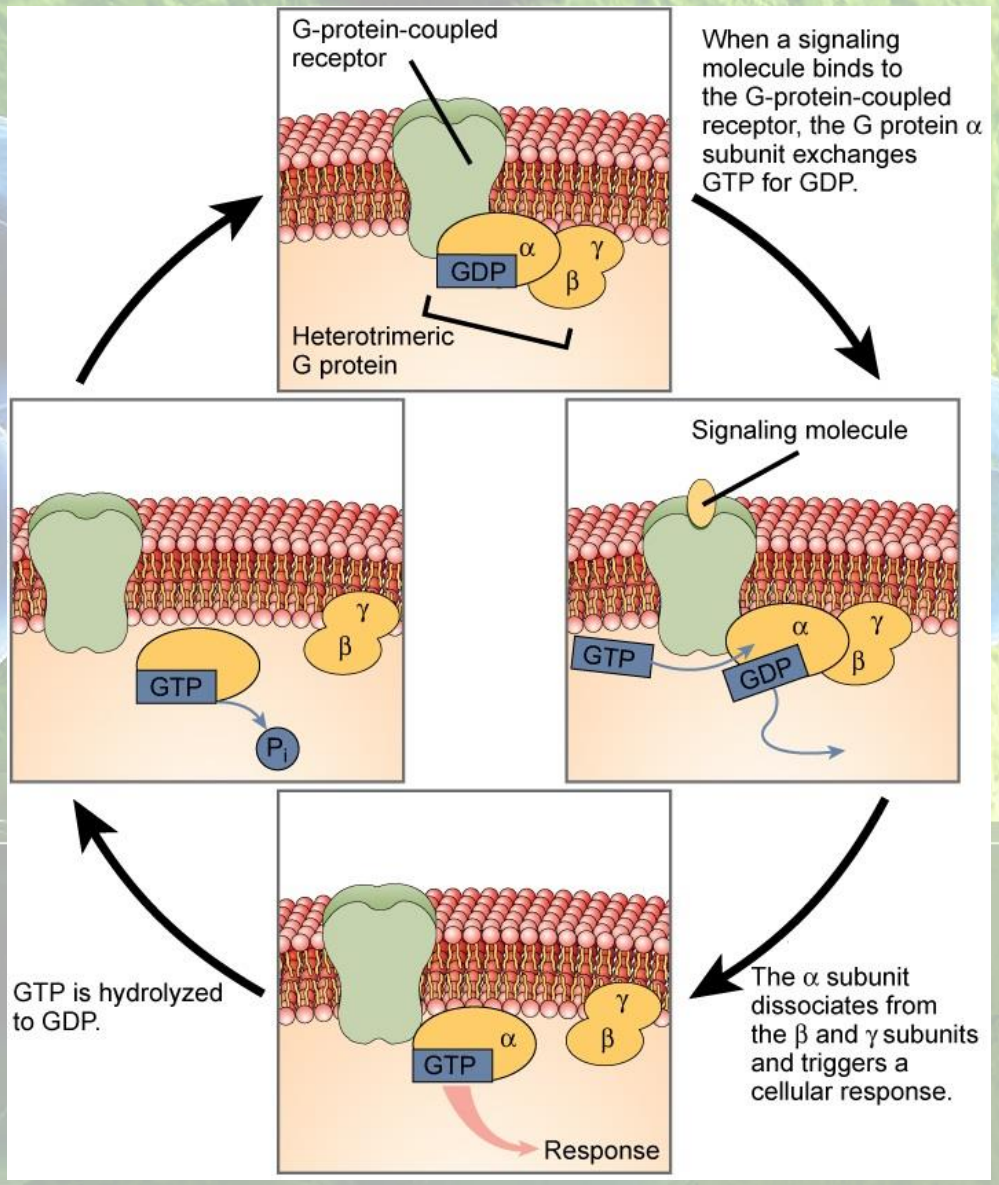
complex made up of 3 subunits : alpha (α), beta (β) and gamma (γ)

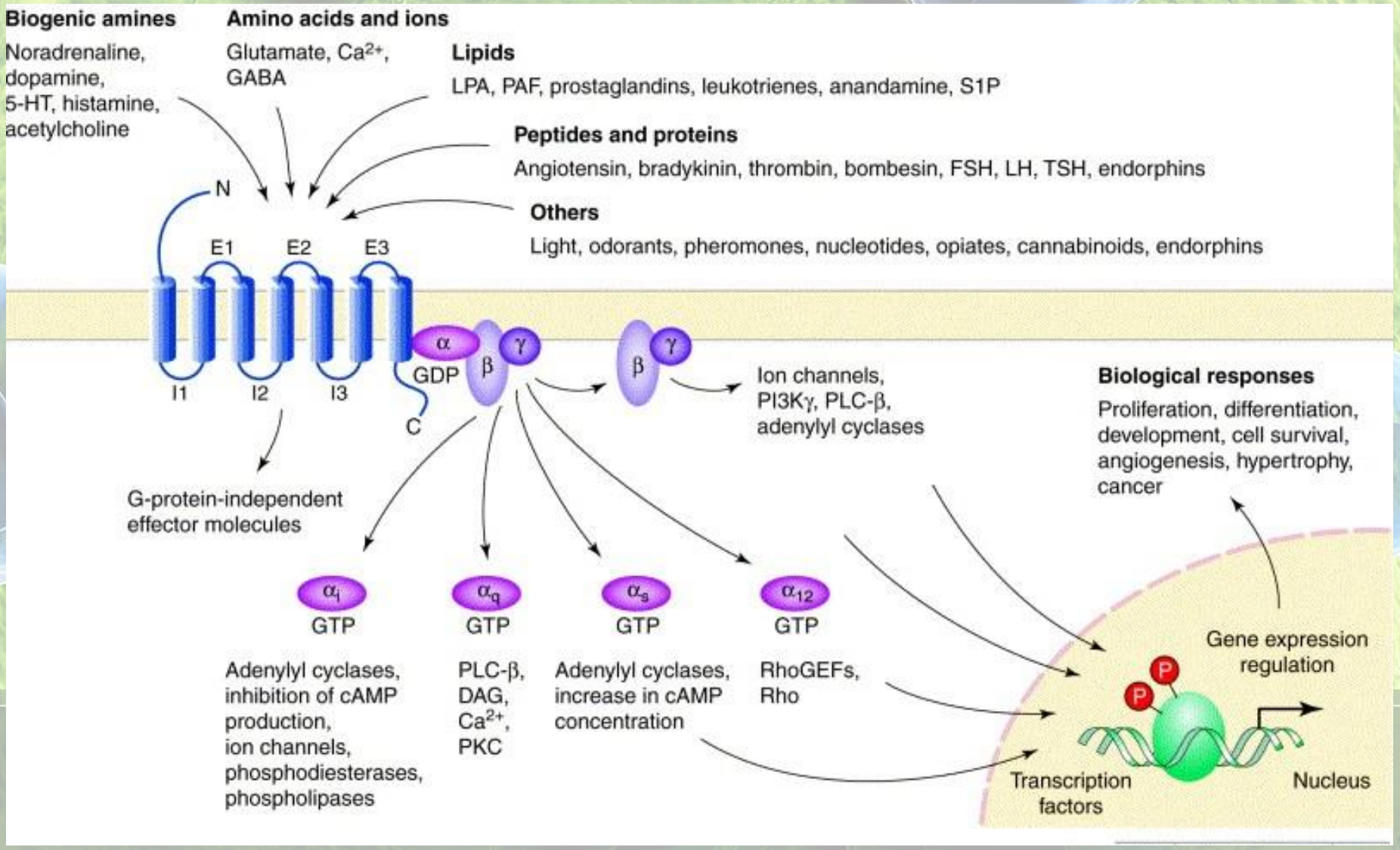
Gα has a GTPase activity

(it hydrolases GTP → GDP)

Requires a second messanger!






Biogenic amines
Noradrenaline, dopamine, 5-HT, histamine, acetylcholine
Amino acids and ions
Glutamate, Ca^{2+}, GABA
Lipids
LPA, PAF, prostaglandins, leukotrienes, anandamine, S1P
Peptides and proteins
Angiotensin, bradykinin, thrombin, bombesin, FSH, LH, TSH, endorphins
Others
Light, odorants, pheromones, nucleotides, opiates, cannabinoids, endorphins
N
E1
E2
E3
I1
I2
I3
C
α
GDP
β
γ
β
γ
Ion channels, PI3Kγ, PLC-β, adenylyl cyclases
Biological responses
Proliferation, differentiation, development, cell survival, angiogenesis, hypertrophy, cancer
G-protein-independent effector molecules
α_i GTP
α_q GTP
α_s GTP
α_{12} GTP
Adenylyl cyclases, inhibition of cAMP production, ion channels, phosphodiesterases, phospholipases
PLC-β, DAG, Ca^{2+}, PKC
Adenylyl cyclases, increase in cAMP concentration
RhoGEFs, Rho
Gene expression regulation
P
P
Transcription factors
Nucleus

(b) **DIRECT ACTIVATION OF KINASES/PHOSPHATASES**

transmission of signal through the membrane is through the kinases, **directly**
second messenger may be involved
engaging of further kinases, mainly **tyrosine kinases** of 3 kinds:

1. **Receptor protein Tyrosine Kinases (RTKs)**

2. **non-Receptor Protein Tyrosine Kinases (nRTKs)**

3. **Cytoplasmic Jak/Tyk Tyrosine Kinases**

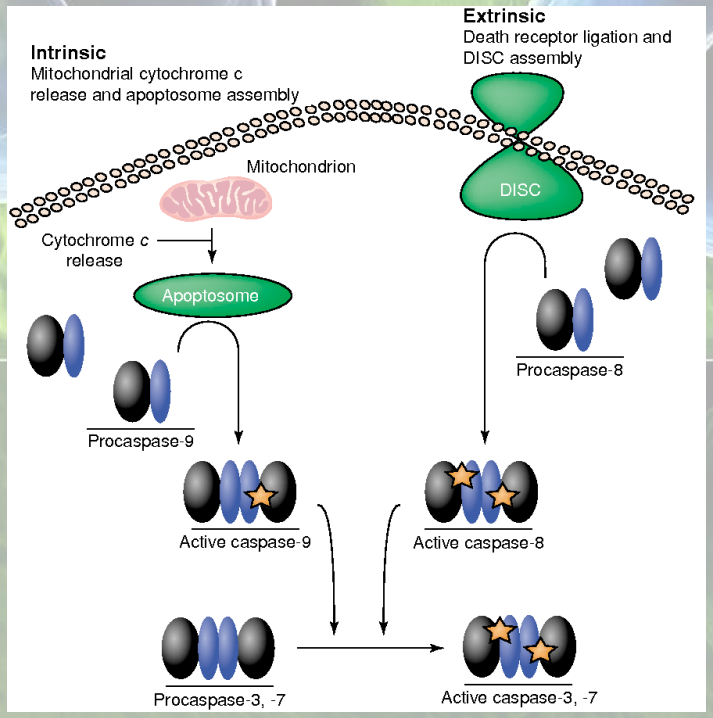
Tyrosine
vs.
Serine/Threonine

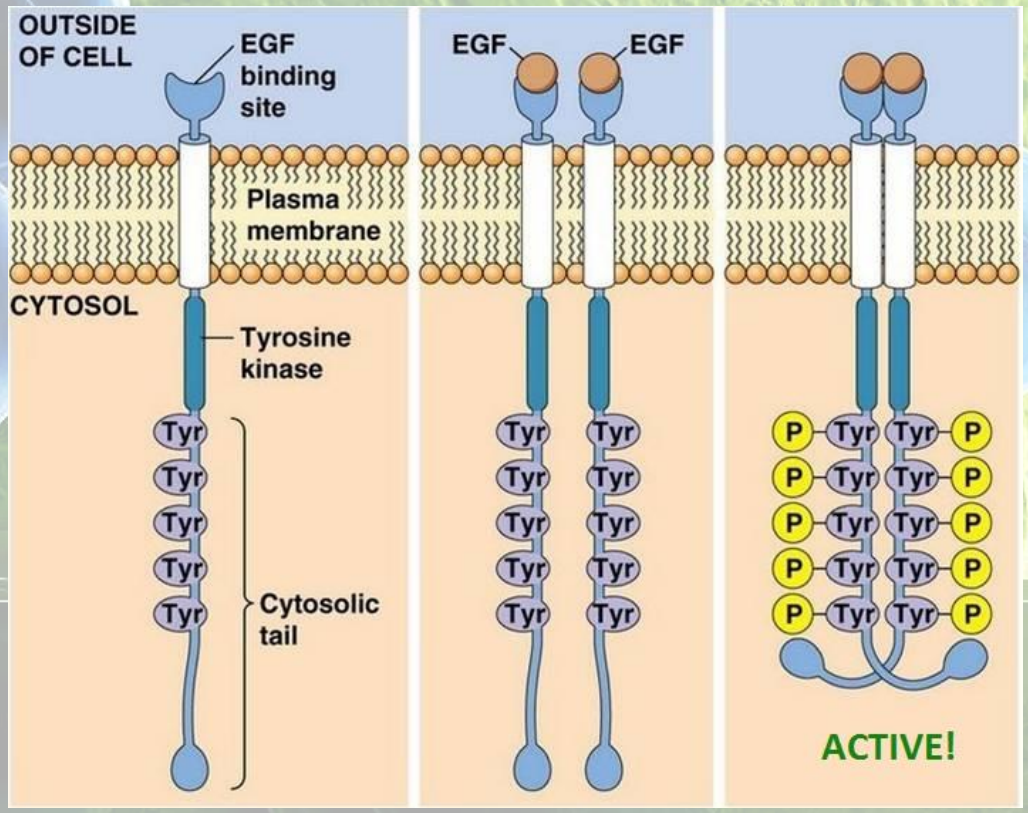
Receptor protein Tyrosine Kinases (RTKs)

HOMODIMERIZATION is required

cross- and auto-phosphorylations of Tyr residues in the C-terminus
recrutation of second messengers (their enzymes)

e.g. GH signaling
EGF signaling
apoptosis induction





Non-Receptor Protein Tyrosine Kinases (nRTKs)

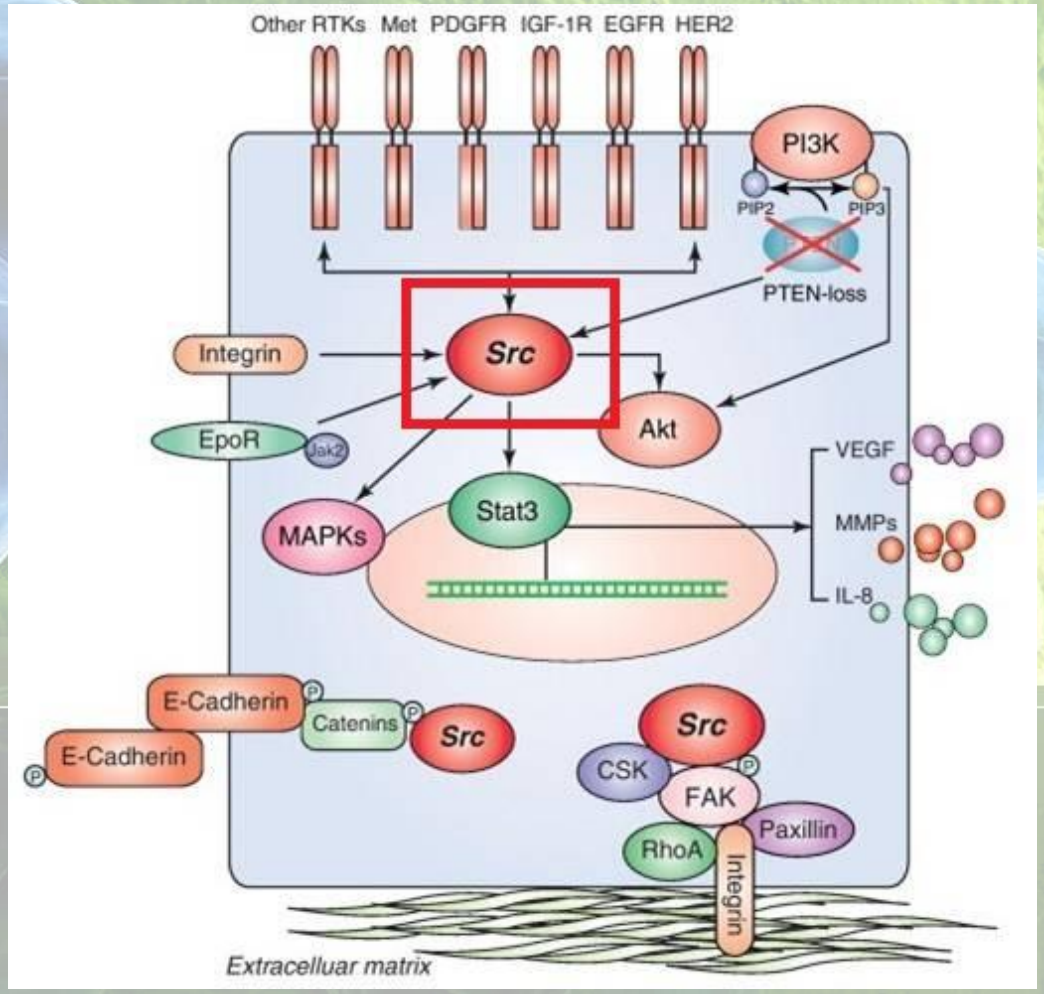
cytoplasmic enzymes

Src family

can be induced by the RTKs

e.g. receptors for the Fc of T cell Ab

- regulation of cell immunity
- migration
- apoptosis
- adhesion
- differentiation



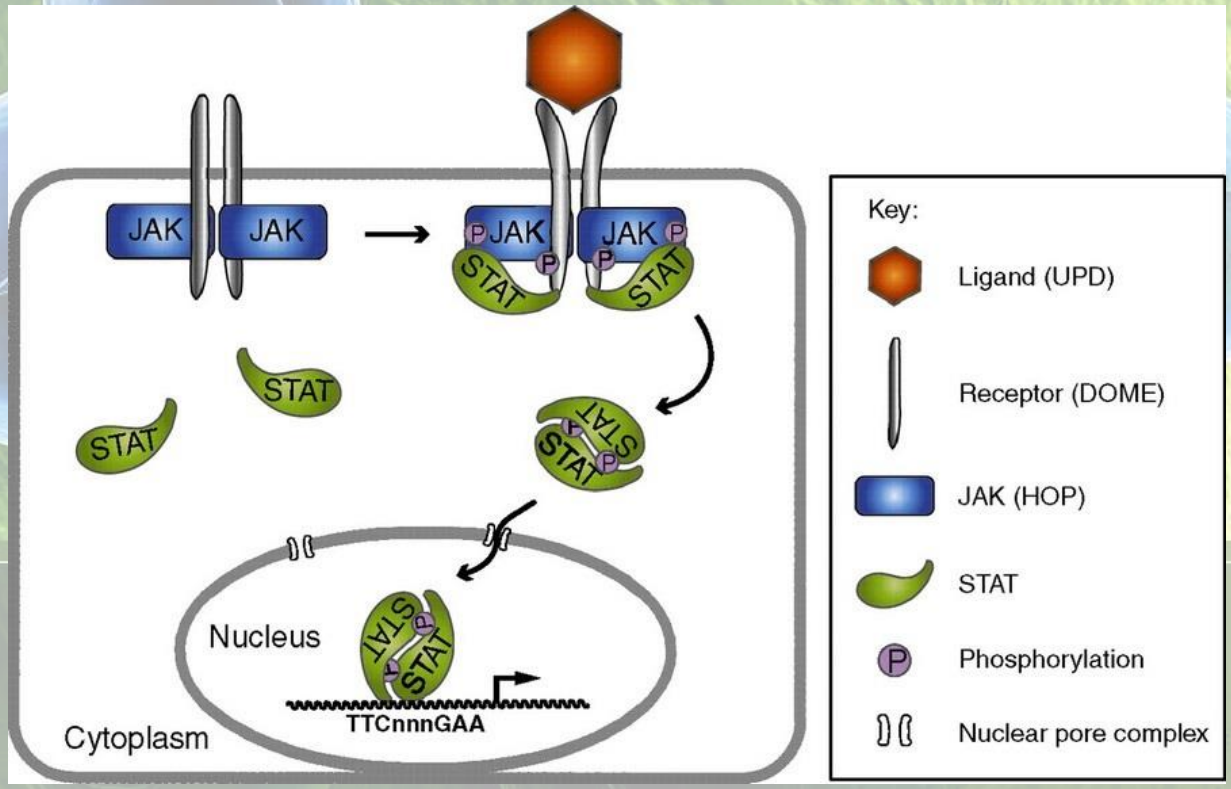
Cytoplasmic Jak/Tyk Tyrosine Kinases

bind to receptors that do not have their own kinase activity

the kinase **directly phosphorylates transcription factors** and enhance gene expression= FAST SIGNALING

NO second messengers!

e.g. cytokines
chemokines
(inflammation process)



Serine/Threonine Kinase Signaling

2 subunits, form HETERODIMER

Smad family

e.g. TGF-β

bone morphogenetic protein BMP

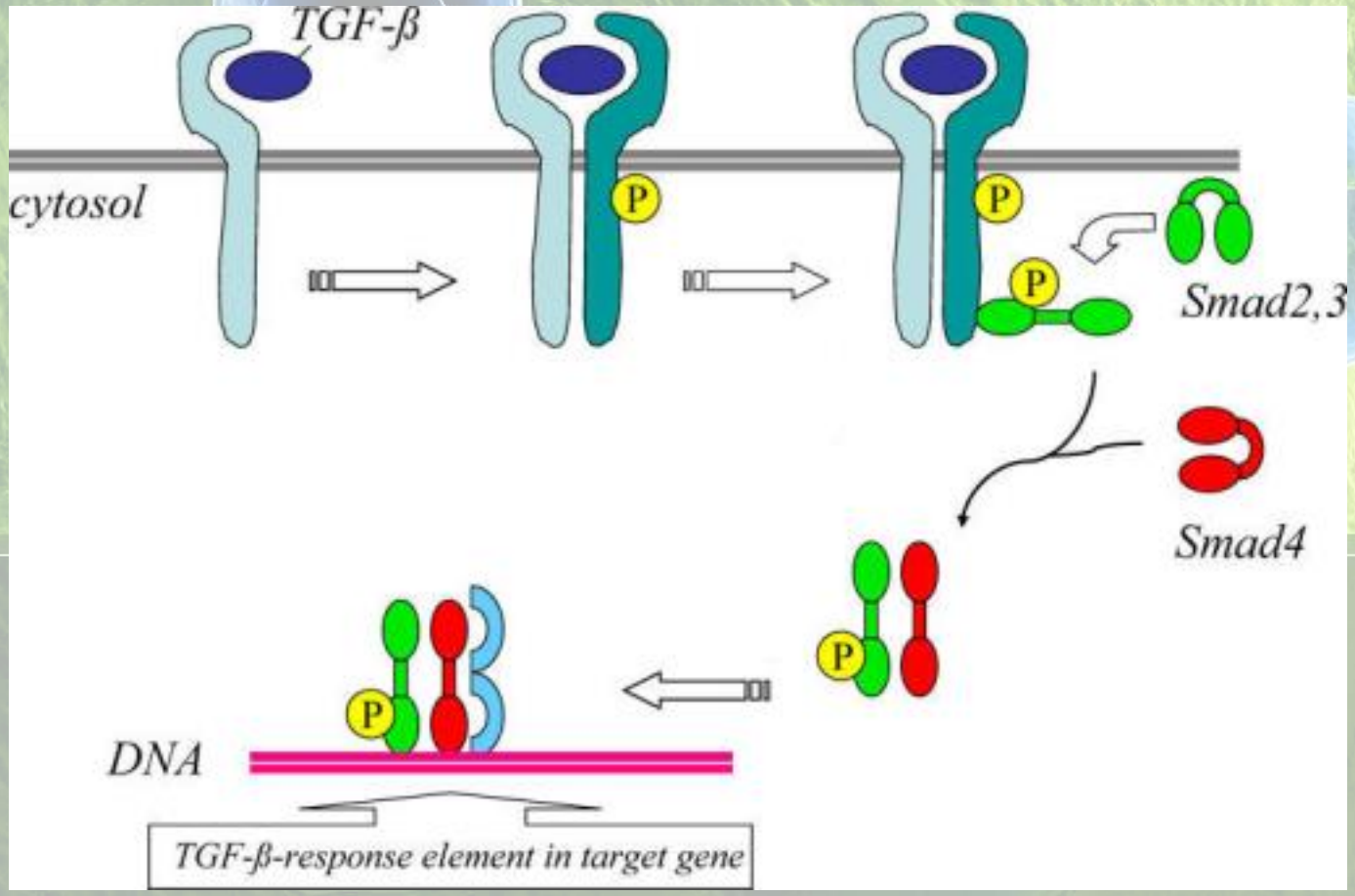
inhibin

actinin

Tyrosine

vs.

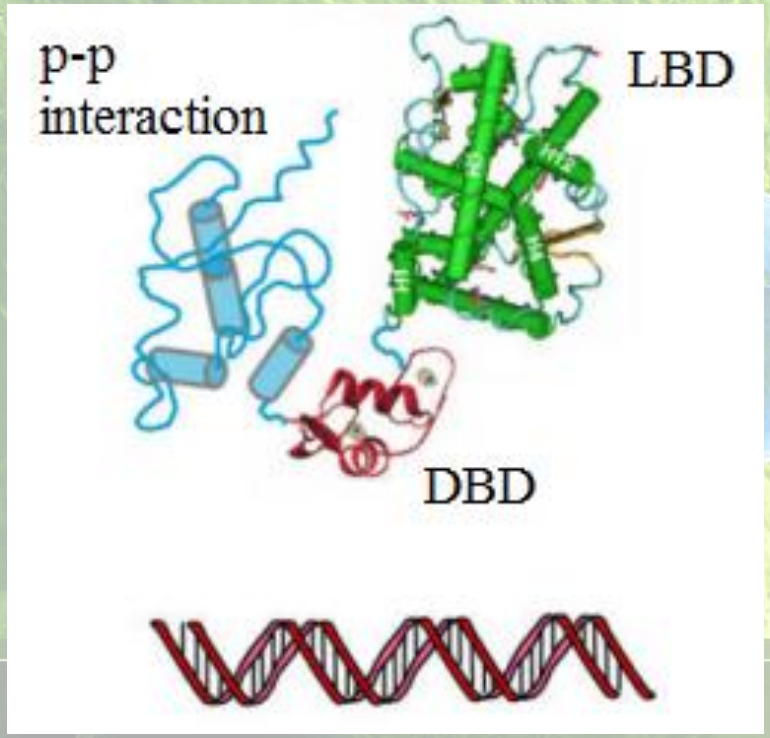
Serine/Threonine



Nuclear Receptors

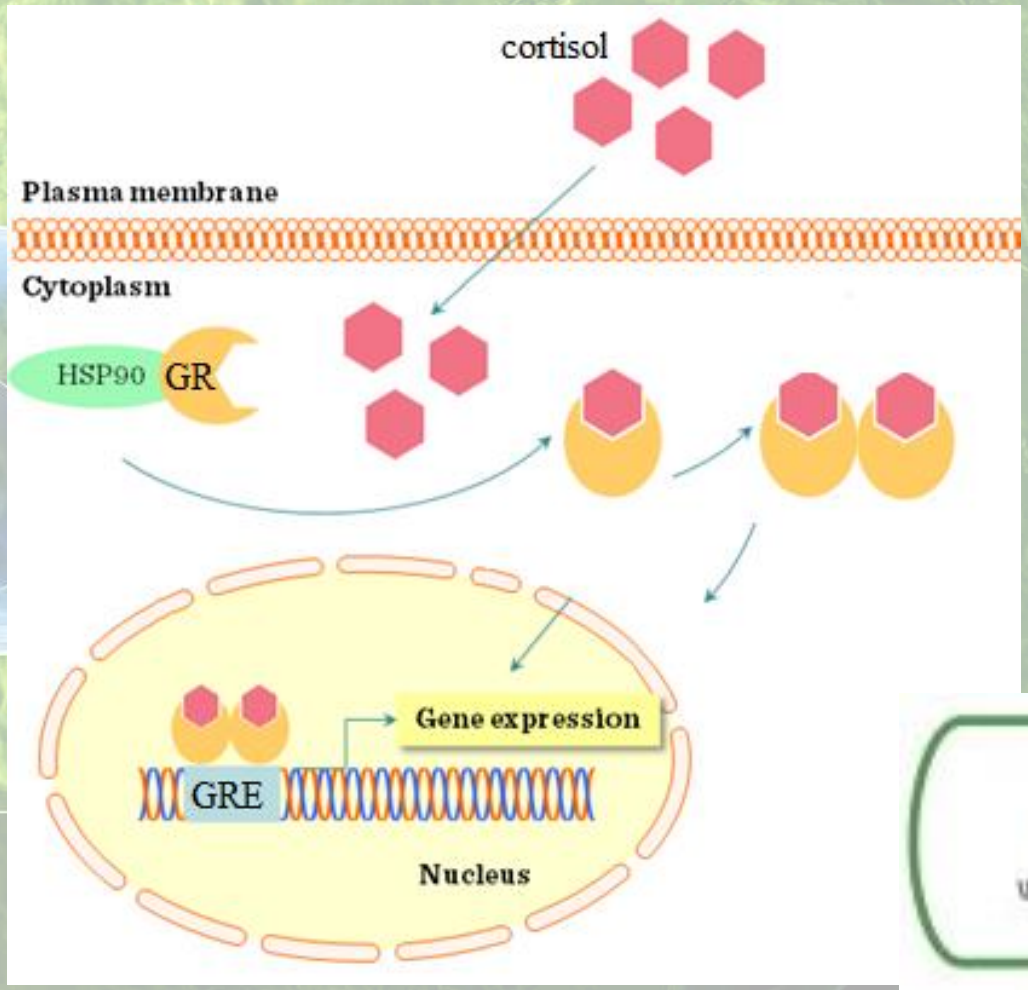
location: in cell **nucleus** or **cytoplasm**
responsible for signaling of ligands that easily go through the plasma membrane:
steroid (glucocorticoids, mineralocorticoids)
thyroid hormones
retinoic acid

structure resembling the one of the transcription factors:
LIGAND BINDING DOMAIN
DNA RECOGNITION DOMIAN
DIMERIZATION DOMAIN/protein-protein interaction domain



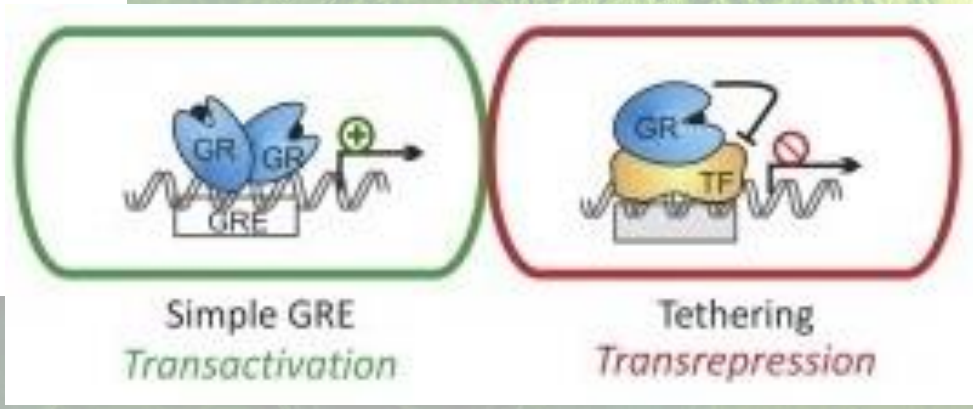
form **homo-** and **hetero-dimer**
can interact with each other
or with other types of proteins

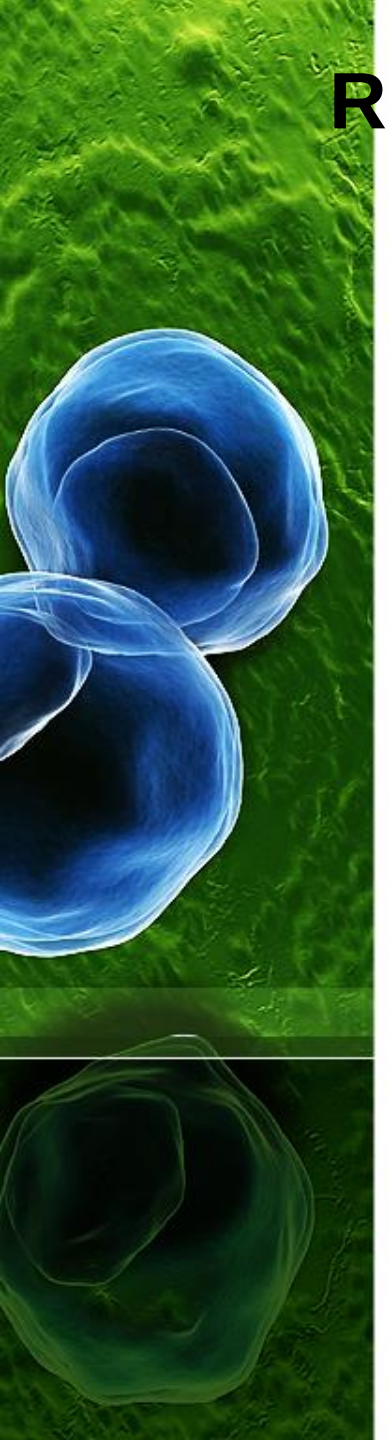
GLUCOCORTICOID RECEPTOR (GR) Signaling



+ TRANSACTIVATION

- TRANSREPRESSION





Regulation of receptors function

UPregulation
DOWNregulation

Mechanisms controlling receptors function:

Intrinsic regulation (regulatory and homeostatic control)

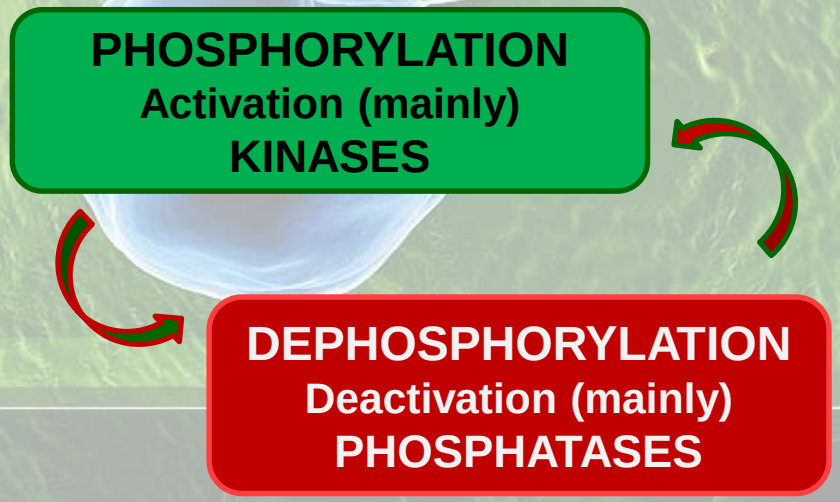
Disease states

Drugs

Mechanisms controlling receptors function

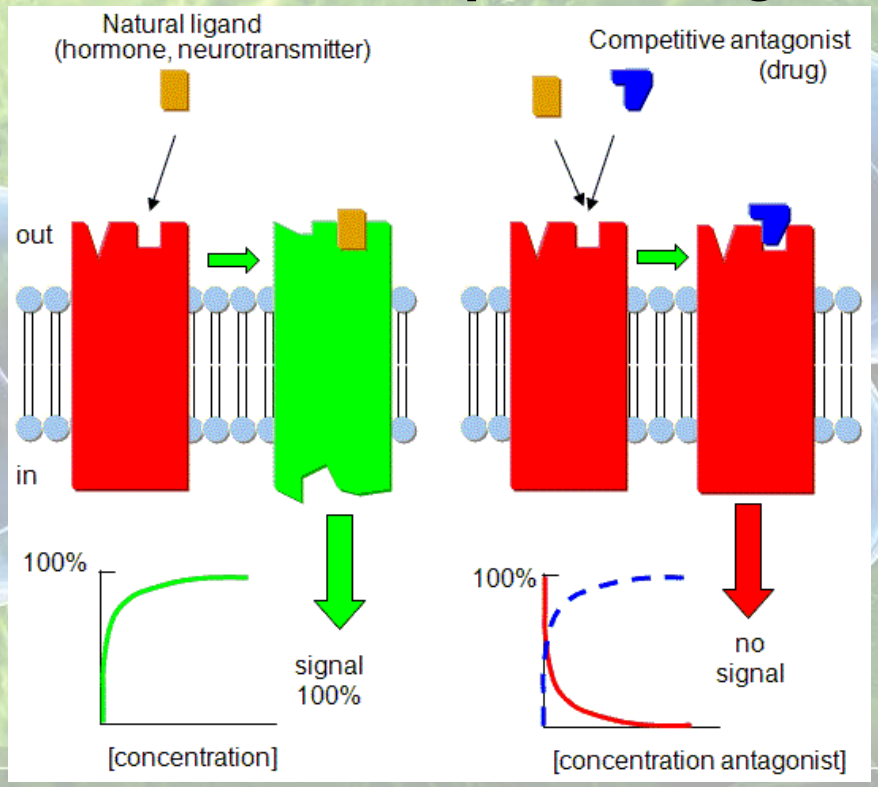
Phosphorylation
and
Dephosphorylation

the fastest!

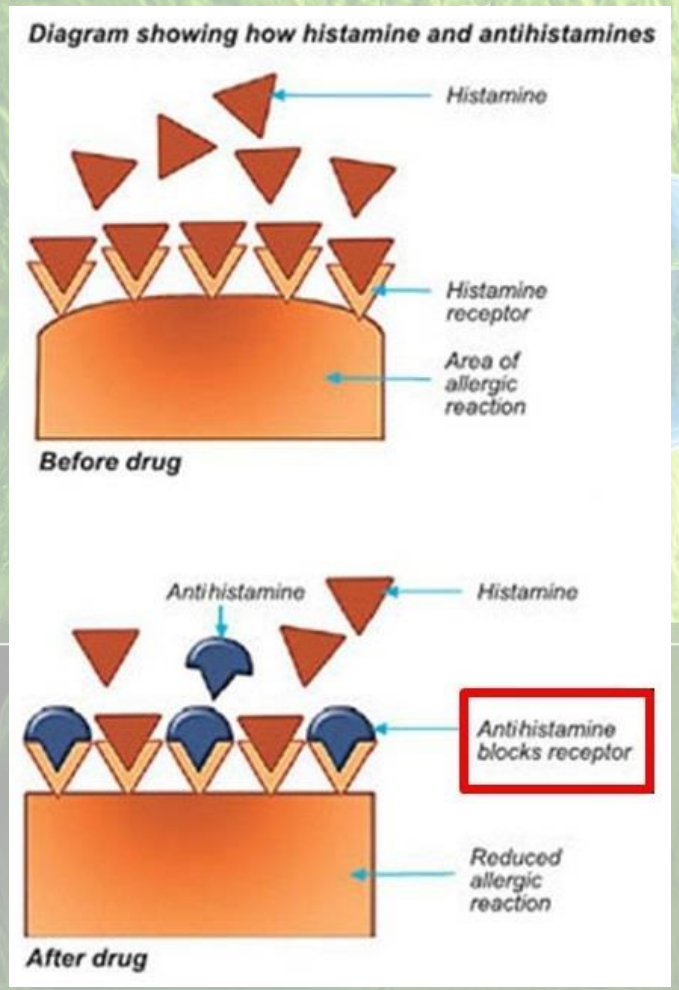


Mechanisms controlling receptors function

Natural or drug **competitive ligands** (antagonists)

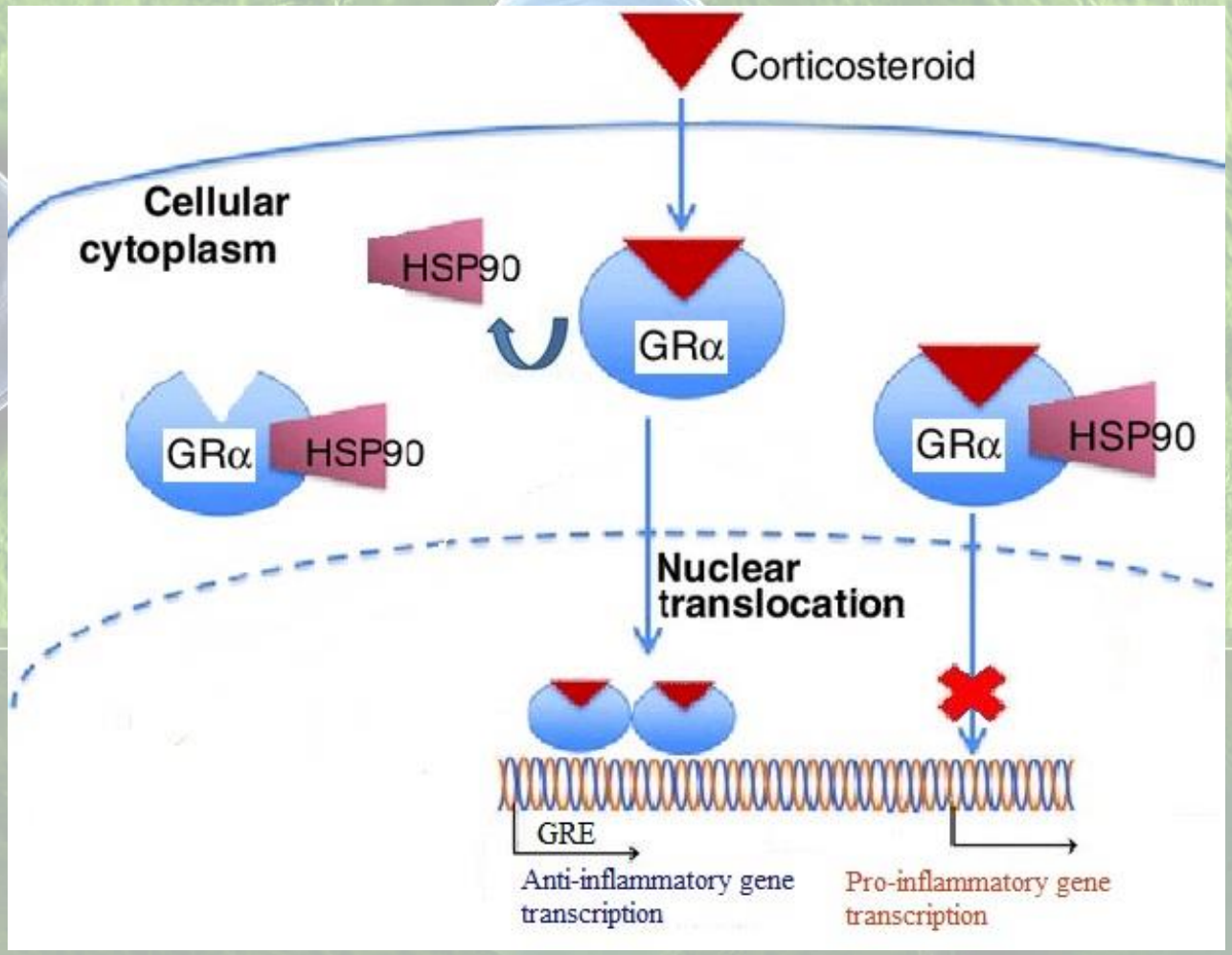


e.g. („-”) Antyhistamine drug action



Mechanisms controlling receptors function

Blocking receptor function by the regulator y proteins

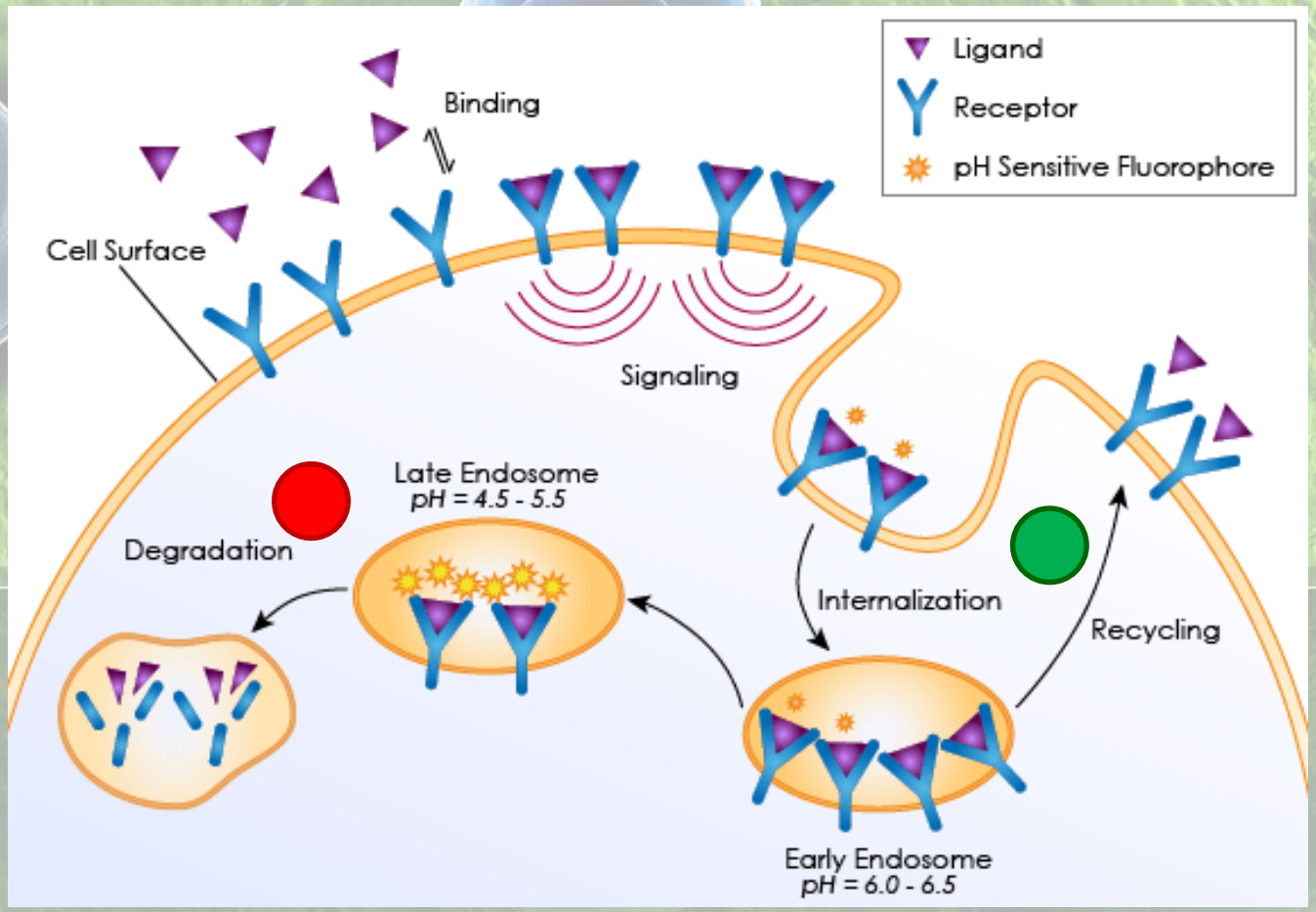


Mechanisms controlling receptors function

Receptor internalization and **degradation**

Endocytosis

Endosome=receptorosome



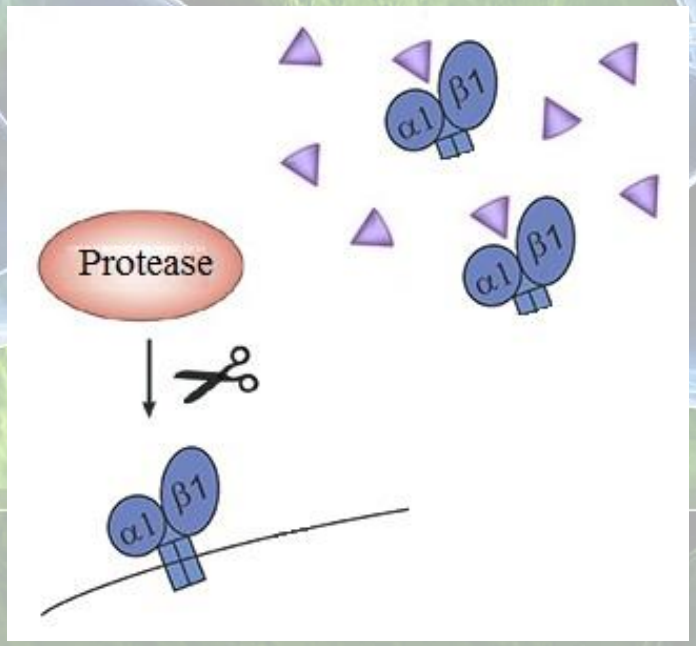
Mechanisms controlling receptors function

Receptor digestion

by the extracellular proteases

~ „peeling” the receptor off the cell surface

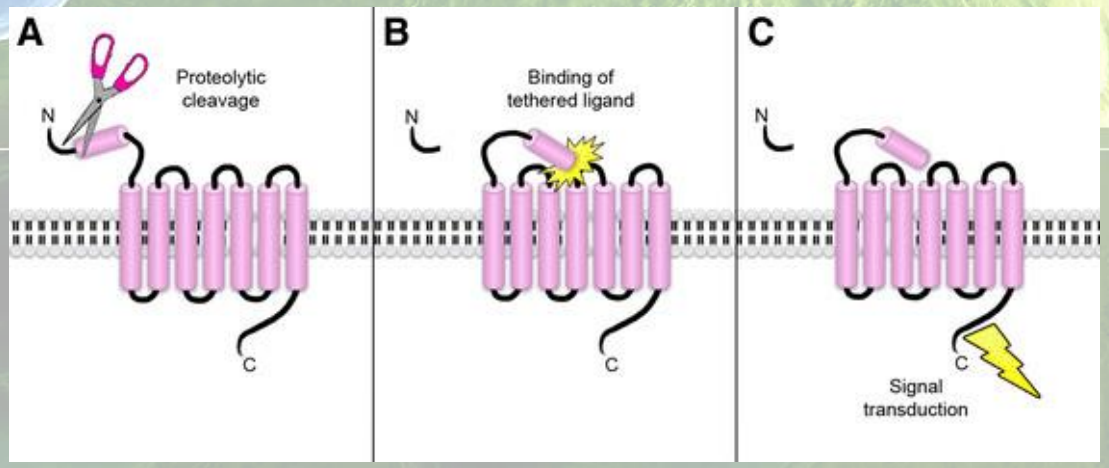
Receptor function **inactivation**

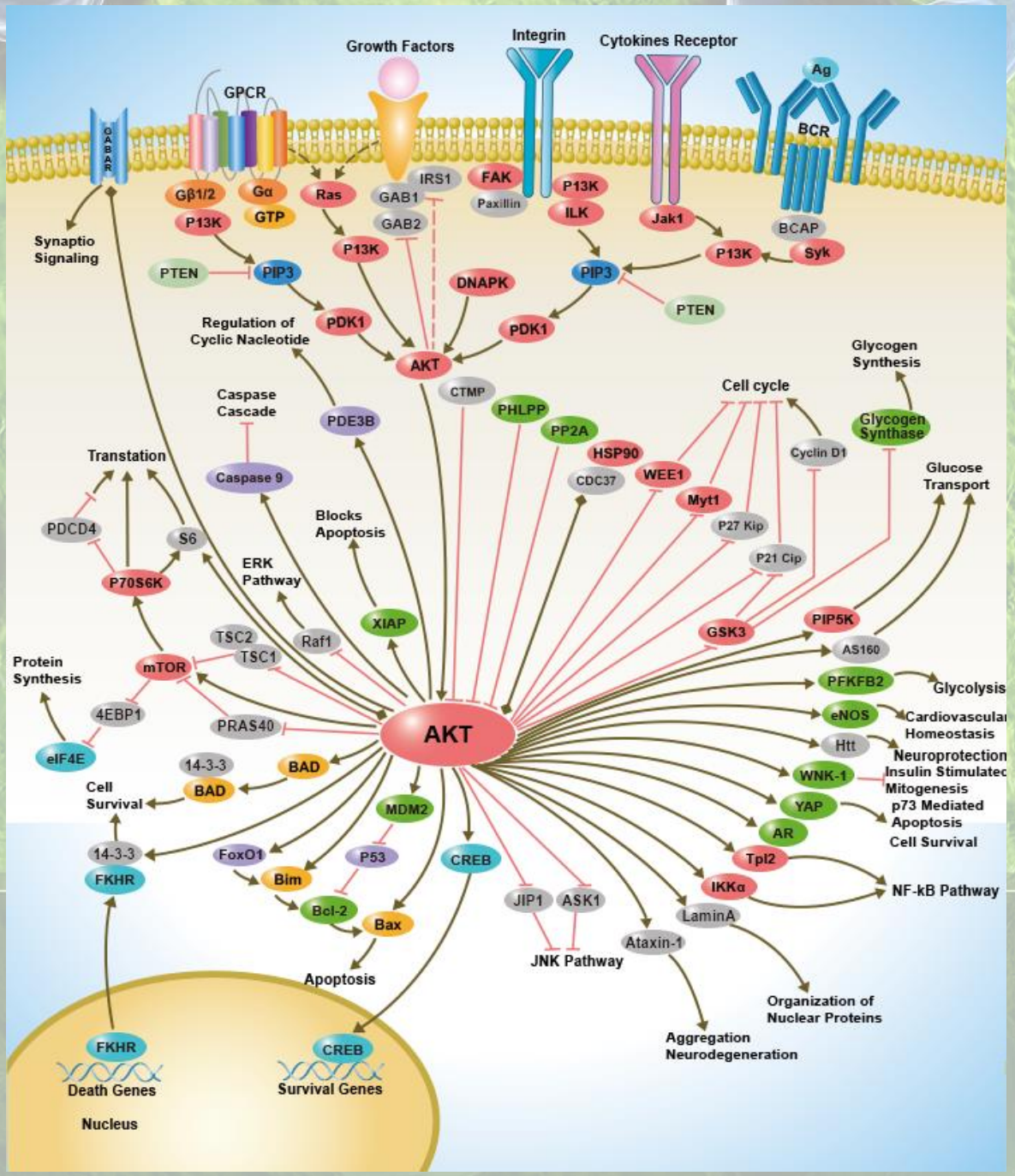


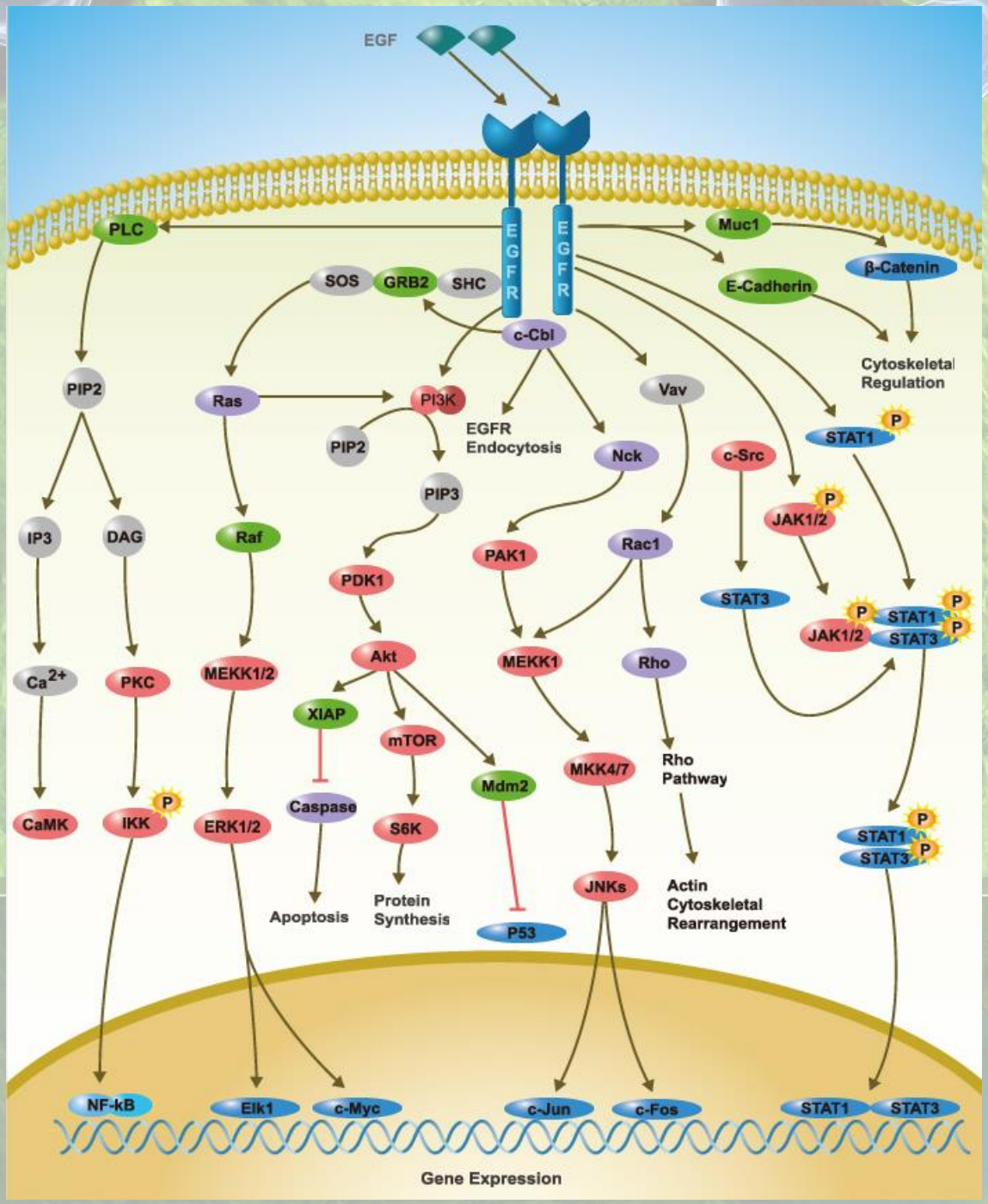
Receptor function **activation**

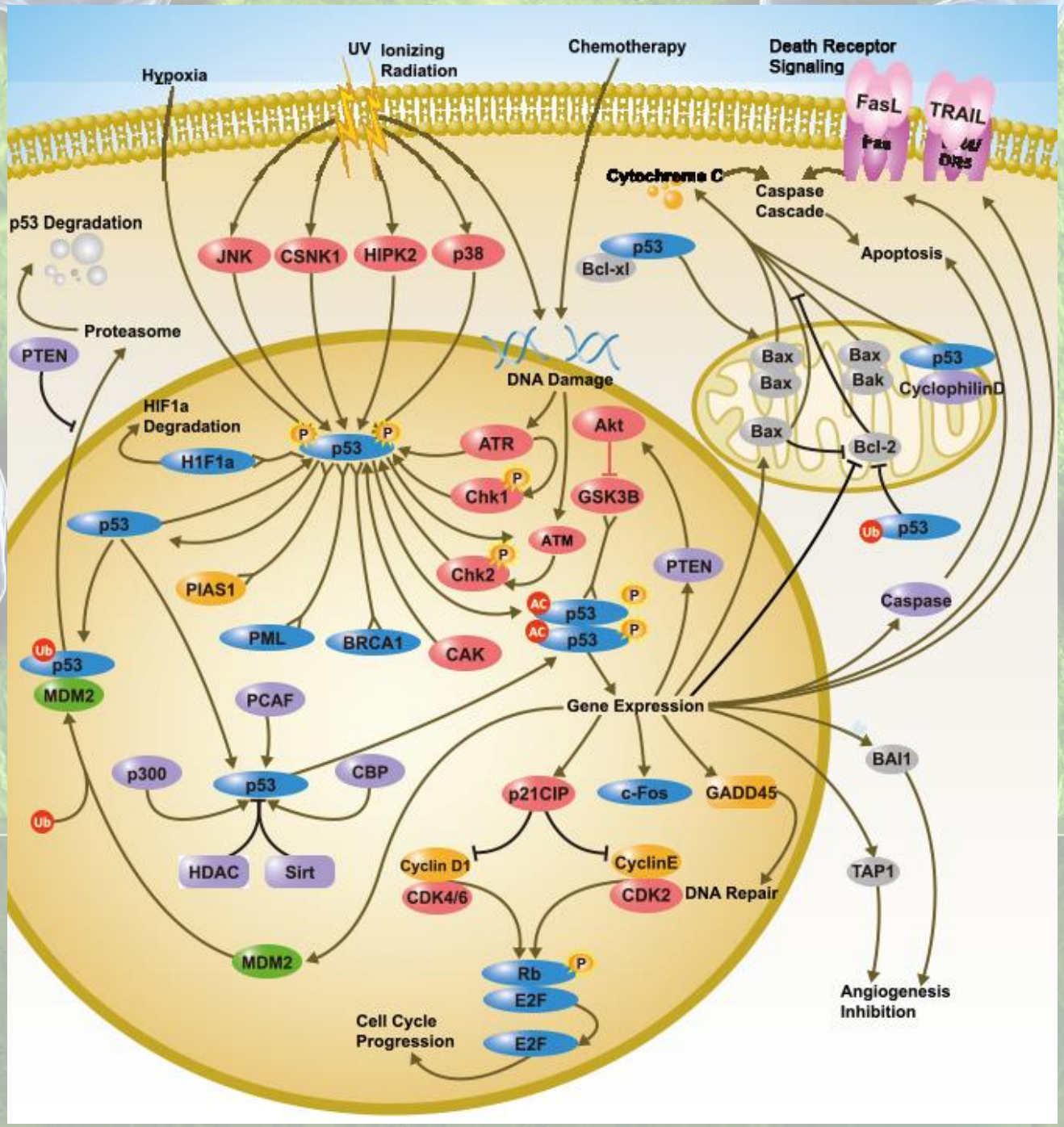
Protease-Activated Receptors (PAR)

e.g. platelets activation during fibrin clot formation in the wounded blood vessel wall




Growth Factors
Integrin
Cytokines Receptor
Ag
BCR
GPCR
GABAR
Gβ1/2
Gα
GTP
Ras
IRS1
GAB1
GAB2
FAK
Paxillin
P13K
ILK
Jak1
BCAP
Syk
Synaptio Signaling
PTEN
PIP3
DNAPK
PDK1
Regulation of Cyclic Nacleotide
AKT
CTMP
PHLPP
PP2A
HSP90
CDC37
WEE1
Myt1
P27 Kip
P21 Cip
Cyclin D1
Cell cycle
Glycogen Synthesis
Glycogen Synthase
Glucose Transport
Caspase Cascade
PDE3B
Caspase 9
Blocks Apoptosis
Transtation
PDCD4
S6
P70S6K
ERK Pathway
XIAP
Raf1
TSC2
TSC1
mTOR
Protein Synthesis
4EBP1
eIF4E
PRAS40
GSK3
PIP5K
AS160
PFKFB2
Glycolysis
eNOS
Cardiovascular Homeostasis
Htt
Neuroprotection
WNK-1
Insulin Stimulated Mitogenesis
YAP
p73 Mediated Apoptosis
AR
Cell Survival
Tpl2
IKKα
NF-kB Pathway
LaminA
Ataxin-1
Organization of Nuclear Proteins
Aggregation Neurodegeneration
JIP1
ASK1
JNK Pathway
14-3-3
BAD
Cell Survival
MDM2
P53
CREB
14-3-3
FKHR
FoxO1
Bim
Bcl-2
Bax
Apoptosis
FKHR
Death Genes
CREB
Survival Genes
Nucleus


EGF
EGFR
EGFR
PLC
Muc1
β-Catenin
E-Cadherin
SOS
GRB2
SHC
c-Cbl
Cytoskeletal Regulation
PIP2
Ras
PI3K
PIP2
EGFR Endocytosis
Vav
Nck
c-Src
STAT1
P
JAK1/2
P
PIP3
IP3
DAG
Raf
PAK1
Rac1
STAT3
PDK1
P
JAK1/2
STAT1
P
STAT3
P
Ca2+
PKC
MEKK1/2
Akt
MEKK1
Rho
XIAP
mTOR
MKK4/7
Rho Pathway
CaMK
IKK
P
ERK1/2
Caspase
S6K
Mdm2
P
STAT1
P
STAT3
Apoptosis
Protein Synthesis
P53
JNKs
Actin Cytoskeletal Rearrangement
NF-kB
Elk1
c-Myc
c-Jun
c-Fos
STAT1
STAT3
Gene Expression


Hypoxia
UV Ionizing Radiation
Chemotherapy
Death Receptor Signaling
FasL
TRAIL
Fas
DR5
Cytochrome C
Caspase Cascade
Apoptosis
p53 Degradation
Proteasome
PTEN
JNK
CSNK1
HIPK2
p38
p53
Bcl-xl
DNA Damage
Bax
Bak
CyclophilinD
HIF1a Degradation
H1F1a
p53
ATR
Akt
Chk1
GSK3B
Bcl-2
Ub
ATM
Chk2
PIAS1
PTEN
AC
Caspase
PML
BRCA1
CAK
Ub
MDM2
PCAF
Gene Expression
BAI1
p300
CBP
p21CIP
c-Fos
GADD45
HDAC
Sirt
Cyclin D1
CyclinE
TAP1
CDK4/6
CDK2
DNA Repair
Rb
E2F
Angiogenesis Inhibition
Cell Cycle Progression