

Corso di Laurea Magistrale in Biotecnologie Mediche
e Genomica funzionale

Segnalazione Cellulare

✓ 3 Crediti Formativi (CFU): 24 ore di lezione





International Centre for
Genetic Engineering and Biotechnology
(ICGEB), Trieste, Italy

Recapito docente

Chiara Collesi

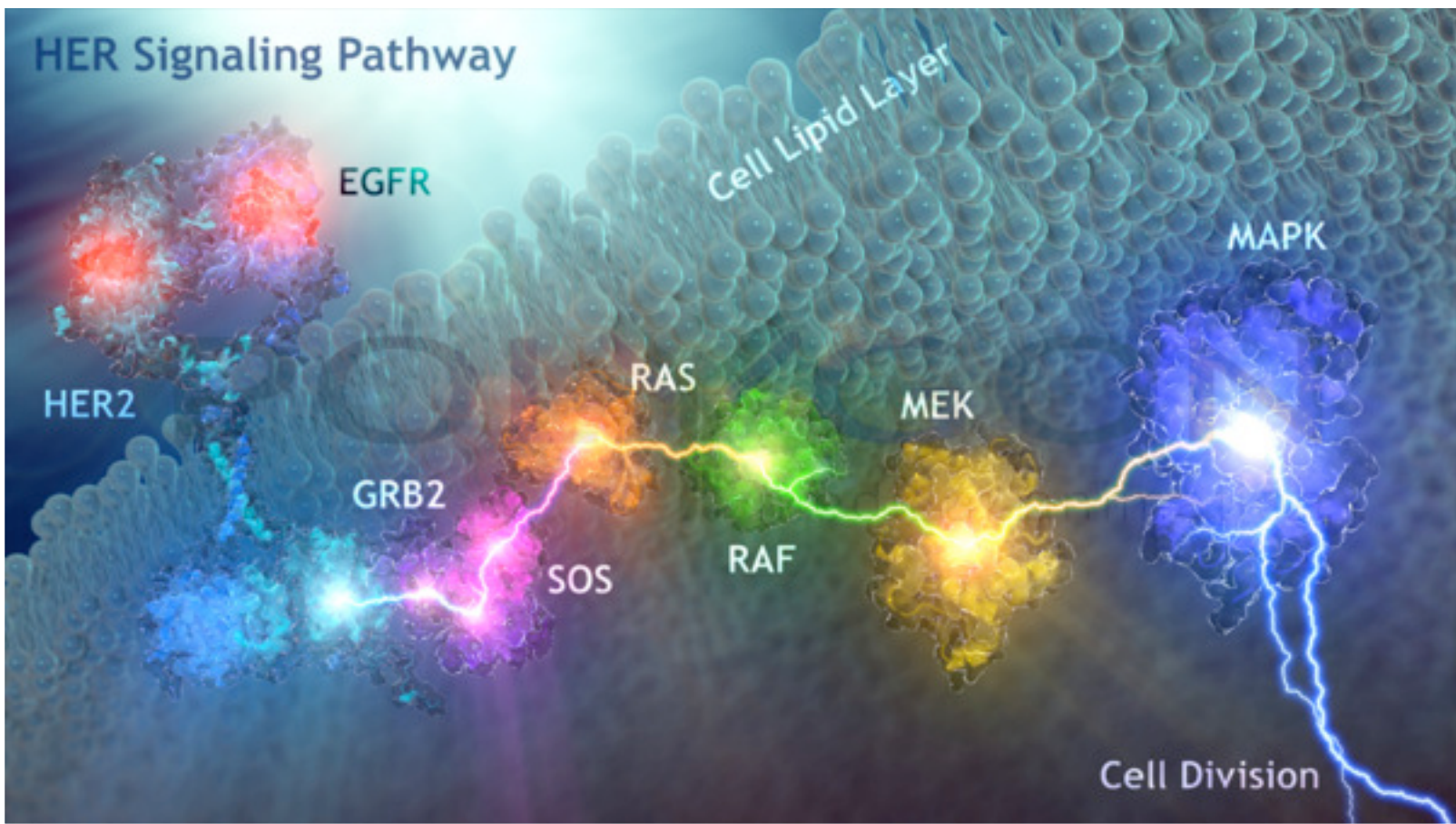
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HER Signaling Pathway



Struttura del corso

Parte introduttiva/propedeutica:

Basi della segnalazione inter-intra cellulare. Seven spanning transmembrane receptors. Recettori associati ad enzimi e recettori con attivita' enzimatica intrinseca. Integrazione e modulazione dei segnali in membrana.

Parte "core":

Il processo di "Rigenerazione" come modello di integrazione e crosstalk delle diverse vie di segnalazione: rigenerazione epatica, intestinale, cardiaca.

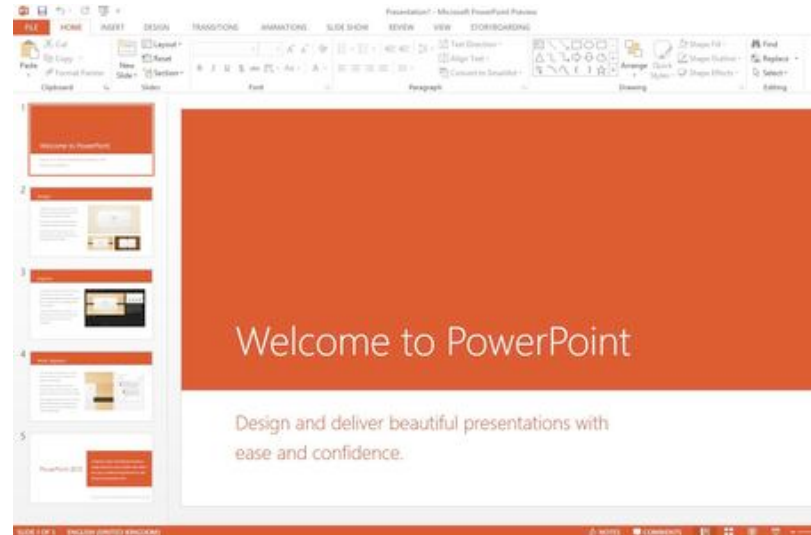
Parte "applicativa":

Come organizzare un journal club, caratteristiche e requisiti delle presentazioni. Journal Clubs su articoli selezionati (se avremo tempo.....).

Moodle+MsTeams

✓ Presentazioni PPT (PDF) di ogni lezione

✓ Video-lezione registrata in audio e video



Testi consigliati



- ✓ F. Amaldi- **BIOLOGIA MOLECOLARE**- Casa Editrice Ambrosiana
 - ✓ B. Alberts et al – **Molecular Biology of the Cell**– Garland Publishing
 - ✓ B. Lewin – **Genes XI**– Oxford University Press
- ✓ Per alcune lezioni che tratteranno argomenti particolarmente innovativi e non sufficientemente descritti nei libri di testo, sarà fornito agli studenti opportuno materiale didattico.

NEWS & VIEWS

CANCER

T cells home in on brain tumours

Immunotherapies activate T cells to destroy tumours, but the approach has failed in some brain cancers. A strategy to improve migration of T cells across the blood-brain barrier could overcome this limitation.



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REVIEW

nature
biotechnology

REVIEW



Cell Signaling in Space and Time: Where Proteins Come Together and When They're Apart

John D. Scott and Tony Pawson
Science **326**, 1220 (2009);
DOI: 10.1126/science.1175668

CRISPR-Cas systems for editing, regulating and targeting genomes

Jeffrey D Sander^{1,2} & J Keith Joung^{1,2}

Esame

✓ Colloquio orale



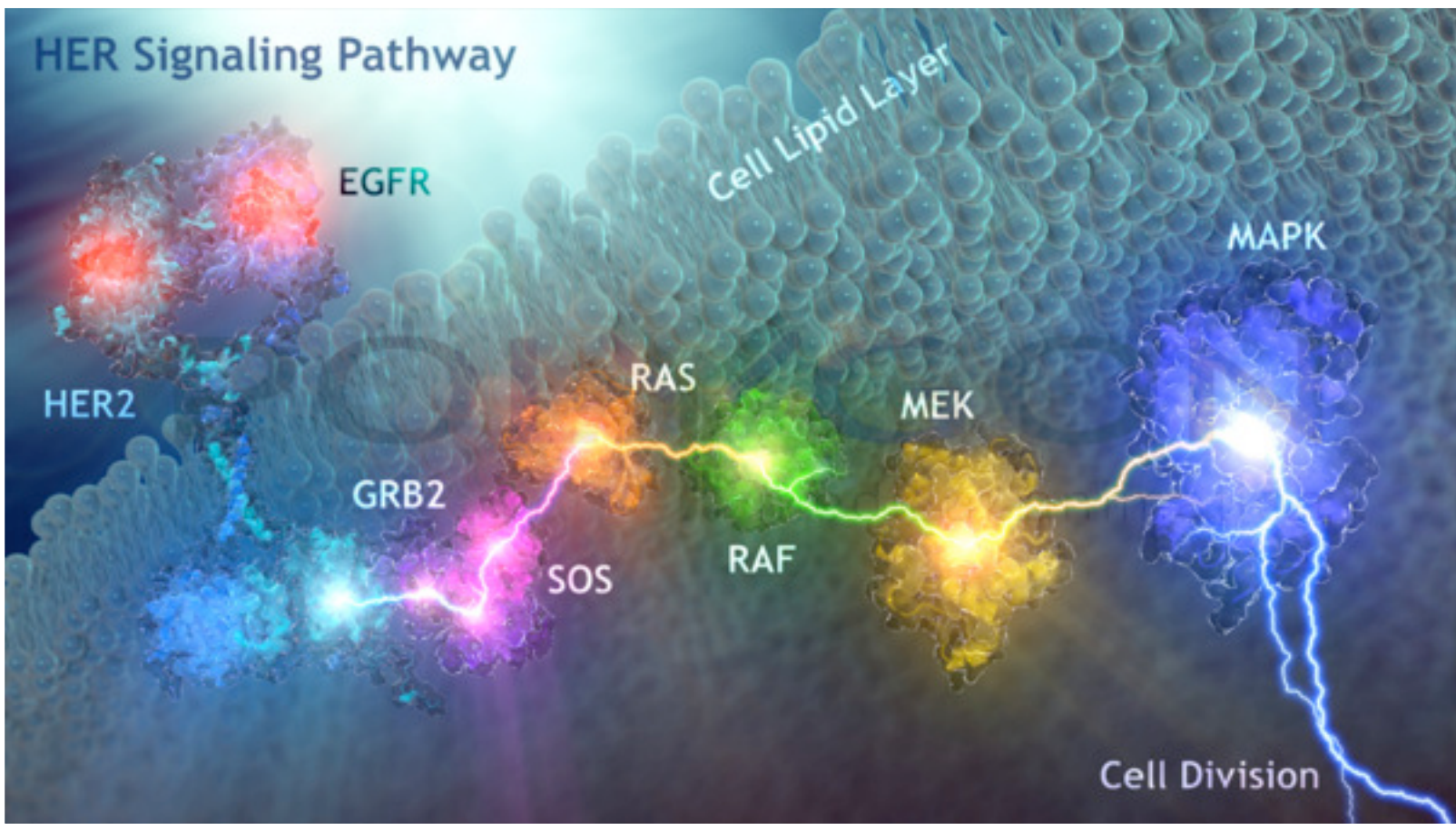
✓ Video-colloquio



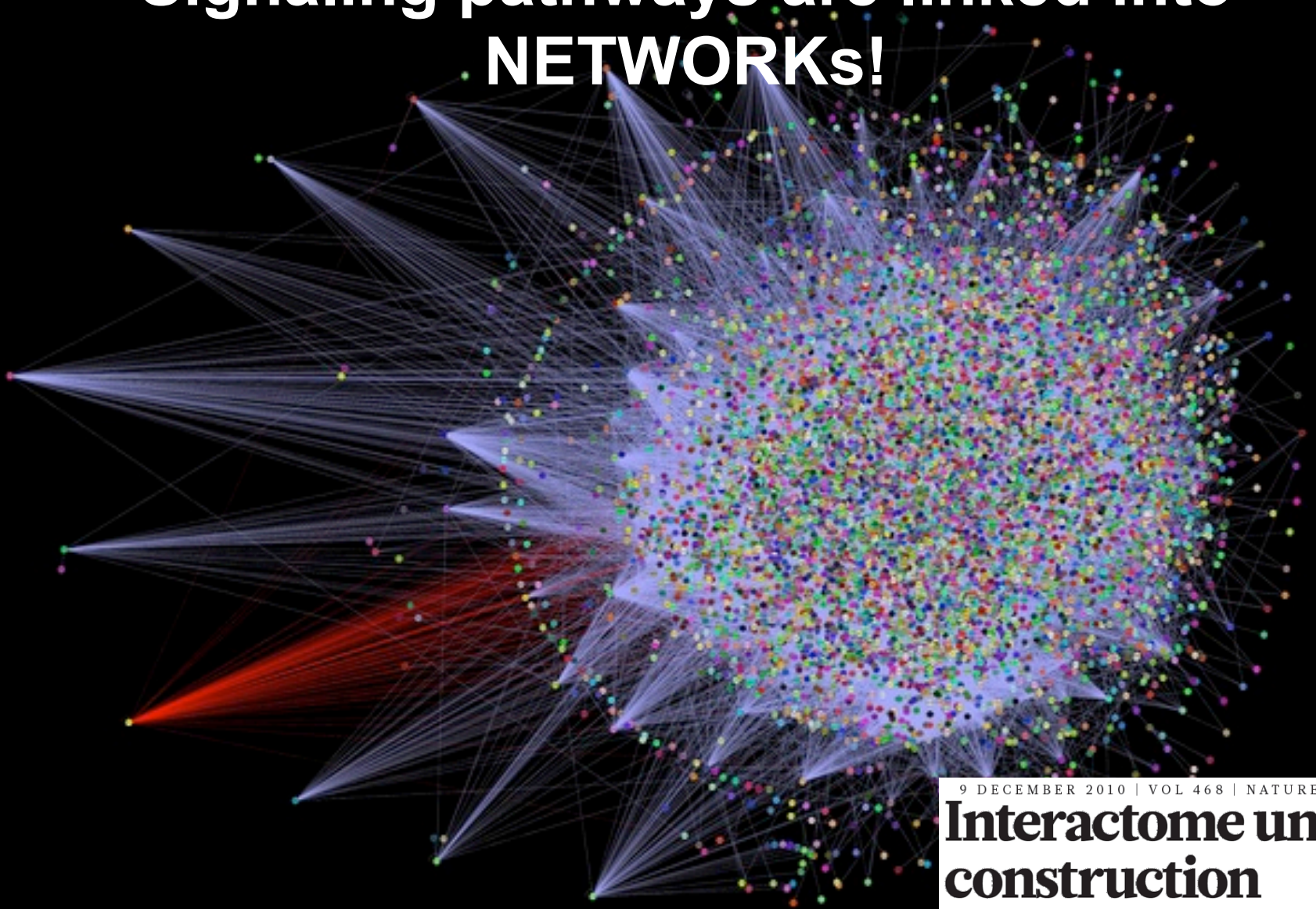
✓ Commento e/o interpretazione articoli scientifici



HER Signaling Pathway



Signaling pathways are linked into **NETWORKS!**



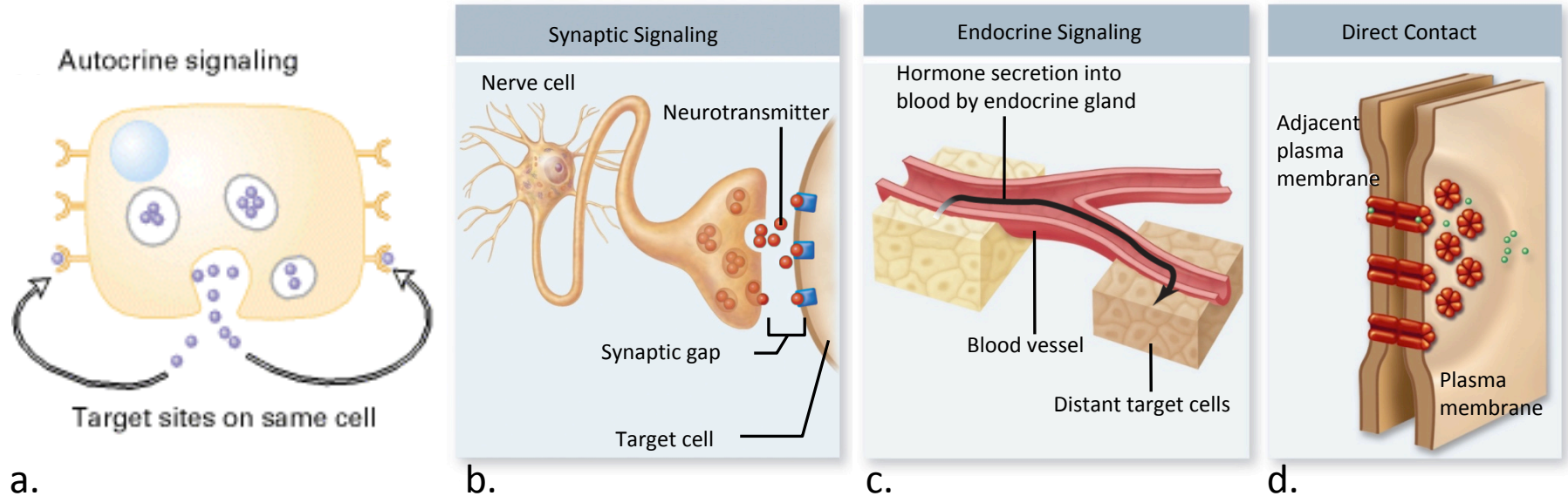
9 DECEMBER 2010 | VOL 468 | NATURE | 851

Interactome under construction

Developing techniques are helping researchers to build the protein interaction networks that underlie all cell functions.

Cellular Messaging: *Inter-cellular signaling*

In multicellular organisms, intercellular exchanges of signals are performed in various ways:



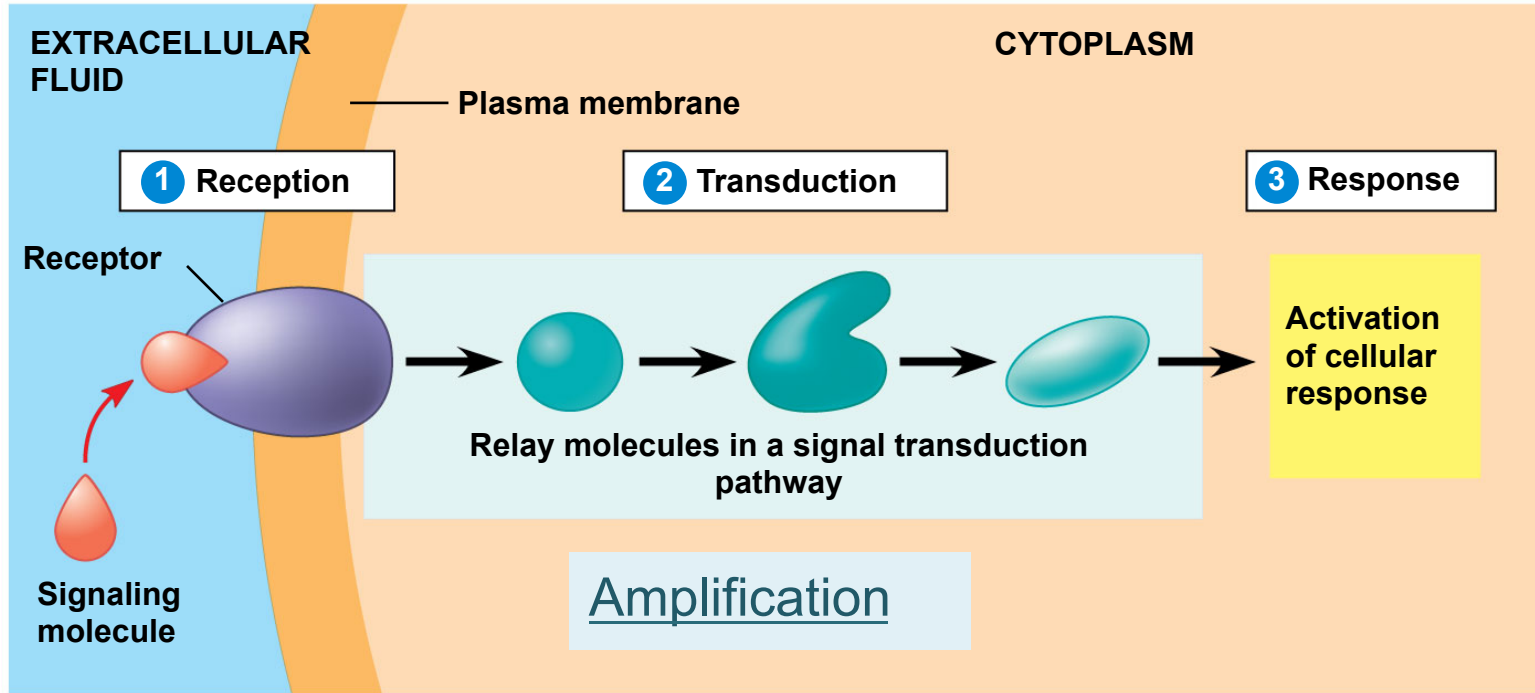
Inter-cellular signaling

Intercellular signaling molecules include hormones, growth factors and cytokines.

Molecules released by cells occurs over distances from a few microns [autocrine (a) and paracrine (b) signaling] to several meters in endocrine (c) signaling. In some instances, receptor proteins attached to the membrane of one cell interact directly with receptors on an adjacent cell (d).

The molecules involved in signal transduction between cells are called first messengers, while the diffusible molecules engaged in intracellular signal transduction in response to first messengers are known as second messengers (e.g., Ca^{2+} and cAMP).

The basic mechanism of *Intra*-cellular signal transduction



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Cells have many receptor proteins on their plasma membrane surface, and molecules that bind specifically to these receptors are called signaling molecules. When bound with signaling molecules, receptors go through structural changes and are activated, which then changes the shape, movement and functions of the cell by activating intracellular signal transduction proteins, and regulates gene expression through the relocation of intracellular signaling molecules to the nucleus.

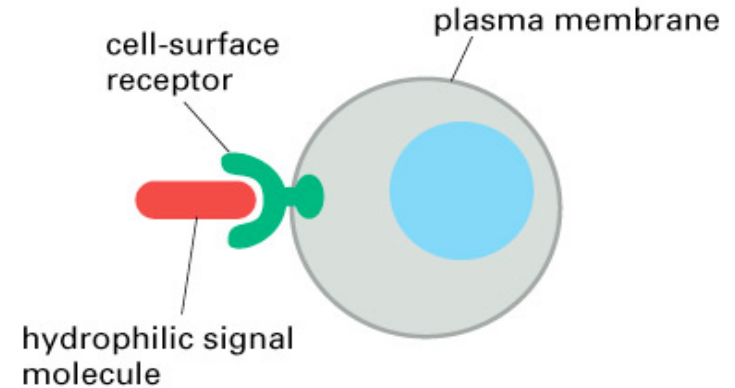
Which are the key players?

- *Ligands*
 - Hormones, growth factors, cytokines, gases
- *Receptors*
 - Specifically bind signaling molecules
 - Either on cell surface or intracellular
- *Second messengers*
 - Molecules which amplify the intracellular response

Extracellular signaling molecules fall into 2 classes:

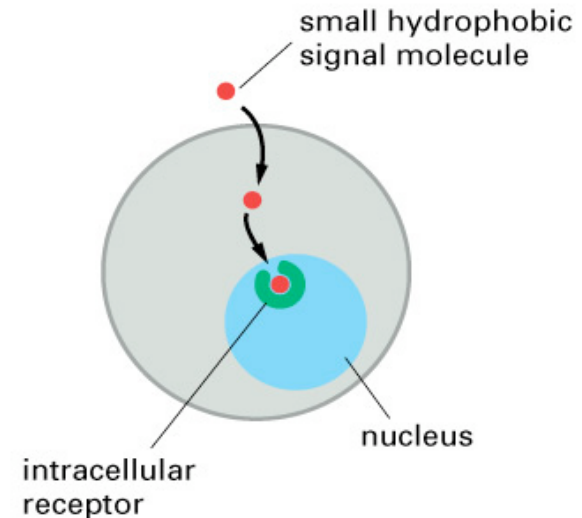
(A) Molecules that are too large or too hydrophilic to cross the plasma membrane - rely on membrane receptors

(A) CELL-SURFACE RECEPTORS



(B) Molecules that are small enough or hydrophobic and pass through the membrane - directly activate intracellular receptors in the cytoplasm or nucleus of target cell

(B) INTRACELLULAR RECEPTORS



Receptor molecules fall into 2 classes:

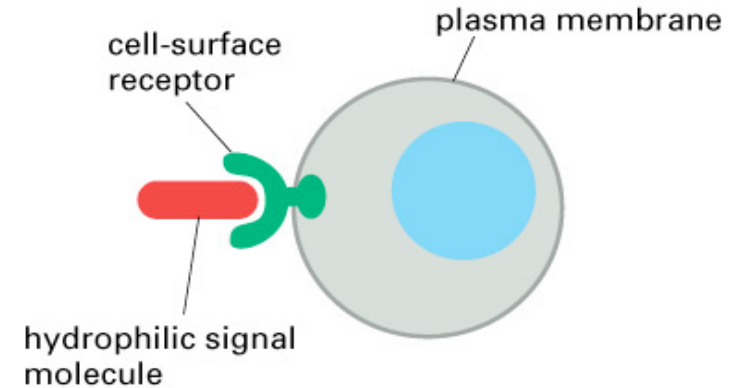
Cell surface receptors:

- Signaling molecules include peptide hormones, growth factors, cytokines etc
- The binding and subsequent events trigger (**a**) an \uparrow or \downarrow in the cytosolic concentration of a second messenger (**b**) the activated receptor acts as a scaffold to recruit and activate other intracellular proteins

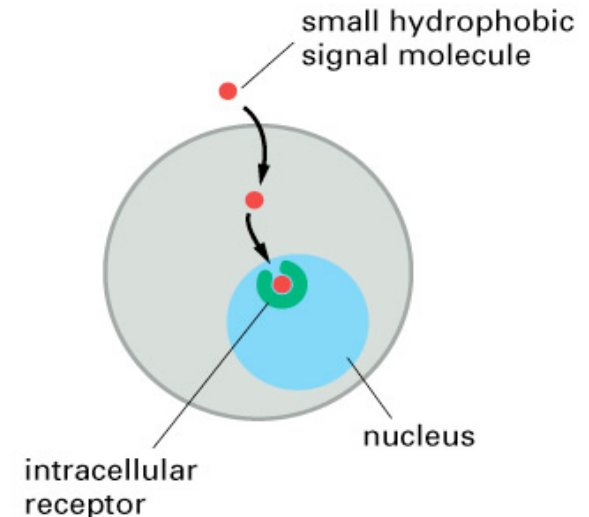
Intracellular receptors

- signaling molecules include steroid hormones, retinoids, thyroxine etc
- receptor-hormone complex acts a **transcription factor** to alter the transcription of target genes

(A) CELL-SURFACE RECEPTORS

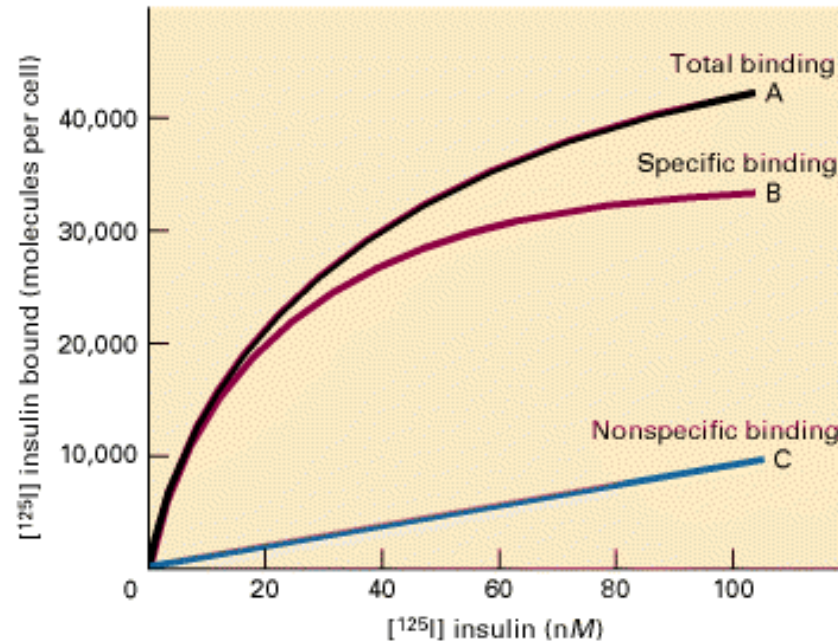


(B) INTRACELLULAR RECEPTORS



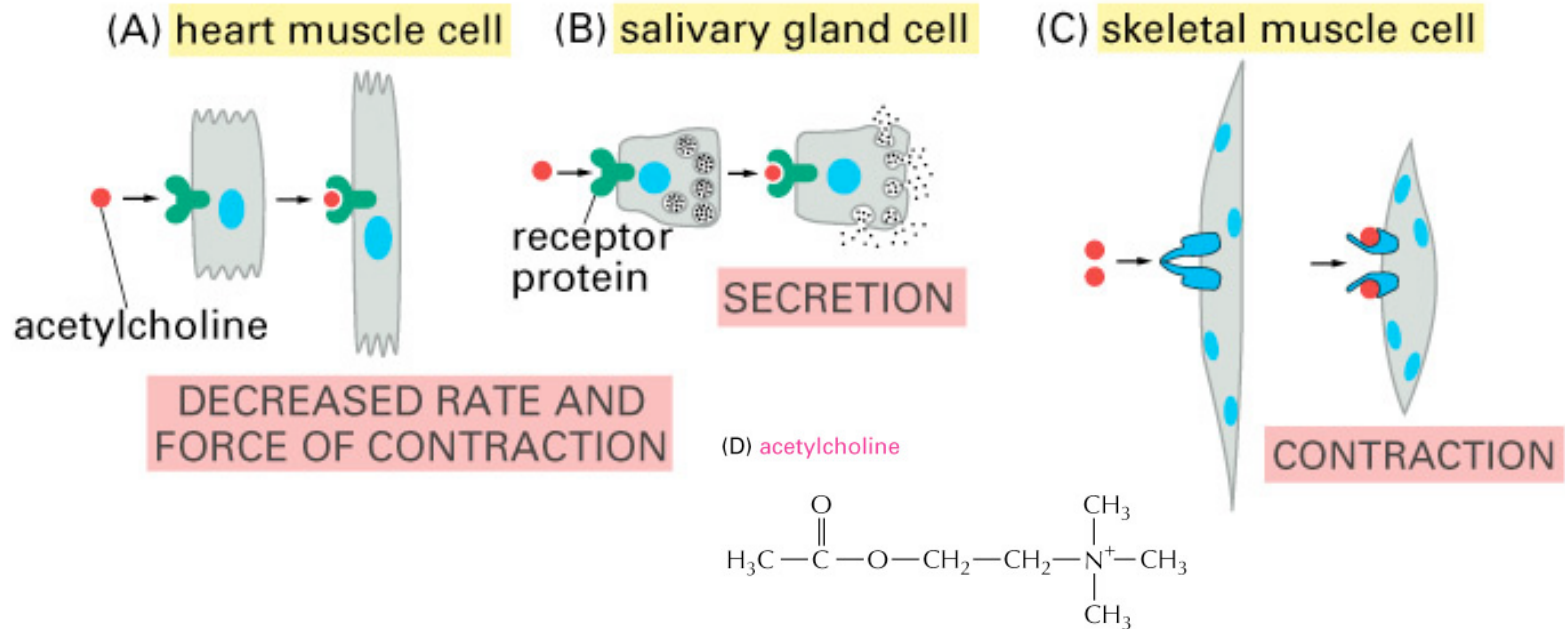
Receptor biochemical features

1. Participates in transduction of the signal from the external messenger to some component of the metabolic machinery
2. Has at least one additional functional site which is altered by ligand binding (allosteric site)
3. Ligand binding to receptors is saturable, resembling Michaelis-Menten kinetics



4. Ligand-receptor interaction characterized by tight binding ($K_d = \text{pM} - \mu\text{M}$)

ADVANTAGES



1. Each cell is programmed to respond to specific combinations of signaling molecules.
2. Different cells can differently respond to the same chemical signal.

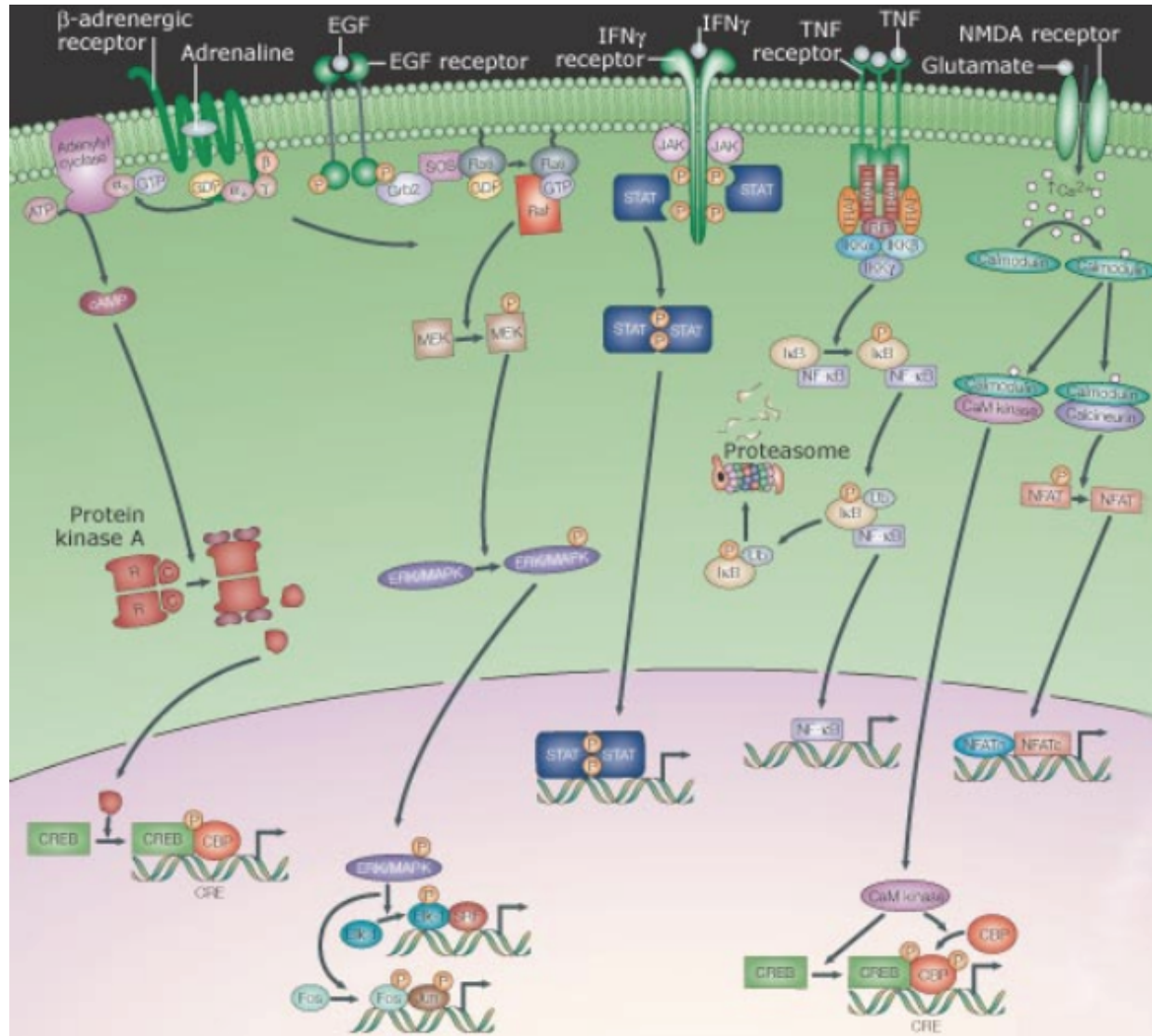
Intracellular Signal Transduction

Intracellular signal transduction is a communication system in which signaling molecules bind to the receptors on the cell surface, triggering signaling within a cell.

Signalling from the membrane to the nucleus

Signalling from cell-surface receptors through relay systems

This group includes receptors that, after engaging their extracellular ligand, undergo a conformational change, which induces them to oligomerize. This results in the production or release of second messengers (ions, lipids) or the post-translational modification (phosphorylation, proteolysis) of cytoplasmic proteins. A series of protein interactions and modifications then relays the signal - sometimes amplifying and diversifying it - to the nucleus, whereupon the activity of transcription factors is altered.

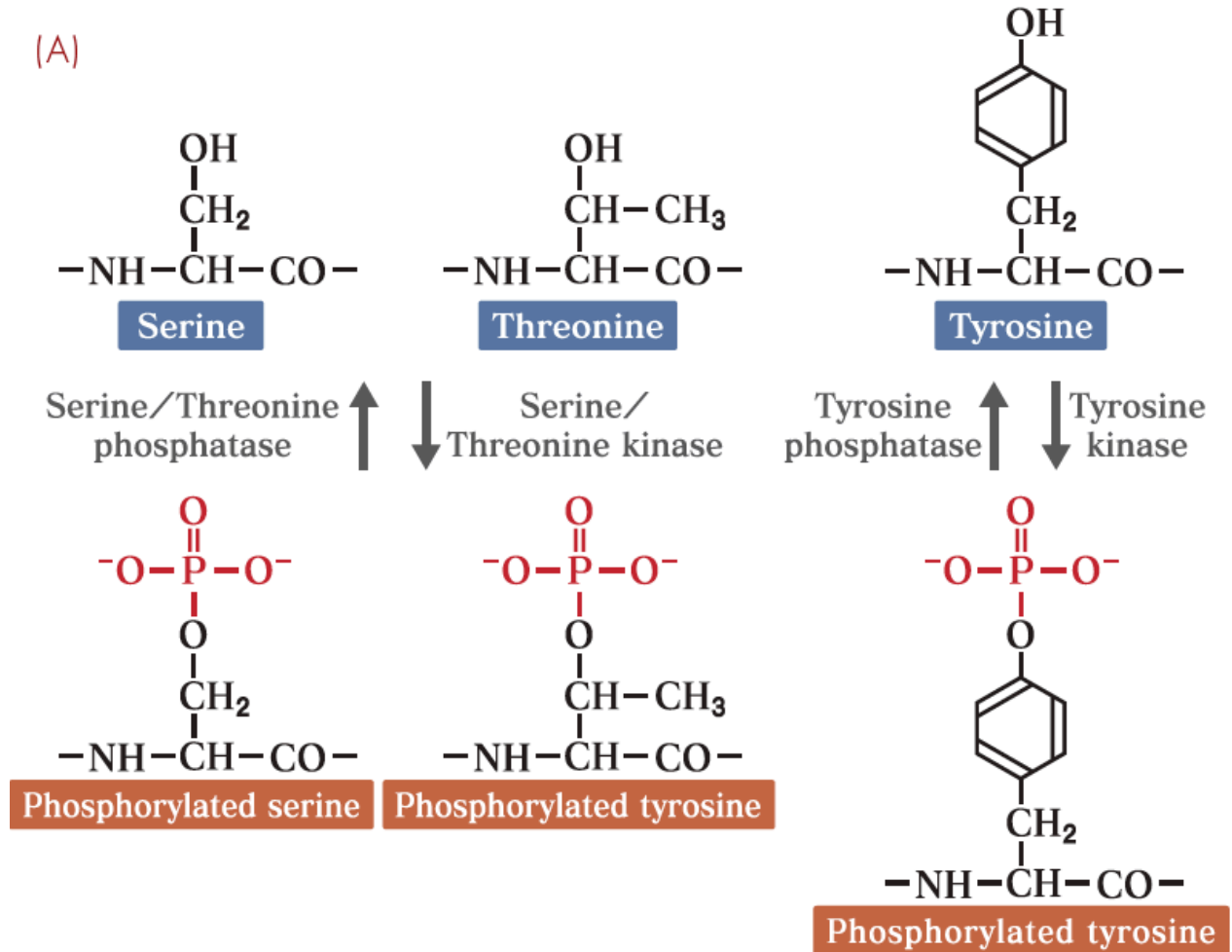


Phosphorylation and Dephosphorylation of Proteins

The most important chemical modification among the intracellular signal transduction mechanisms is the **phosphorylation** of the side chains of tyrosine, serine and threonine in proteins.

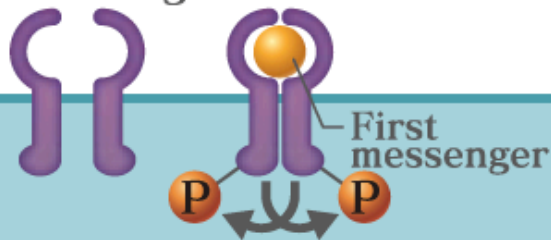
Phosphorylation is one of the most effective ways of **changing the structure of proteins** due to the large size and negative charge of the phosphate group; for the same reason, it is also effective as a **recognition marker** for other proteins.

(A)

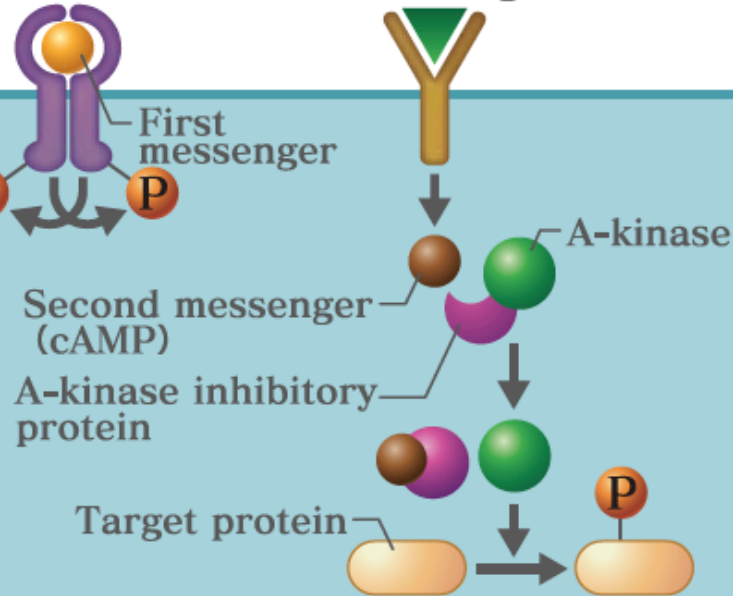


The three activation patterns of phosphorylation

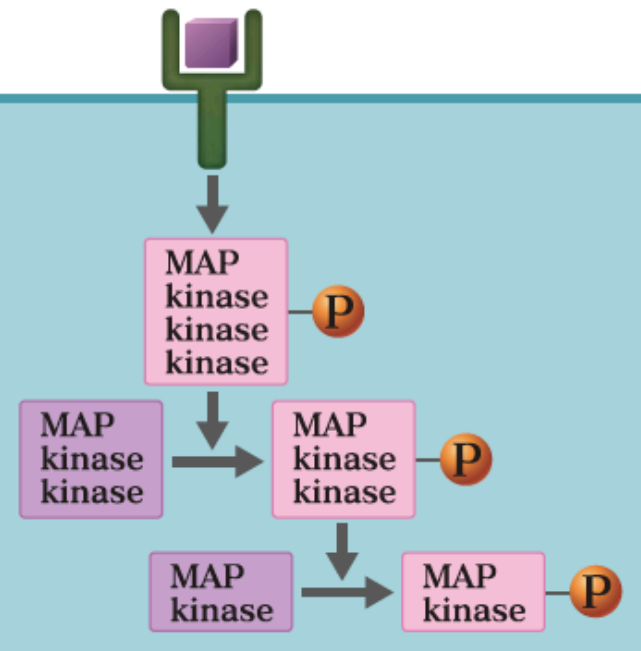
(a) Activation of receptor kinases by first messengers (hormones)



(b) Activation of kinases by intracellular second messengers



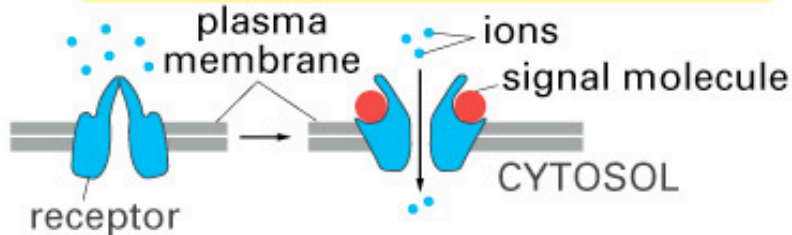
(c) Chain reaction of phosphorylation kinases (kinase cascade)



- Receptors themselves may have kinase activity. In such cases, receptors on the plasma membrane bind a signaling molecule (i.e., a first messenger), oligomerize, thereby activating their kinase activity within the cell.
- A kinase may bind with a second messenger located in the cell and become activated. A-kinase, which is activated by cAMP, is normally inactive when bound to an inhibitory protein. When cAMP binds PKA, the kinase and the inhibitor are separated, thereby activating PKA.
- Kinases activated in the cell may induce chain reactions. This phenomenon is called a kinase cascade, since a series of reactions occur in the same way as a waterfall flowing over a cliff. A well-known example is that of MAPK (mitogen-activated protein kinase), signaling cascade, which results in the activation of various transcription factors.

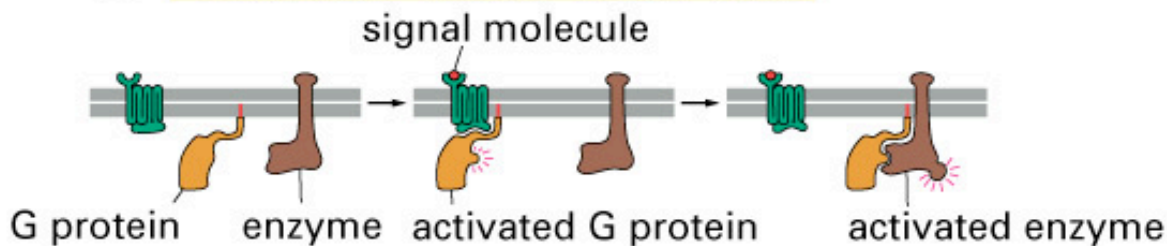
Plasma Membrane receptors fall into 3 main classes

(A) ION-CHANNEL-LINKED RECEPTOR



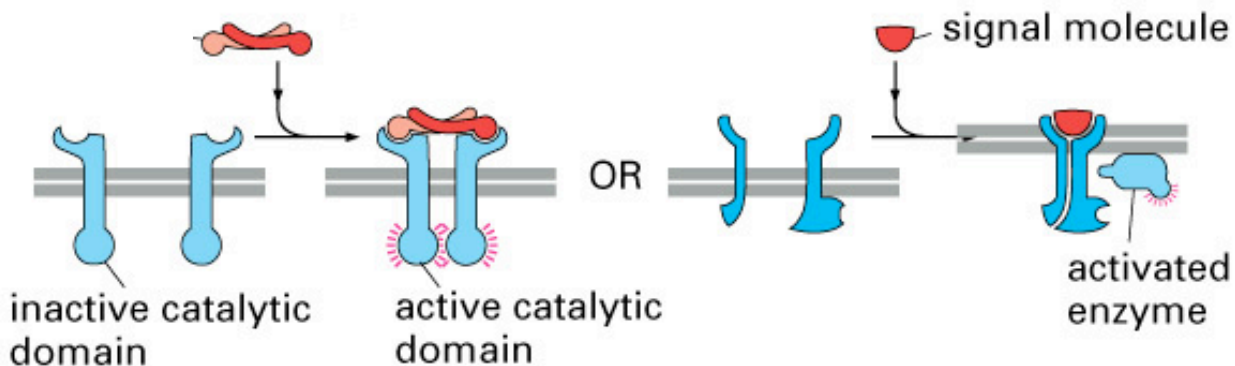
- Major use in the Nervous System
- Ach NICOTINIC receptor

(B) G-PROTEIN-LINKED RECEPTORS



- 7 trans-membrane receptors; Ach MUSCARINIC receptor; involved in **light** and **odorant** detection, detection of certain hormones and neurotransmitters

(C) ENZYME-LINKED RECEPTORS



- Genes involved in 30% of human cancers are activated by these types of receptors

Enzyme-linked receptors fall into 3 categories:

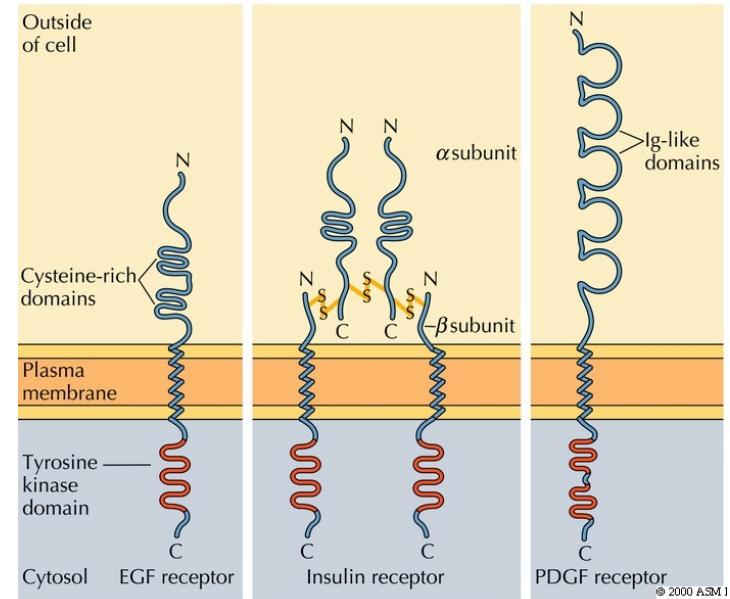
1- Tyrosine Kinase Receptors

- Not only a receptor
- Also an enzyme: Tyrosine kinase

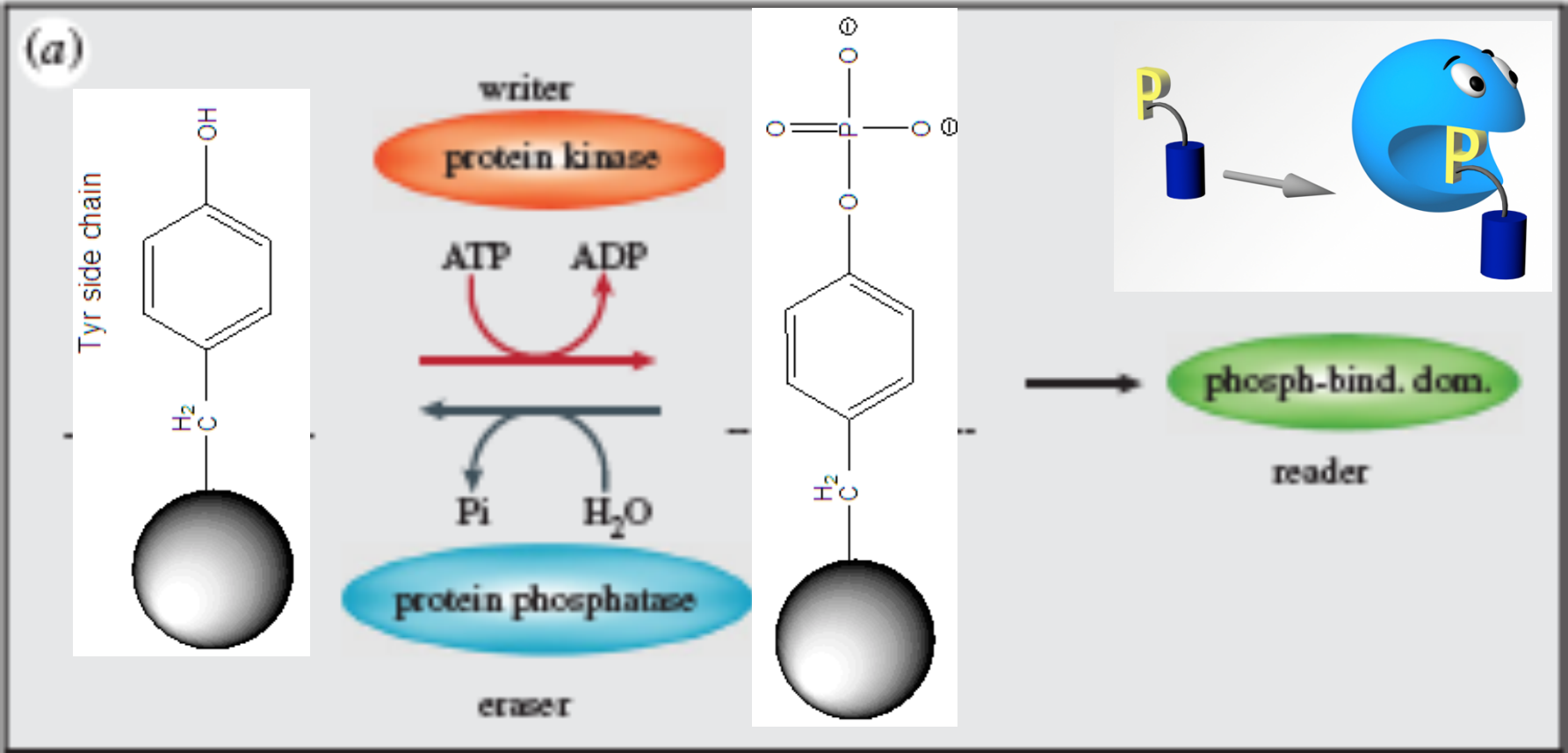
2- TGF- β receptors

3- Cytokine superfamily receptors

- No catalytic domain
- Interact with non receptor protein-tyrosine kinases
 - Src family
 - JAK family

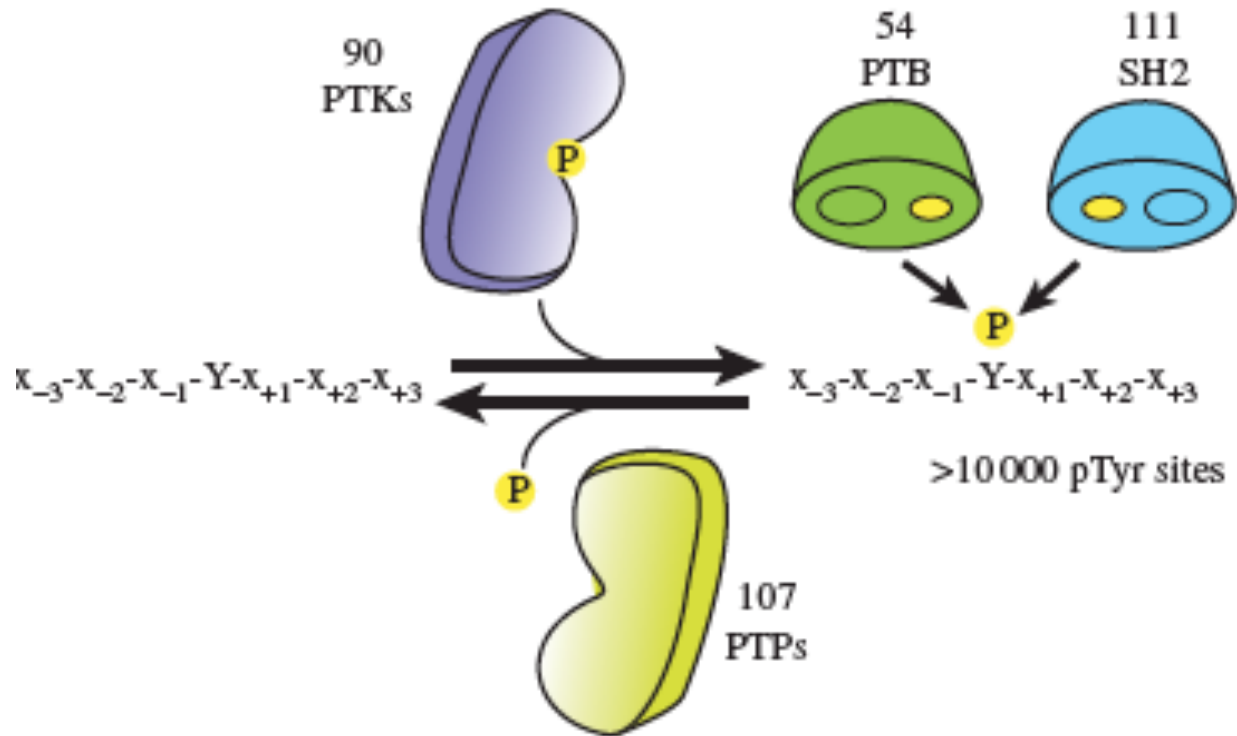


Key concepts



Key concepts

The eukaryotic phosphorylation-based network is operated by a modular kinase-phosphatase-interaction domain toolkit



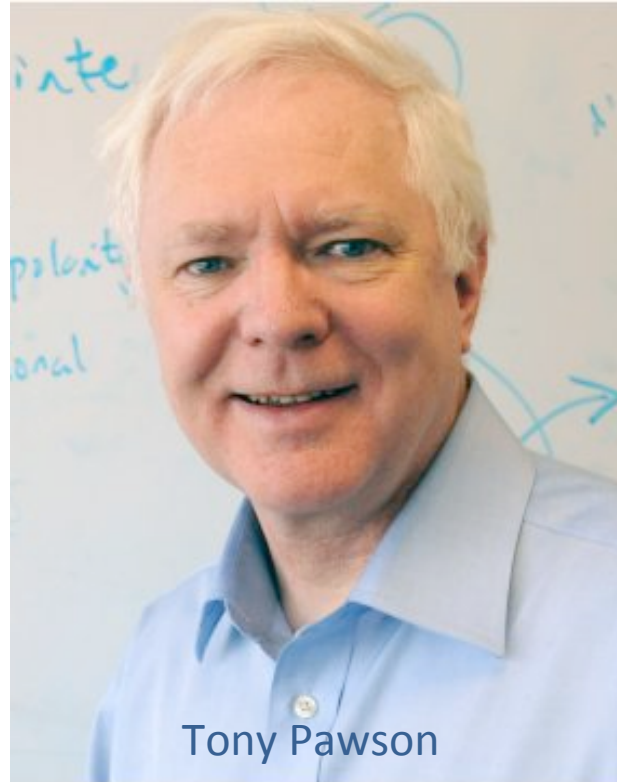
Yossi Yarden



Key people



Joseph
Schlessinger



Tony Pawson

