

# **Receptors: key structures in cell signaling**

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# Signal transduction in multicellular organism

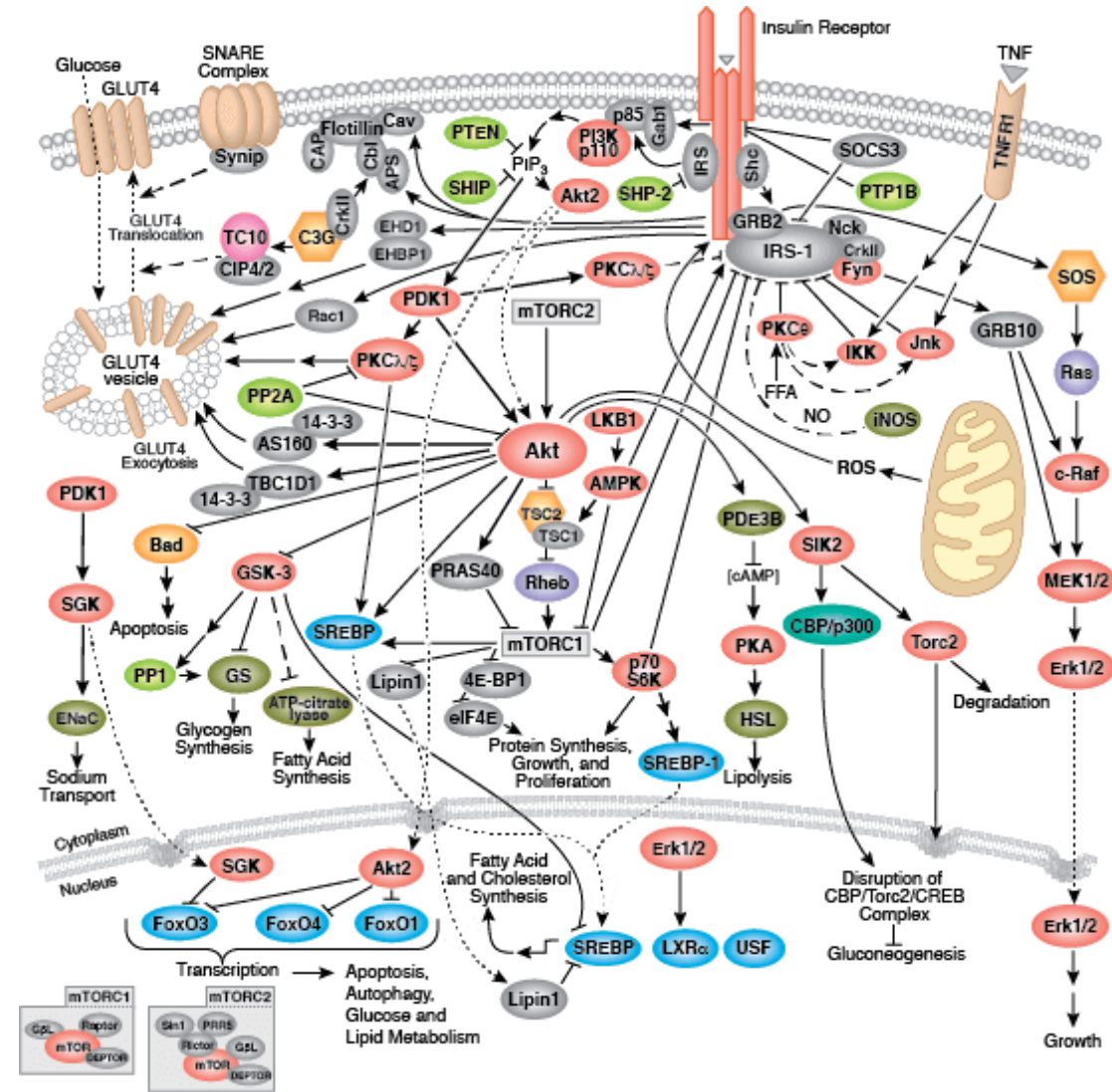
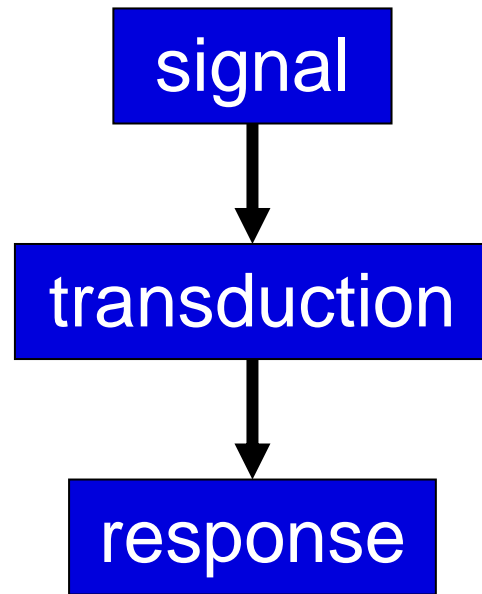


Neuronal signalling



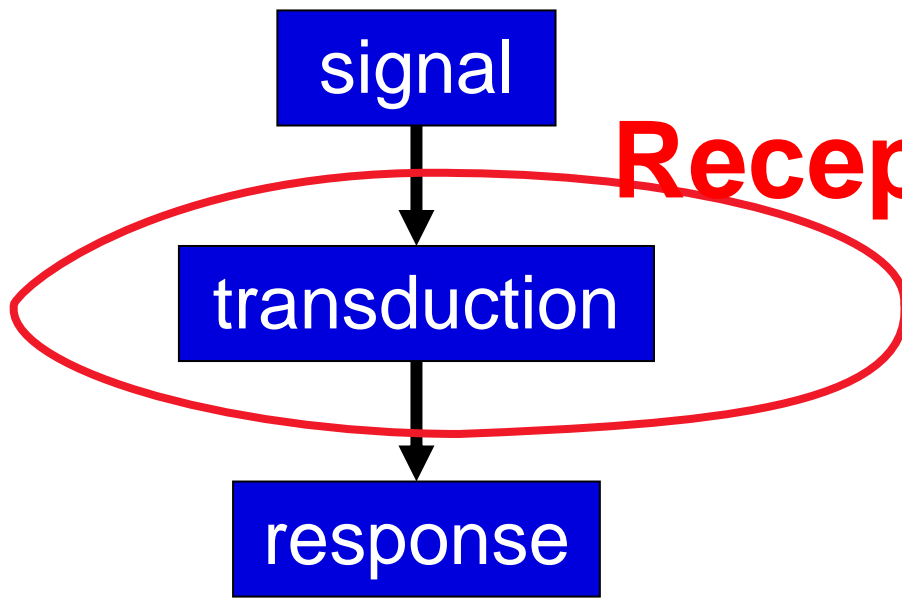
Humoral signalling

# Cellular signaling

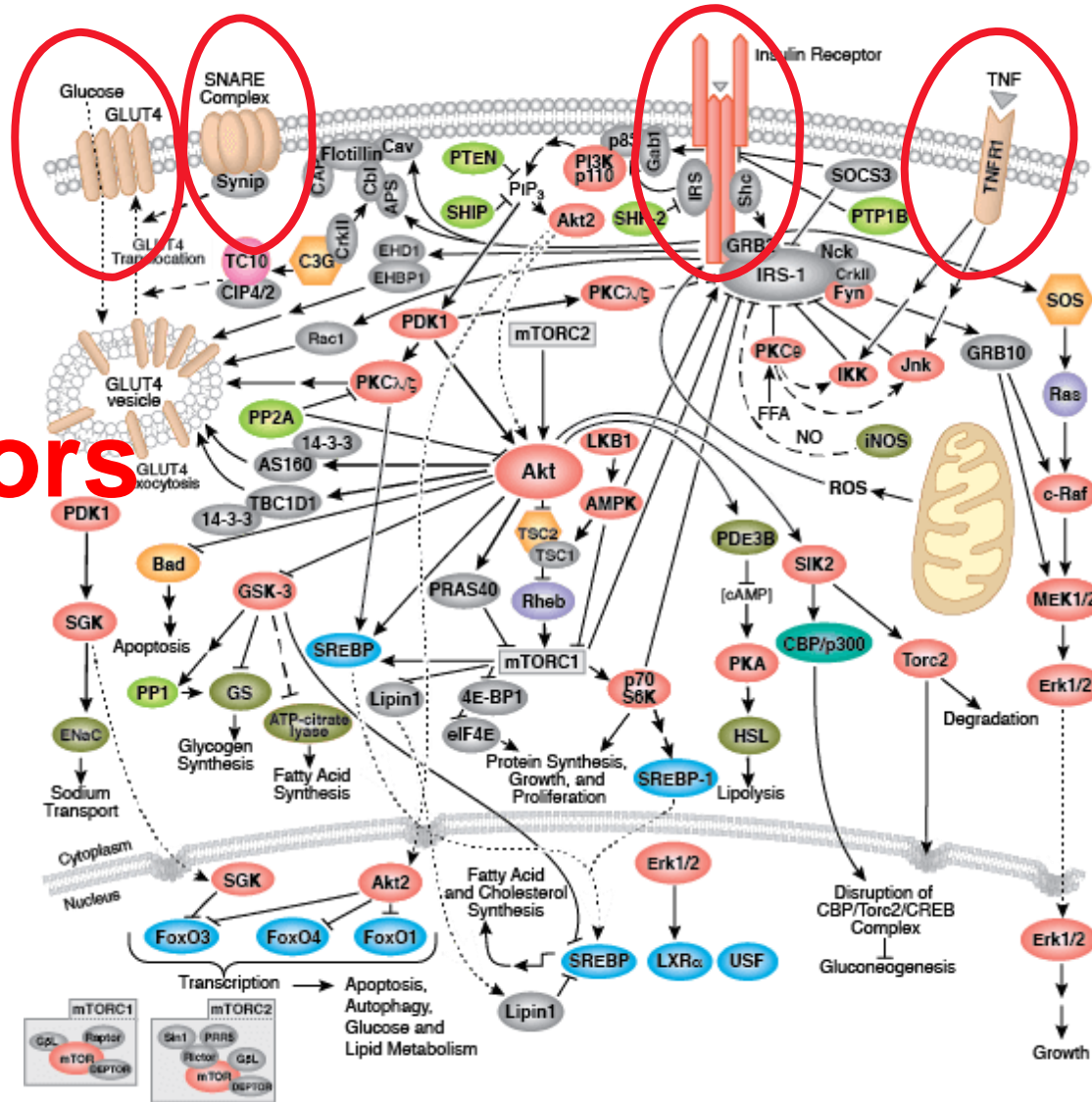


<https://www.cellsignal.com/contents/science-cst-pathways-cellular-metabolism/insulin-receptor-signaling/pathways-irs>

# Cellular signaling



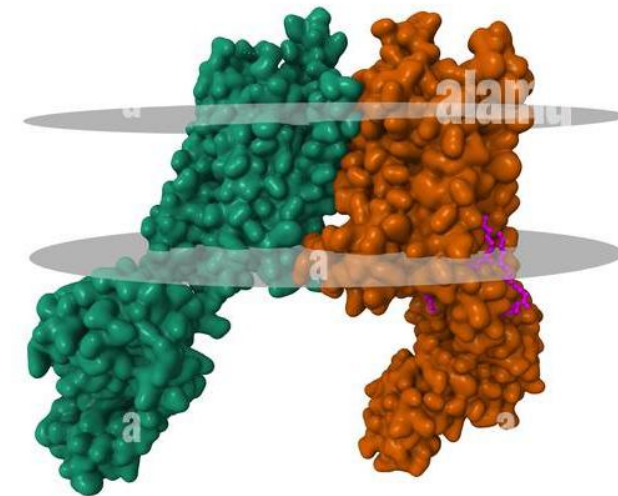
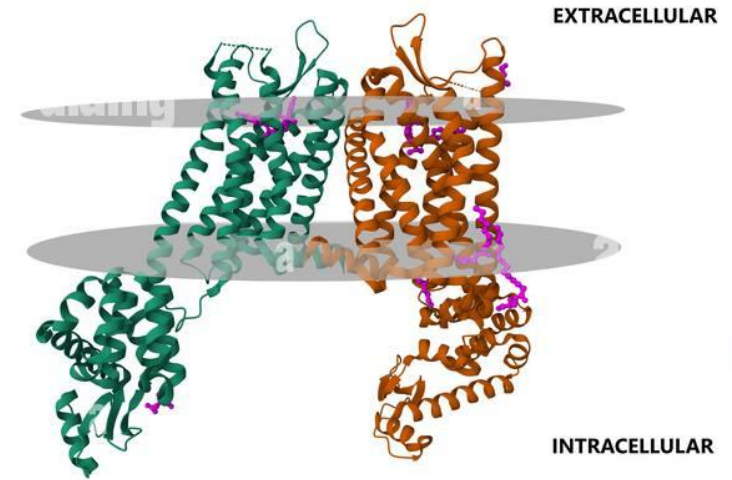
Receptors



<https://www.cellsignal.com/contents/science-cst-pathways-cellular-metabolism/insulin-receptor-signaling/pathways-irs>

# Receptors

- Protein-based structures
- Receive and transduce signals
- Integrated in signalling pathways



Kappa opioid receptor  
(source: <https://c8.alamy.com>)

# Classification

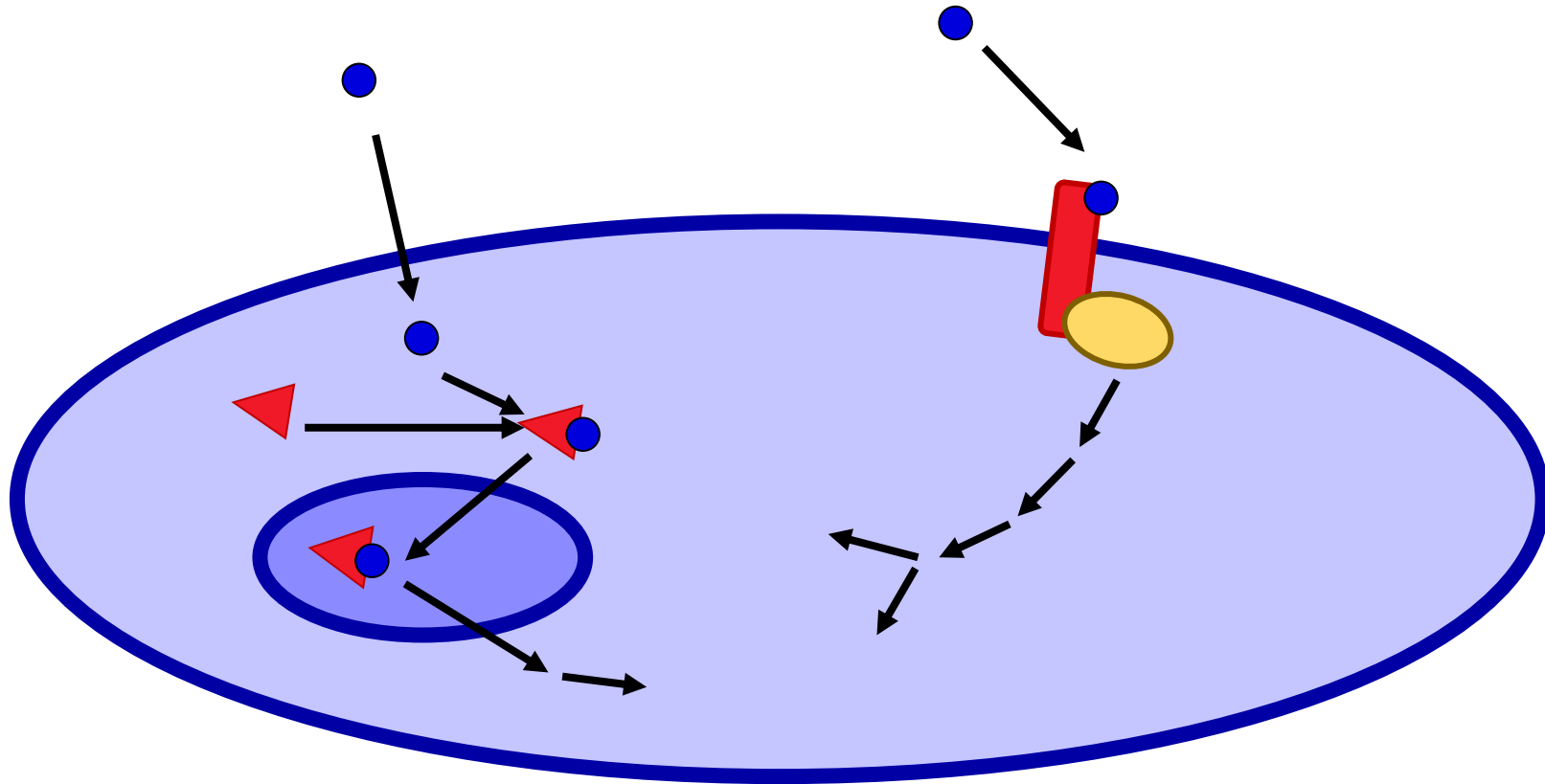
## – Location:

- Intracellular
- Cell surface

## – Function

- Ionotropic = ligand-gated ion channels
- G protein-coupled
- Enzyme-linked
  - Tyrosine kinases
  - Histidine kinases

# Intracellular vs. cell-surface receptors



# Ionotropic receptors

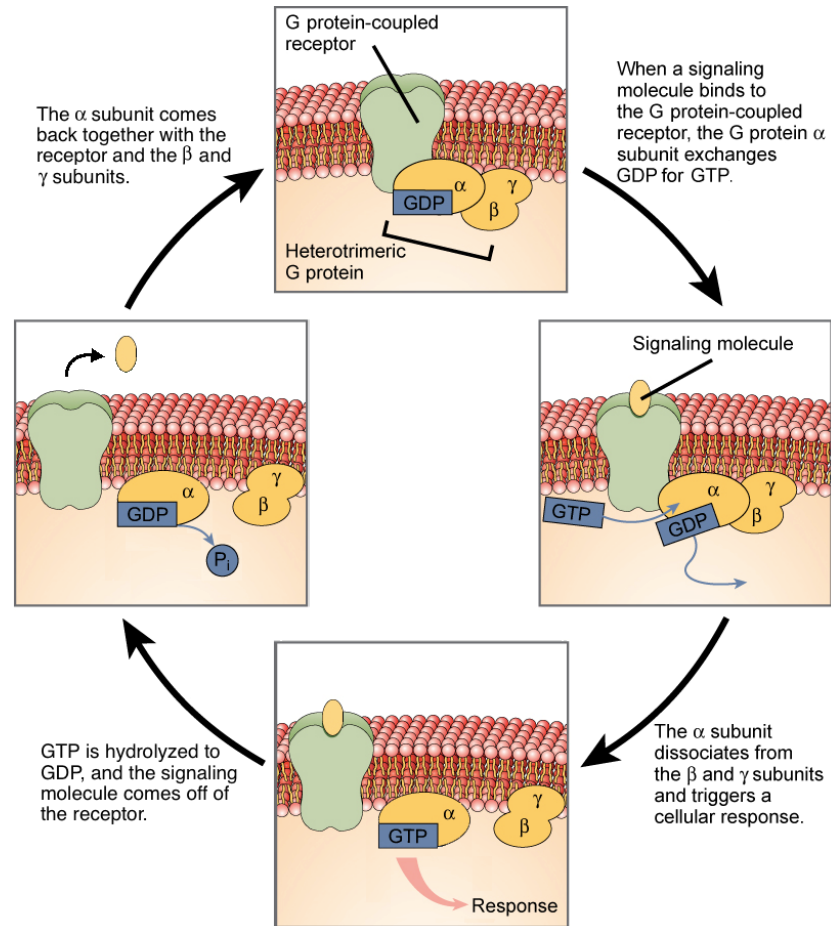
- Ligand-gated ion channels
- Direct change of membrane voltage and/or intracellular concentration of the ion



# Metabotropic receptors

- Production of second messenger
- G protein-coupled receptors
- Enzyme-linked receptors

# G protein-coupled receptors



<https://www.khanacademy.org/science/biology/cell-signaling/mechanisms-of-cell-signaling/a/signal-perception>

– Production of second messengers:

cAMP, cGMP, DAG, IP3, Ca<sup>2+</sup>

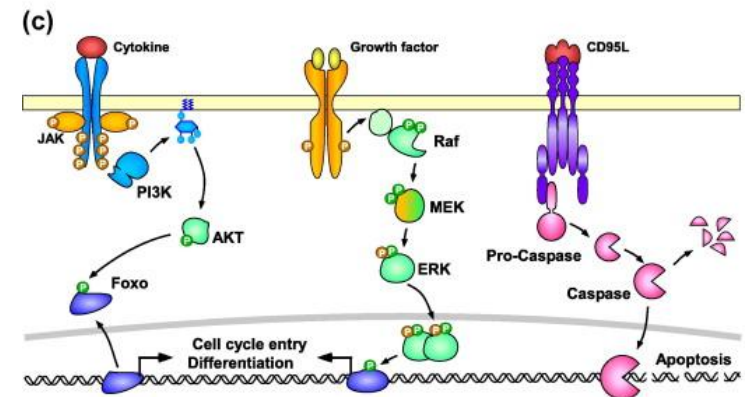
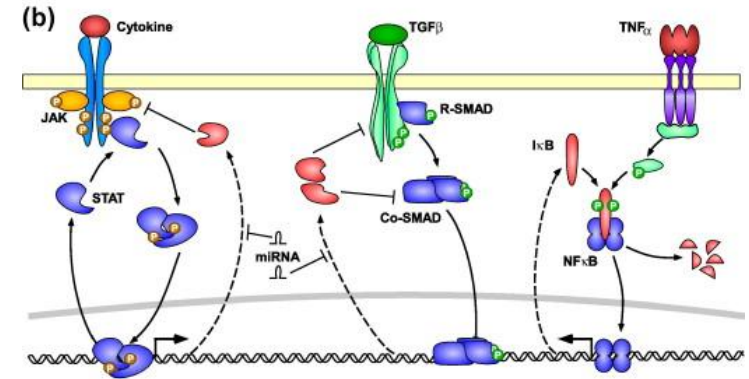
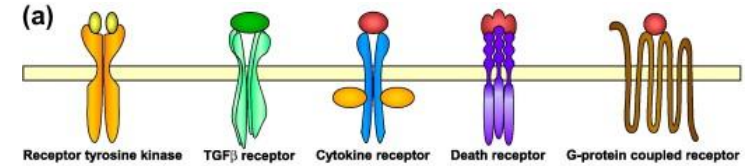
– G<sub>s</sub>

– G<sub>i</sub>

– G<sub>q</sub>

# Enzyme-linked receptors

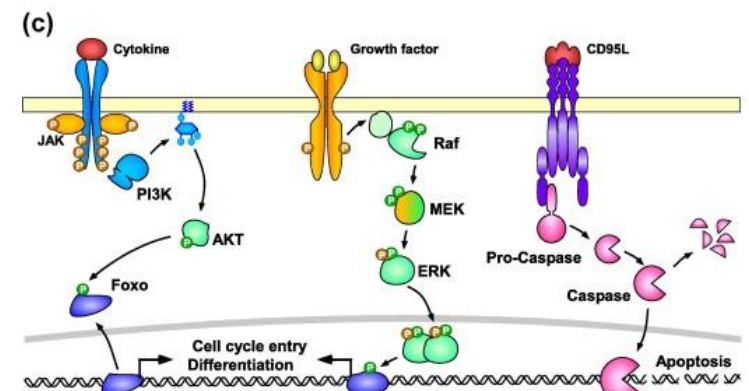
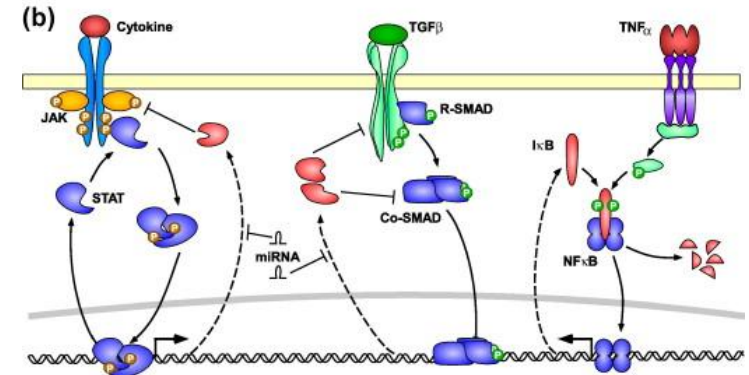
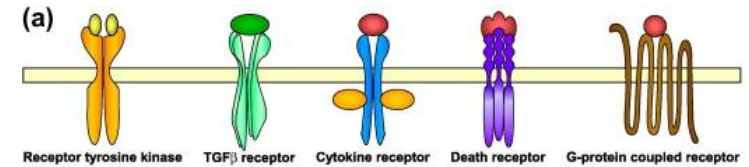
- Tyrosine kinases
- Guanylyl cyclase
- Serin/threonin kinases
- Tyrosine-kinase associated
- Tyrosine phosphatases



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# Receptor tyrosine kinases

- signal transduction: peptide hormones (insulin) and growth factors (epidermal growth factor)
- cell growth and differentiation: embryonic development, cell proliferation, migration and tissue repair



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# Regulation of receptor response

## Down-regulation

- Decrease of number and/or sensitivity of the receptors due to increased ligand stimulation
- Desensitisation
- Internalisation

# Regulation of receptor response

## Up-regulation

- Increase of number and/or sensitivity of the receptors due to decreased ligand stimulation
- (Re)sensitisation
- Externalisation
- Synthesis de novo

# Receptor families

- Classification according to **ligand(s)**

# Adrenergic receptors

- G protein-coupled receptors
  
- Ligands: catecholamines
  - Epinephrine (adrenaline)
  - Norepinephrine (noradrenaline)
  - Dopamine



# Adrenergic receptors - subtypes

## Alpha

- $\alpha 1$  (Gq) – DAG+IP3; smooth muscle contraction, mydriasis
- $\alpha 2$  (Gi) – cAMP; platelet activation

## Beta (Gs)

- $\beta 1$  – heart (SA node)
- $\beta 2$  – smooth muscle relaxation (bronchodilation)
- $\beta 3$  – lipolysis, urination

# Dopamine receptors

- G protein-coupled receptors
- Ligand: dopamine
- Expression:
  - CNS – neurotransmission, neuromodulation
  - peripheral (non-)neural tissues

# Dopamine receptors - subtypes

**D1-like family**  
(Gs): D1, D5

**D2-like family**  
(Gi): D2, D3, D4

- Dimerization
  - Heterodimers (e.g. D1-D2)
  - Non-isoreceptor heterodimers (e.g. D2-Adenosine A2R)
- Protein interactions

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- Dimerization
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# Acetylcholine (cholinergic) receptors

**M type =  
Muscarinic  
acetylcholine  
receptors**

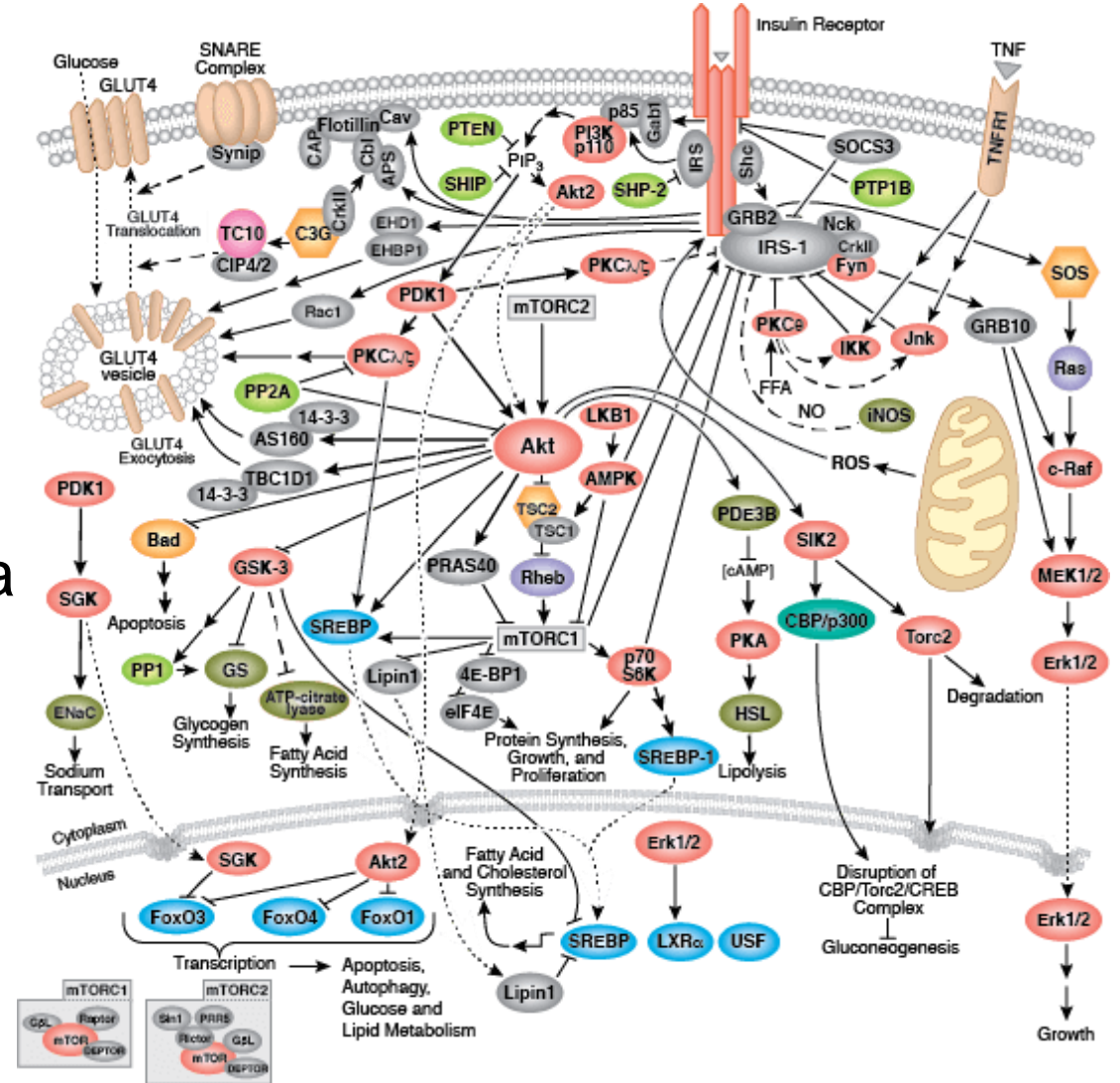
- Metabotropic receptors – G-protein coupled receptors
- Subtypes
  - M1 – CNS, autonomic ganglia, salivary glands, stomach
  - M2 – heart (SA node, atria, AV node), CNS
  - M3 – smooth muscle (e.g. vessels, bronchi), endocrine+exocrine glands, GIT, eyes, CNS
  - M4+M5 – CNS

**N type = Nicotinic  
acetylcholine  
receptors**

- Ionotropic receptors – ligand-gated ion channels
- Subtypes (according to subunits)
  - Nm – „muscular“ type – neuromuscular junction
  - Nn – „neuronal“ type – autonomic ganglia, adrenal medulla

# Insulin receptor

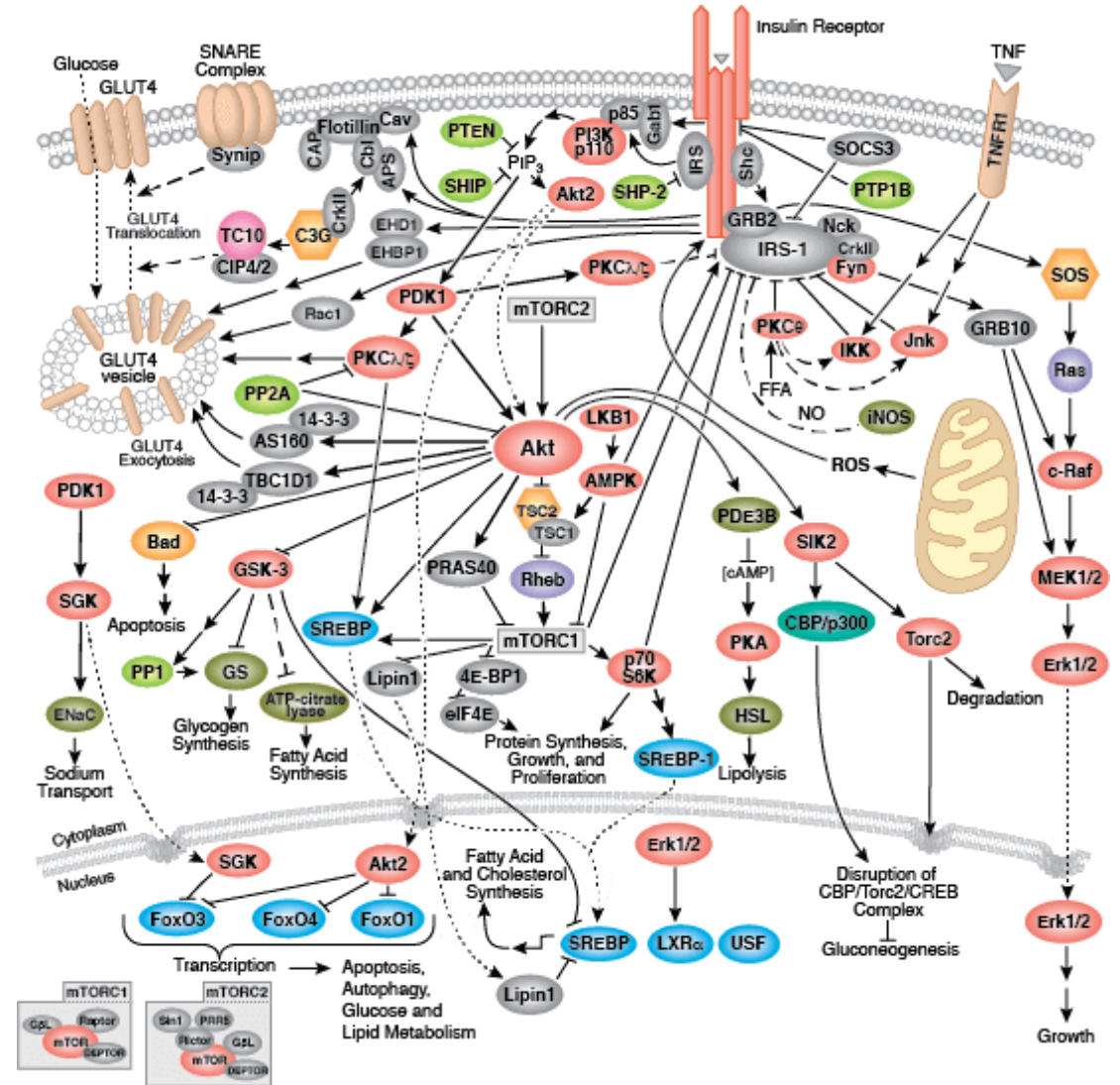
- Ligands: **insulin**, IGF-I, IGF-II
- Receptor Activation: Insulin binding causes the insulin receptor to undergo a conformational change, leading to **autophosphorylation**
- Transduction: tyrosine kinase activity



<https://www.cellsignal.com/contents/science-cst-pathways-cellular-metabolism/insulin-receptor-signaling/pathways-irs>

# Insulin receptor

- Signalling: various intracellular signalling pathways, including PI3K/Akt and MAPK
- Effects:
  - **Glucose Uptake:** glucose transporter 4 (GLUT4) externalisation, particularly in muscle and adipose tissues
  - **Glycogen Synthesis:** activating glycogen synthase
  - **Protein Synthesis:** enhancing the activity of ribosomal protein S6 kinase and other translation initiation factors
  - **Lipid Metabolism:** inhibits lipolysis and promotes lipogenesis by regulating key enzymes involved in lipid metabolism



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# Vascular endothelial growth factor (VEGF) receptors

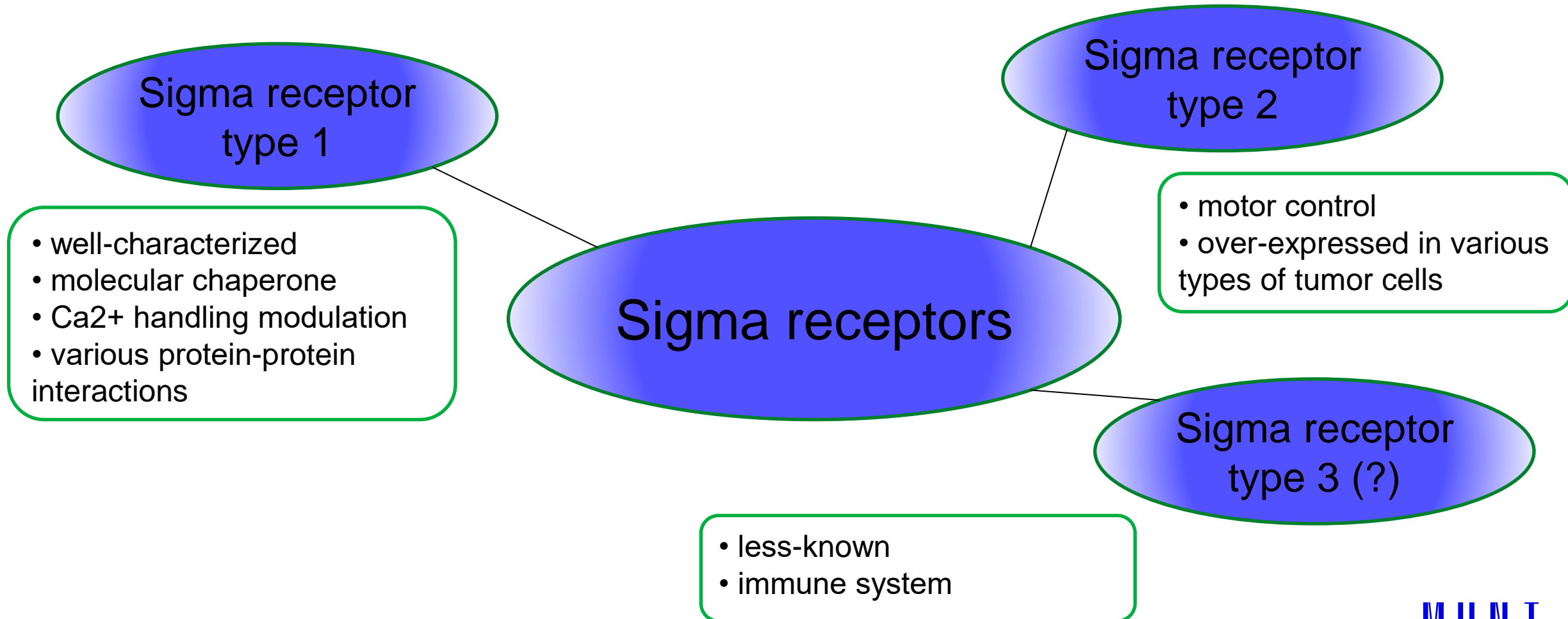
- Membrane (mbVEGFR) or soluble (sVEGFR) receptors
- Tyrosine kinase activity
- Three main subtypes: VEGFR-1, VEGFR-2, VEGFR-3
- Angiogenesis, vascular permeability, endothelial functions, lymphangiogenesis (VEGFR-3), tissue response to hypoxia



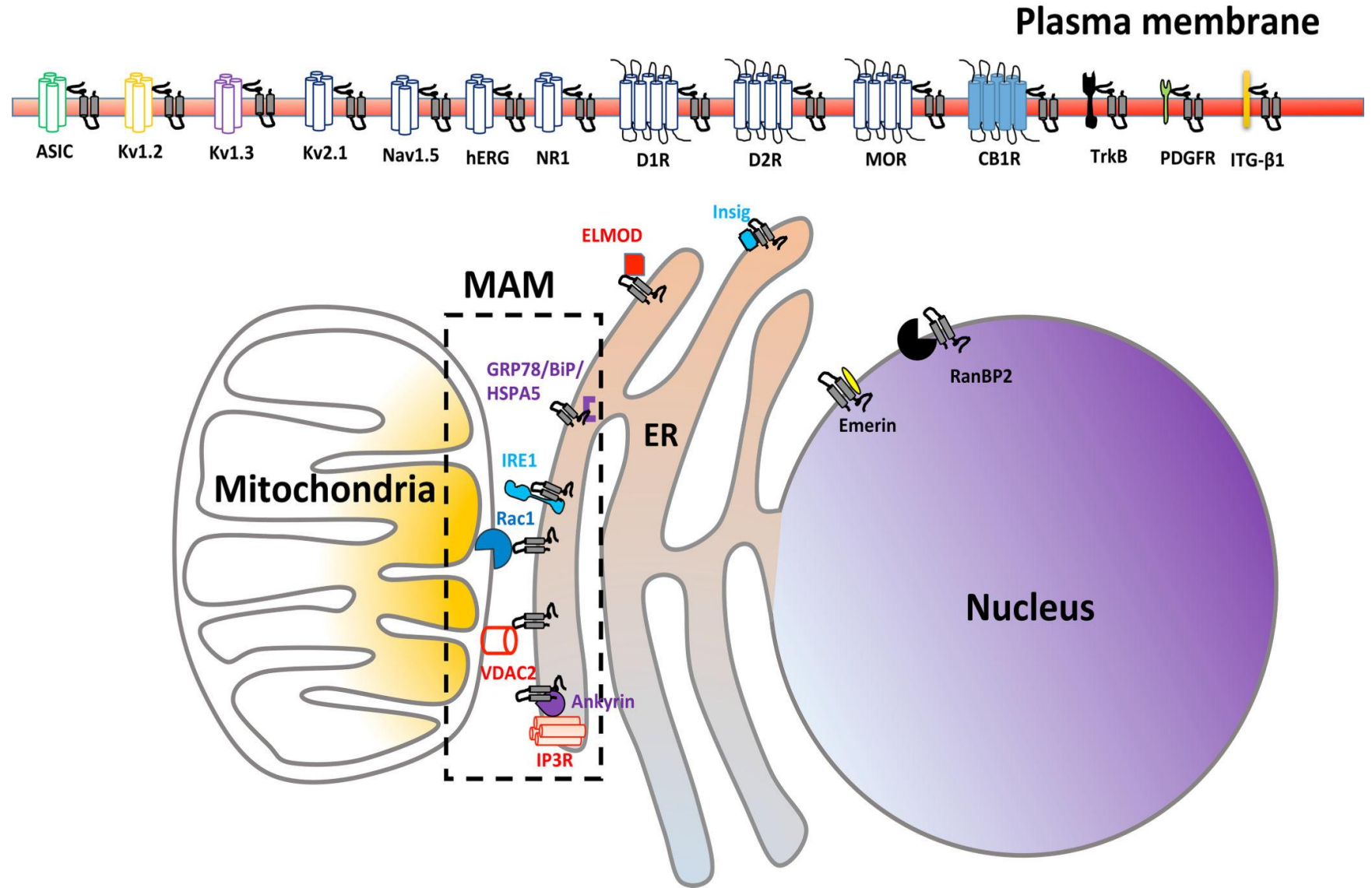
# Inositol-tris-phosphate (IP3) receptors

- Intracellular receptors - endoplasmic reticulum, mitochondria
- Types: IP3R1, IP3R2, IP3R3
- Function: ligand-gated Ca<sup>2+</sup> channels
- Dimerisation and protein-protein interactions

# Sigma receptors



# Sigma 1 receptors



Su et al., 2016.  
*Trends Pharmacol Sci.* 2016; 37(4): 262–278. doi:10.1016/j.tips.2016.01.003

# Take home messages

Receptors are crucial structures in cell signalling.

Receptors play an important role in pathophysiology of many diseases.

Receptors are targets for pharmacotherapy.

