Imperial College London

Receptors and signalling: Lecture 1

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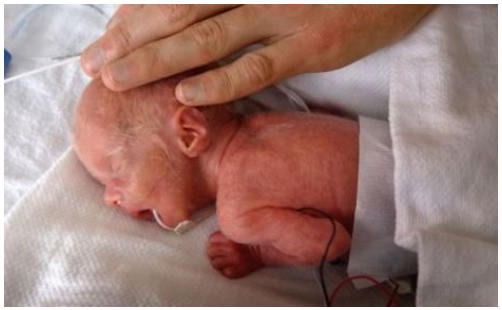
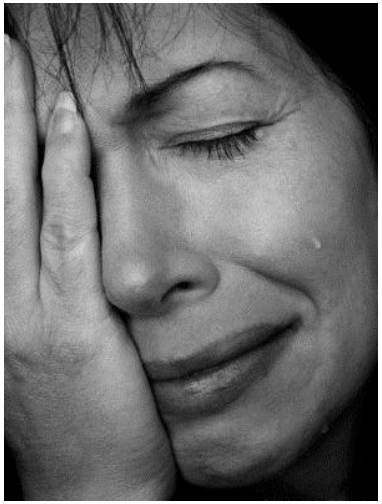
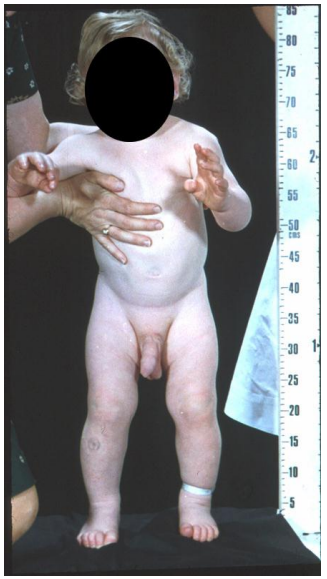
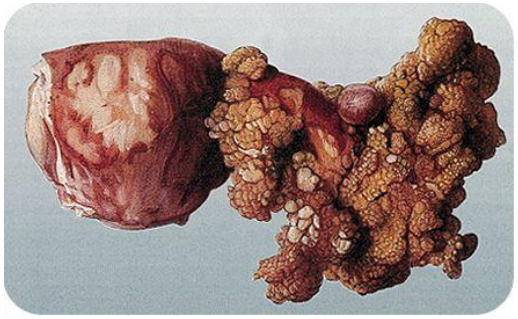
What do these have in common?



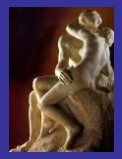






It’s a receptor world



How we develop and sense/respond to our environment







Stimuli



Cell surface receptors

When receptor activity goes wrong:

Cancer
Diabetes
Obesity
Infertility
Blindness
Schizophrenia
Depression
Preeclampsia
Congestive heart failure

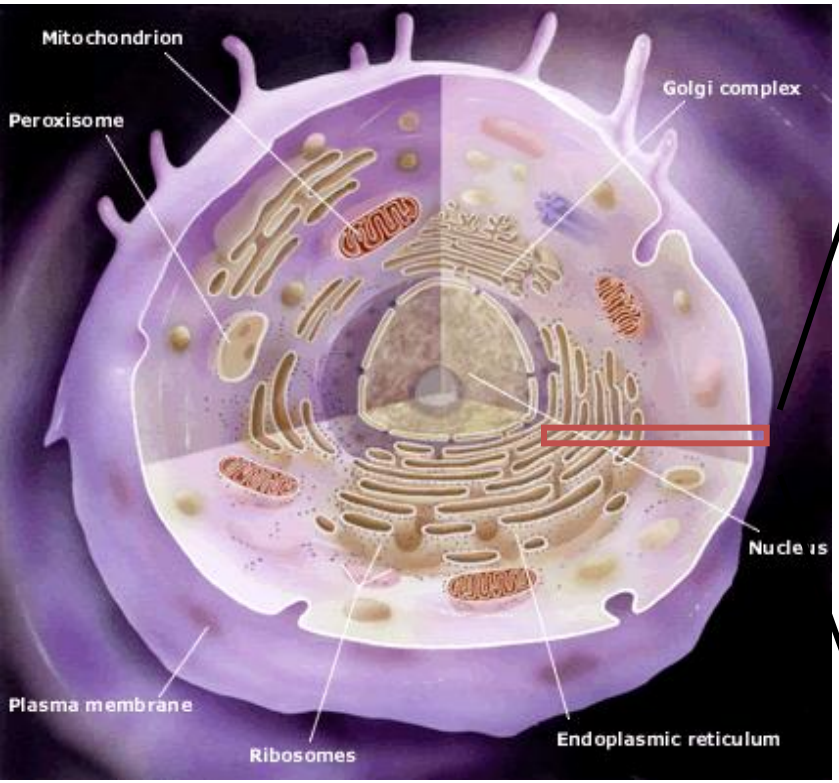
Learning Objectives:

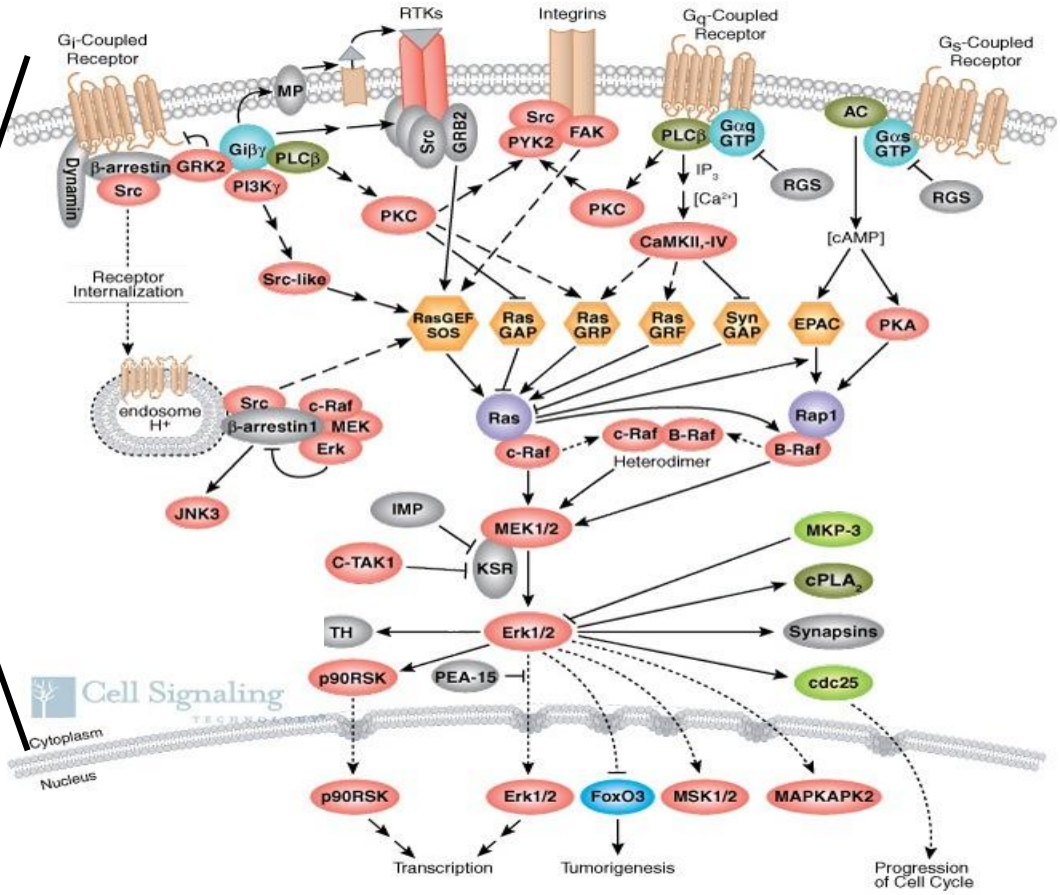
List the main types of cell surface receptor and describe their main structural features

Compare and contrast the activation modes and signalling pathways induced by each type of cell surface receptor

Give examples of how disruption of communication in receptor signalling results in human disease

A single cell is exposed to multiple ligands to activate multiple signalling networks





How do cells regulate the dynamics and strength of signalling that results in precise control of a specific physiological response?

Main Types Of Cell Surface Receptors

* 1. Tyrosine kinase receptors

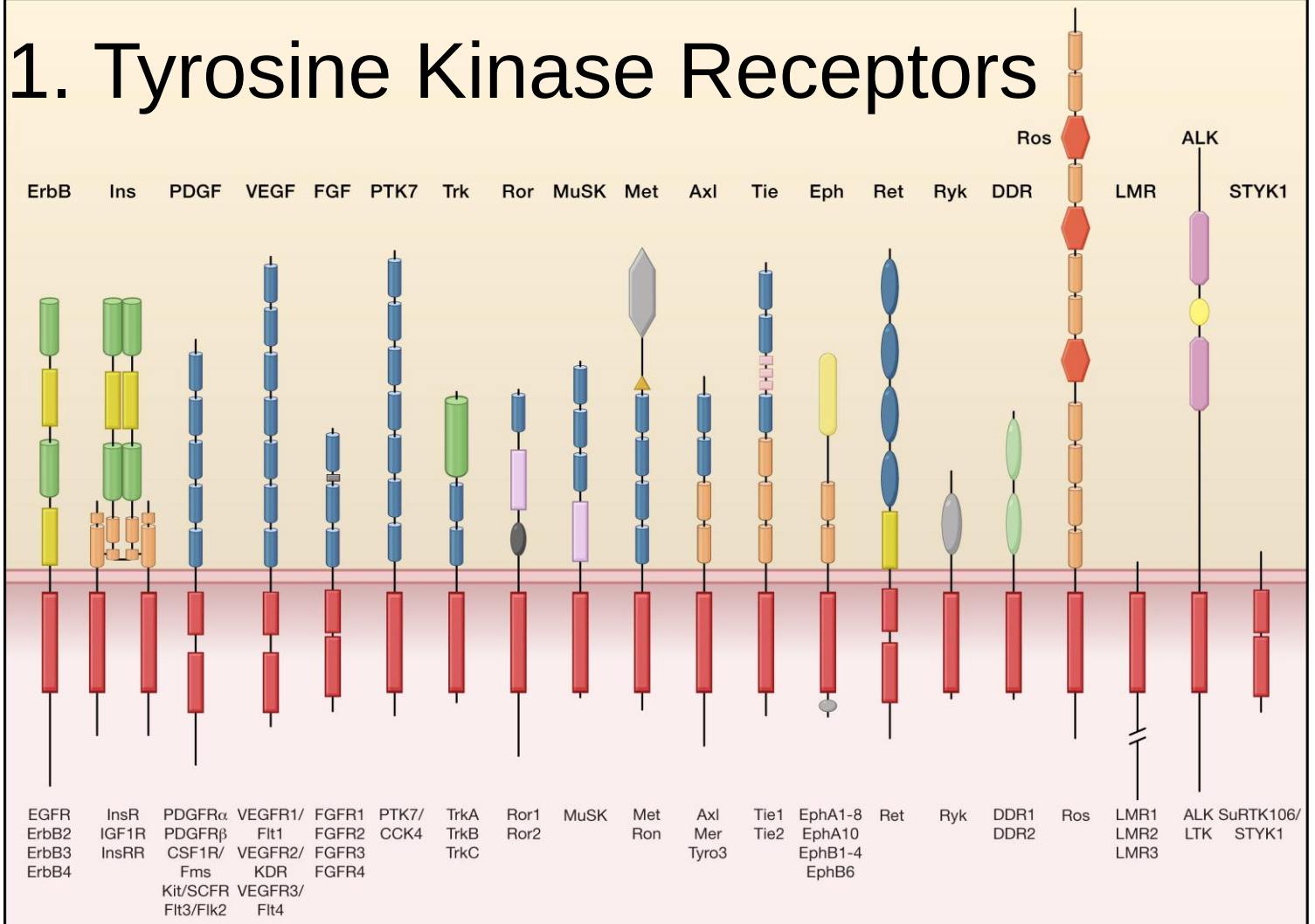
2. Enzyme-associated receptors

* (tyrosine, serine/threonine (TGFbeta, BMPs), phosphatases (CD45), guanyl cyclase (ANP, BNP)

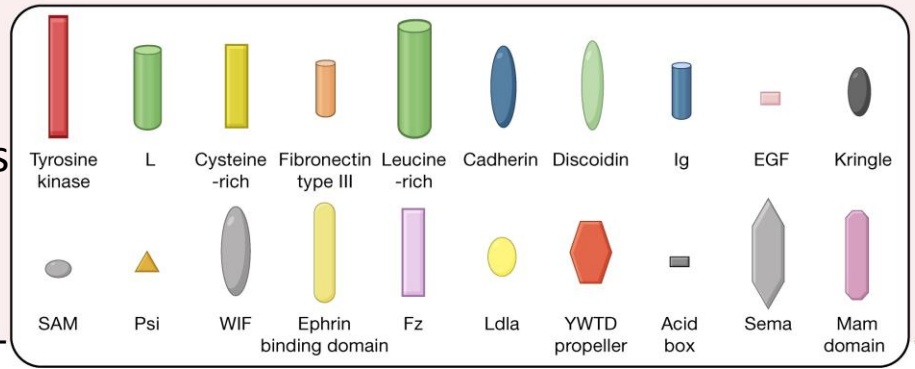
3. Ligand-gated Ion Channels

* 4. G-protein coupled receptors (GPCRs)

1. Tyrosine Kinase Receptors

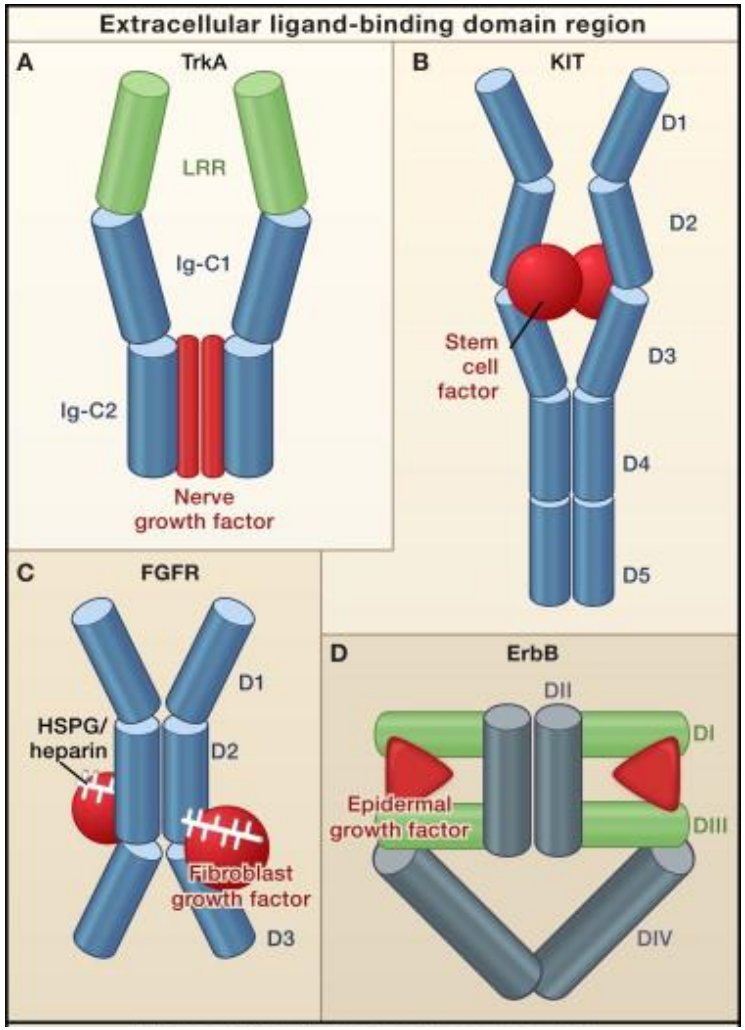


58 RTK's
20 subfamilies



Cell. 2010. 141:1117

RTK's and Dimerization



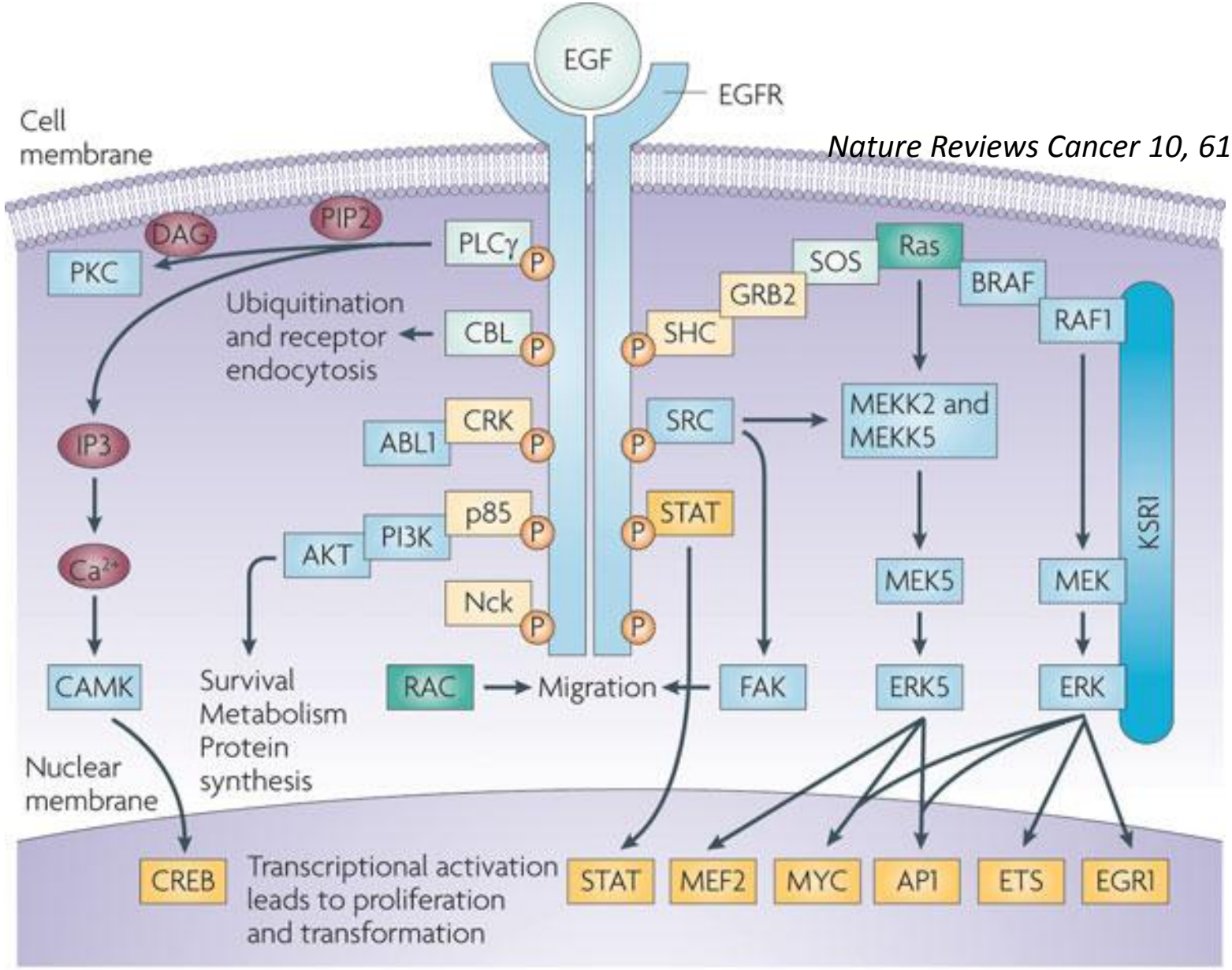
TrkA receptor: Ligand-mediated dimerization. NGF is a dimer, no direct receptor contact.

KIT: Stem cell factor is a dimer plus receptor-mediated dimerization

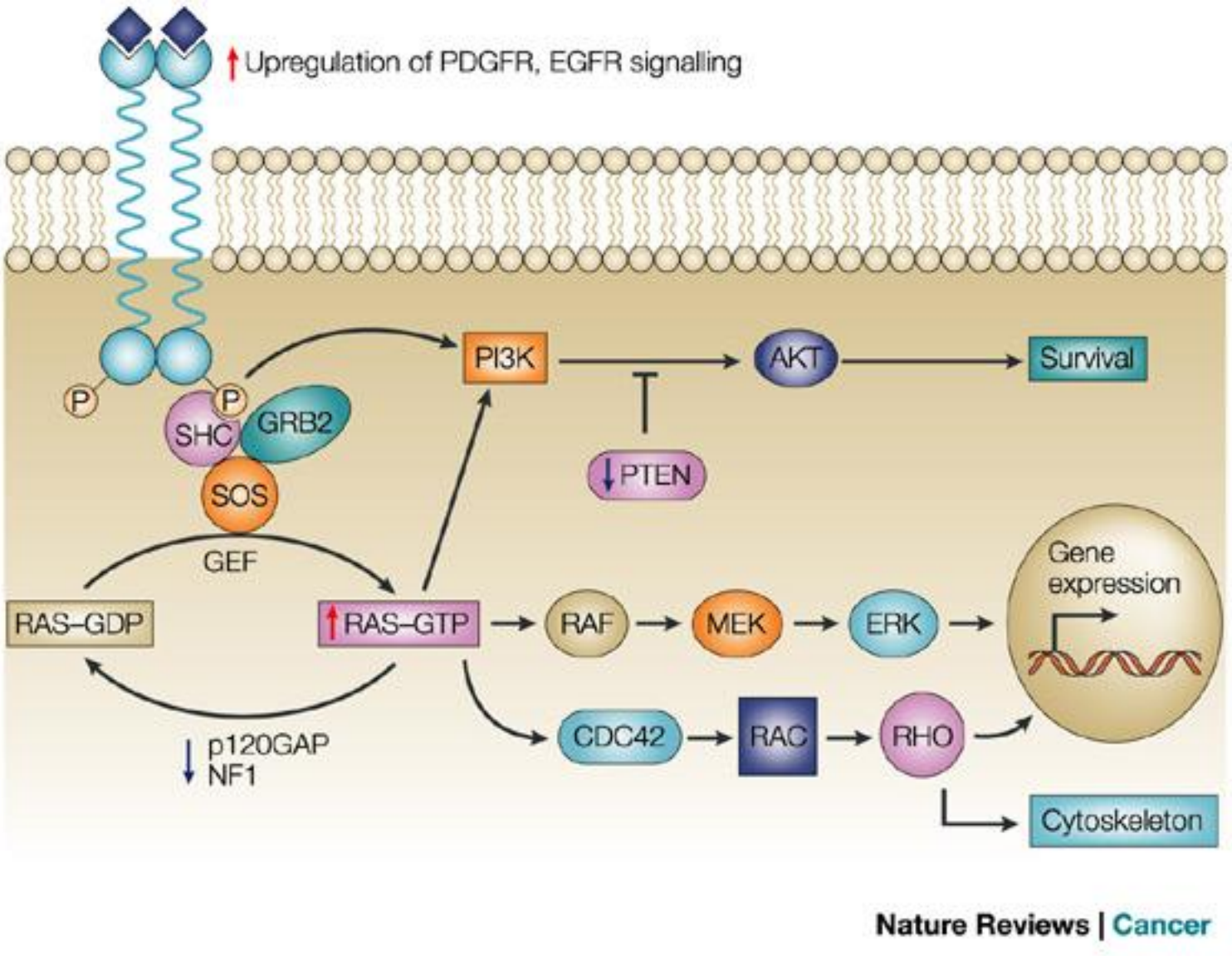
FGFR: receptor-mediated dimerization induced by FGF and the accessory molecule heparin

ErbB receptor: Dimerization is mediated entirely by the receptor. The ligand drives conformational changes in the receptor that exposes a dimerization site.

Signalling pathways activated by RTK's

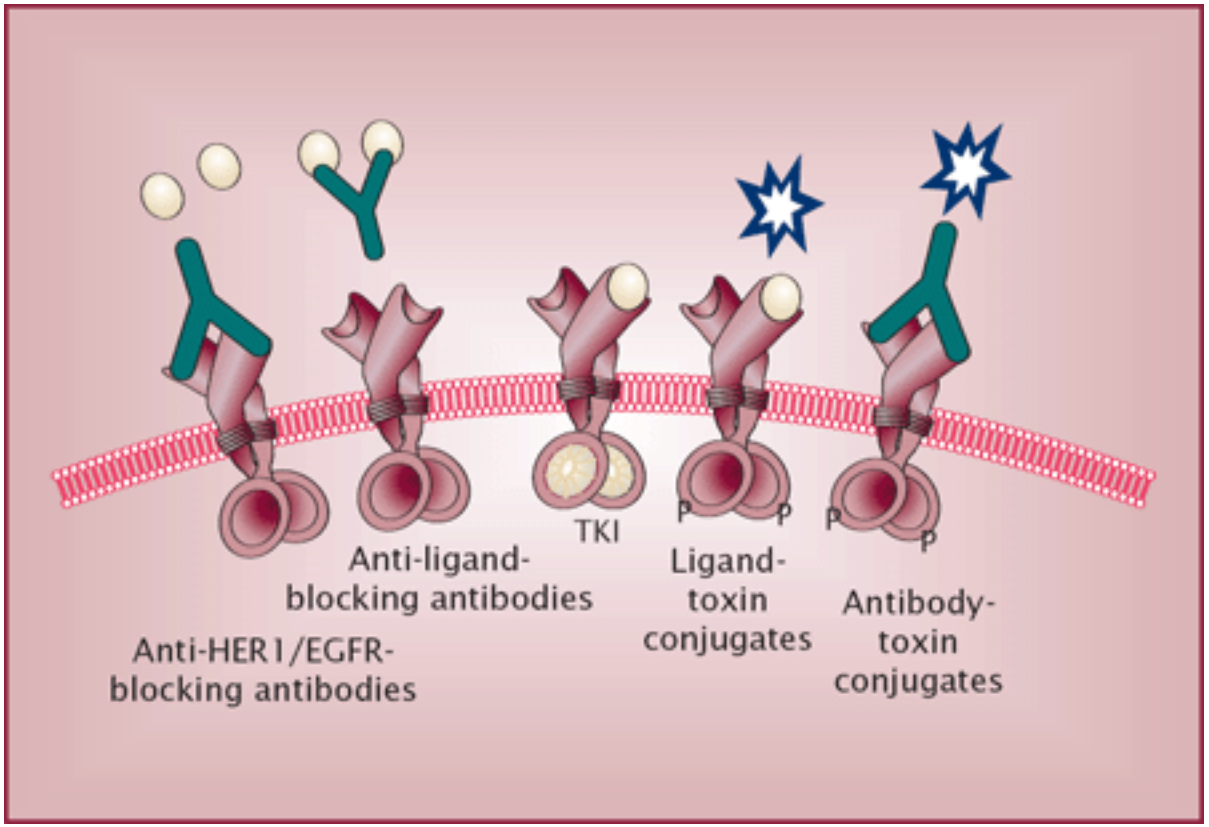


RTK signalling and disease



Nature Reviews Cancer 2, 616-626 (August 2002)

Approaches in targeting RTK's in Cancer



Because of their key roles in mediating cellular proliferation, RTKs are attractive candidates for therapeutic intervention.

2. Enzyme-Linked Receptors- Cytokine receptors

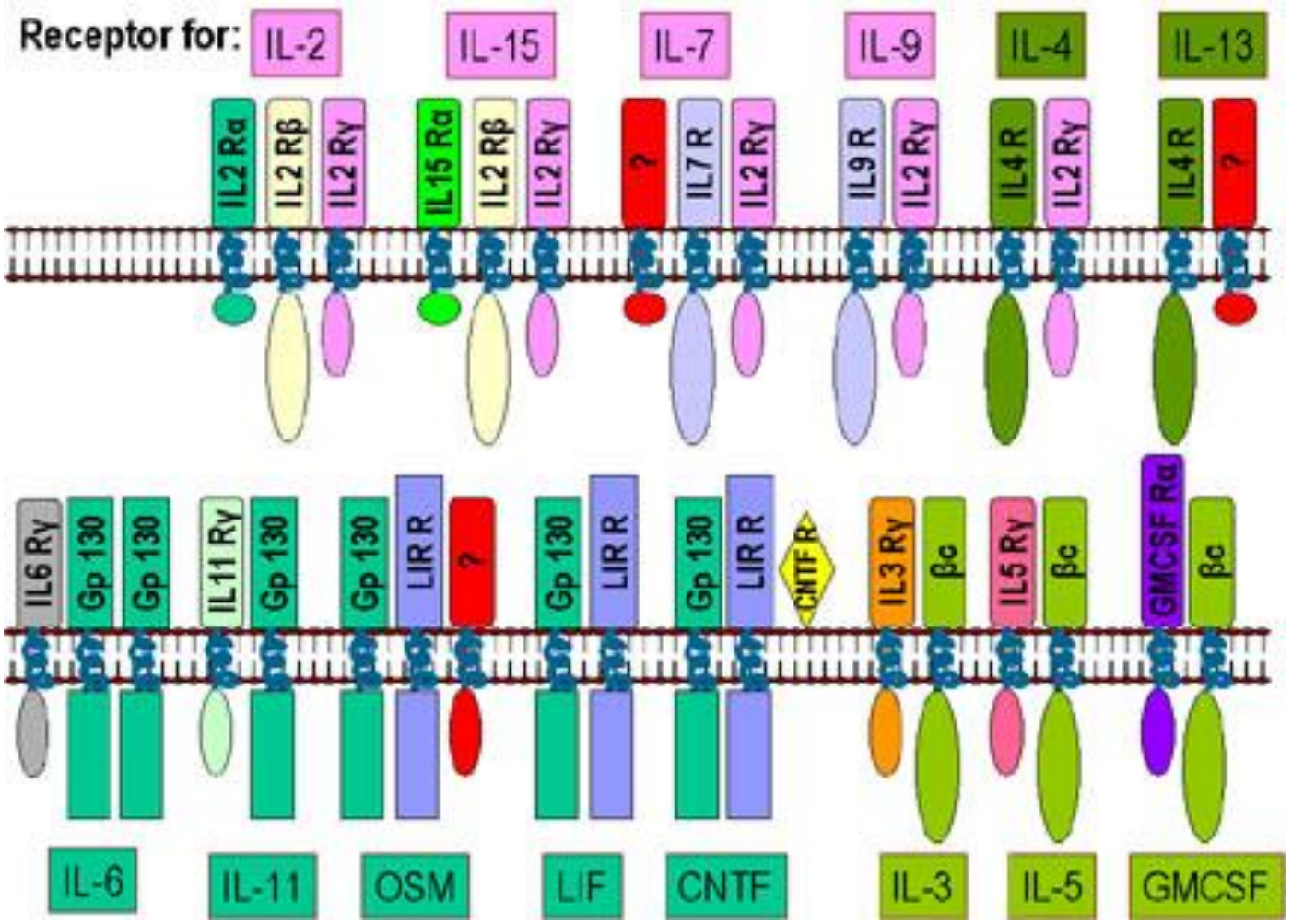
Cytokines play pivotal roles in immunity and inflammation by regulating the survival, proliferation, differentiation not just in haematopoiesis but in other cellular systems.

- Type 1:
  - IL3, IL4, IL5, IL6, IL7, IL9, IL11, IL12
  - GM-CSF, G-CSF
  - Tumor necrosis factor-α
  - Leukemia inhibitory factor (LIF)
  - Erythropoietin
  - Growth hormone
  - Prolactin
- Type 2:

  IFN-alpha, IFN-beta, IFN-gamma, IL10, TF (tissue factor), IL22
- Chemokines*
  - IL-8, RANTES

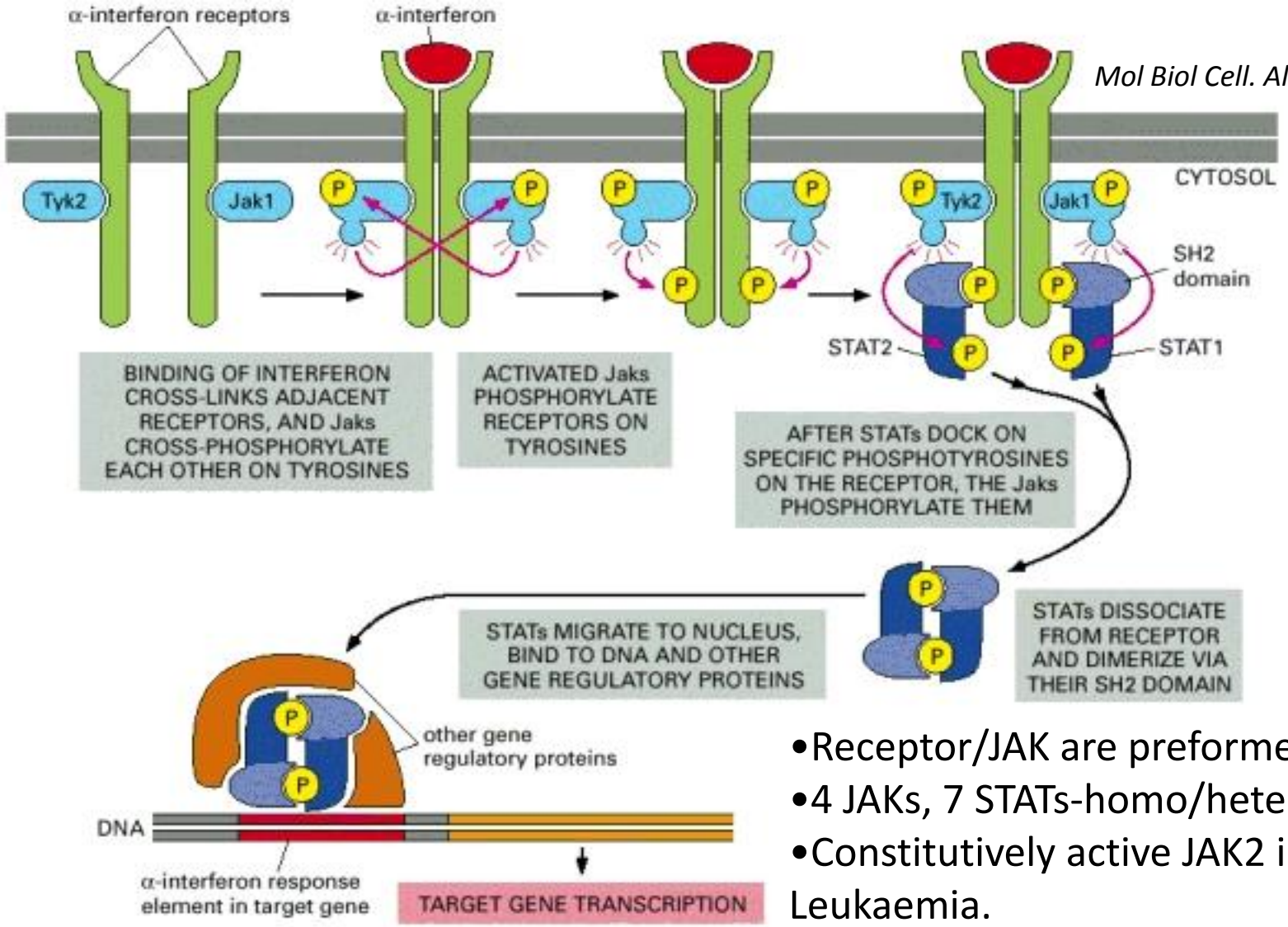
* GPCR

CYTOKINE RECEPTORS ARE ASSEMBLED FROM TWO TO THREE DIFFERENT POLYPEPTIDE CHAINS ENCODED BY DIFFERENT GENES



Cytokine receptors cluster into families that share the same receptor subunit (IL- interleukin, OSM- oncostatin, CNTF-Ciliary neurotrophic factor, GMCSF; granulocyte-macrophage colony-stimulating hormone)

The JAK/STAT pathway is the canonical signalling for Cytokine Receptors

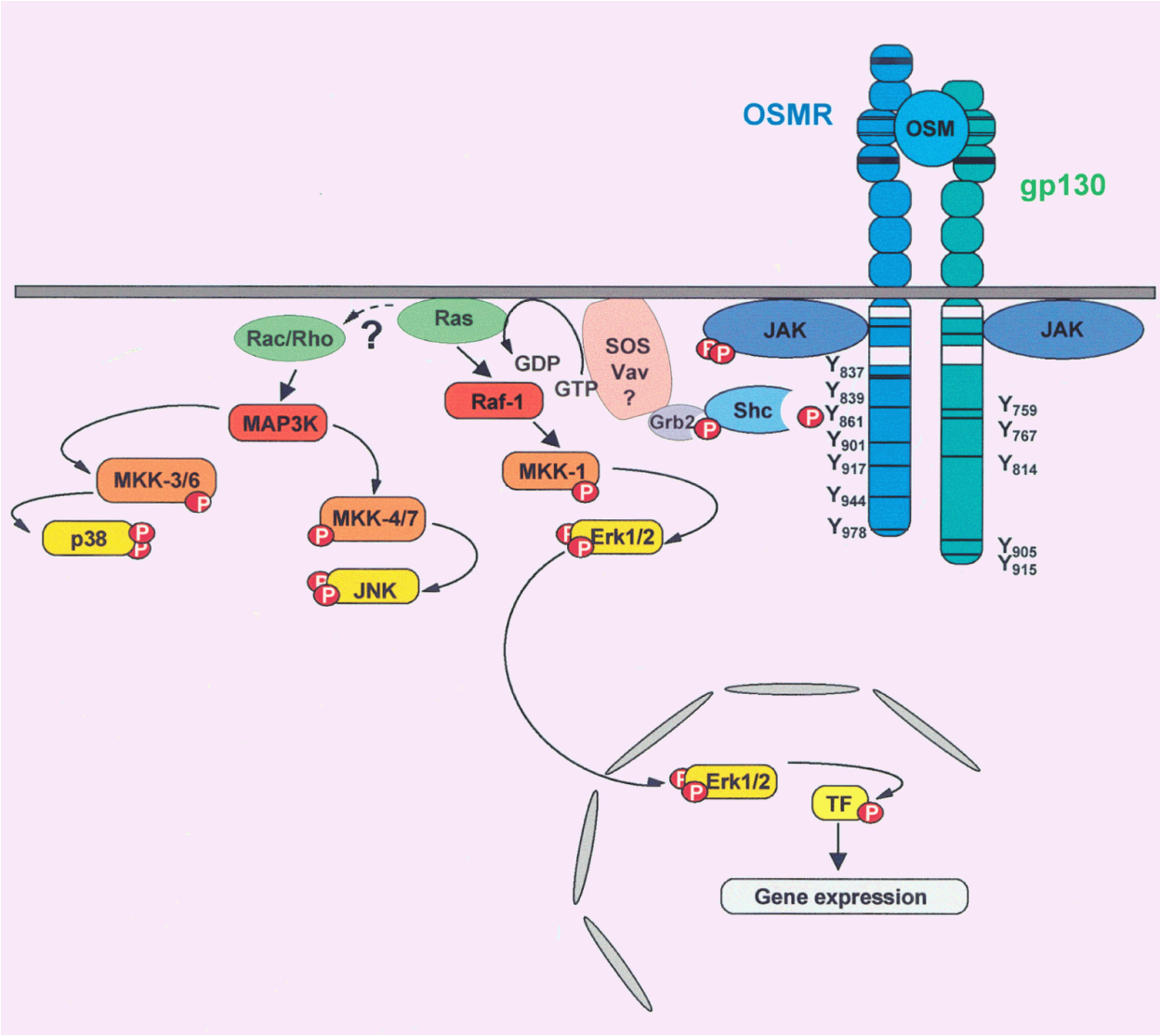


Mol Biol Cell. Alberts et al, Chapter 15

- Receptor/JAK are preformed
- 4 JAKs, 7 STATs-homo/heterodimerize
- Constitutively active JAK2 implicated in Leukaemia.

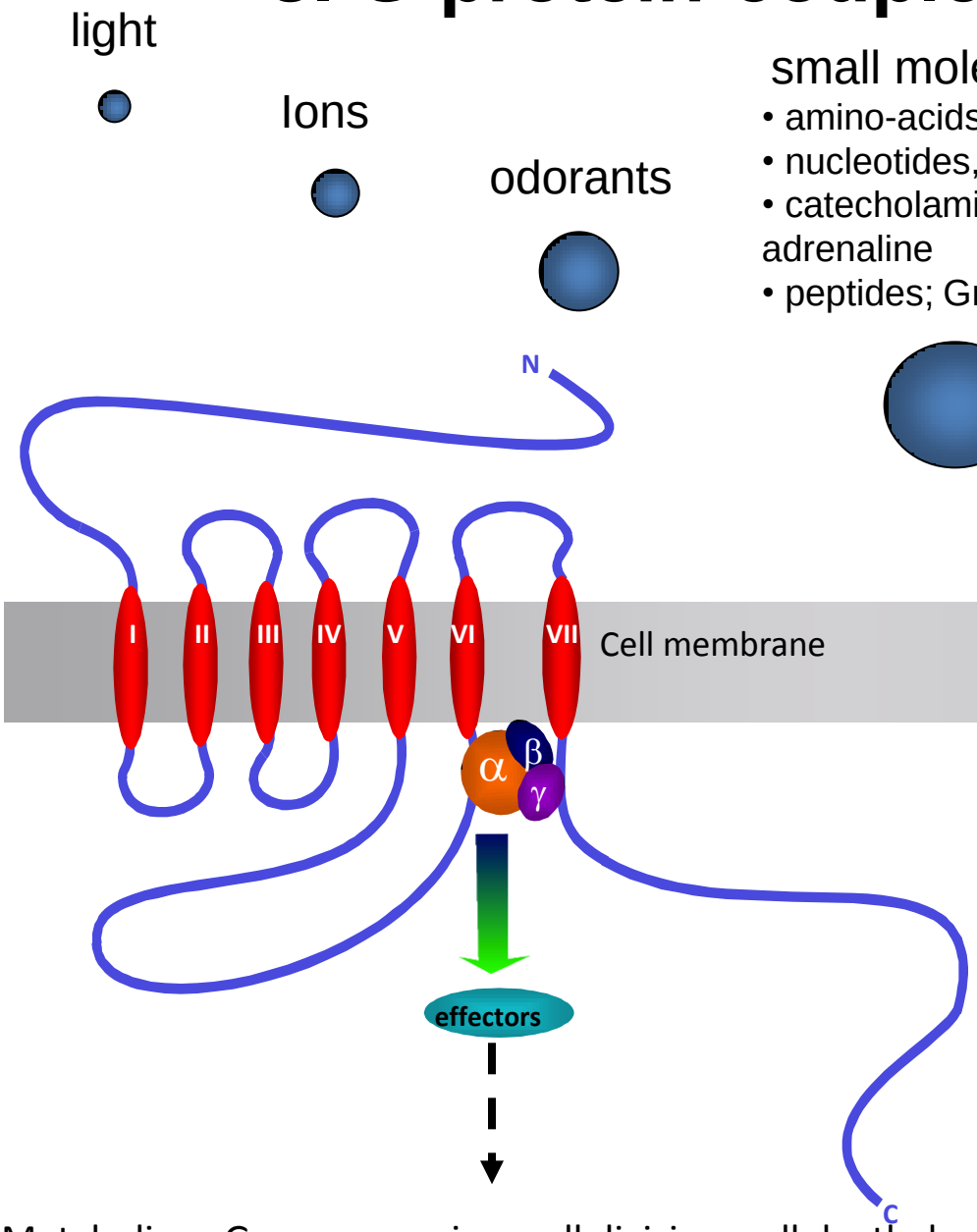
Cytokine receptors can also activate MAPK pathways

OSMR induces activation of the Ras–Raf–MAPK pathway by the adaptor protein Shc (SH2- and collagen-homology-domain-containing protein)



Biochem. J. (2003) **374** (1–20) Heinrich et al.

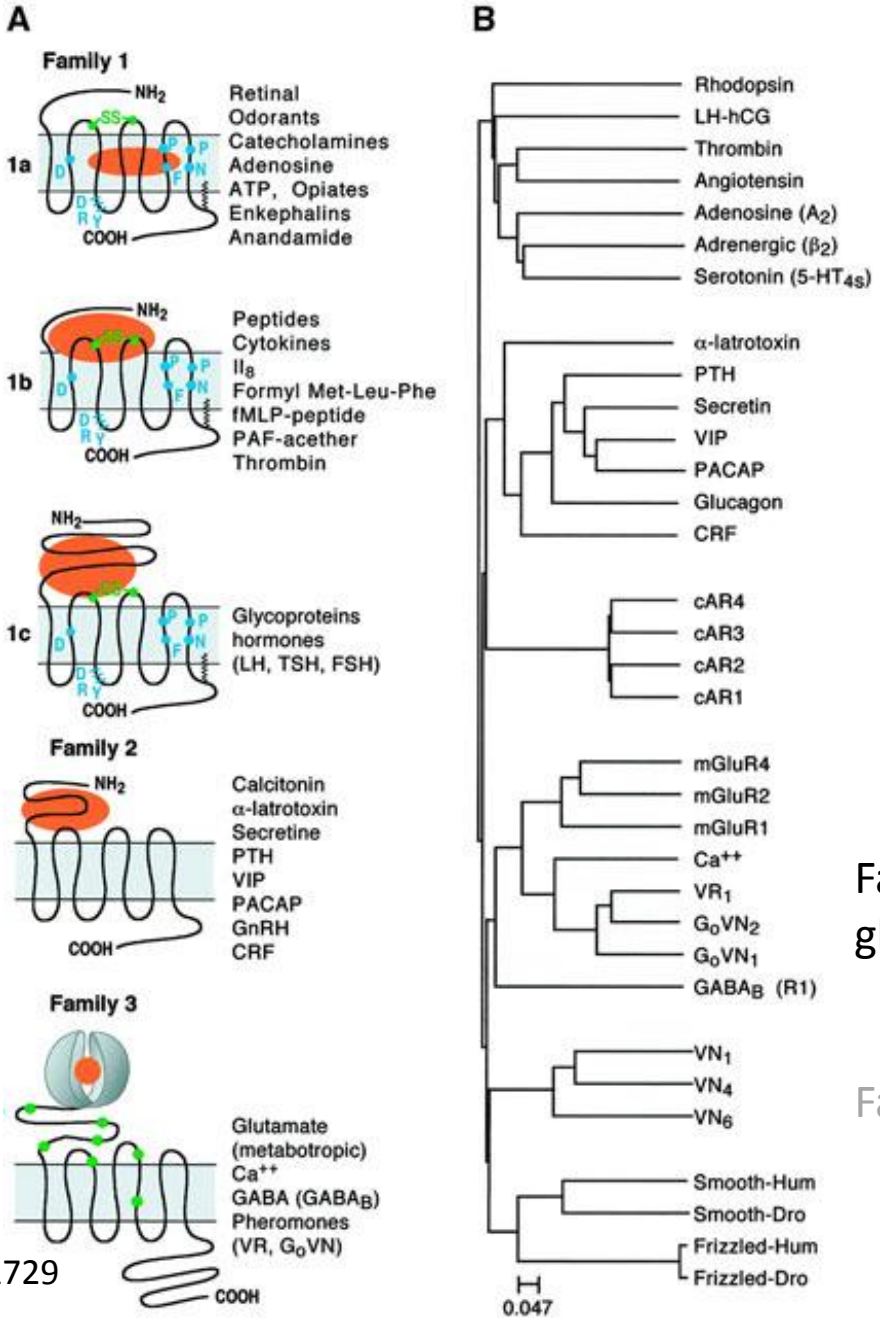
3. G protein-coupled receptors (GPCRs)



Metabolism, Gene expression, cell division, cell death, hormone secretion, contraction, migration

- GPCRs play a central role in all physiological systems
- Overstimulation or inhibition of activity lead to abnormal cellular function and disease
- >40% drugs target GPCRs

The Superfamily of GPCRs



Family 1/A (Rhodopsin-like)

Family 2/B (Secretin-like)

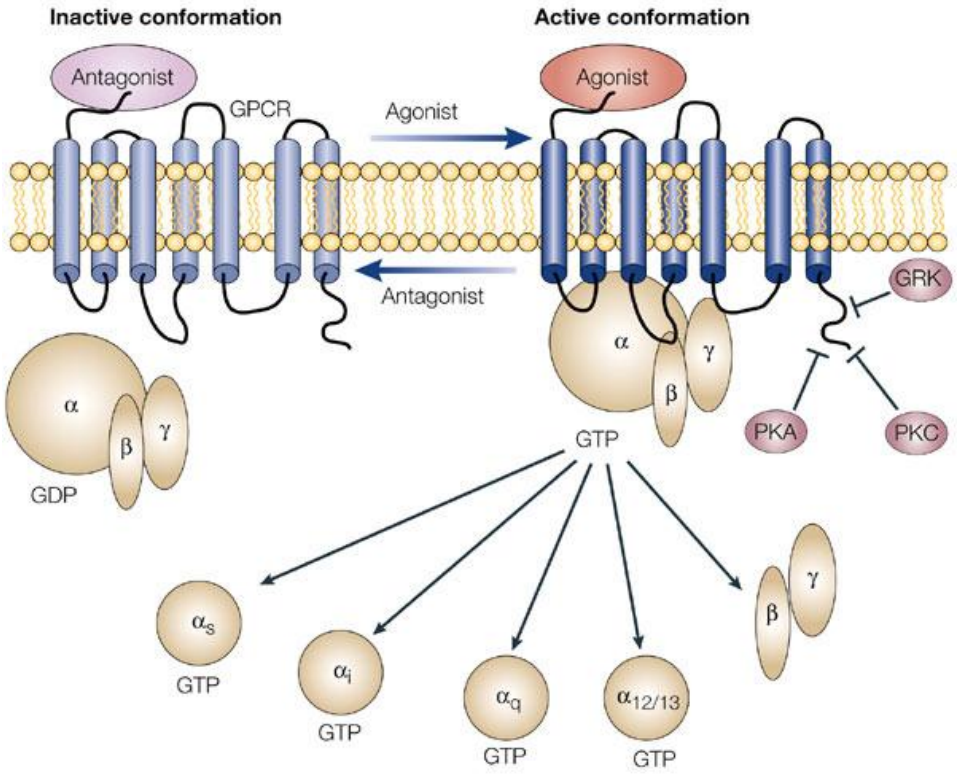
Family 5/E (cAMP receptors)

Family 3/C (Metabotropic glutamate / pheromone-like)

Family 4/D

Frizzled/Smoothened family

EMBO J (1999) **18,** 1723–1729



Family	α_s	α_i	α_q	$\alpha_{12/13}$	βγ
Members	$G\alpha_s$	$G\alpha_{i1/i2/i3}$	$G\alpha_q$, $G\alpha_{14}$	$G\alpha_{12}$	β (1–5)
	$G\alpha_{sXL}$	$G\alpha_o$, $G\alpha_t$	$G\alpha_{11}$, $G\alpha_{15/16}$	$G\alpha_{13}$	γ (1–8)
	$G\alpha_{olf}$	$G\alpha_z$, $G\alpha_{gust}$			
Effectors	Adenylyl cyclases	Adenylyl cyclases	PLCβ	Rho GEFs	Ion channels
	Increased cAMP	Inhibition of cAMP	DAG	Rho	PI3Kγ
	PKA	Ion channels	Ca^{2+}		PLCβ
		Phosphodiesterases	PKC		Adenylyl cyclases
		Phospholipases			

Nature Reviews | Molecular Cell Biology

Receptor activation…

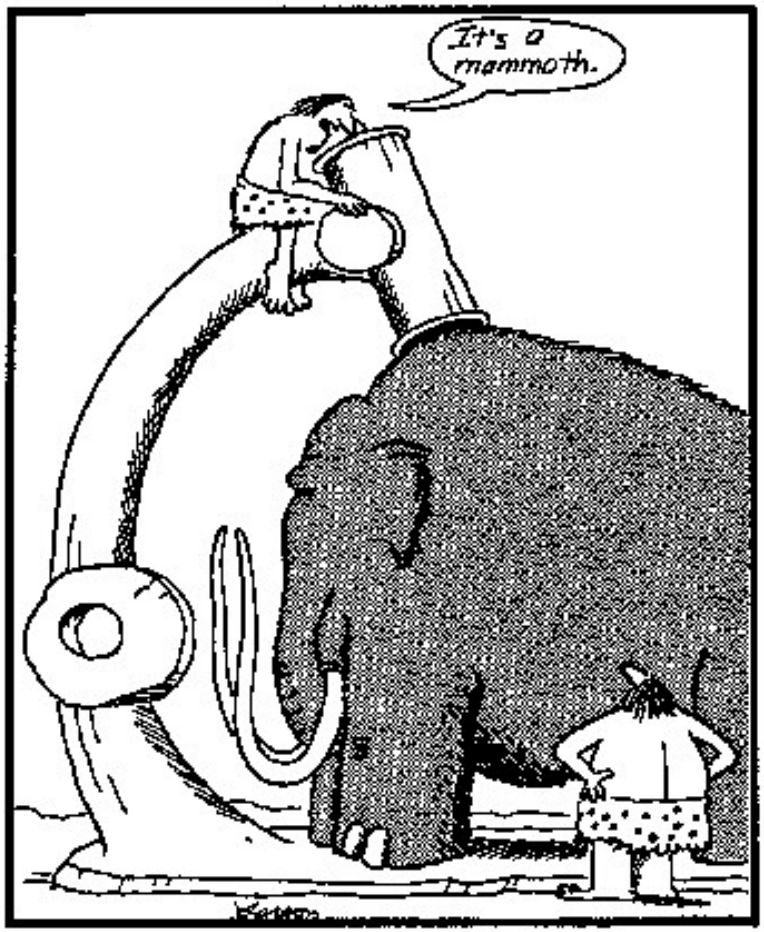
GPCRs activate different sub-classes of heterotrimeric G-proteins and effector systems.

GPCRs act as guanine nucleotide exchange factors (GEFs) that exchanges GDP for GTP on the Gα subunit.

Gα subunit has intrinsic GTPase activity. A group of proteins called RGSs, act as GTPase-activating proteins (GAPs) and accelerate hydrolysis of GTP to GDP.

An individual GPCR can be promiscuous in its G protein coupling.

(Atosiban)



Early microscope

Real time imaging of ligand-induced Gq signaling observed by Ca2+ indicator dye

Diversification of GPCR function and cellular response by dimerization/oligomerization

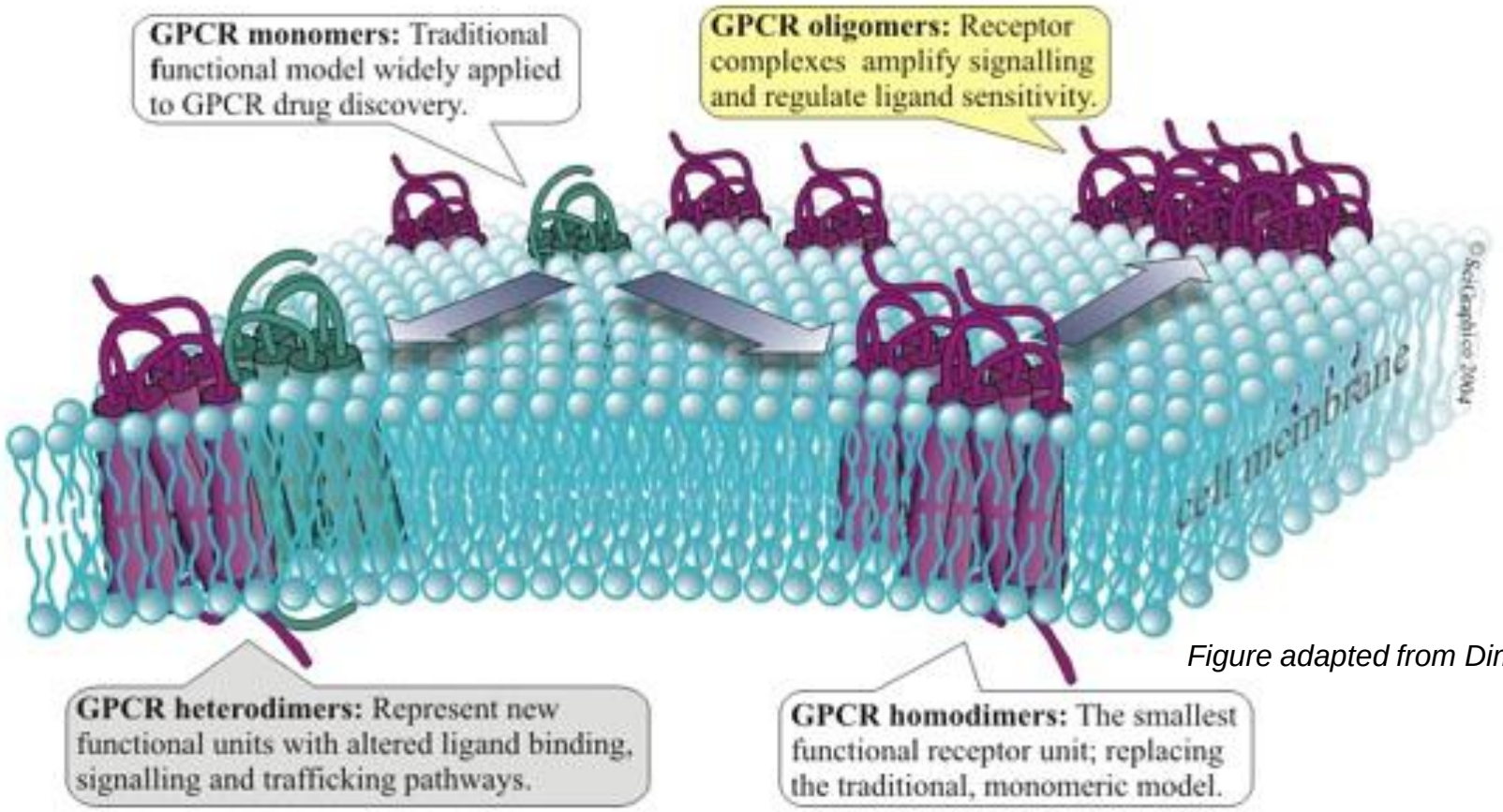
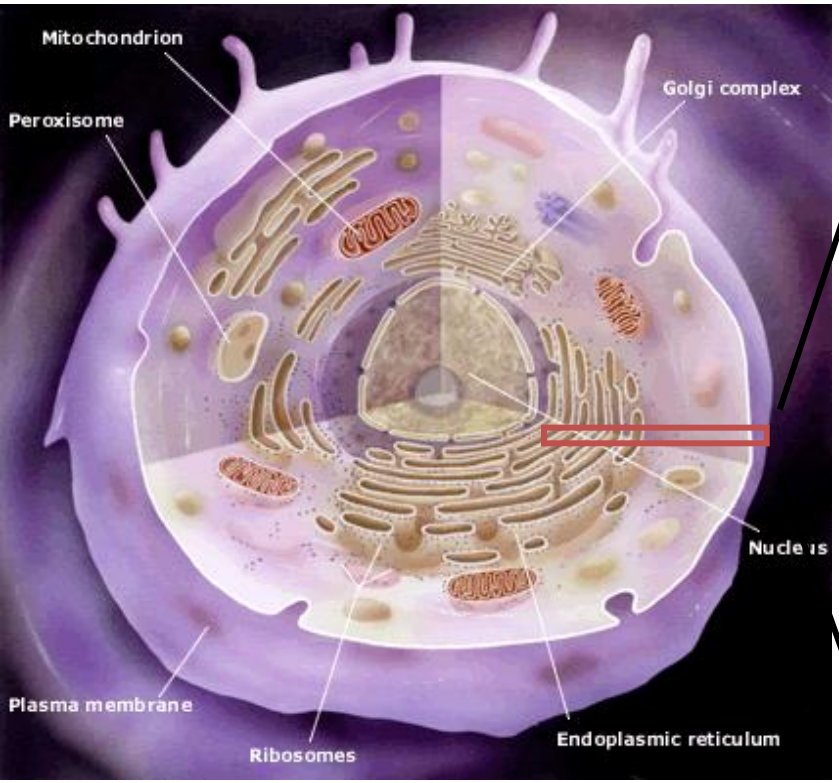


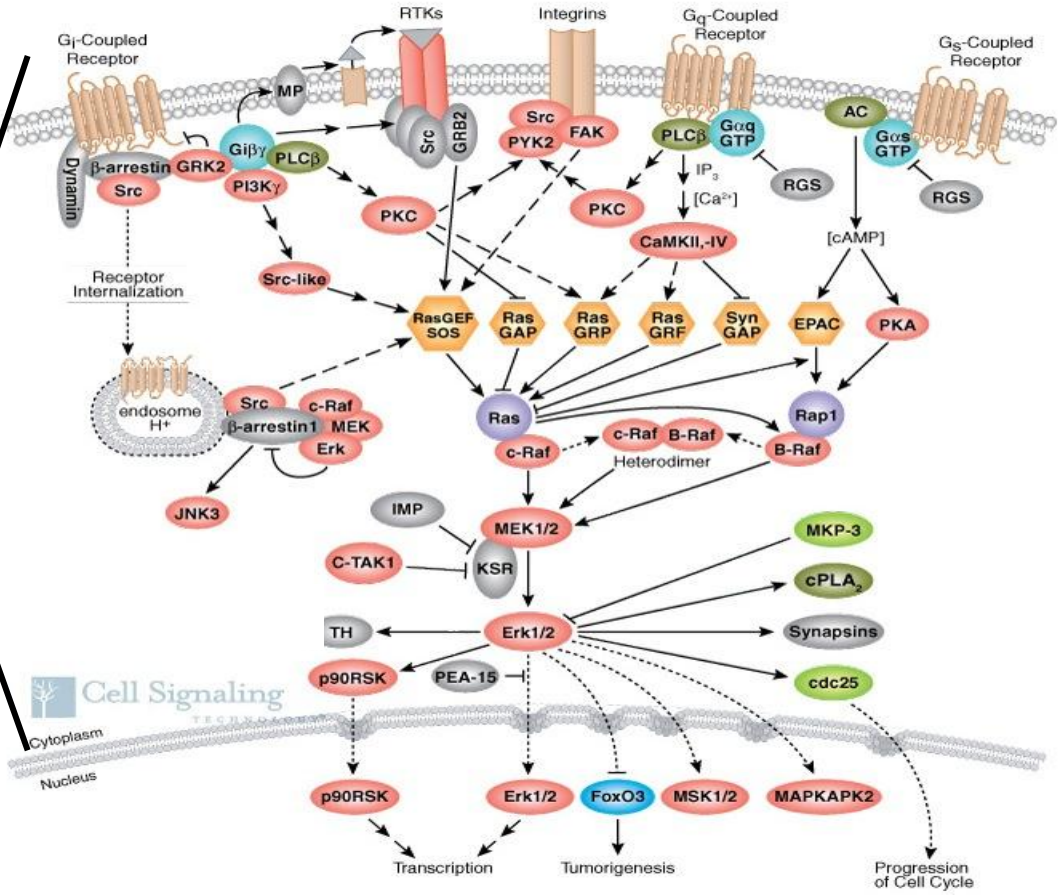
Figure adapted from Dimerix.com

- Additional level of regulation of receptor function and cellular response
- Possible target for next generation of therapeutic compounds?

e.g Dugs specifically targeting heterodimers, or combination therapies (e.g A2aR antagonists & D2R agonist (L-Dopa) in Parkinson's Disease, improves motor abilities without causing dyskinesia)

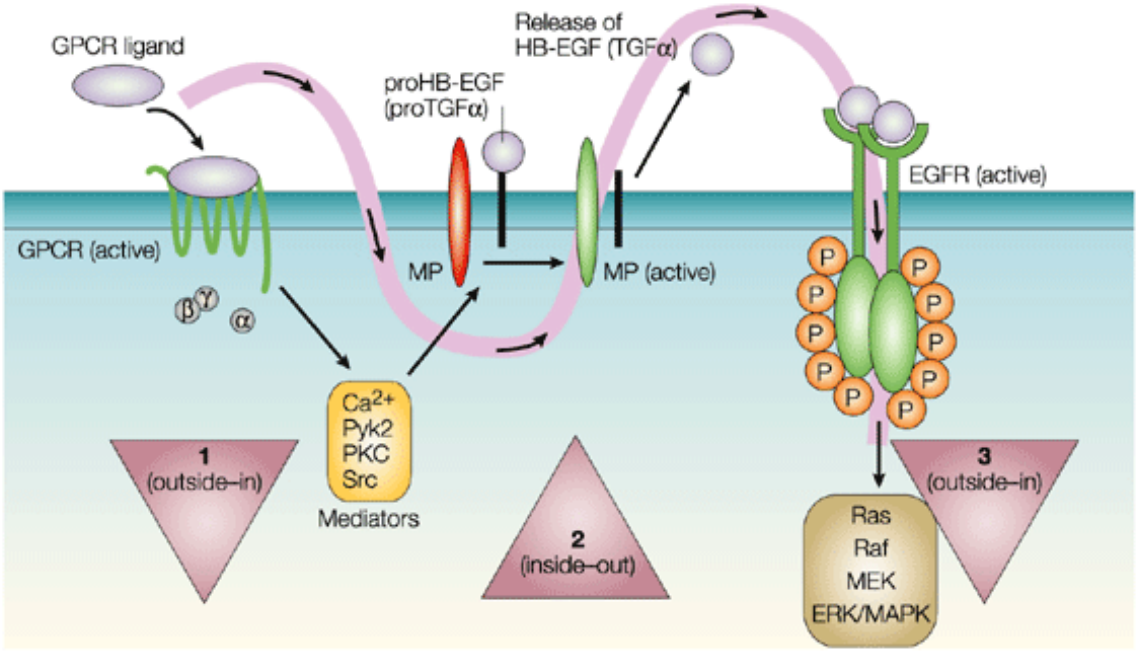
A single cell is exposed to multiple ligands to activate multiple signalling networks

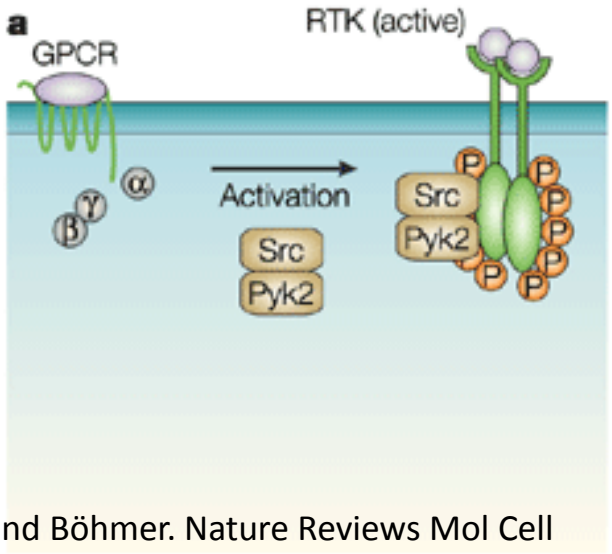


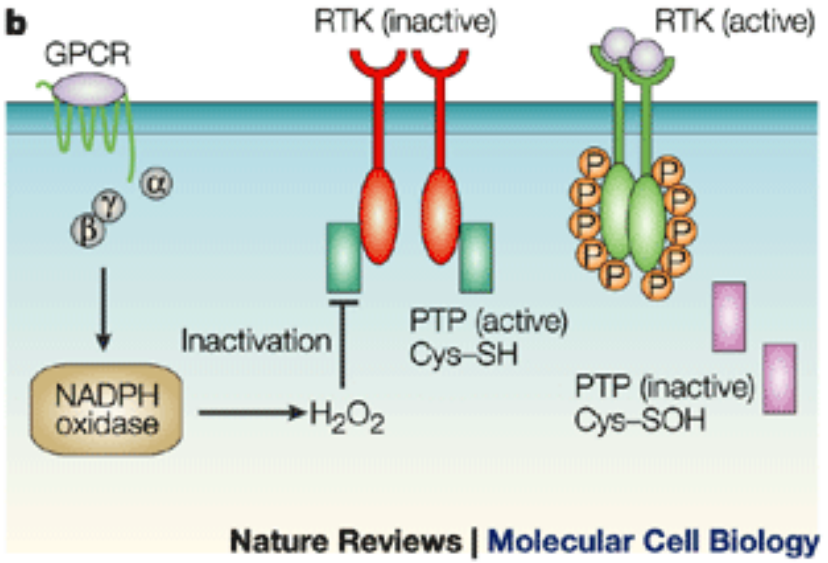


How do cells regulate the dynamics and strength of signalling that results in precise control of a specific physiological response?

GPCRs ‘talk’ to other cell surface receptors-Transactivation







Wetzker and Böhmer. Nature Reviews Mol Cell Biol. 4, 651-657

Learning Objectives:

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Compare and contrast the activation modes and signalling pathways induced by each type of cell surface receptor

Give examples of how disruption of communication in receptor signalling results in human disease

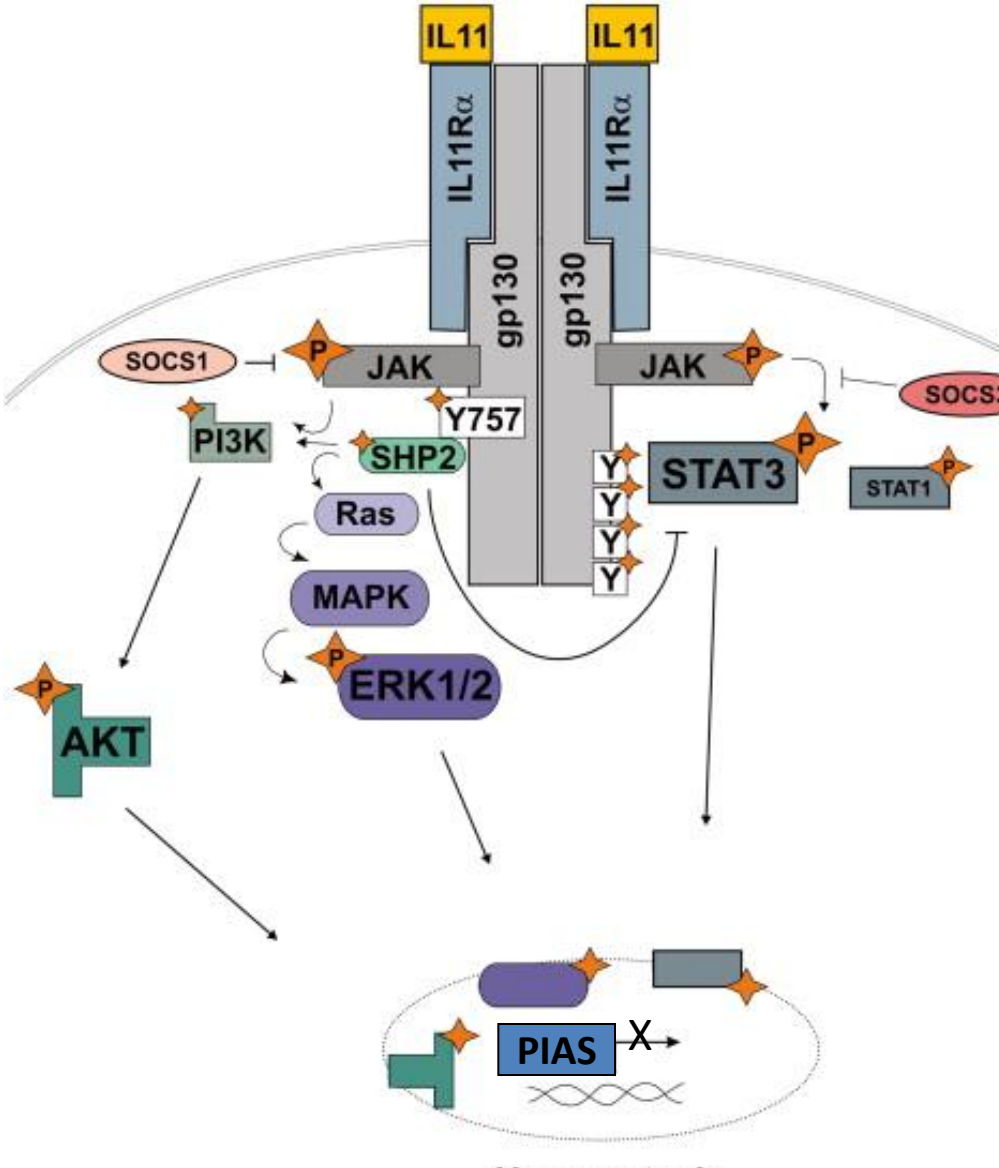
Regulation of receptor signalling

Cytokine receptor signaling is tightly regulated by a number of mechanisms:

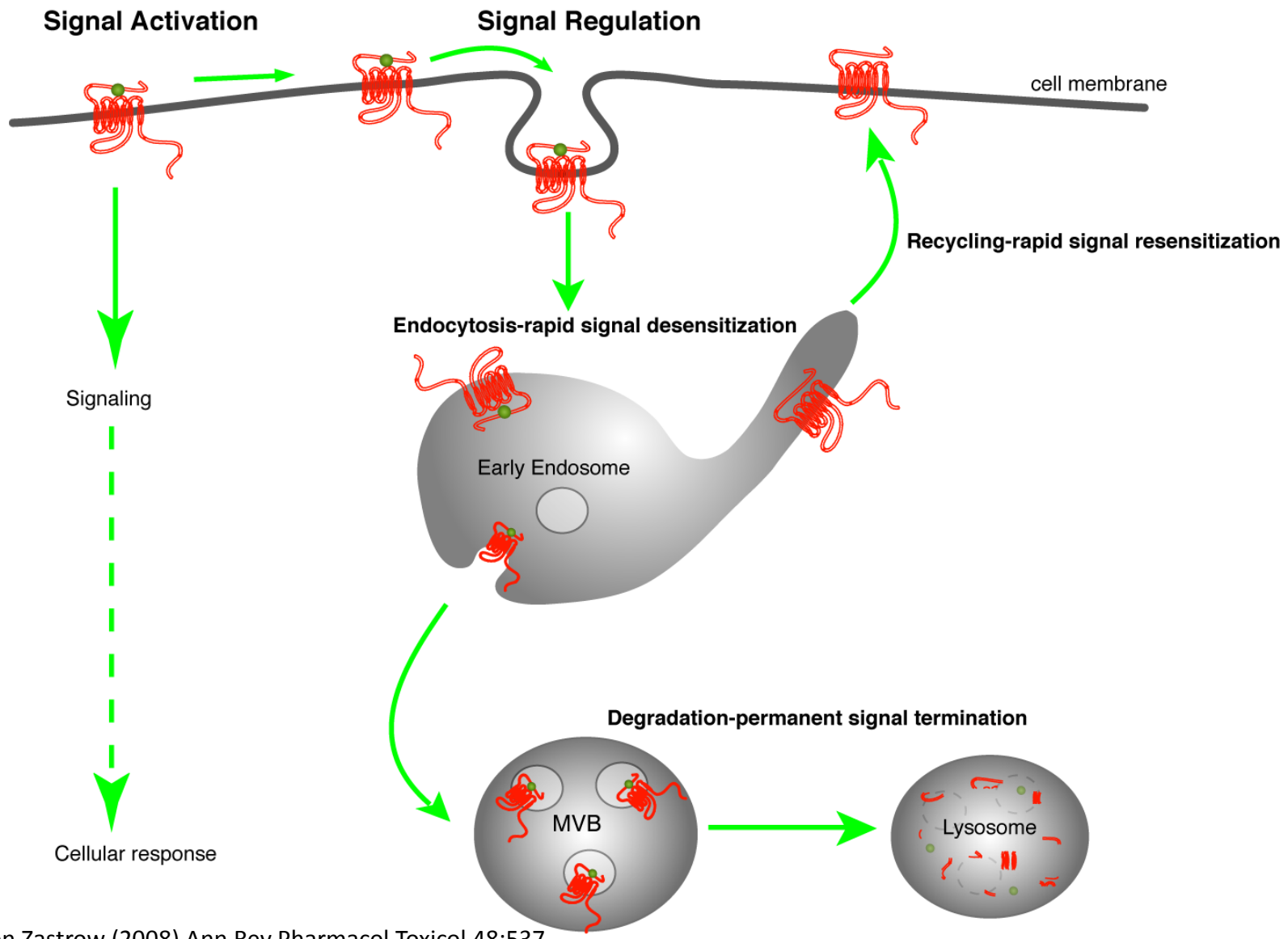
Protein tyrosine phosphatases remove phosphates from cytokine receptors and activated STATs.

Suppressor of cytokine signalling (SOCS)-1 binds directly to activated JAKs while SOCS-3 binds to phospho-gp130 and inhibits STAT3 signalling by competing for receptor binding.

Protein Inhibitors of Activated STATs (PIAS), negatively regulate STAT signalling by inhibiting transcriptional activation by STATs by for e.g. blocking access to STAT DNA recognition sequences.



Membrane trafficking dictates pattern of receptor signalling and tissue hormonal responsiveness



Hanyaloglu & von Zastrow (2008) Ann Rev Pharmacol Toxicol 48:537

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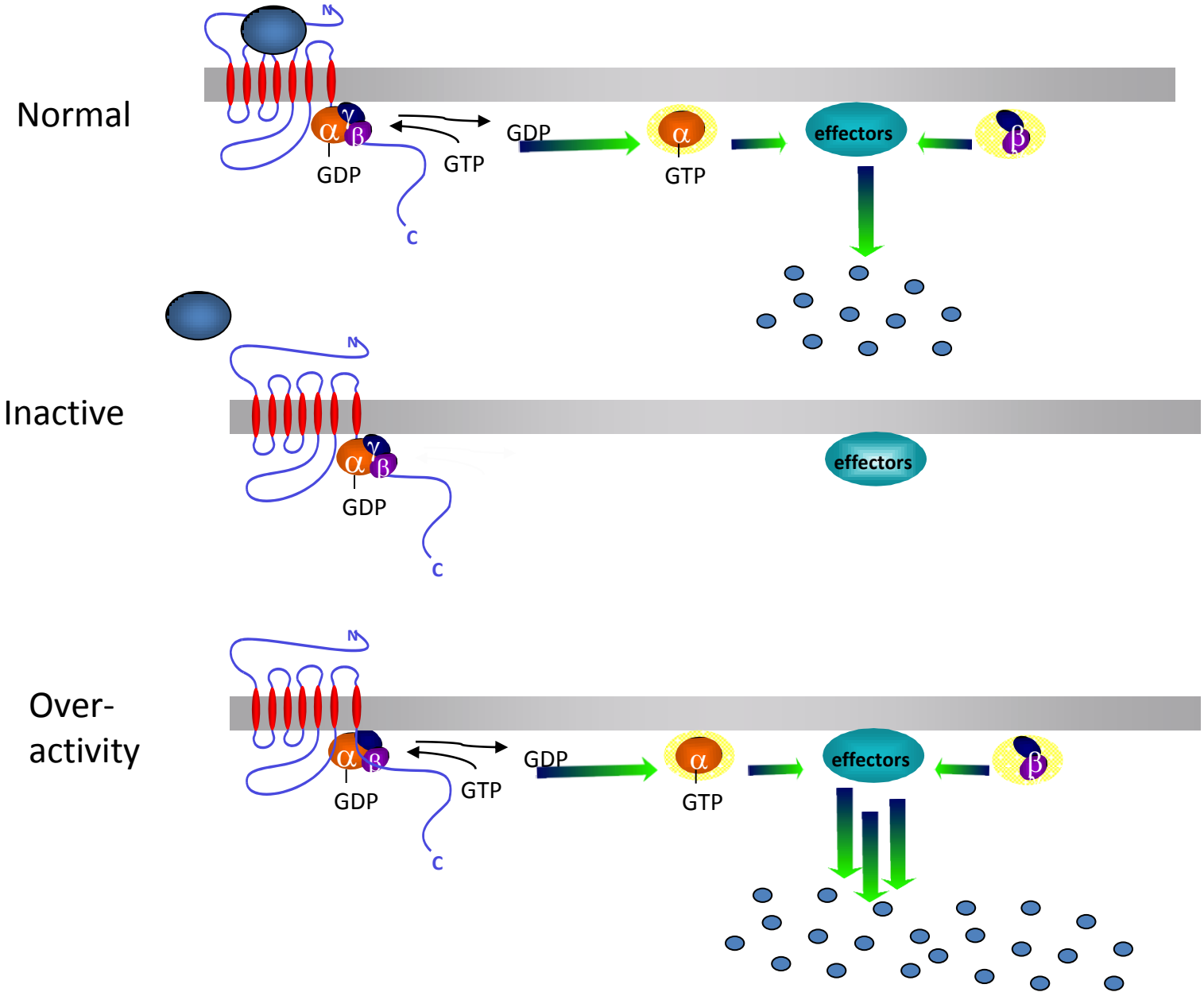
Group Task: Cell surface Receptors and Disease



Perspectives…….

Cell surface receptors signal to highly diverse signal networks each of which are exquisitely regulated to provide very specific responses.

The majority of research in this field studies activation of a single receptor, yet a single cell would control activity of multiple receptors. Therefore, the next big challenge is in translating the possible permutations of signaling outputs, to biological end-points in specific physiological systems- 'Systems biology'.

As we understand more of how these pathways impact downstream cellular programs in specific physiological systems, will in turn open up numerous possibilities for therapeutic intervention for treatment of a number of human diseases.

Reading

Molecular Biology of The Cell 4th Edition. Alberts *et al.* Chapter 15. Cell Communication.

Lemmon & Schlessinger. 2010. *Signaling by Receptor Tyrosine Kinases. Cell.* 141(7):1117-1134

Heinrich *et al*. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem. J.* (2003) **374** (1–20)

Pierce *et al*., 2002 *Seven-transmembrane receptors. Nature Reviews/Mol Cell Biol* (9):639-50