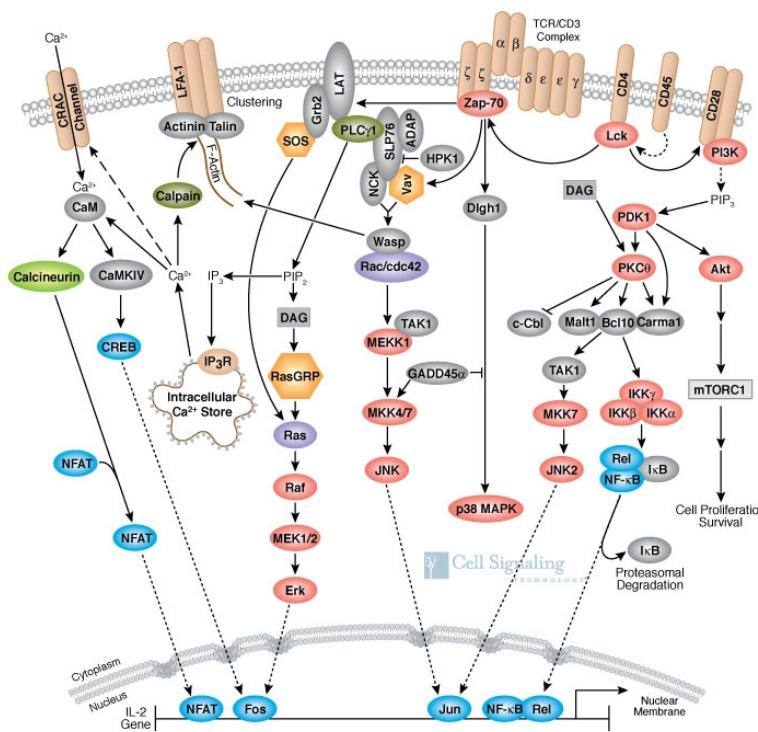


Introduction to Molecular and Cellular Biology

LECTURES 19-20:

Cellular signaling



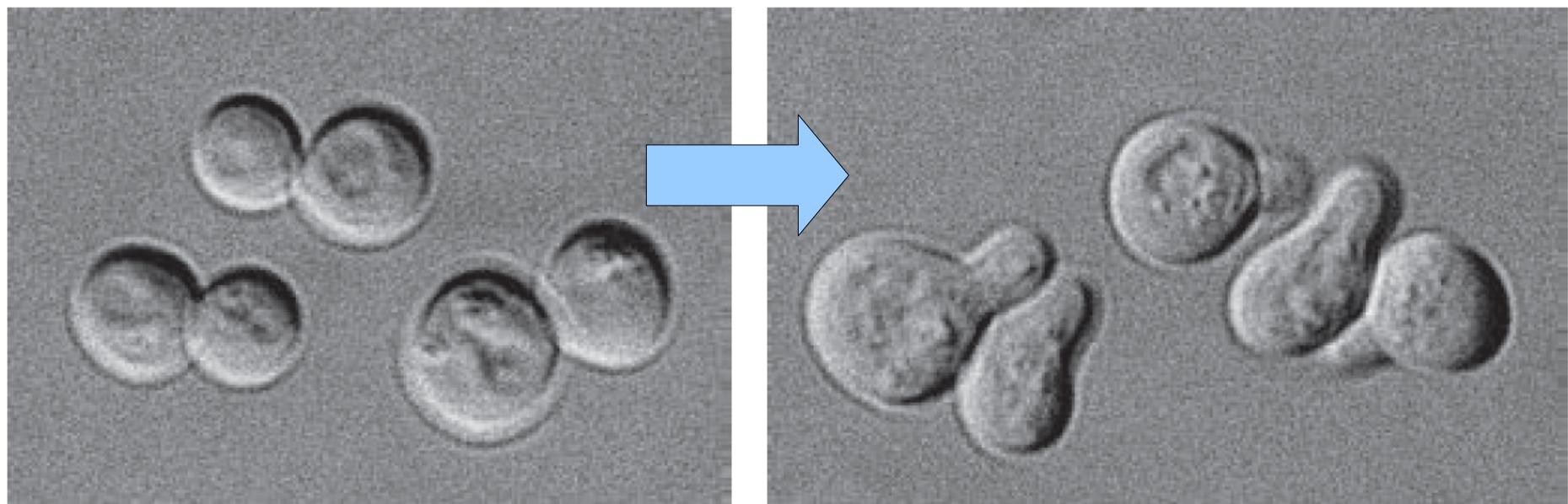
LECTURES 19-20: CELLULAR SIGNALING

- Basic principles
- Nuclear receptors
- Signaling through G-protein, secondary messengers
- Signaling through enzyme-linked cell receptors:
 - key role of phosphorylation/dephosphorylation
- Signaling pathways depending on regulated proteolysis:
 - Notch, Wnt, Hedgehog, NF-κB

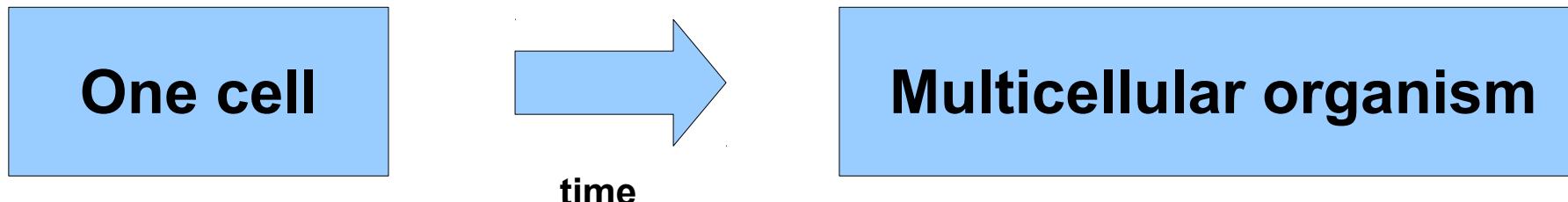


INTRODUCTION

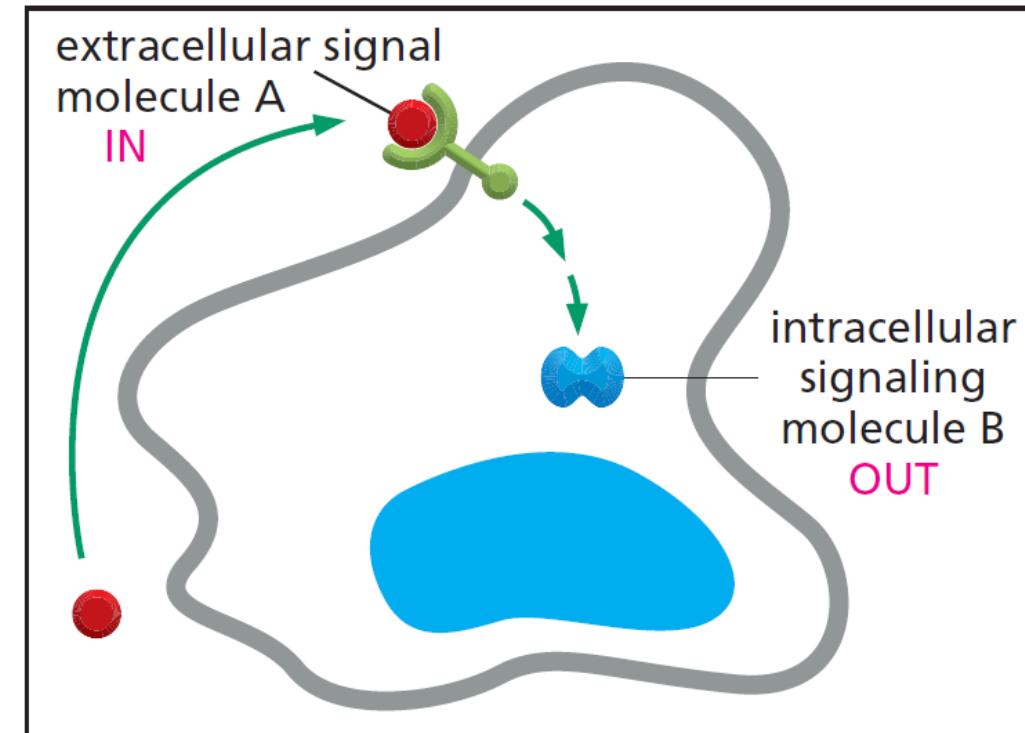
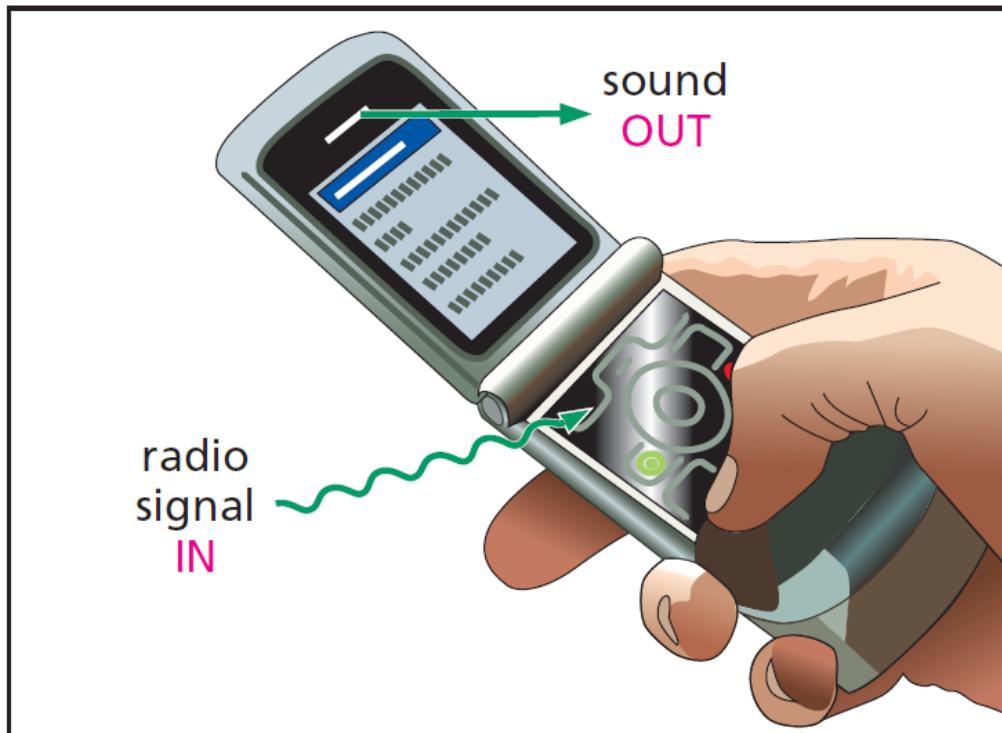
- Cell communication => long evolution of multicellular organisms
- Signal molecules: extracellular molecules produced to 'talk' with neighbours
- Signal molecules => receptor proteins => target proteins



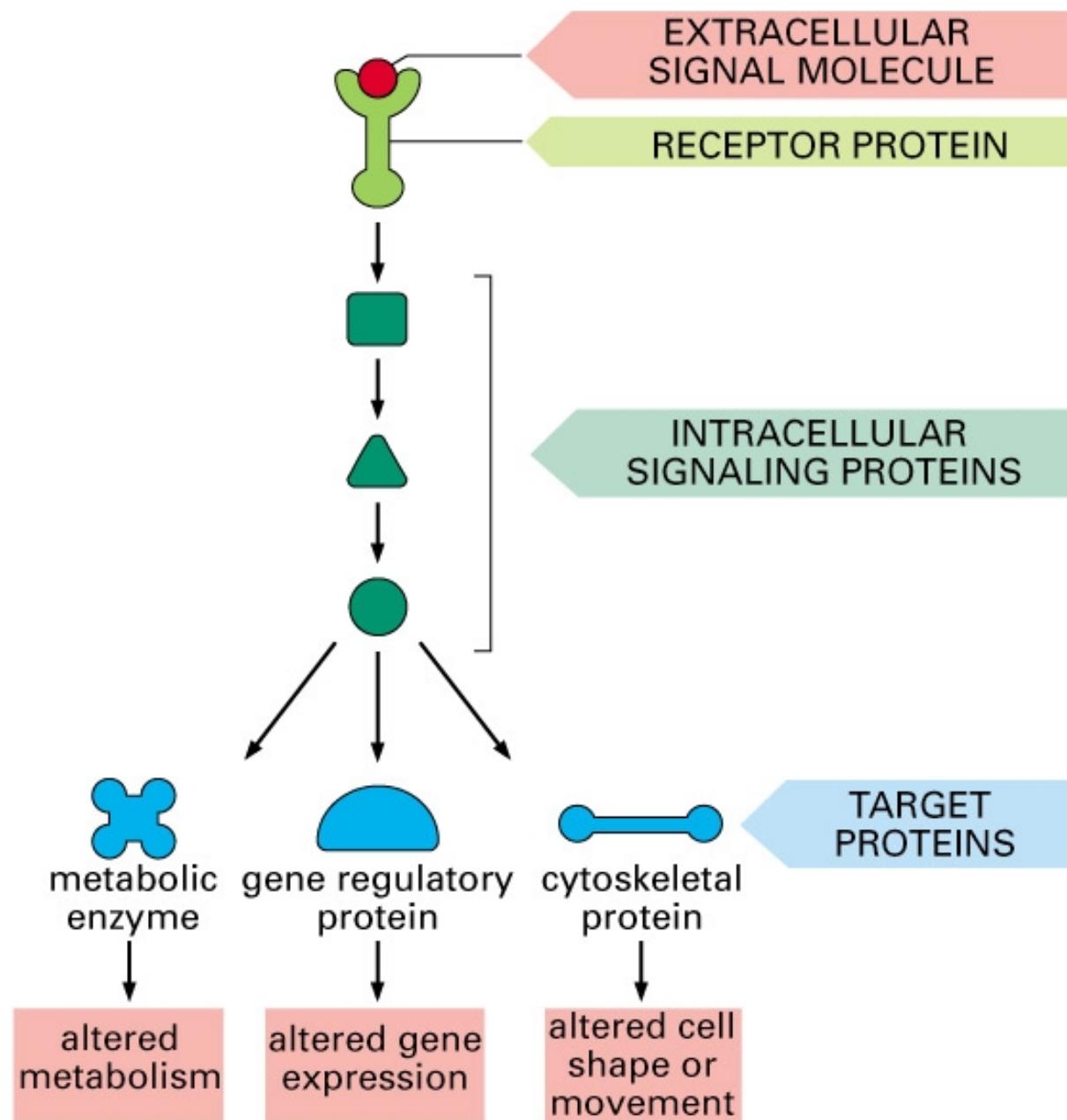
Mating yeast: response to mating factor



INTRODUCTION

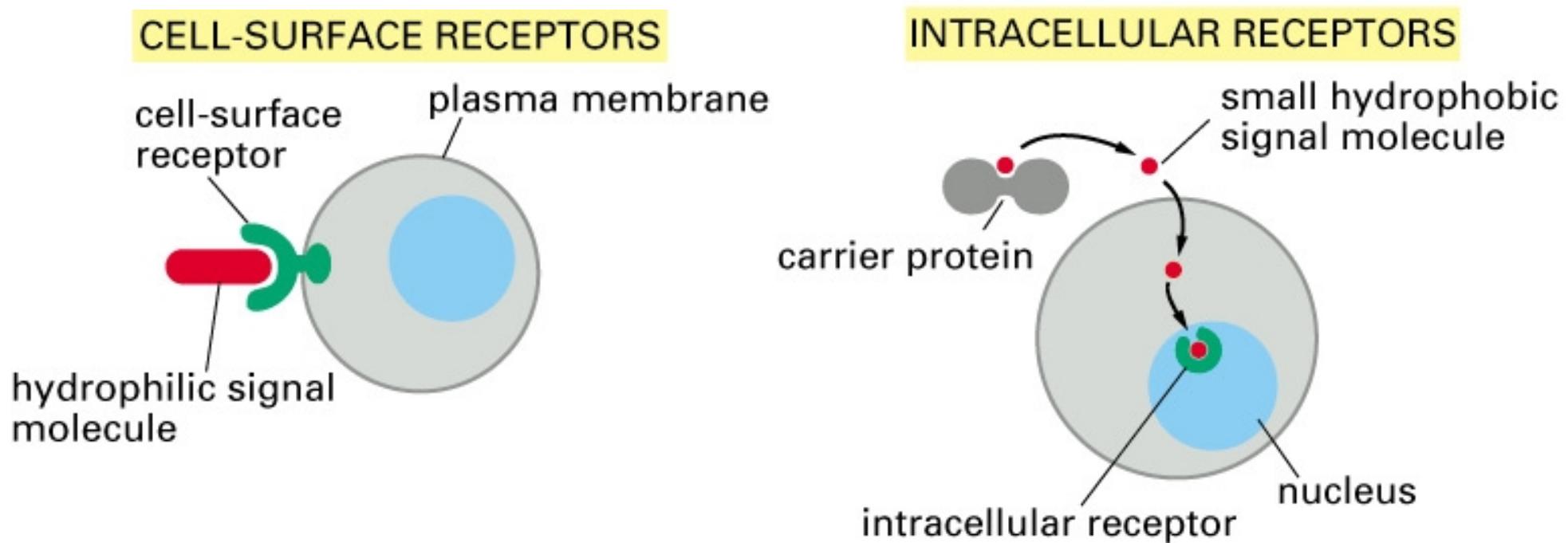


CELL COMMUNICATION: GENERAL SCHEME



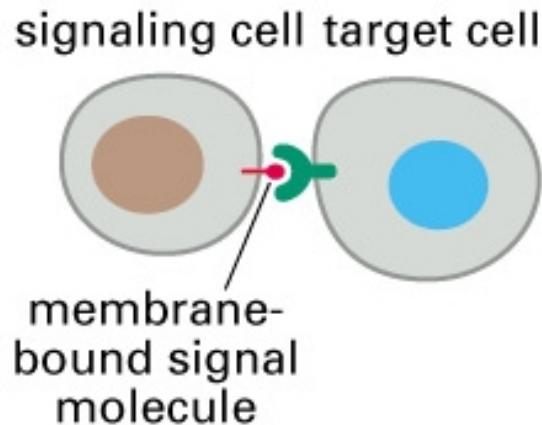
SIGNAL MOLECULES

- Vast diversity: proteins, peptides, amino acids, nucleotides, steroids, retinoids, fatty acids derivatives, NO, CO etc.
- Source: secretion, diffusion
- Types: hydrophilic/hydrophobic => binding to extra/intracellular receptors
- Affinity $\sim 10^{-8}$ M

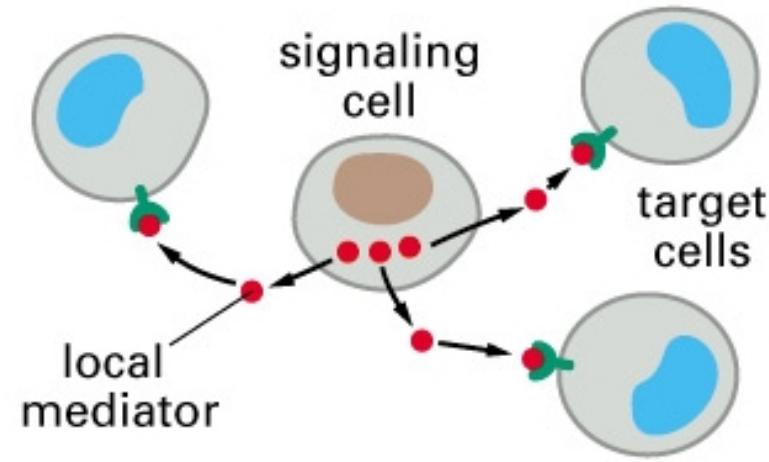


SIGNAL MOLECULES: ACTION DISTANCE

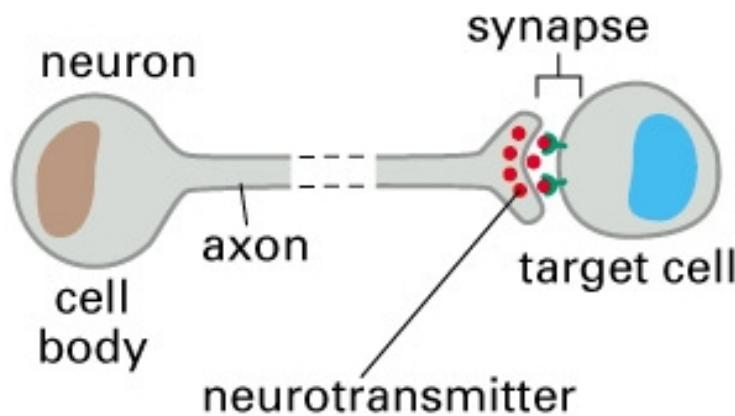
CONTACT-DEPENDENT



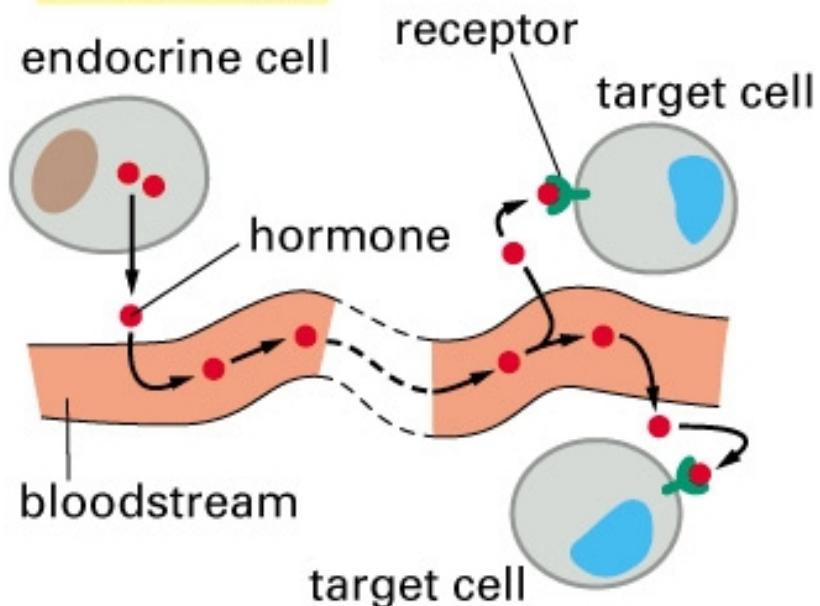
PARACRINE



SYNAPTIC



ENDOCRINE



SIGNAL MOLECULES: ACTION DISTANCE

➤ Local mediators:

- affect immediate environment of the cell in paracrine signaling
- usually destroyed or immobilized afterwards

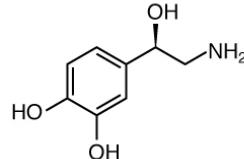
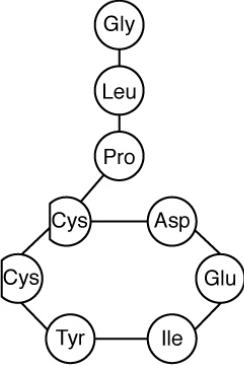
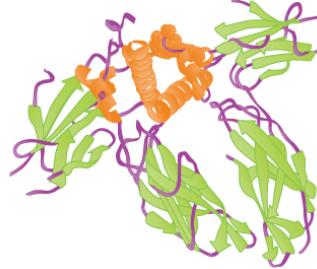
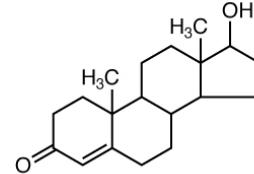
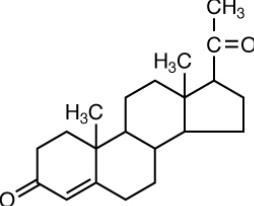
➤ Neurotransmitters:

- synaptic signalling
- very high concentration of signal molecule
- very fast (~100m/s)
- retrieved afterwards

➤ Hormones:

- long-range action in endocrine signaling
- very low concentrations
- slow
- destroyed afterwards

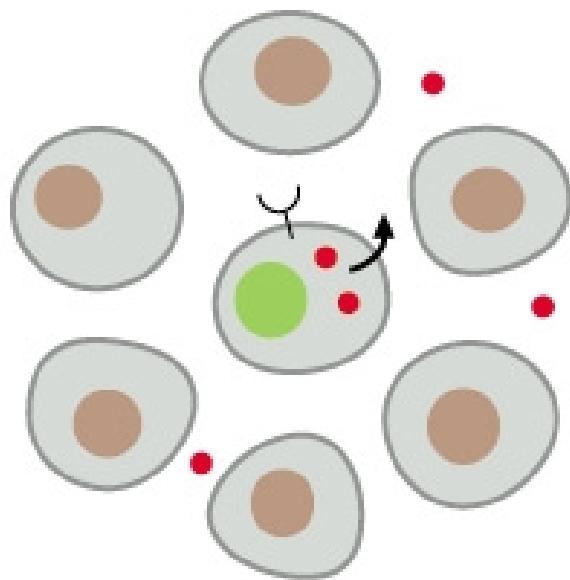
HORMONES DIVERSITY

| Hormone Class | Components | Example(s) |
|------------------|---|---|
| Amine Hormone | Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring) | Norepinephrine  |
| Peptide Hormone | Short chains of linked amino acids | Oxytocin  |
| Protein Hormone | Long chains of linked amino acids | Human Growth Hormone  |
| Steroid Hormones | Derived from the lipid cholesterol | Testosterone  Progesterone  |

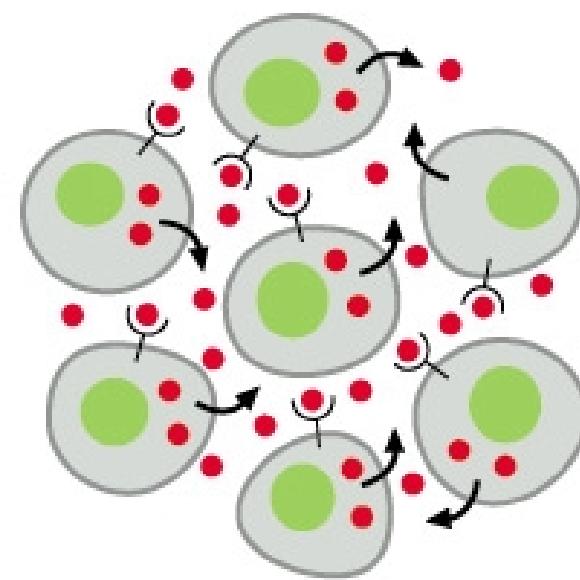
AUTOCRINE SIGNALING

Coordination of the decision by groups of identical cells

- Attenuation of weak signals
- Involvement in cancer



A SINGLE SIGNALING CELL RECEIVES A WEAK AUTOCRINE SIGNAL



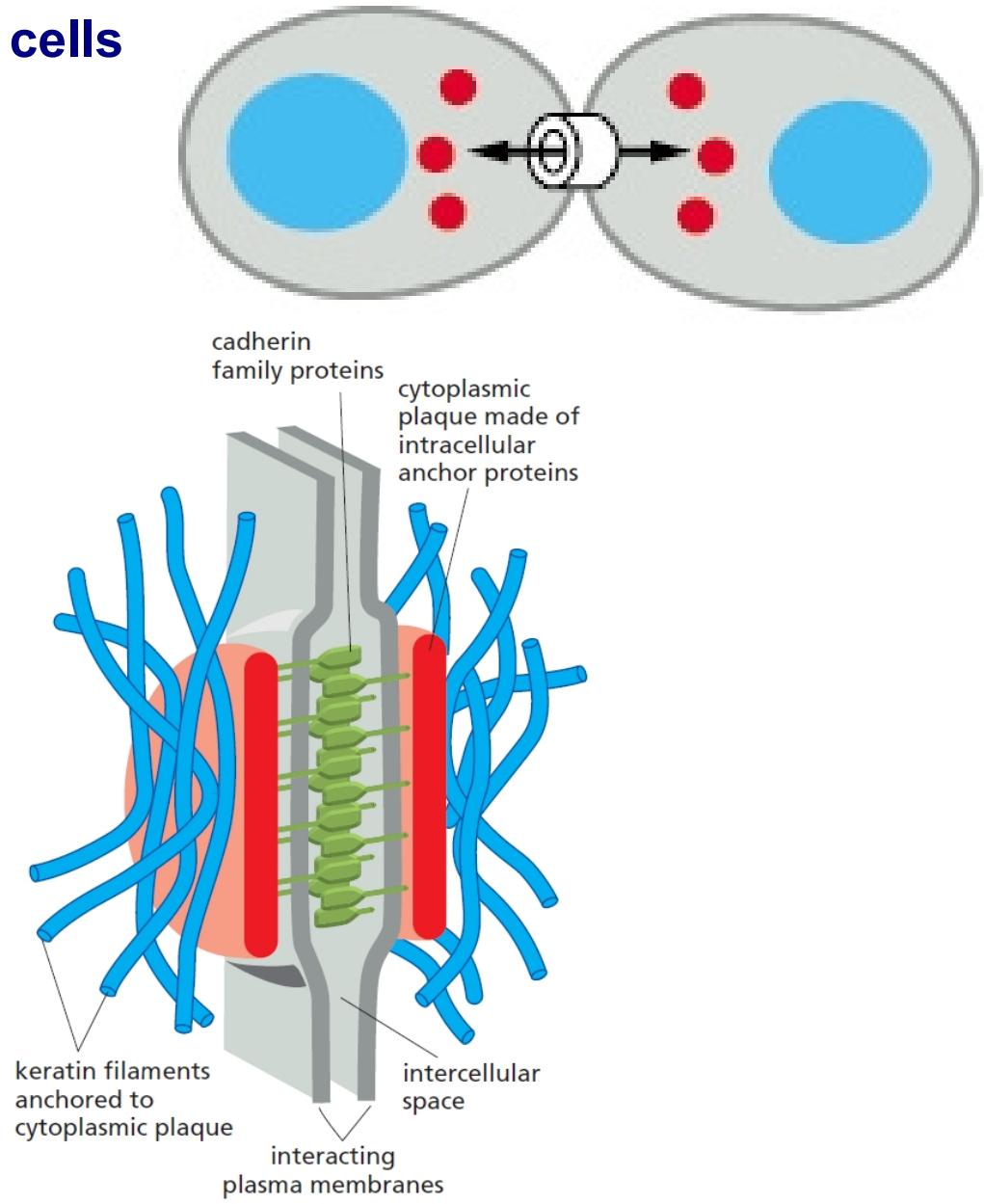
IN A GROUP OF IDENTICAL SIGNALING CELLS, EACH CELL RECEIVES A STRONG AUTOCRINE SIGNAL

GAP JUNCTIONS

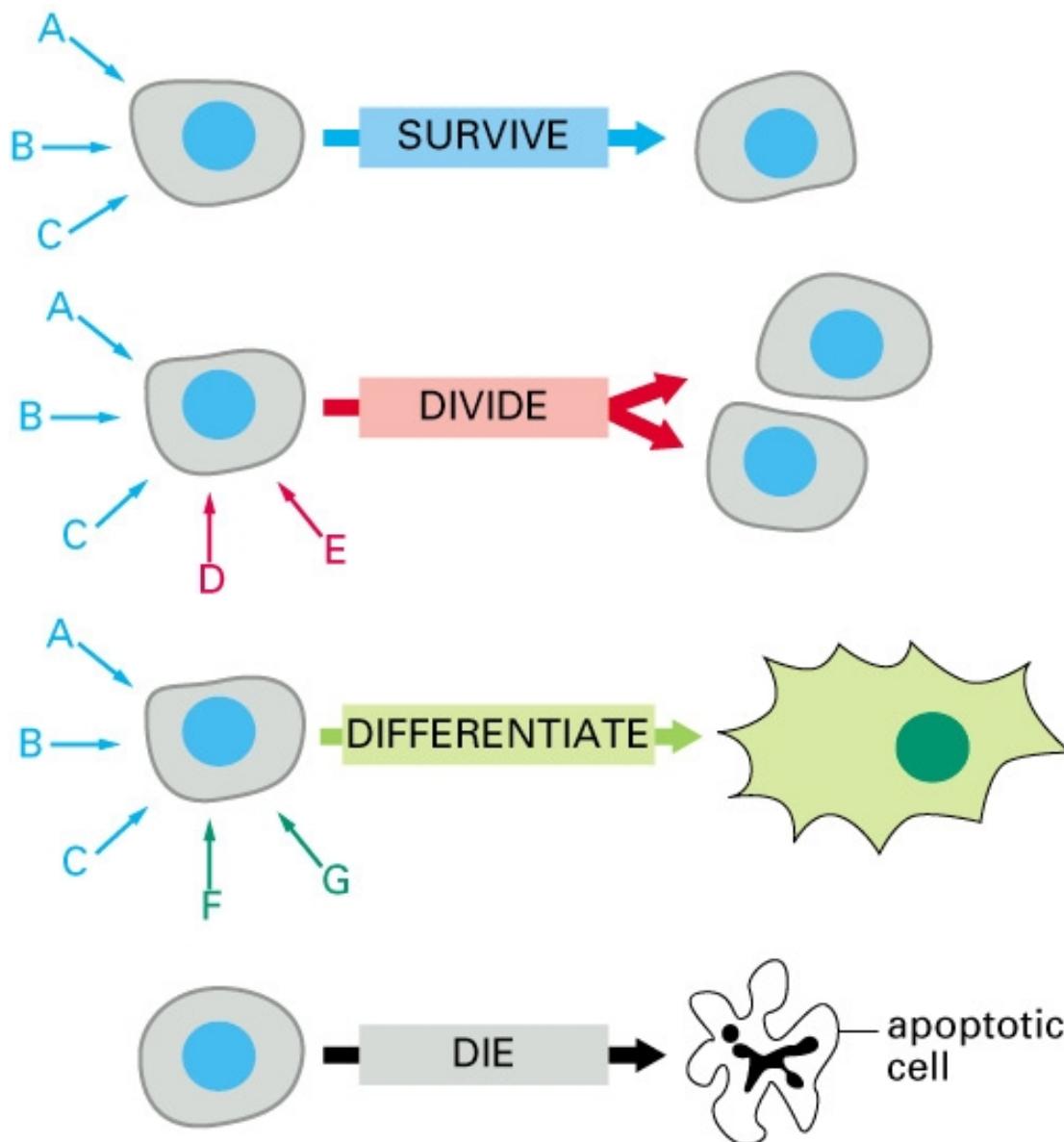
- Channels permeable for small molecules: Ca^{2+} , cAMP etc.
- Coordination in groups of identical cells



0.1 μm

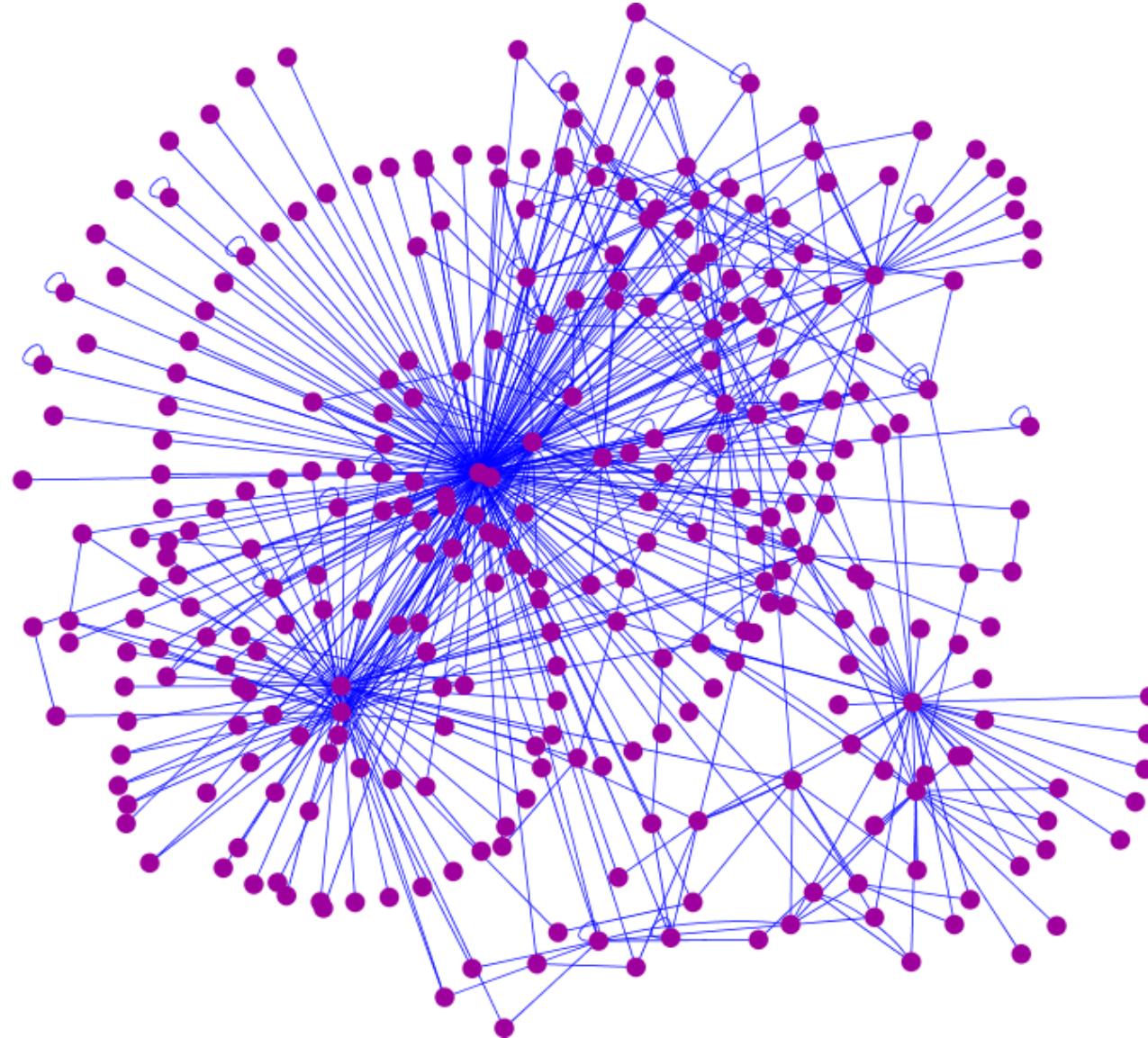


CELL REACTS TO THE COMBINATION SIGNALS



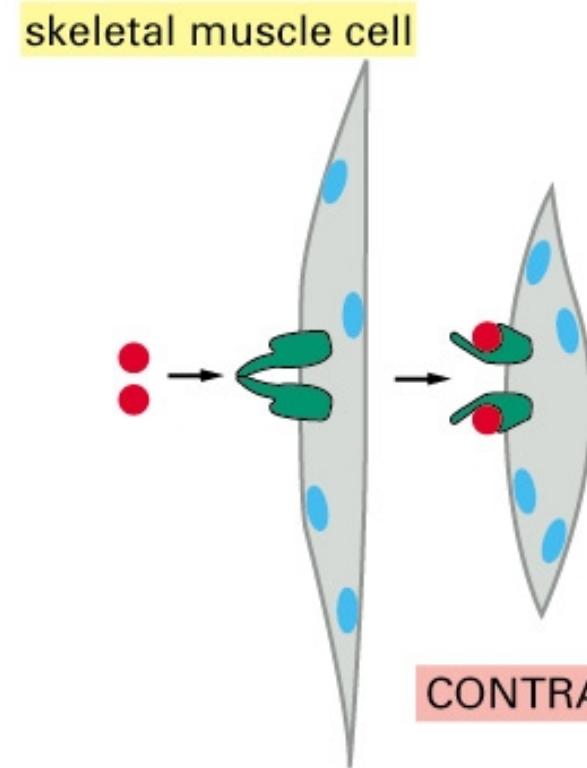
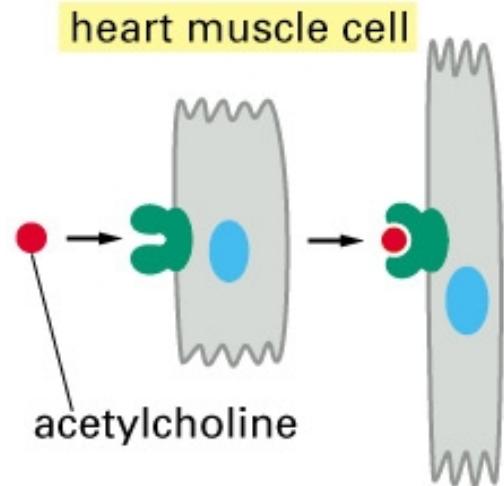
NETWORK ANALOGY

Combination of signals + cells can be seen as nodes and edges



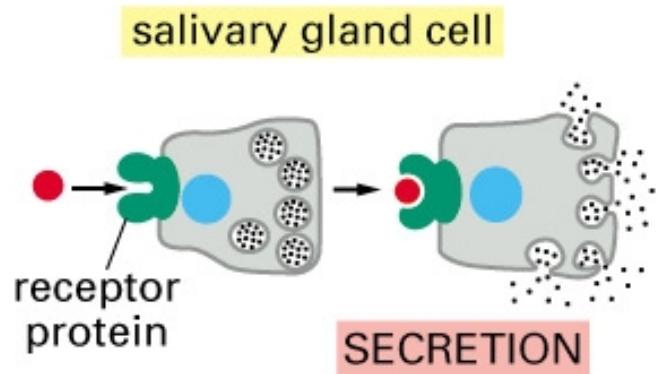
DIFFERENT CELLS => DIFFERENT RESPONSE

➤ Differences: receptors, pathways, condicions



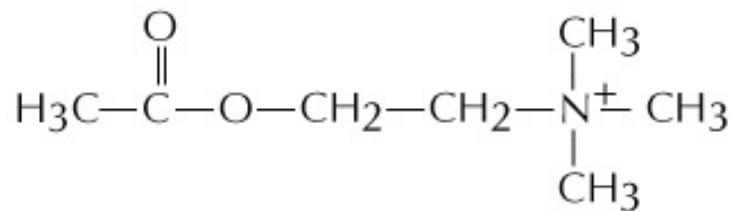
DECREASED RATE AND
FORCE OF CONTRACTION

CONTRACTION



SECRETION

acetylcholine



THE ROLE OF SIGNAL CONCENTRATION CHANGING RATE

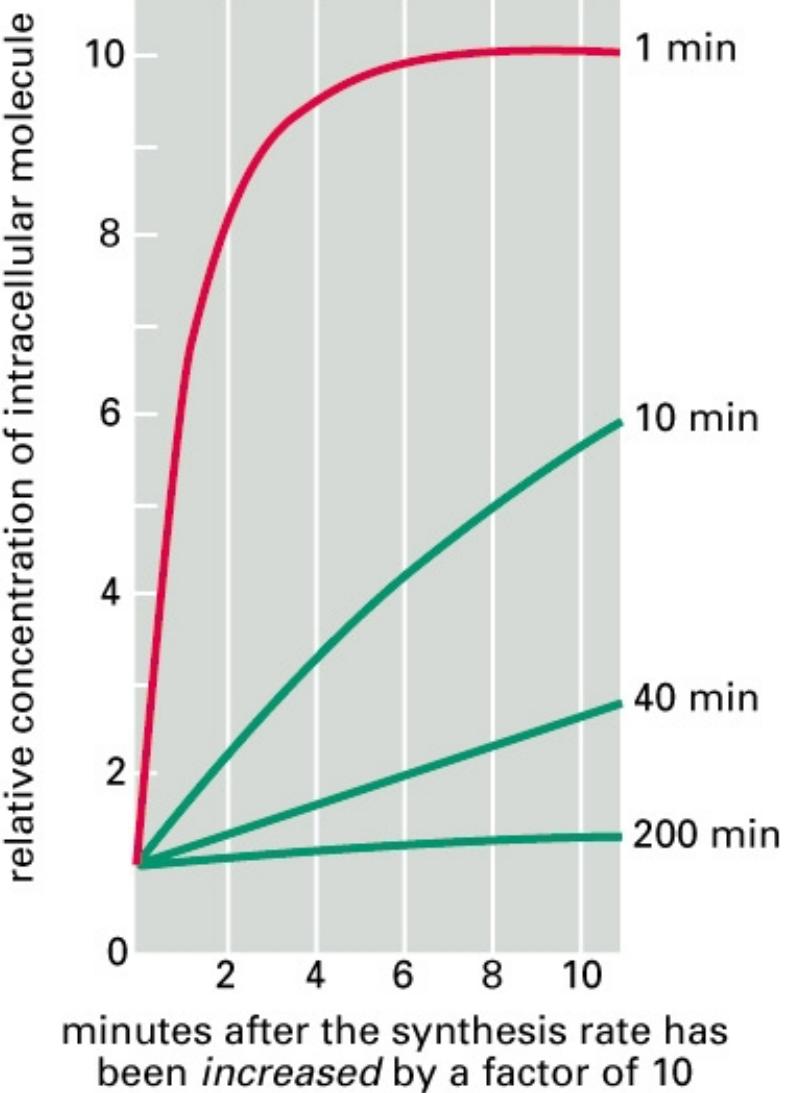
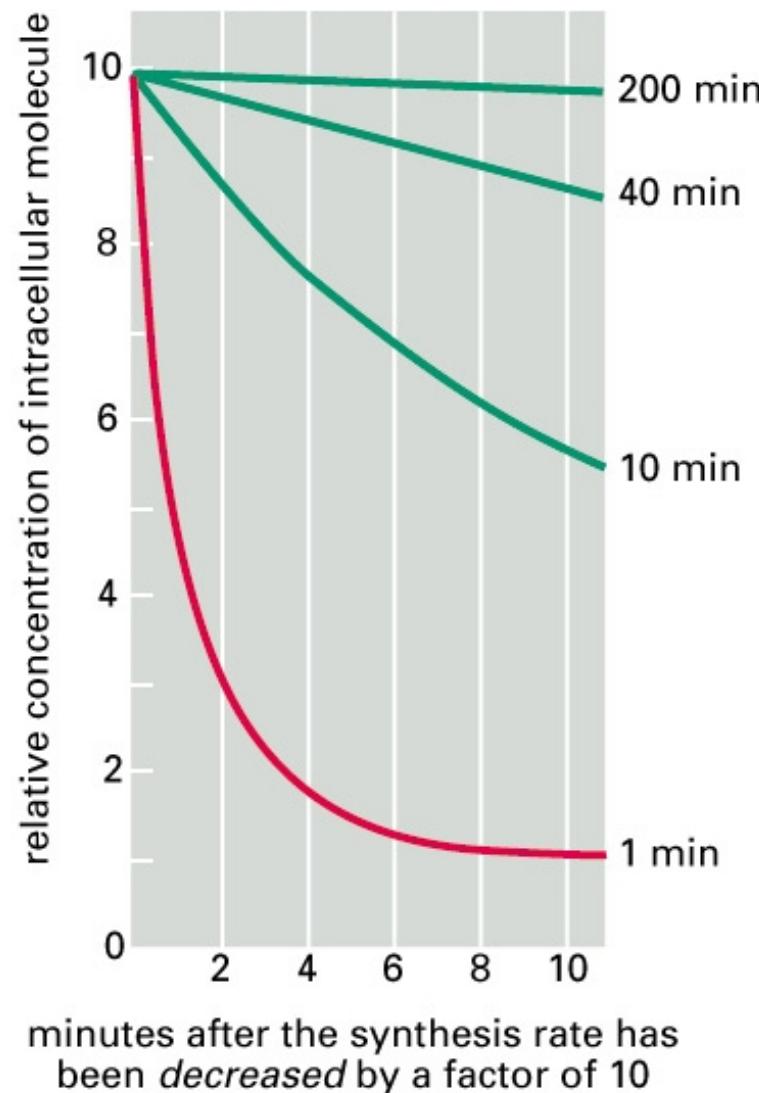
➤ Synthesis rate

➤ Degradation rate



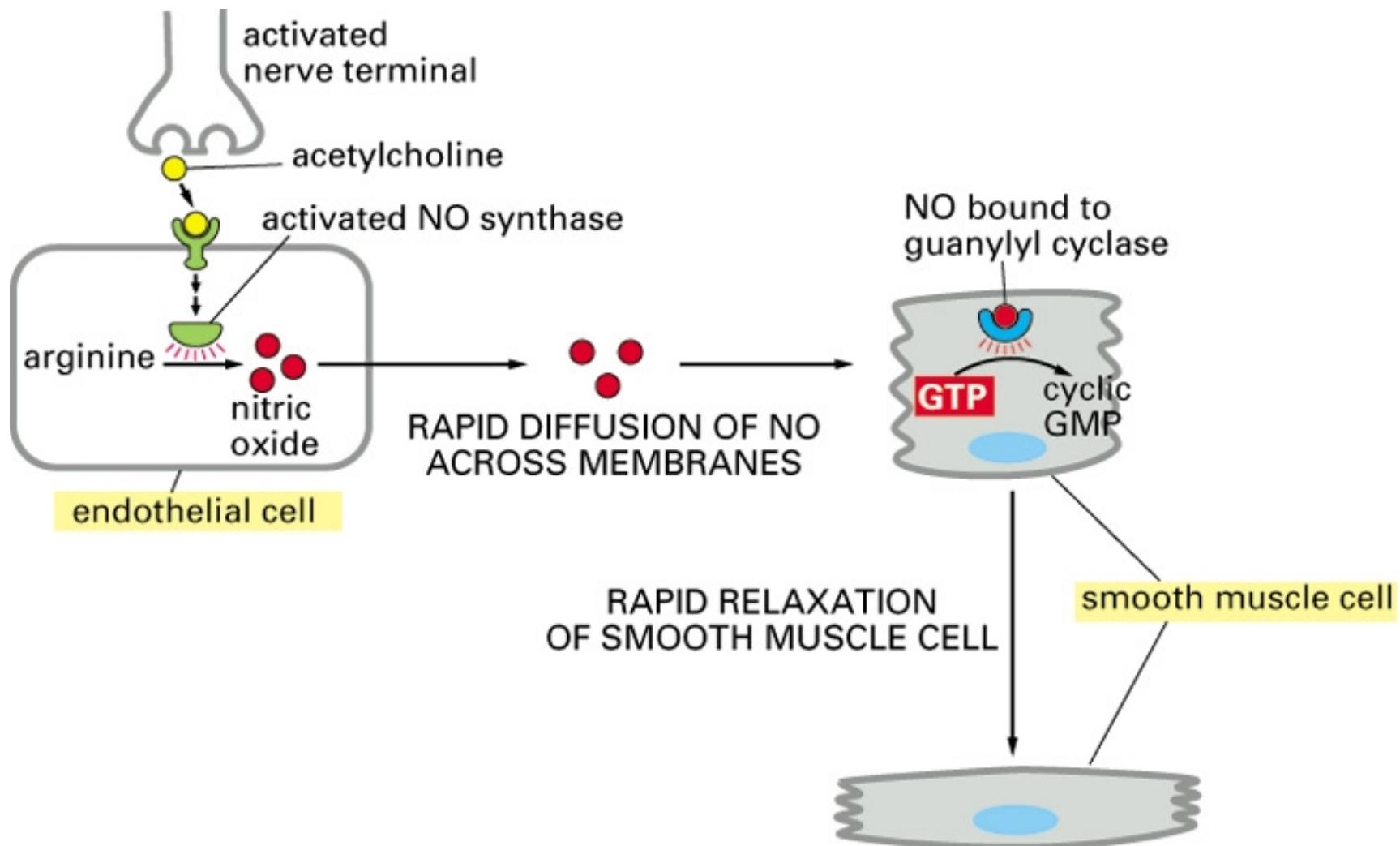
➤ Signaling effect~turnover = f (lifetime)

➤ Lifetime



NITRIC OXIDE BINDS DIRECTLY IN THE CELL

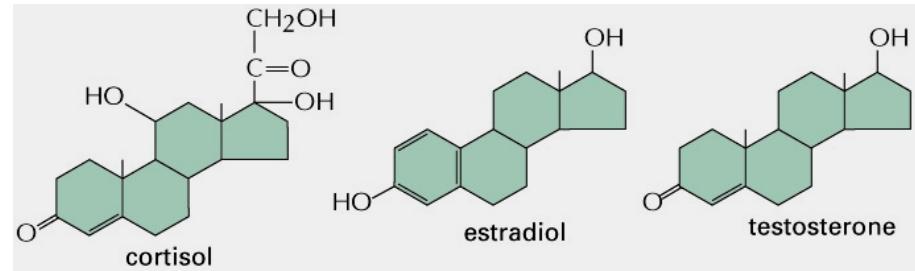
- Hydrophobic, small => permeability
- Lifetime: 5-10 s
- CO works in the same way



NUCLEAR RECEPTORS

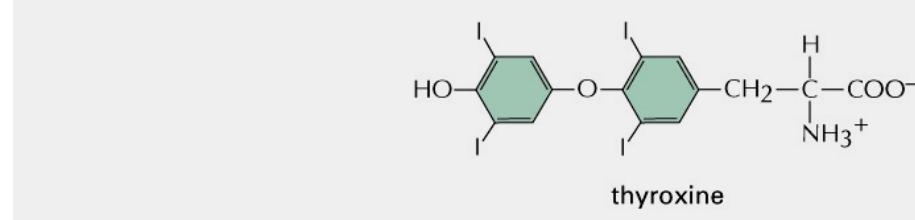
Ligand-activated gene regulatory proteins

- Orphan NR: no ligands are identified



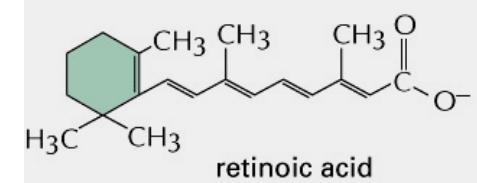
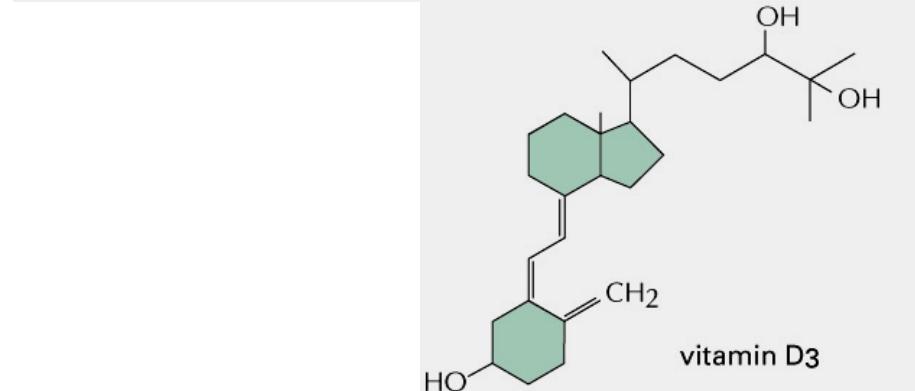
- Ligands:

- cortisol (cortex of adrenal glands)
- sex hormones (testes, ovaries)
- vitamin D (skin) => Ca^{2+}
- thyroid hormones (thyroid gland)
- retinoids => vertebrate development



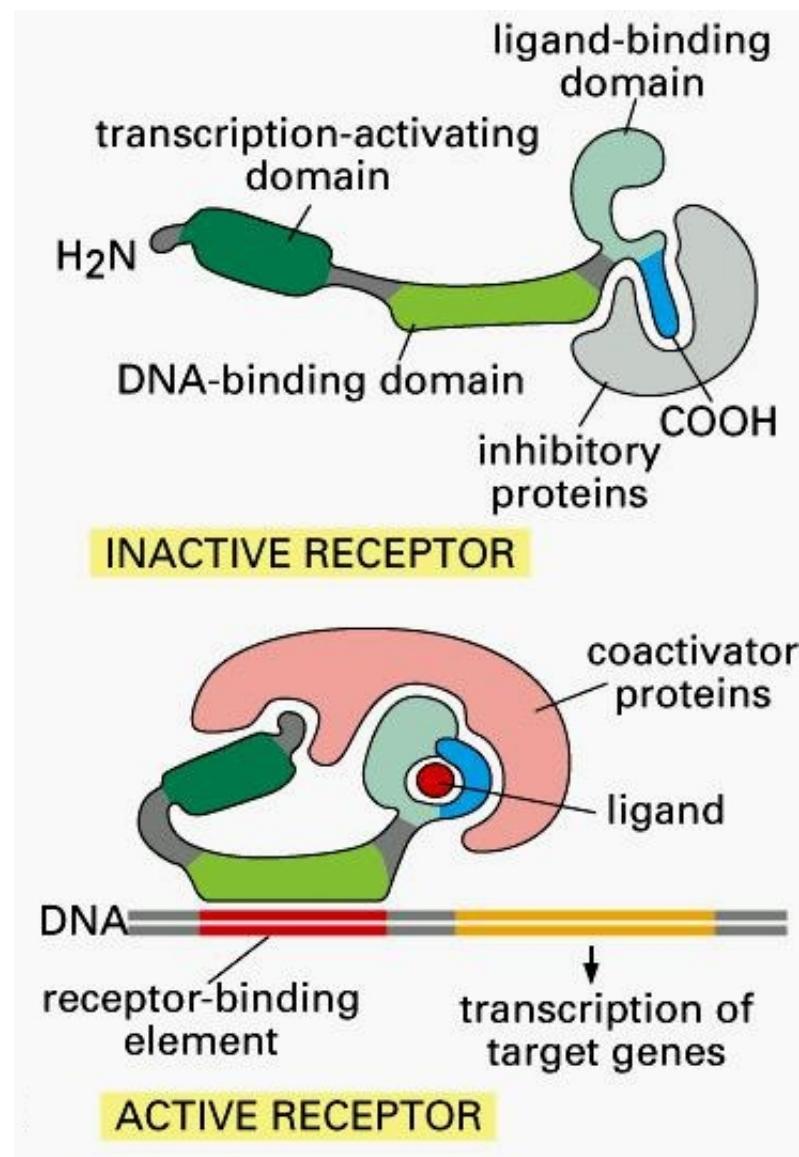
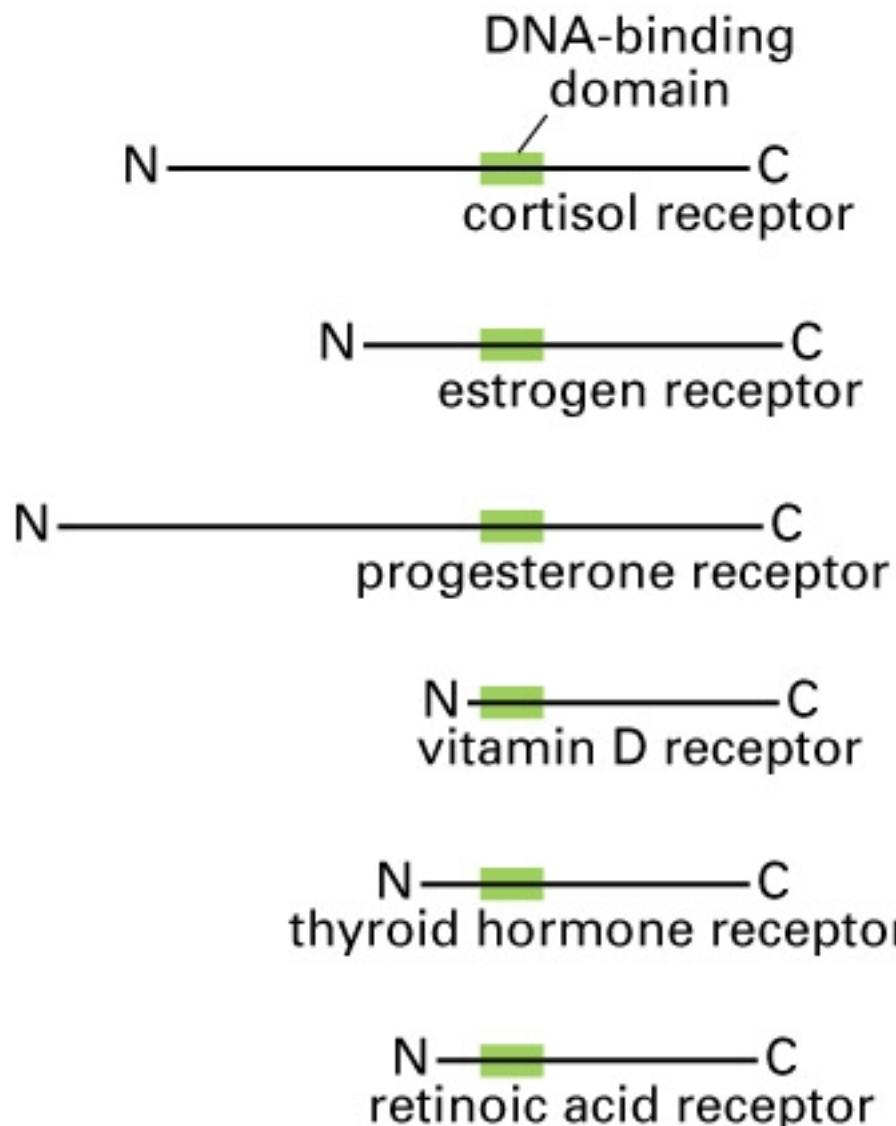
- Solubility:

- soluble (shorter lifetime)
- insoluble (longer lifetime)

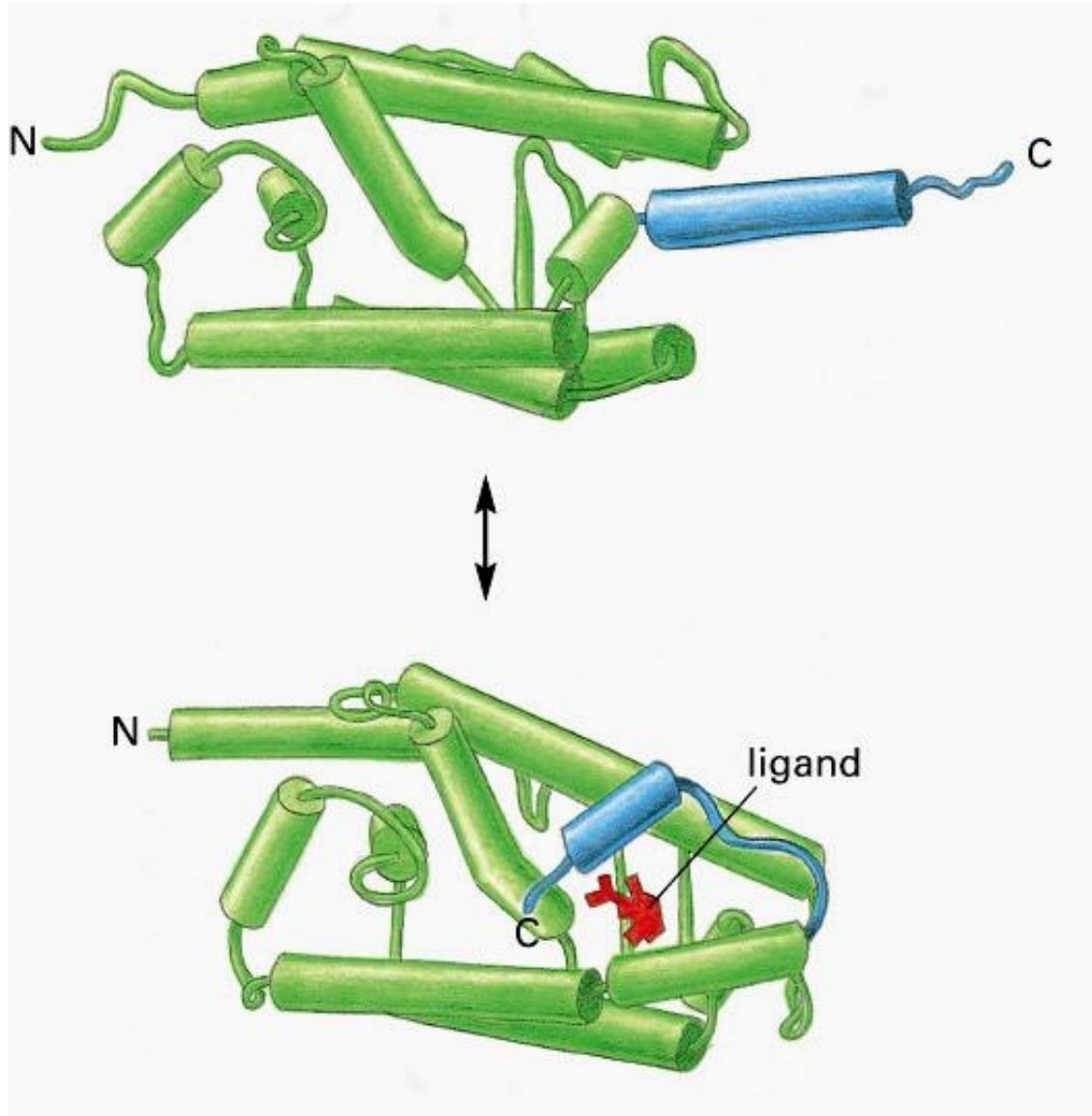


NUCLEAR RECEPTORS: STRUCTURE AND MECHANISM

➤ Localization: cytosolic or nuclear

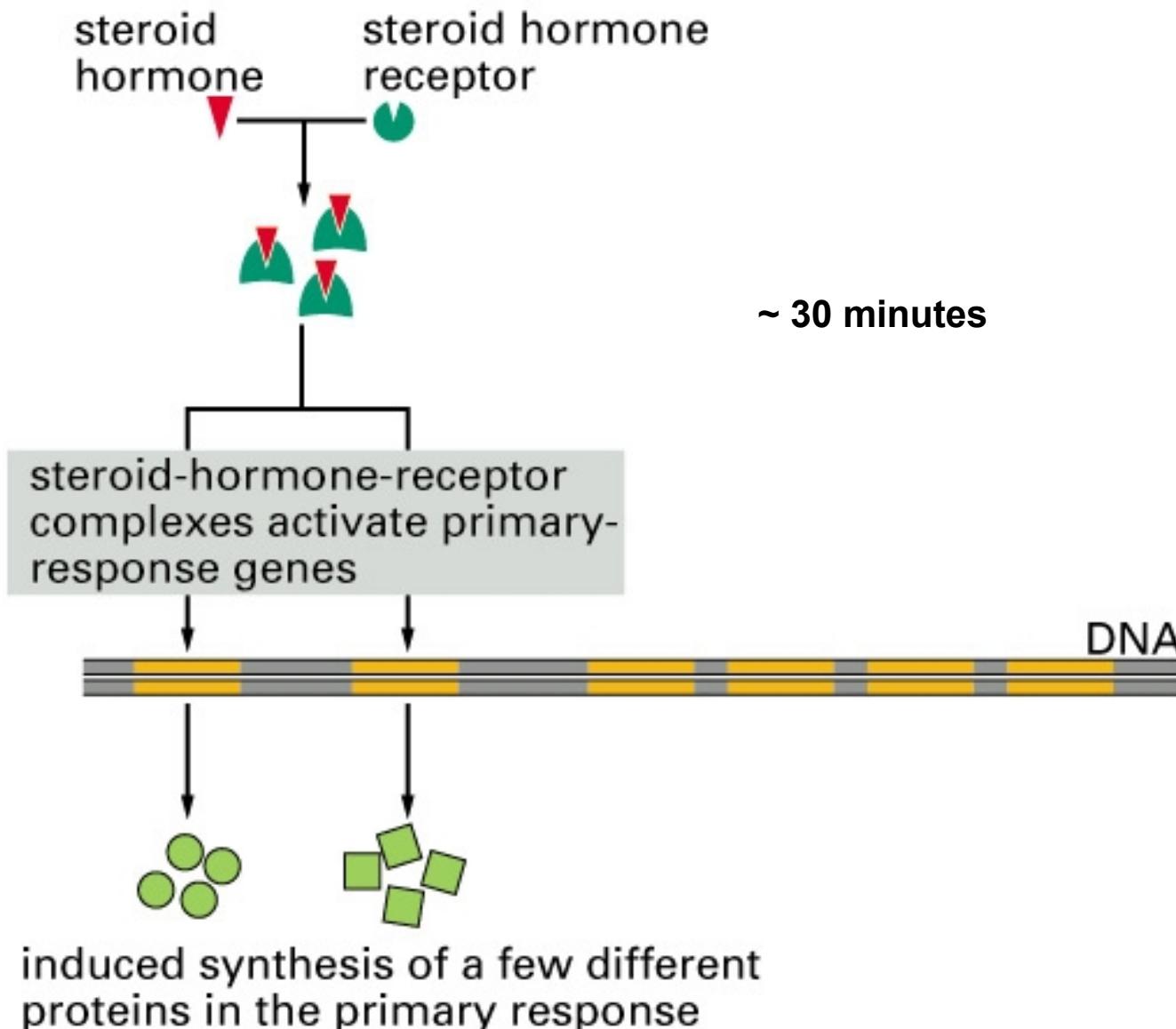


NUCLEAR RECEPTORS: STRUCTURE AND MECHANISM



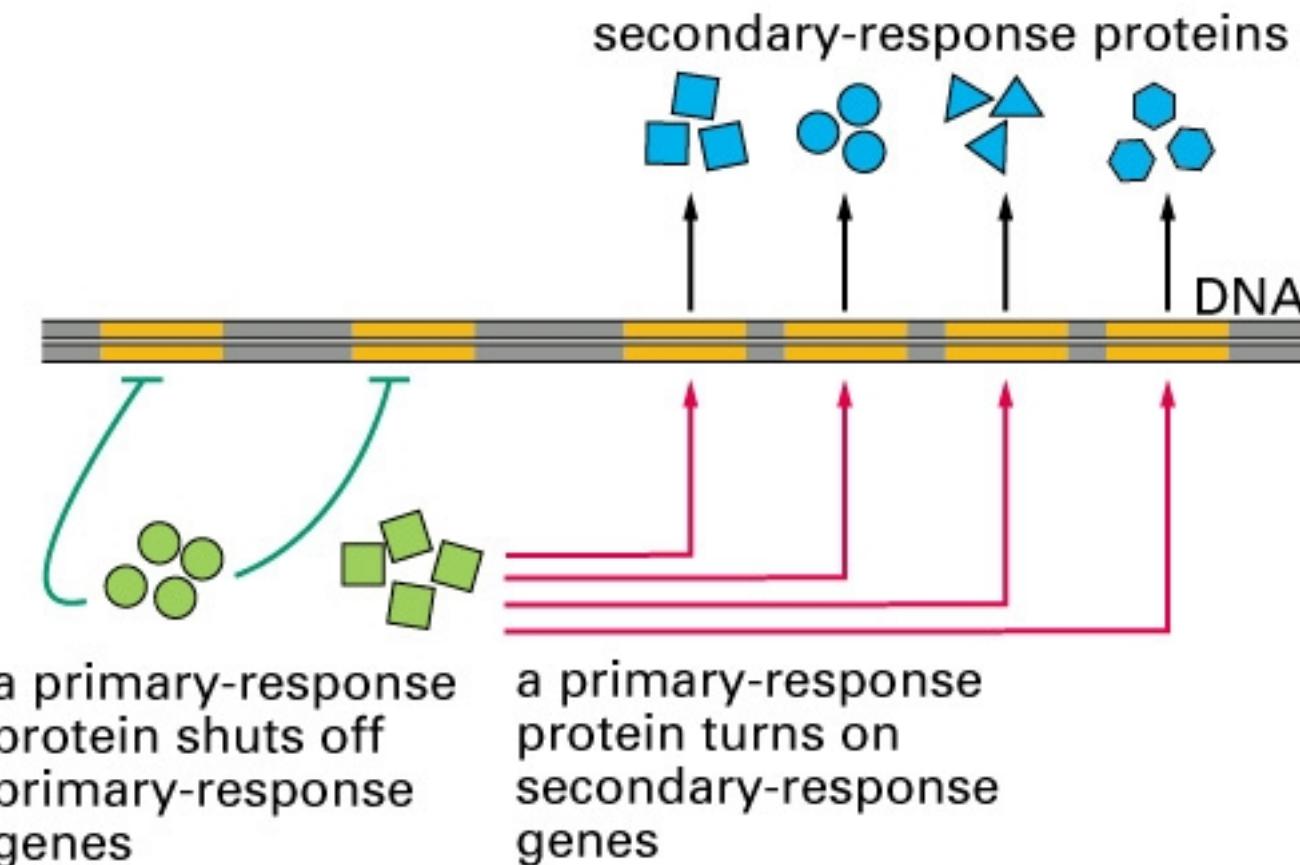
NUCLEAR RECEPTORS: PRIMARY RESPONSE

EARLY PRIMARY RESPONSE TO STEROID HORMONE



NUCLEAR RECEPTORS: SECONDARY RESPONSE

DELAYED SECONDARY RESPONSE TO STEROID HORMONE

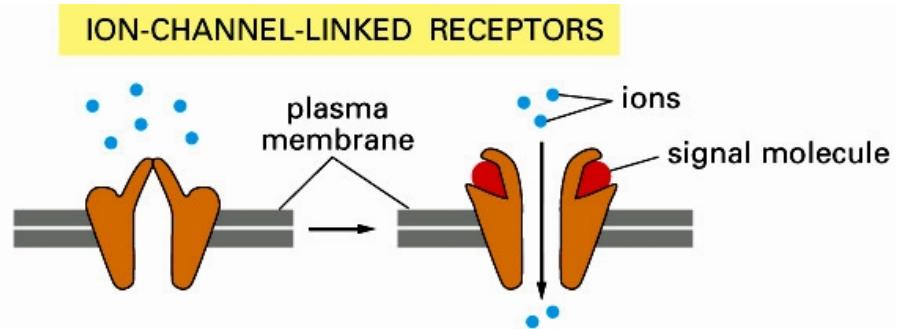


NUCLEAR RECEPTORS

- The chain of responses can be very long and complex.
- Response:
 - ligand
 - cell type
- Gene activation: combination of all factors
- Hormone effect:
 - availability of the receptor
 - availability of other proteins which collaborate with the receptor

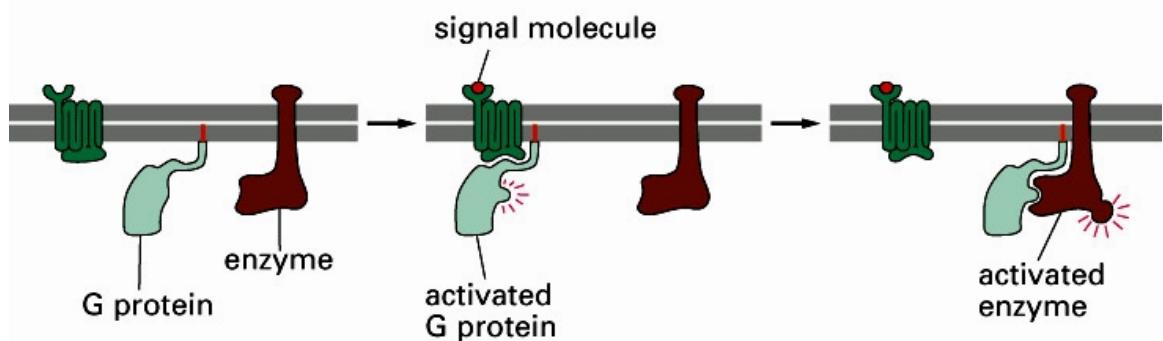
CELL-SURFACE RECEPTORS

➤ Ion-channel-linked



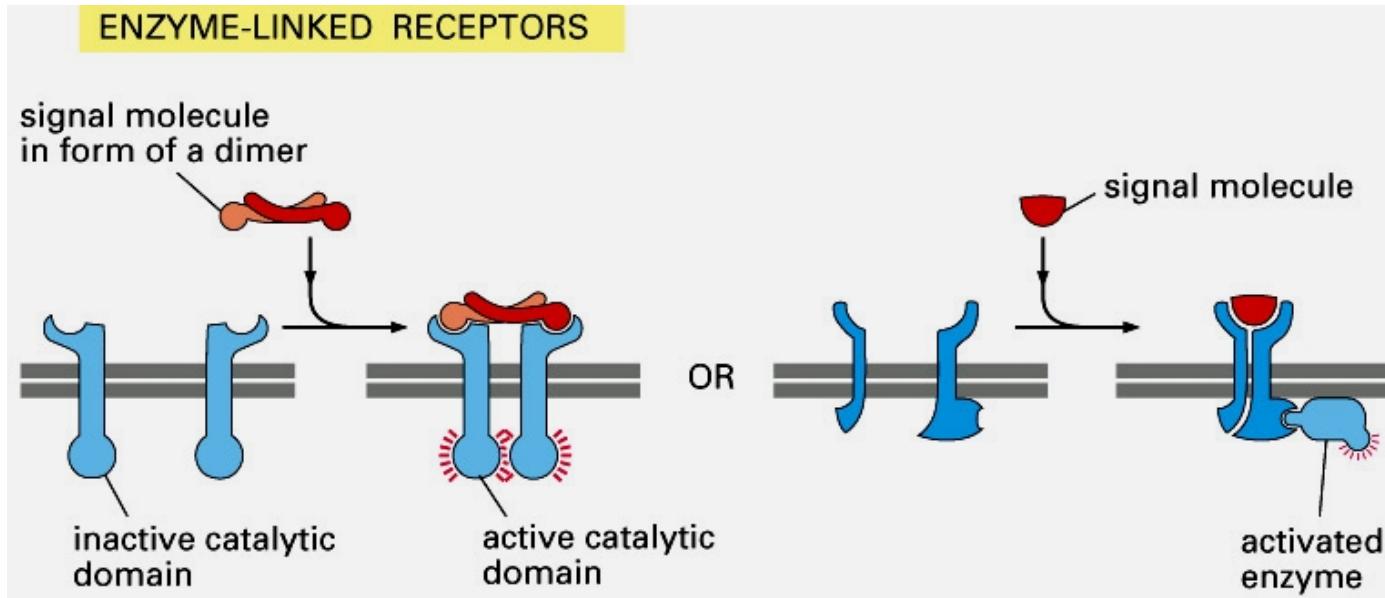
➤ G-protein-linked:

- activates enzyme
- opens channel



➤ Enzyme-linked

- 1 TMD
- most are kinases



➤ Others

CELL-SURFACE RECEPTORS

Small intracellular mediators = secondary messengers:

➤ Water-soluble => cytosol:

- cAMP

- Ca²⁺

➤ Lipid-soluble => PM:

- diacylglycerol

➤ Bind intracellular signaling proteins:

- relay

- messenger

- adaptor

- amplifier

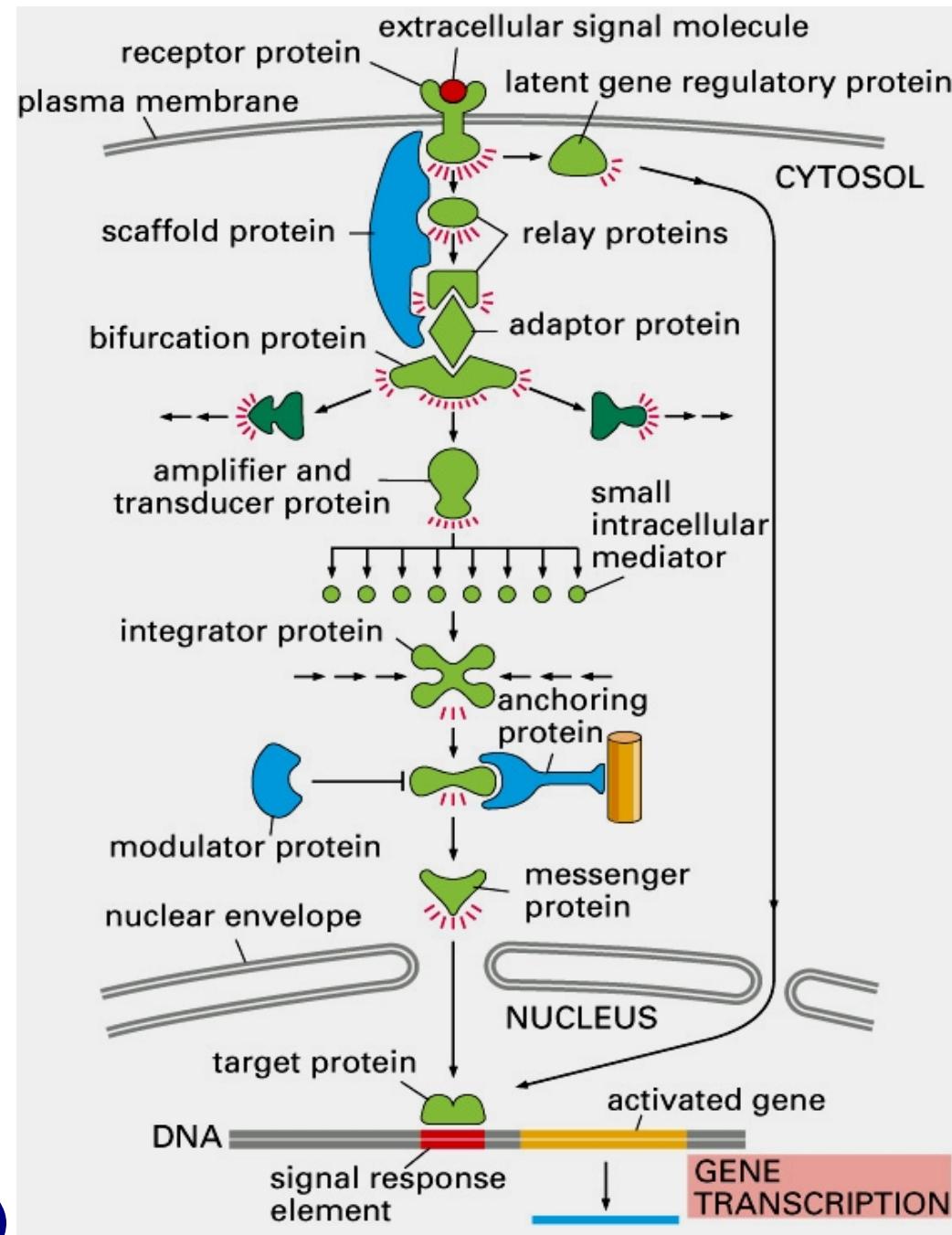
- transducer

- bifurcation

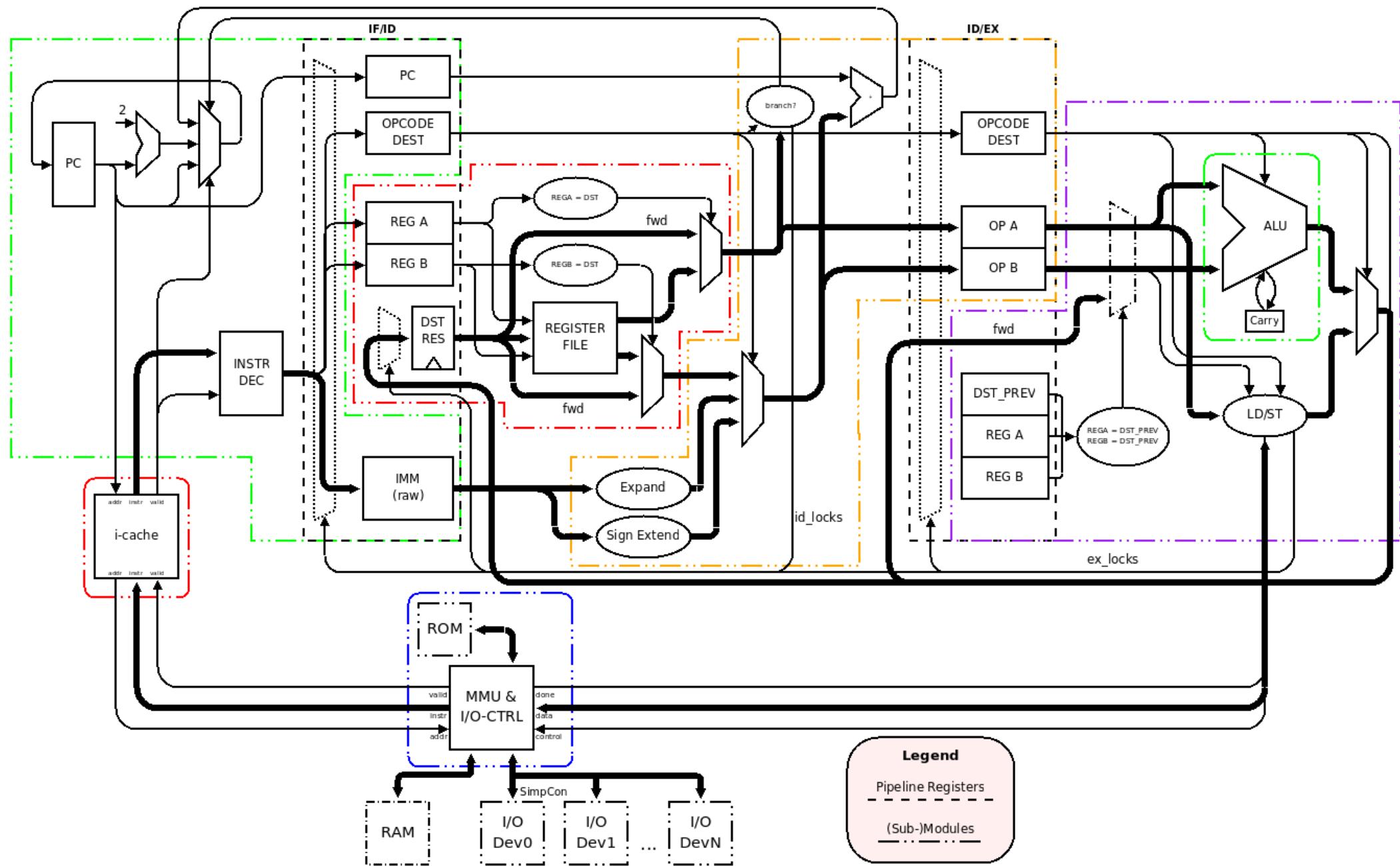
- integrator

- latent gene regulatory

- others (scaffold, anchoring, modulator)

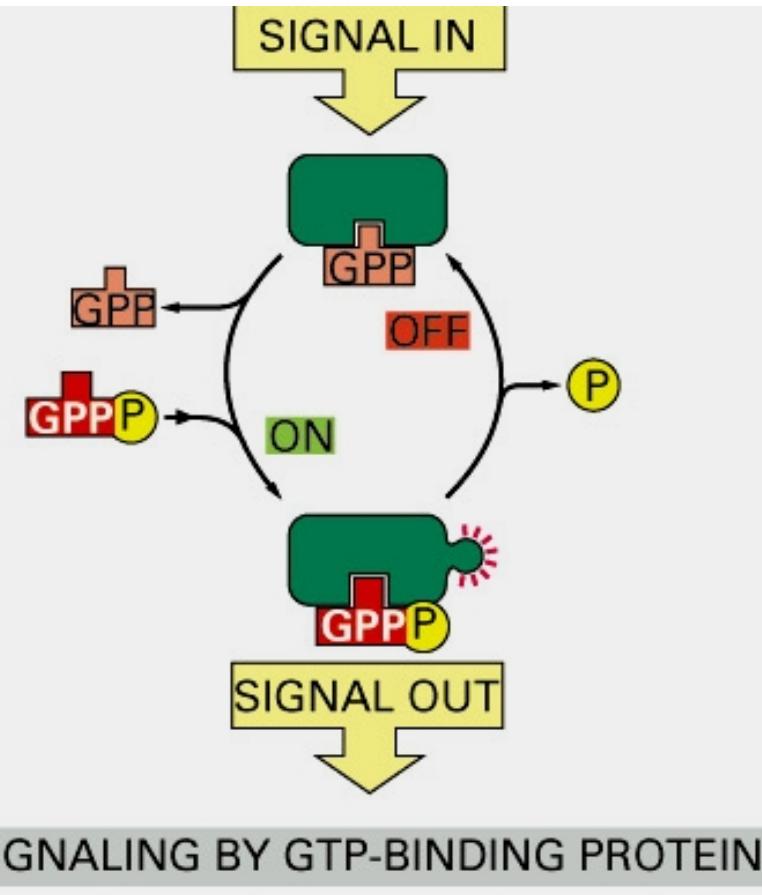
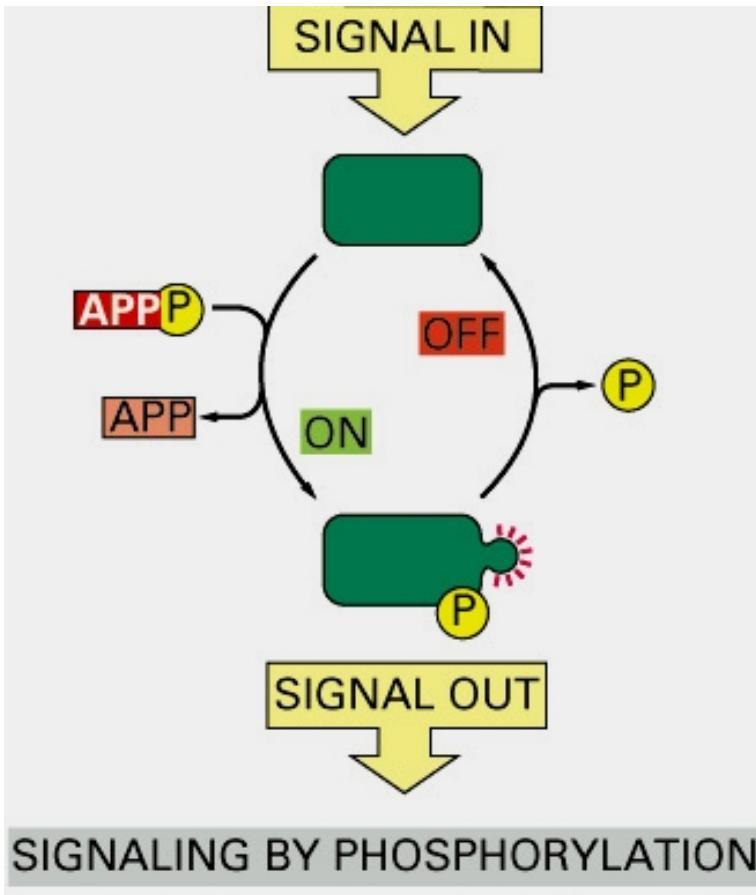


ANALOGY: COMPUTER ARCHITECTURE



MOLECULAR SWITCHES

Switches: inactive state \Leftrightarrow active state



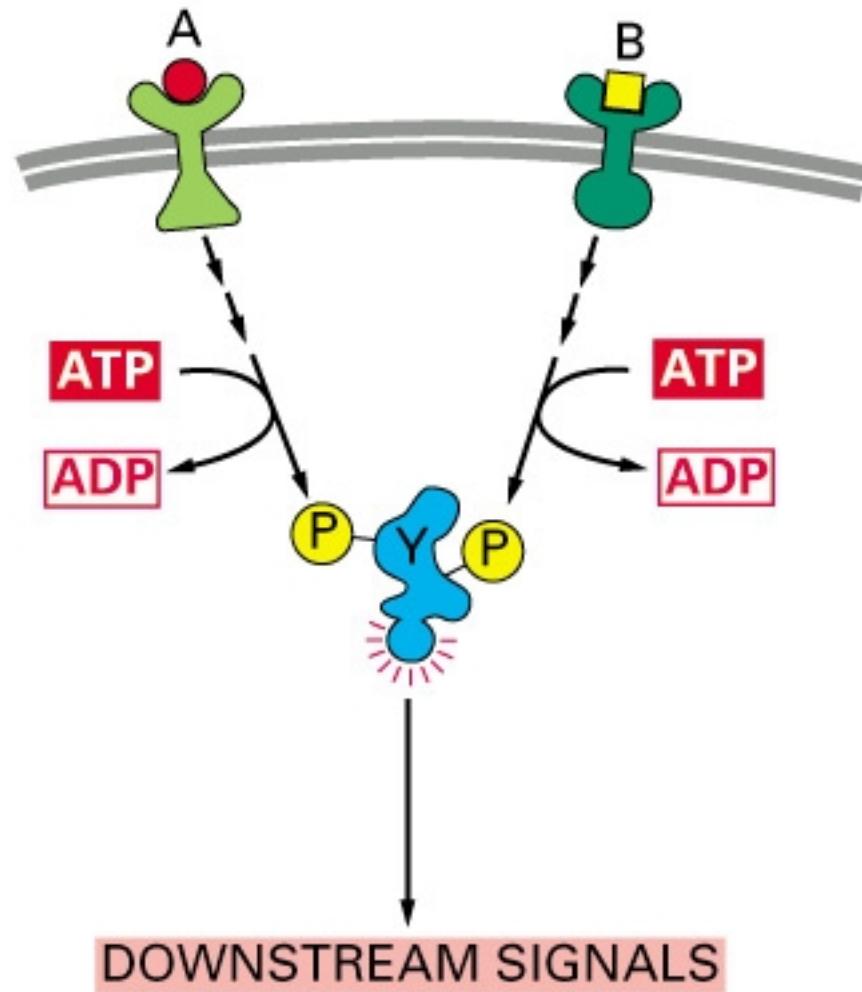
~2% of human genes

- (576 kinases):
- Ser-kinases
 - Thr-kinases
 - Others

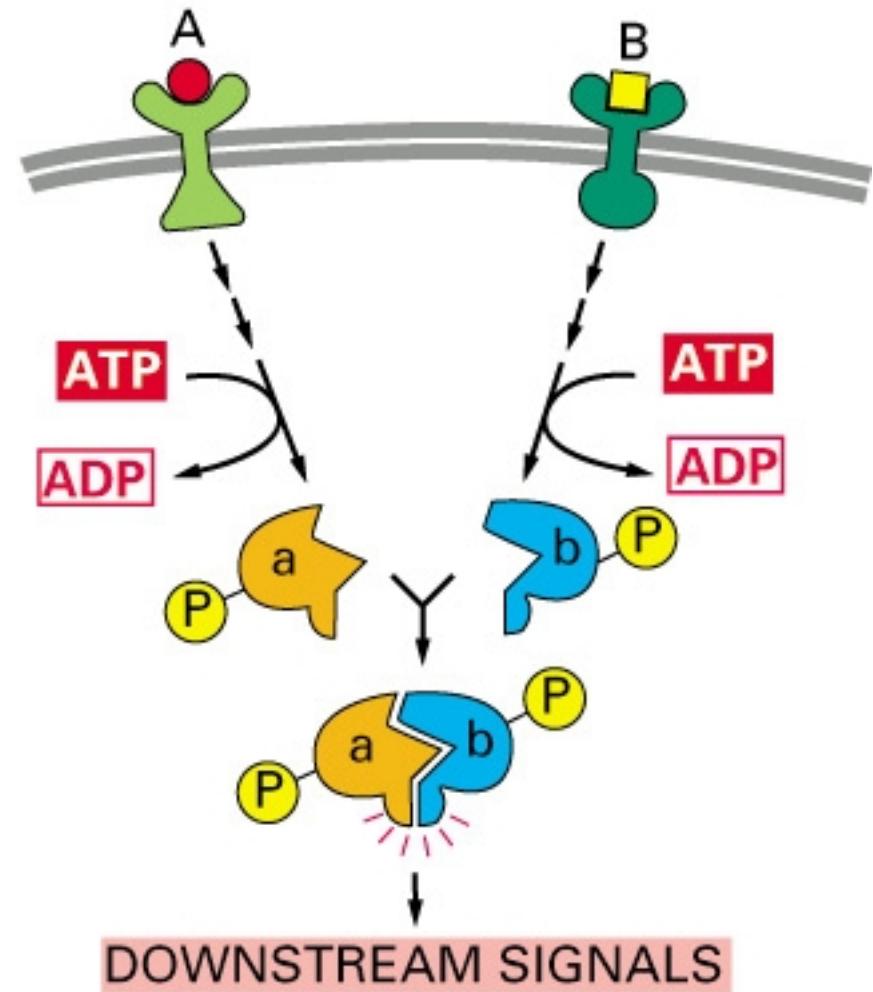
GTpases:

- monomeric
- trimeric (G-proteins)

MECHANISM OF SIGNAL INTEGRATION

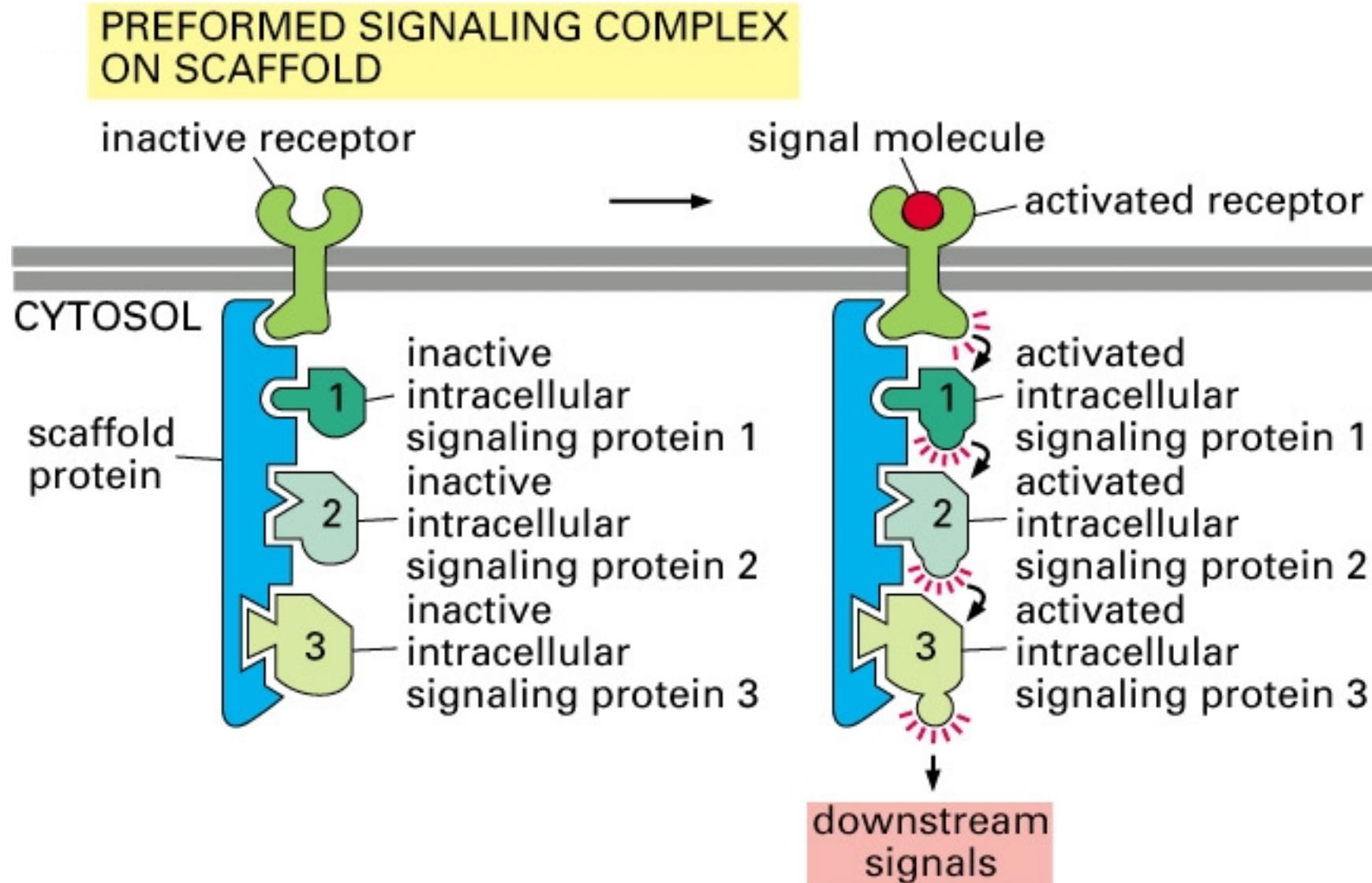


A^*B



$(A^*a)^*(B^*b)$

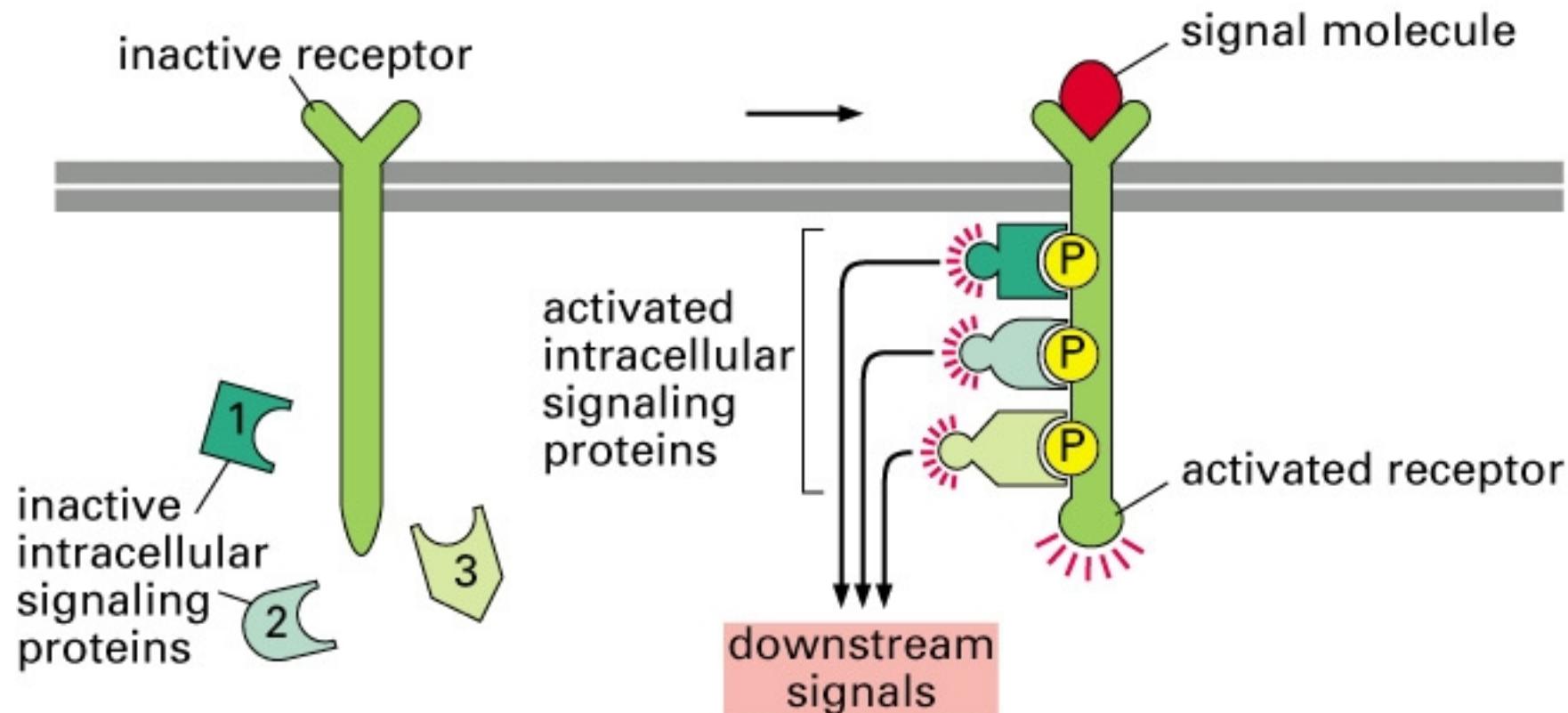
MECHANISM OF SINGALING COMPLEXES: SCAFFOLD



Usually some components are diffusible => amplification

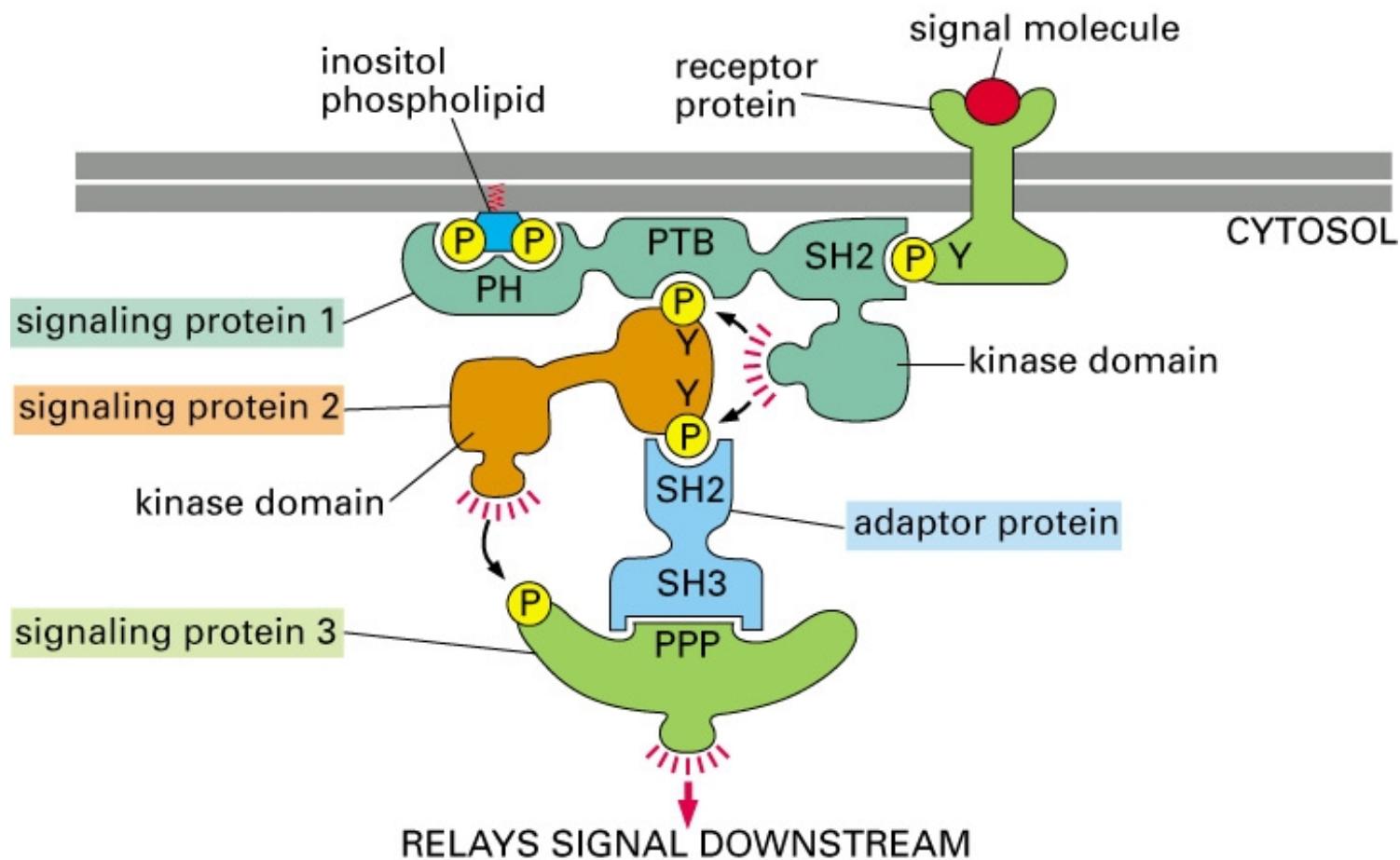
MECHANISM OF SINGALING COMPLEXES: TRANSIENT

ASSEMBLY OF SIGNALING COMPLEX FOLLOWING RECEPTOR ACTIVATION



Usually very rapid dissociation

MODULAR BINDING DOMAINS



BINDING DOMAIN

PH = Pleckstrin homology domain

PTB = phosphotyrosine-binding domain

SH2 = Src homology 2 domain

SH3 = Src homology 3 domain

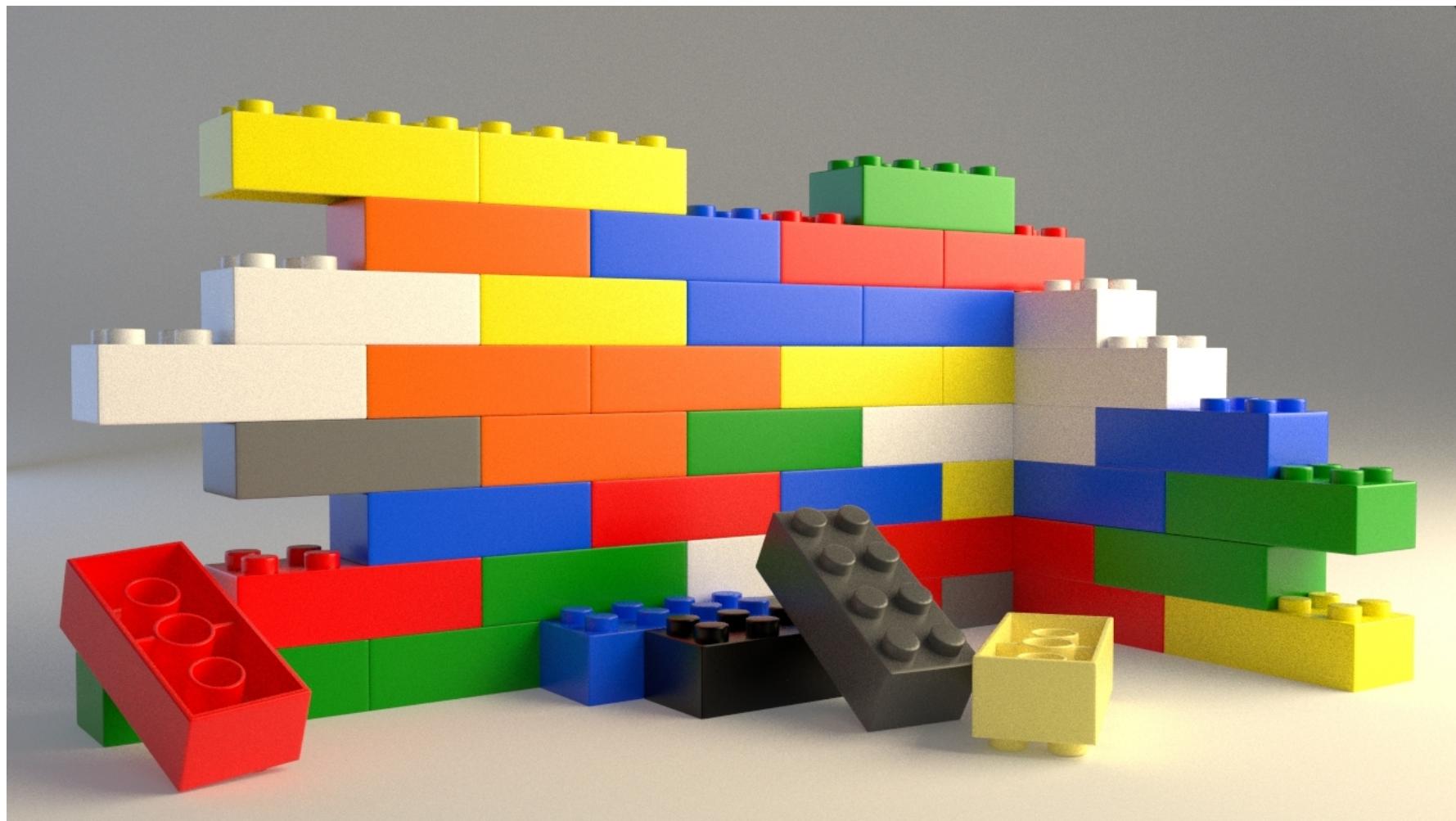
MOTIF RECOGNIZED

= phosphorylated inositol phospholipid

Y = phosphotyrosine

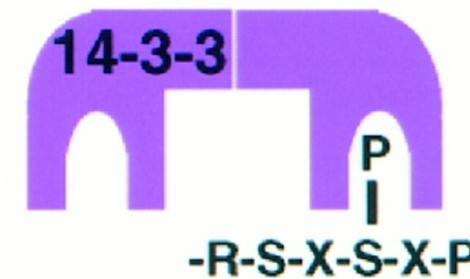
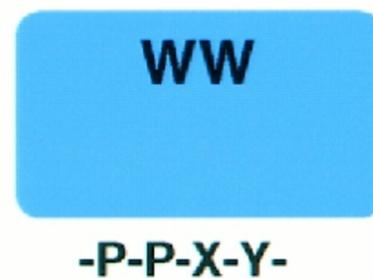
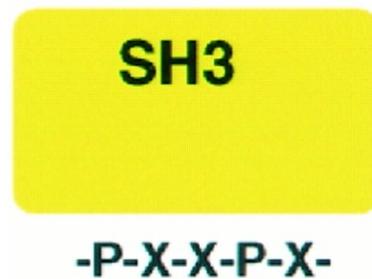
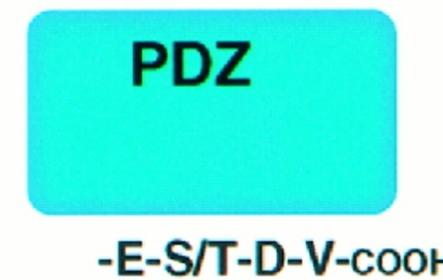
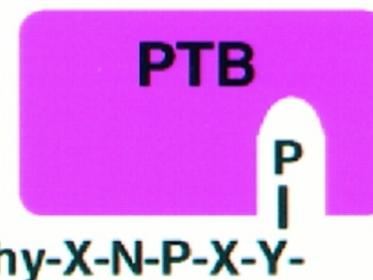
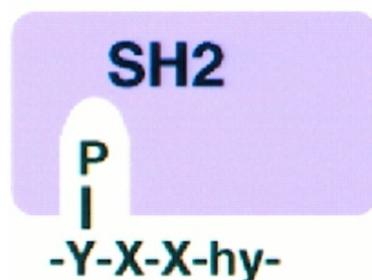
= proline-rich motif

ANALOGY: LEGO

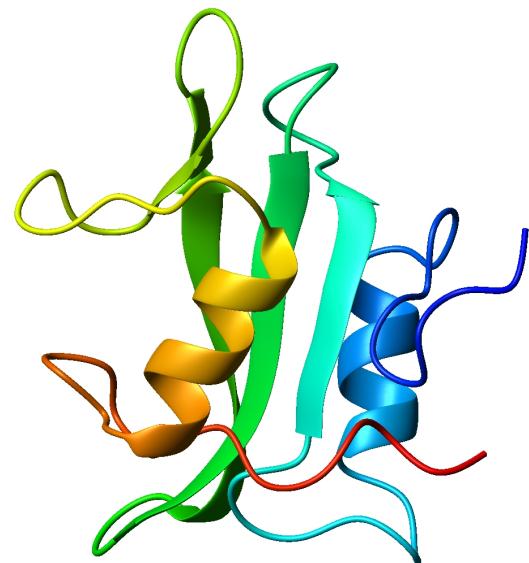


MODULAR BINDING DOMAINS

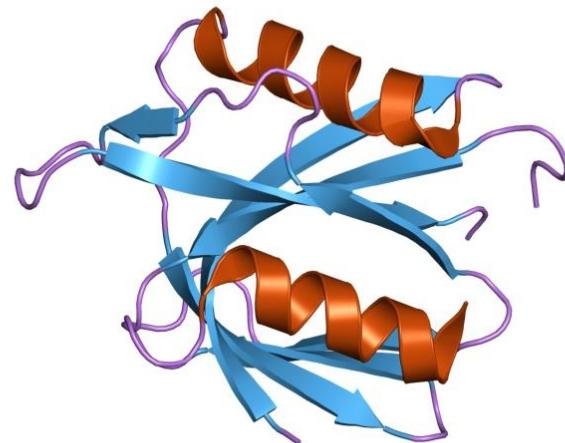
Recognition of short peptides



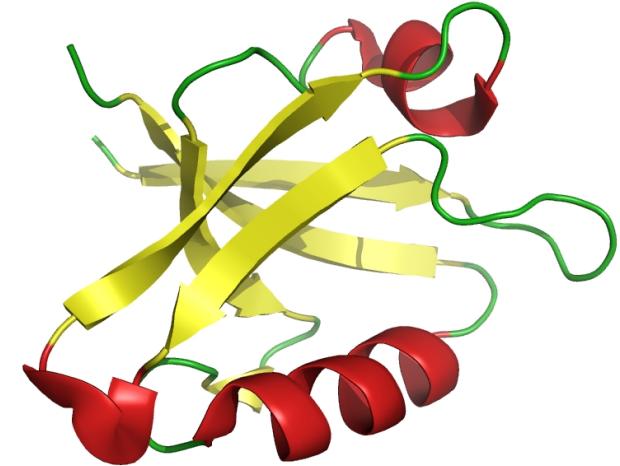
MODULAR BINDING DOMAINS



SH2



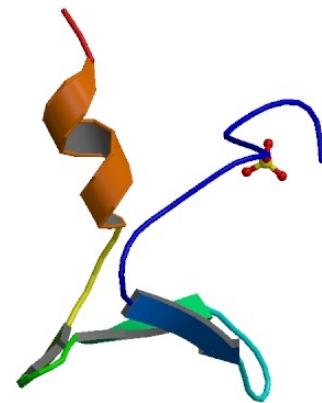
PTB



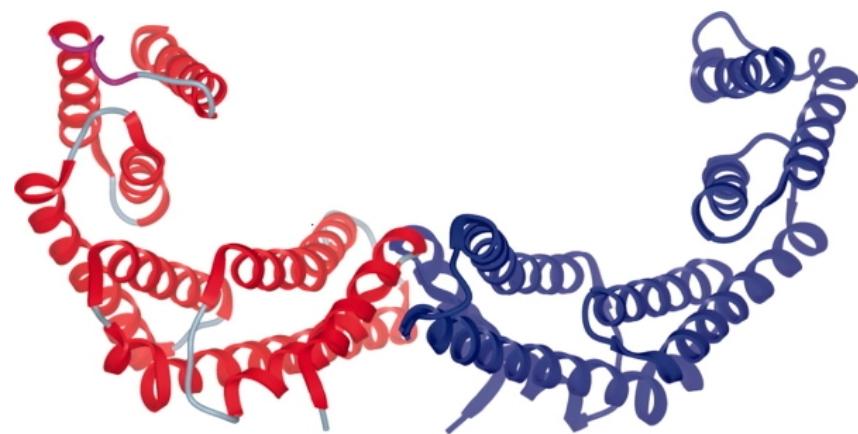
PDZ



SH3



WW



14-3-3

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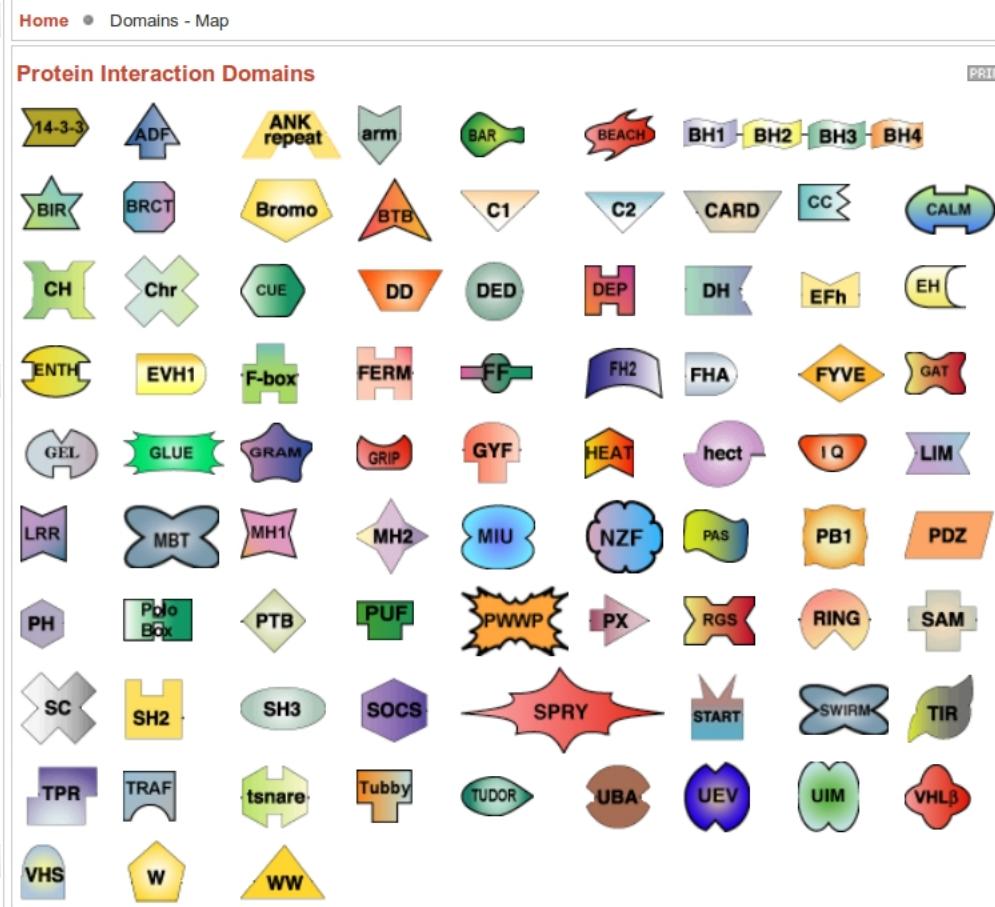
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The Pawson Lab Researching Signal Transduction



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CELL RESPONSE TO SIGNAL

➤ ~ [signal ligand] (f.i.: primary response to steroids)

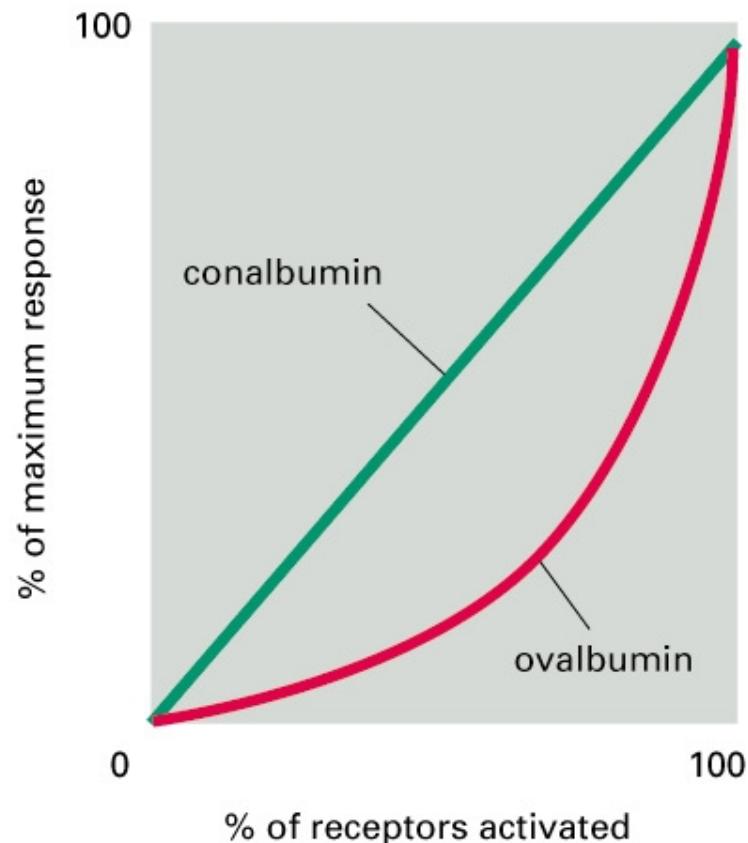
➤ Abrupt

➤ All-or-nothing (positive feedback => action potential)

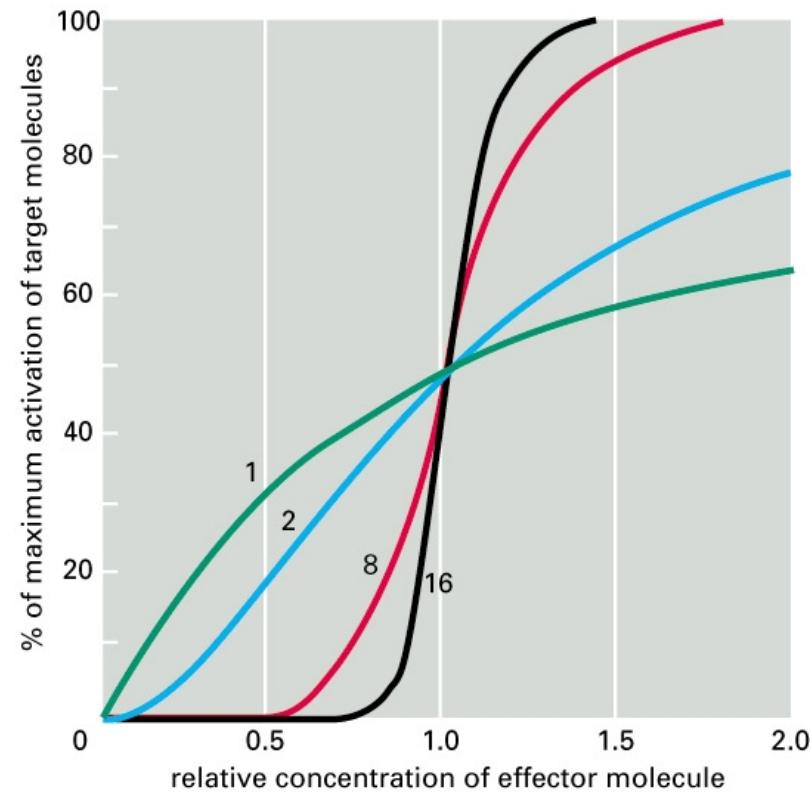
➤ Cooperativity

➤ Threshold

➤ Cell memory

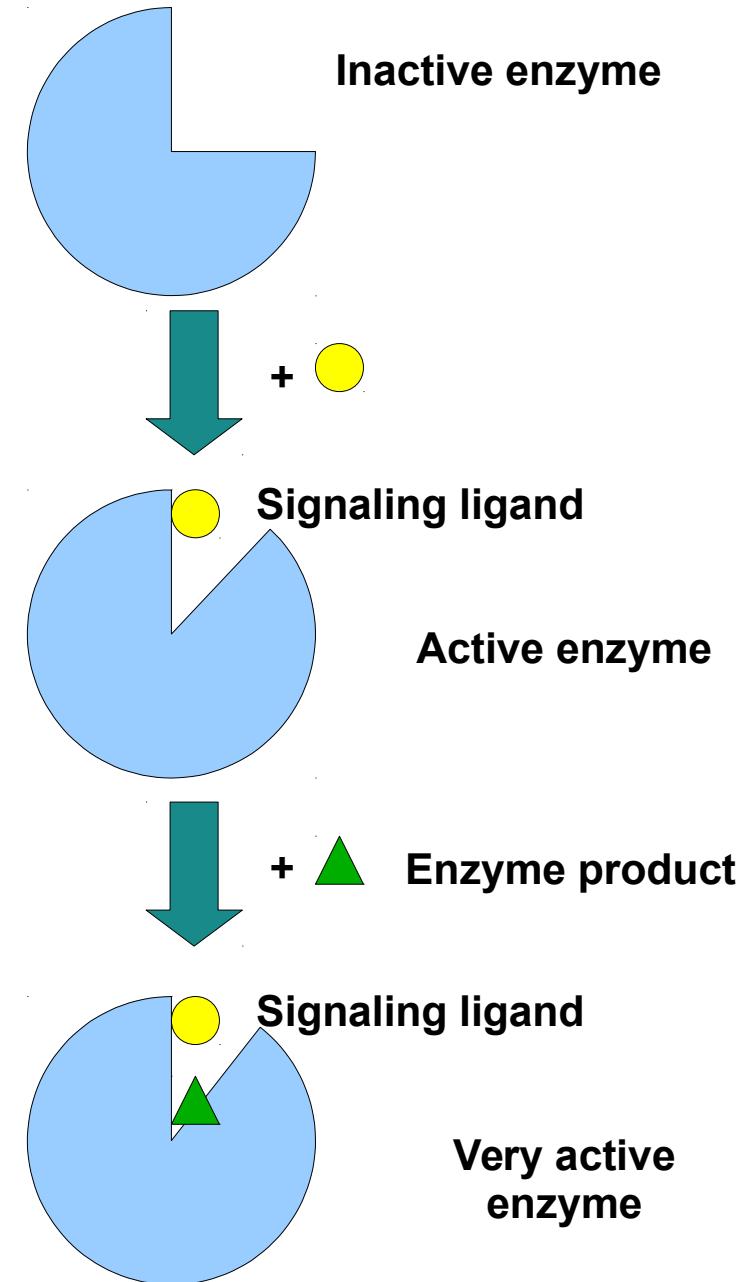
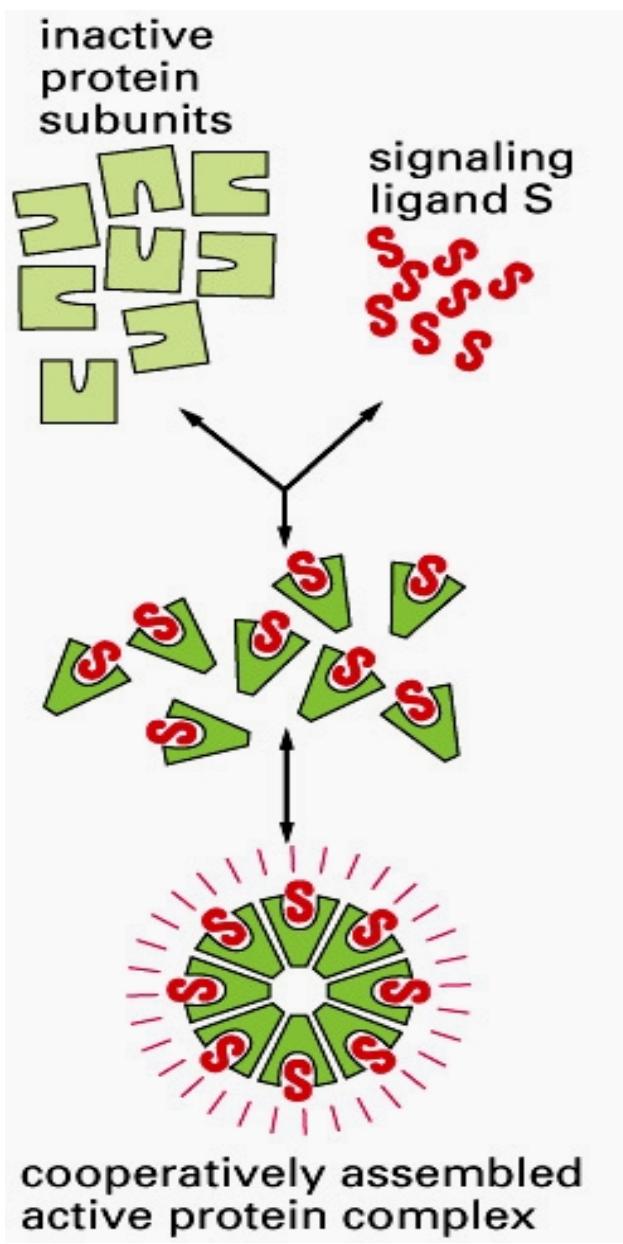


Chicken oviduct cells
stimulated by estradiol



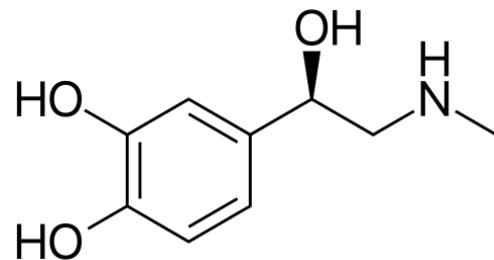
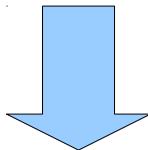
Simultaneous binding of
several effectors

CELL RESPONSE TO SIGNAL

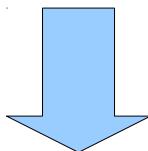


CELL RESPONSE TO SIGNAL

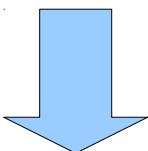
Adrenaline



G-linked protein

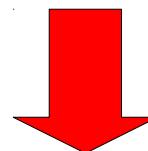


Increase in cAMP



Enzyme 1

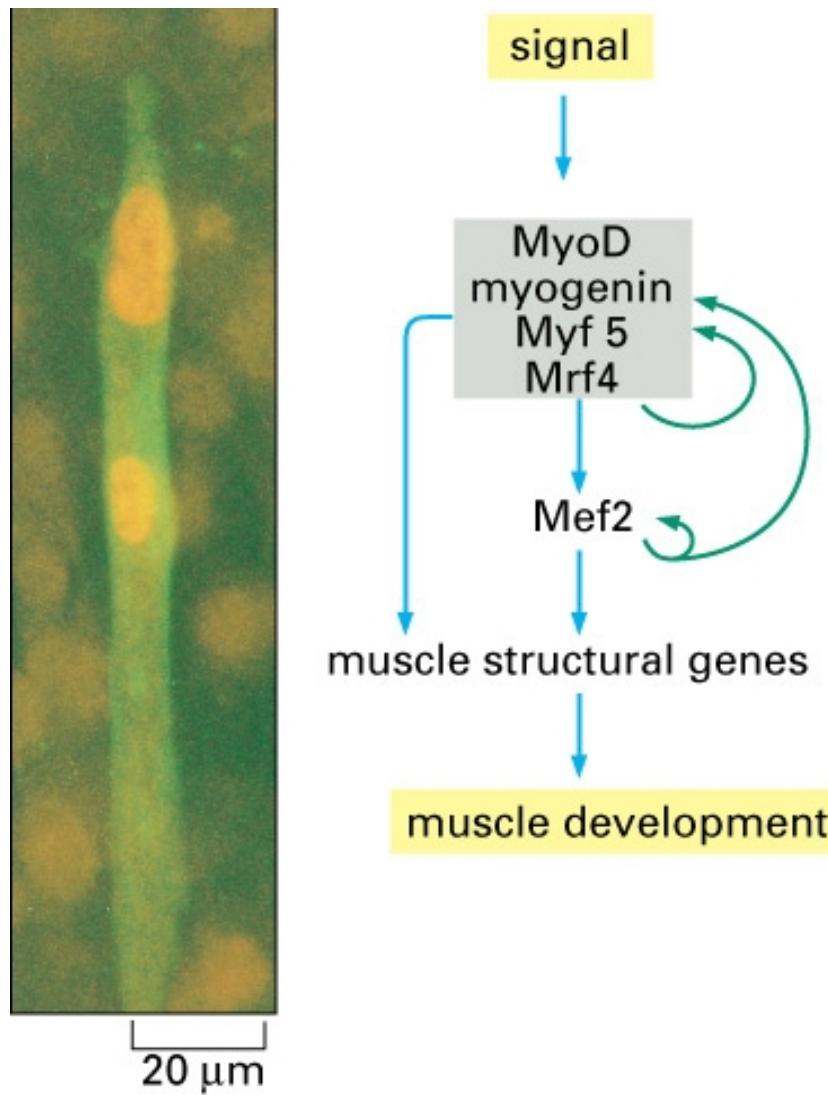
(glycogen breakdown)



Enzyme 2

(glycogen synthesis)

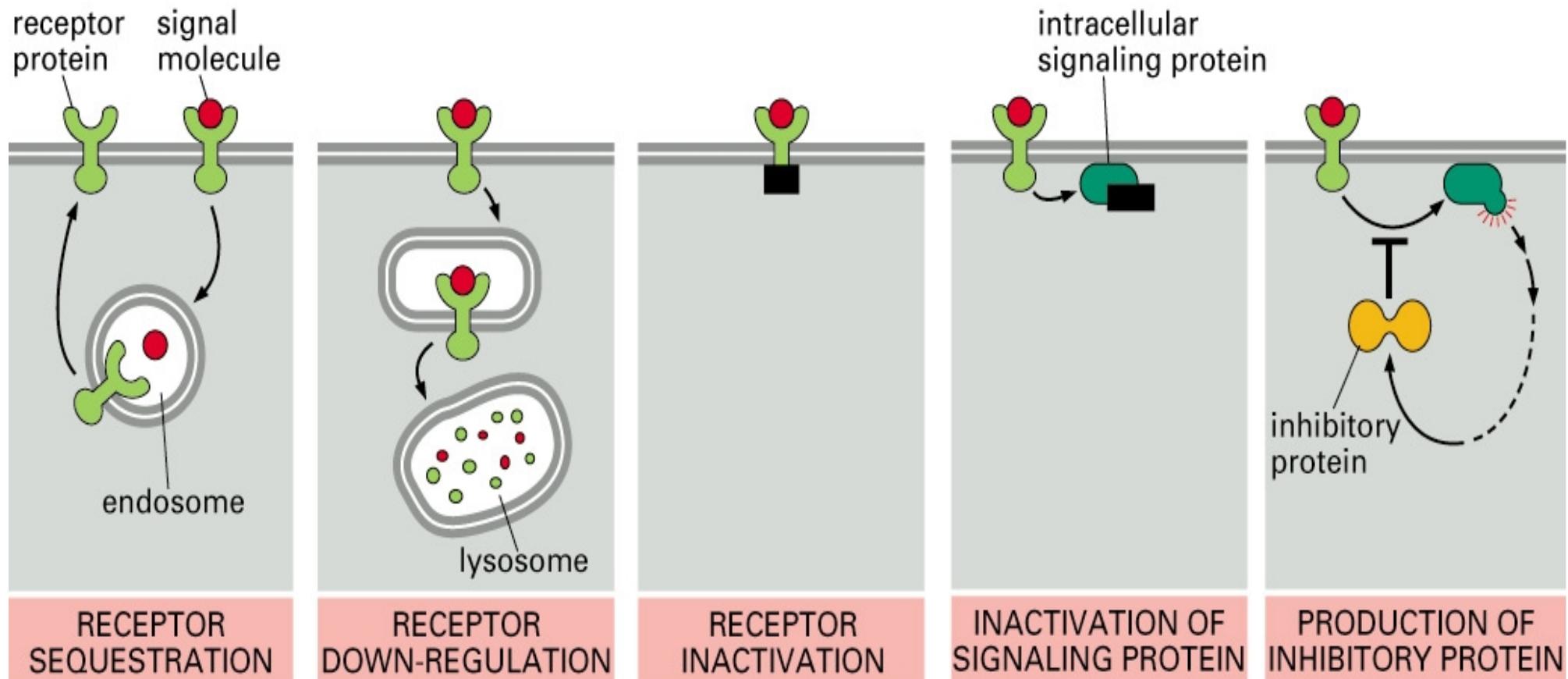
CELL MEMORY IN CELL DEVELOPMENT



Fibroblast develop into muscle cell after gene injection.

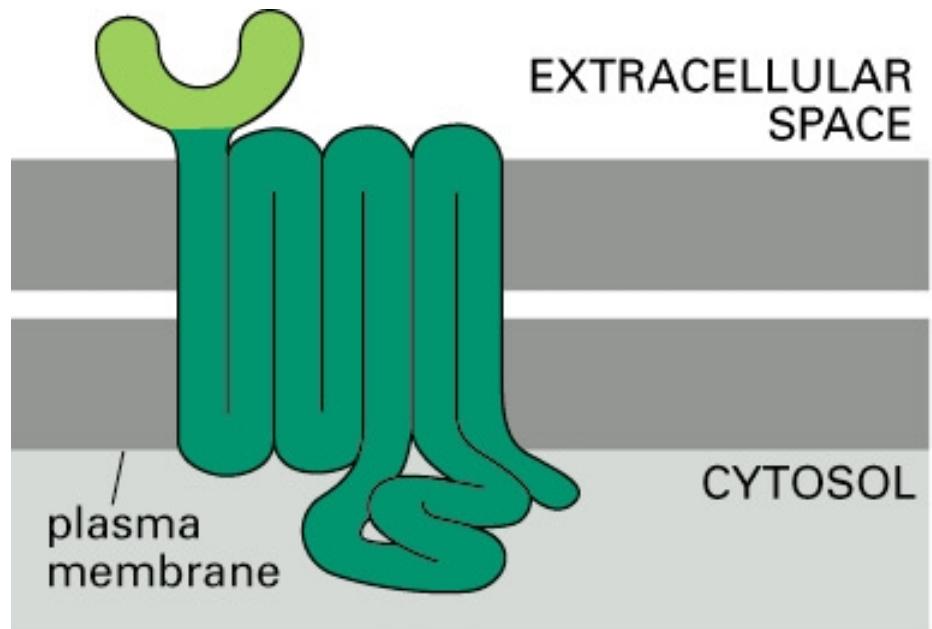
CELLS ADJUST SENSITIVITY TO A SIGNAL

- Reversible changes/adaptation to the concentrations of signals
- Negative feedback with a delay



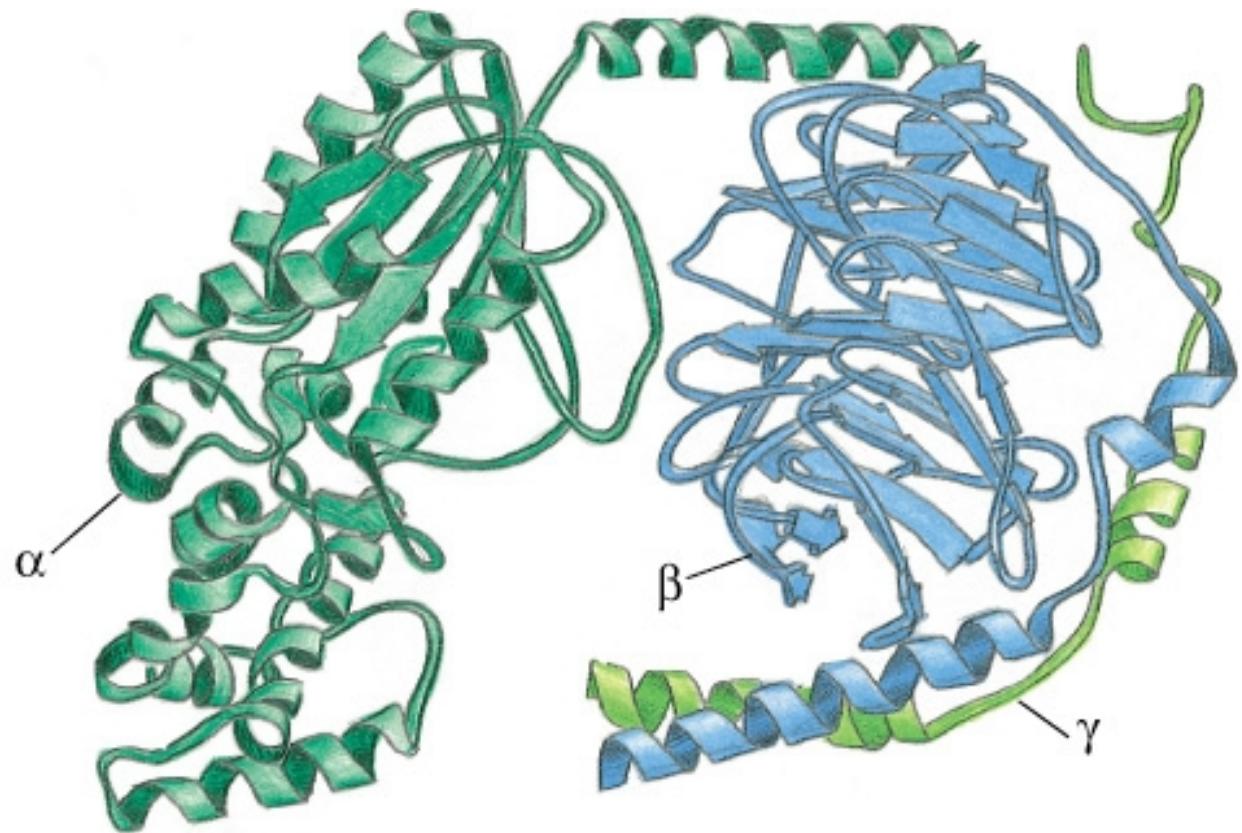
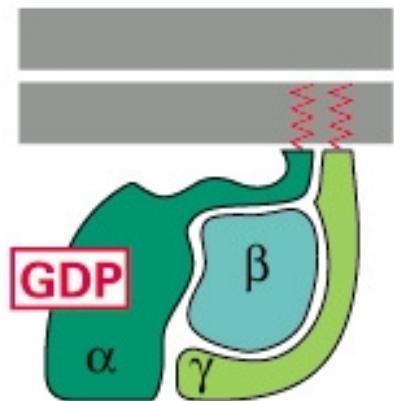
G-PROTEIN-LINKED RECEPTORS

- In all eukaryotes
- 5% of genes in *C. elegans*
- ~ 10^3 genes in mammals
- Variable signal molecules:
 - proteins
 - peptides
 - aa and fatty acid derivatives
- The same ligand => different receptors
 - adrenaline
 - acetylcholine
 - serotonin
- Similar structure (7 TMD)
- Function in senses
- Major target for drug discovery

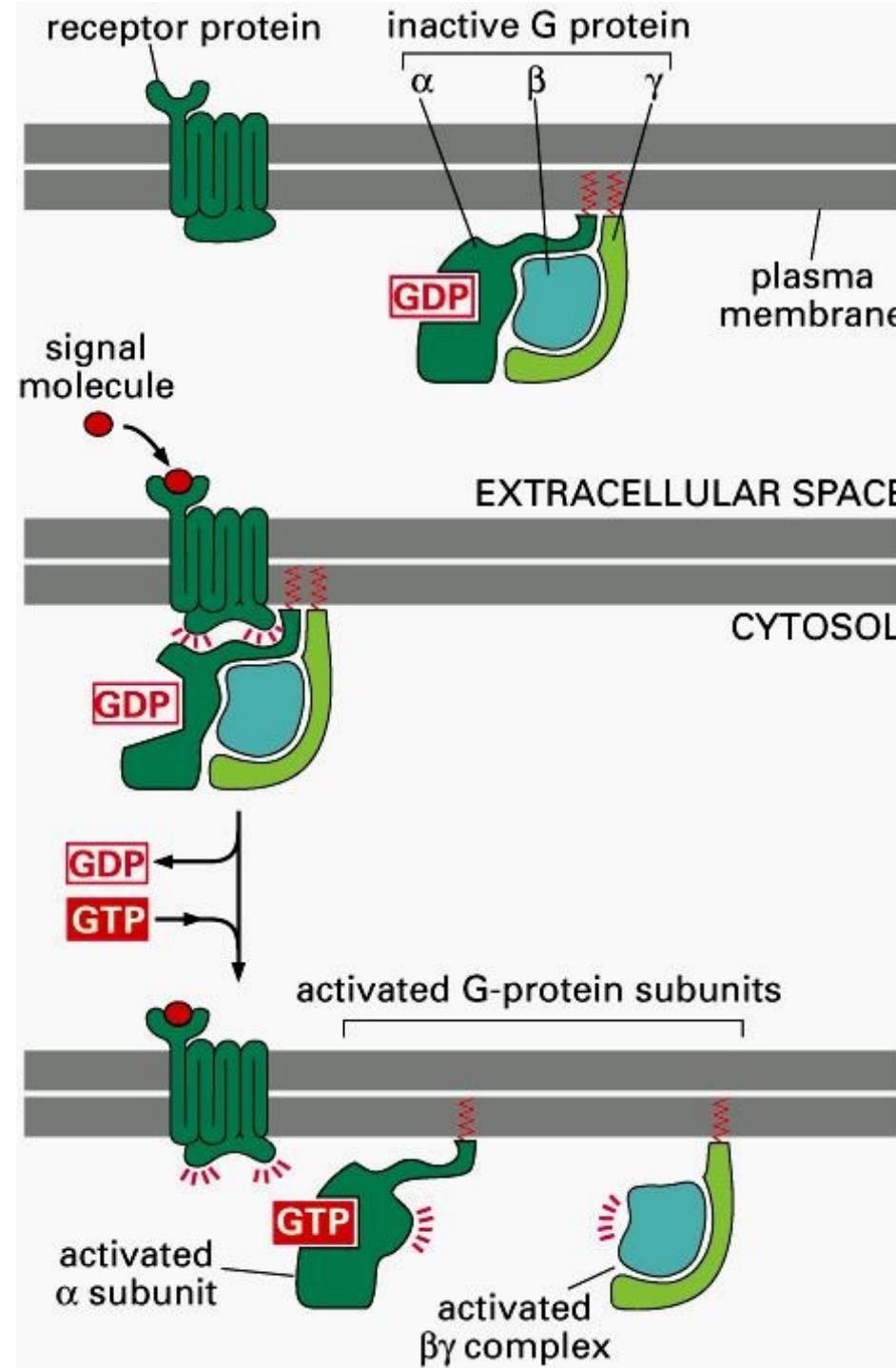


G-PROTEINS

GTP-binding proteins anchored by lipids

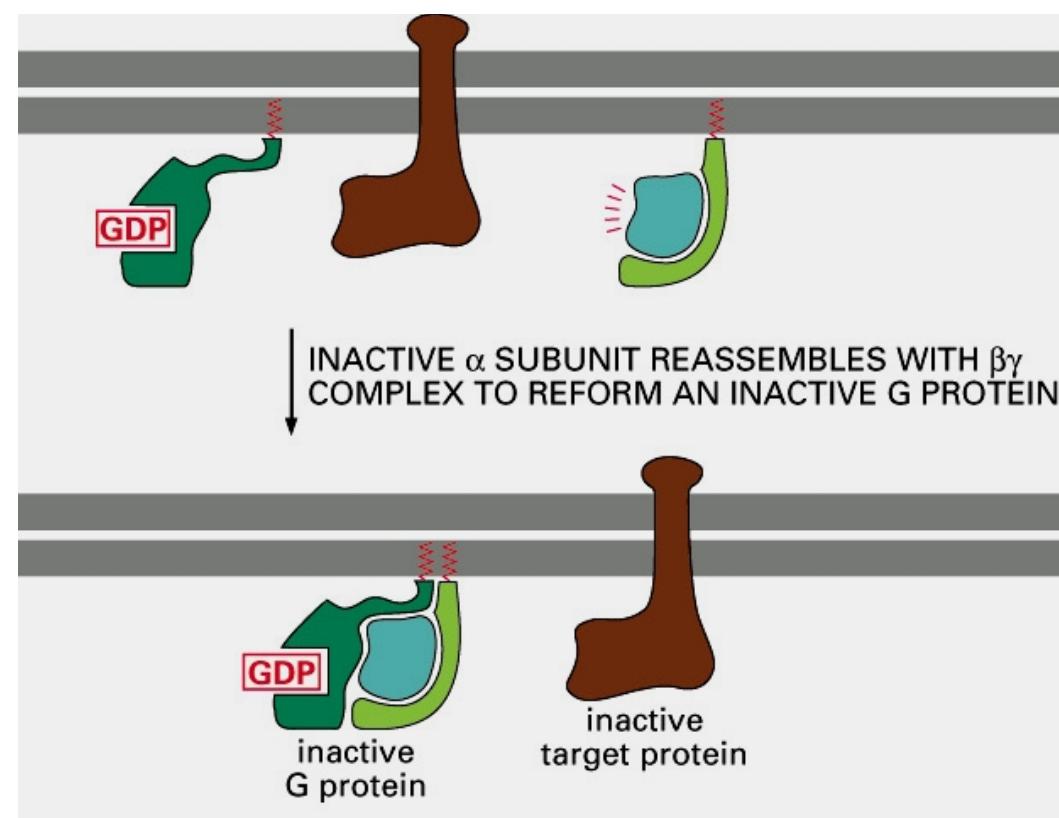
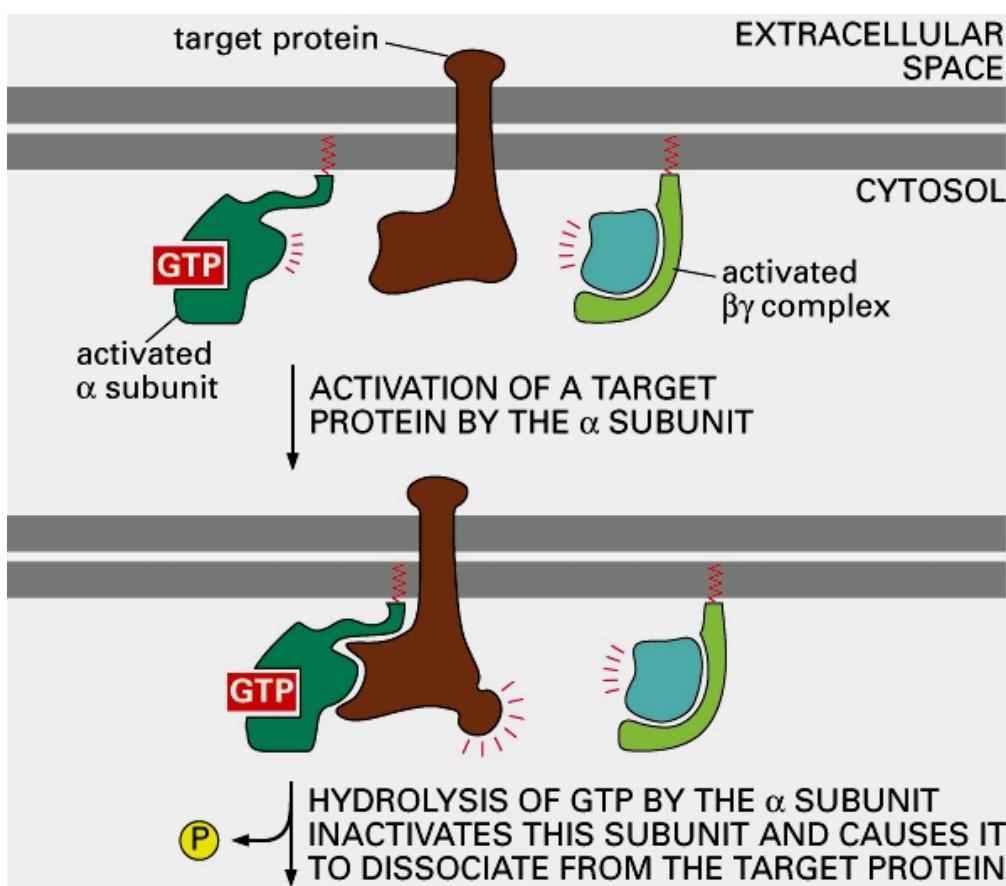


G-PROTEINS ACTIVATION

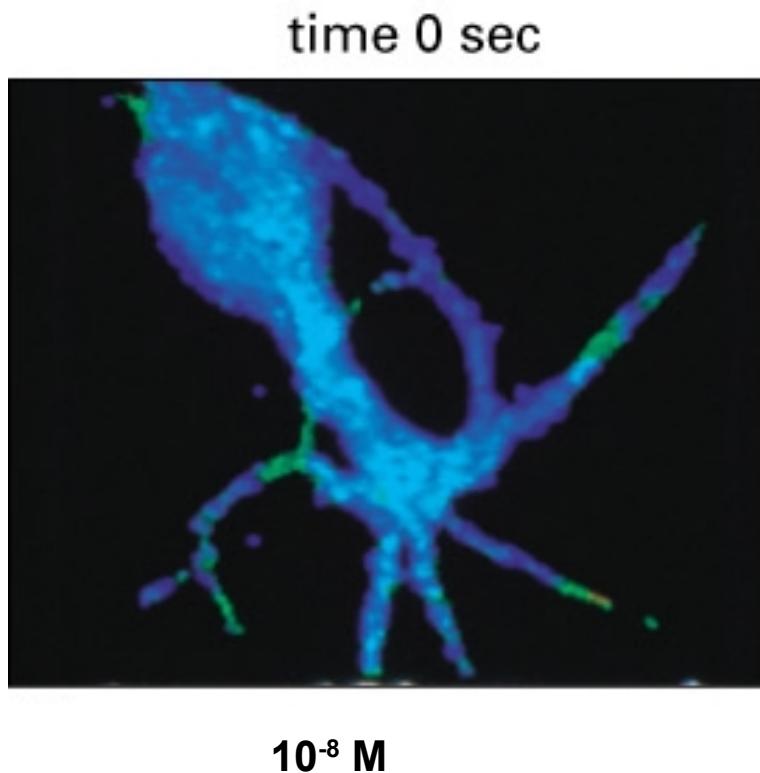


G-PROTEINS ACTIVATION

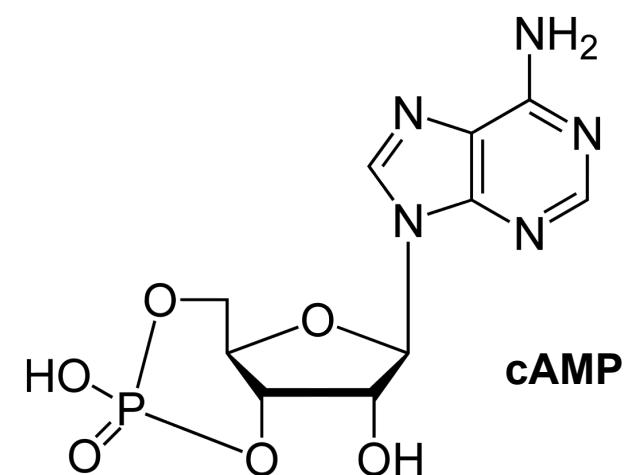
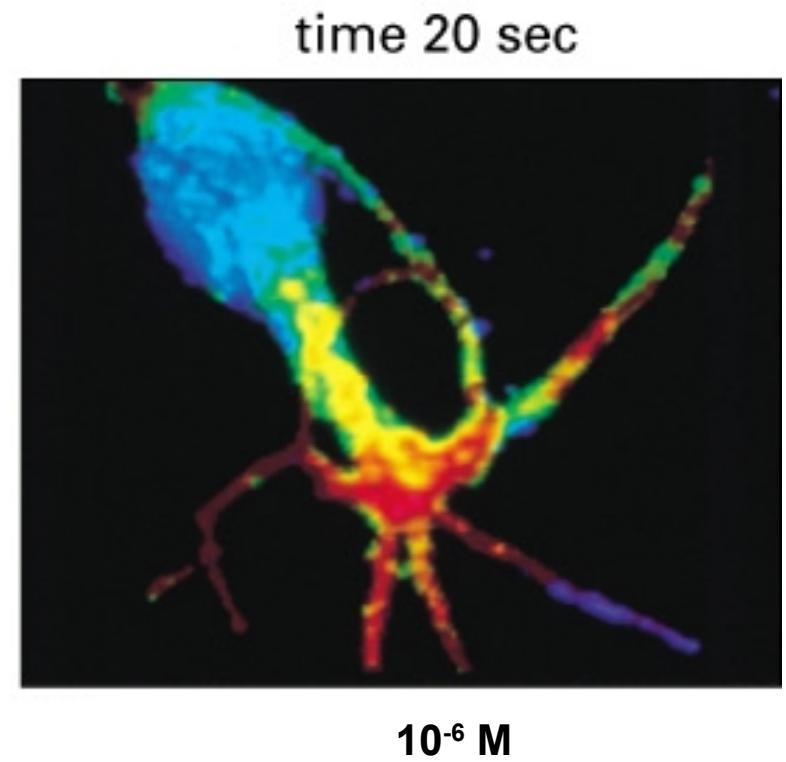
- α -subunit is GTPase activated by conformational changes through unbinding
- Regulator of G-protein signaling (RGS) proteins: enhancing α -subunit activity
- 25 RGS proteins in human



REGULATION OF CYCLIC AMP PRODUCTION THROUGH G-PROTEIN SIGNALING

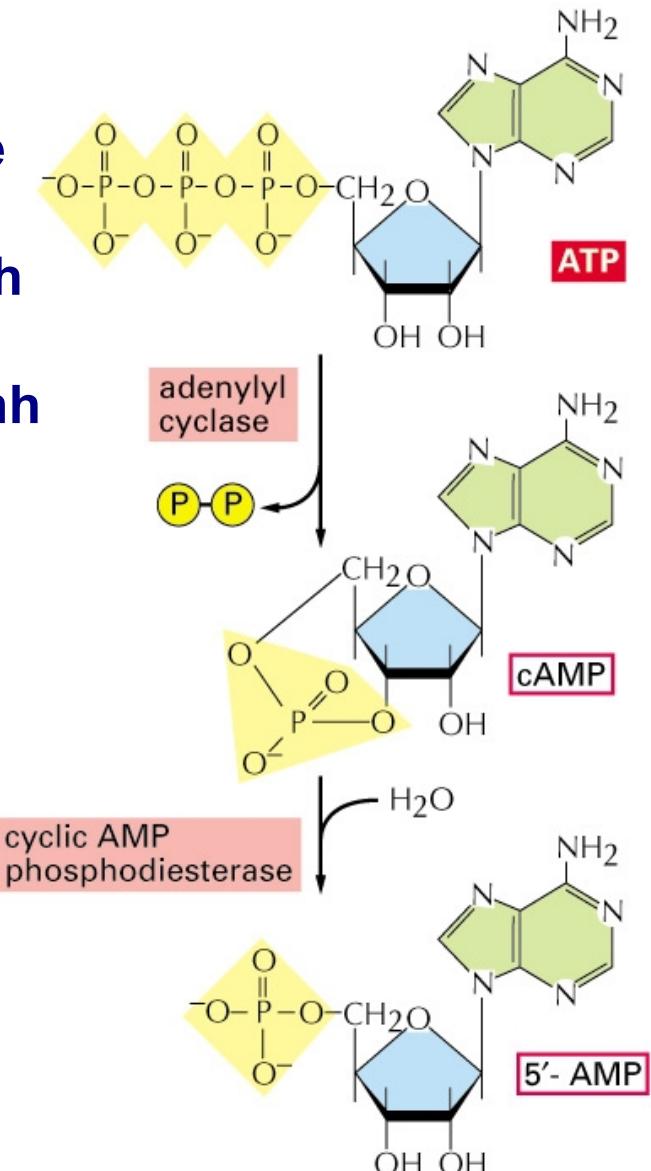


+ serotonin
→



REGULATION OF CYCLIC AMP PRODUCTION THROUGH G-PROTEIN SIGNALING

- One G-protein (G_s) activates adenylyl cyclase
- An another G-protein (G_i) inhibits adenylyl cyclase
- Cholera toxin: ADP-ribose $\Rightarrow \alpha$ -subunit of $G_s \Rightarrow$ inh
- Petruissis toxin: ADP-ribose $\Rightarrow \alpha$ -subunit of $G_i \Rightarrow$ inh
- At least 4 hormones-activators

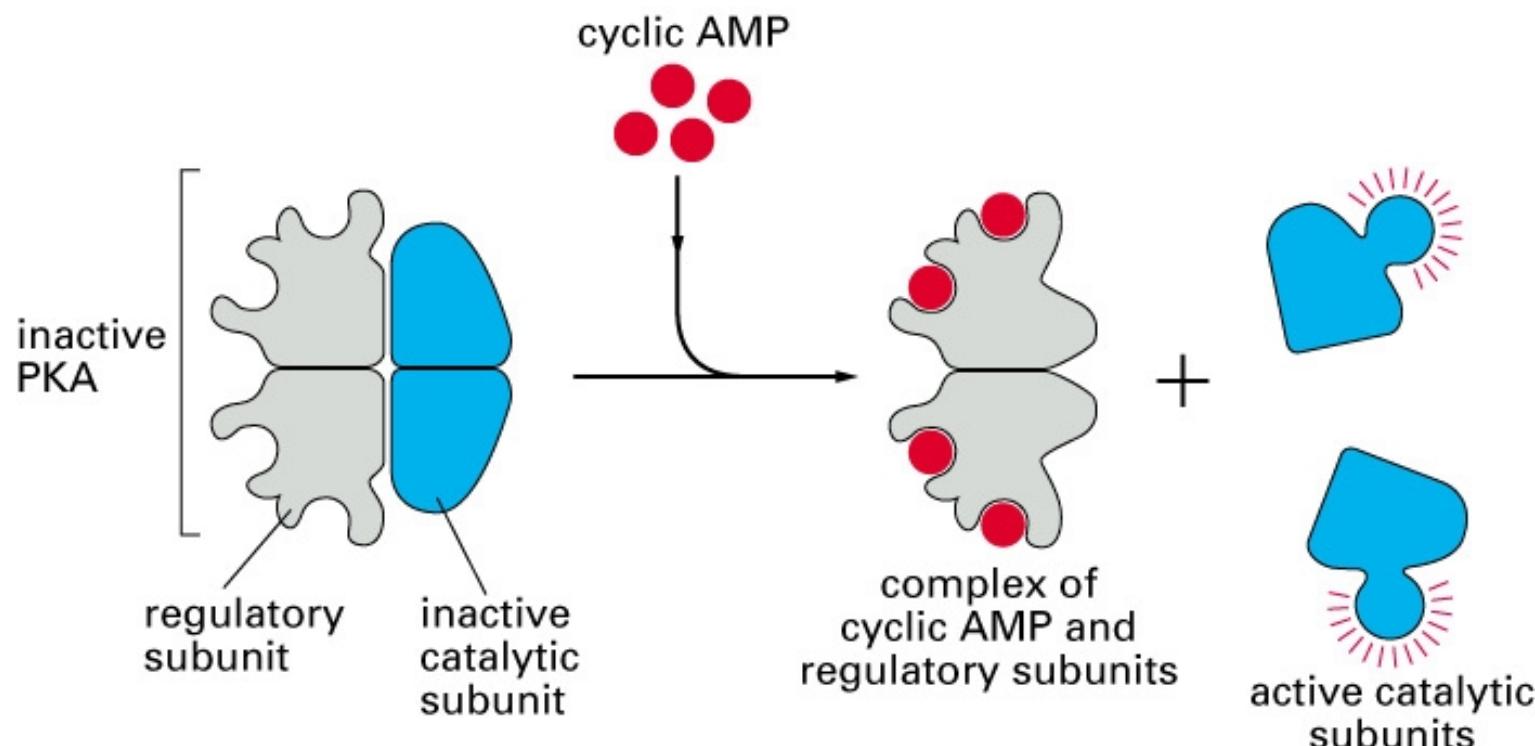


HORMONE-INDUCED RESPONSES MEDIATED BY CYCLIC AMP

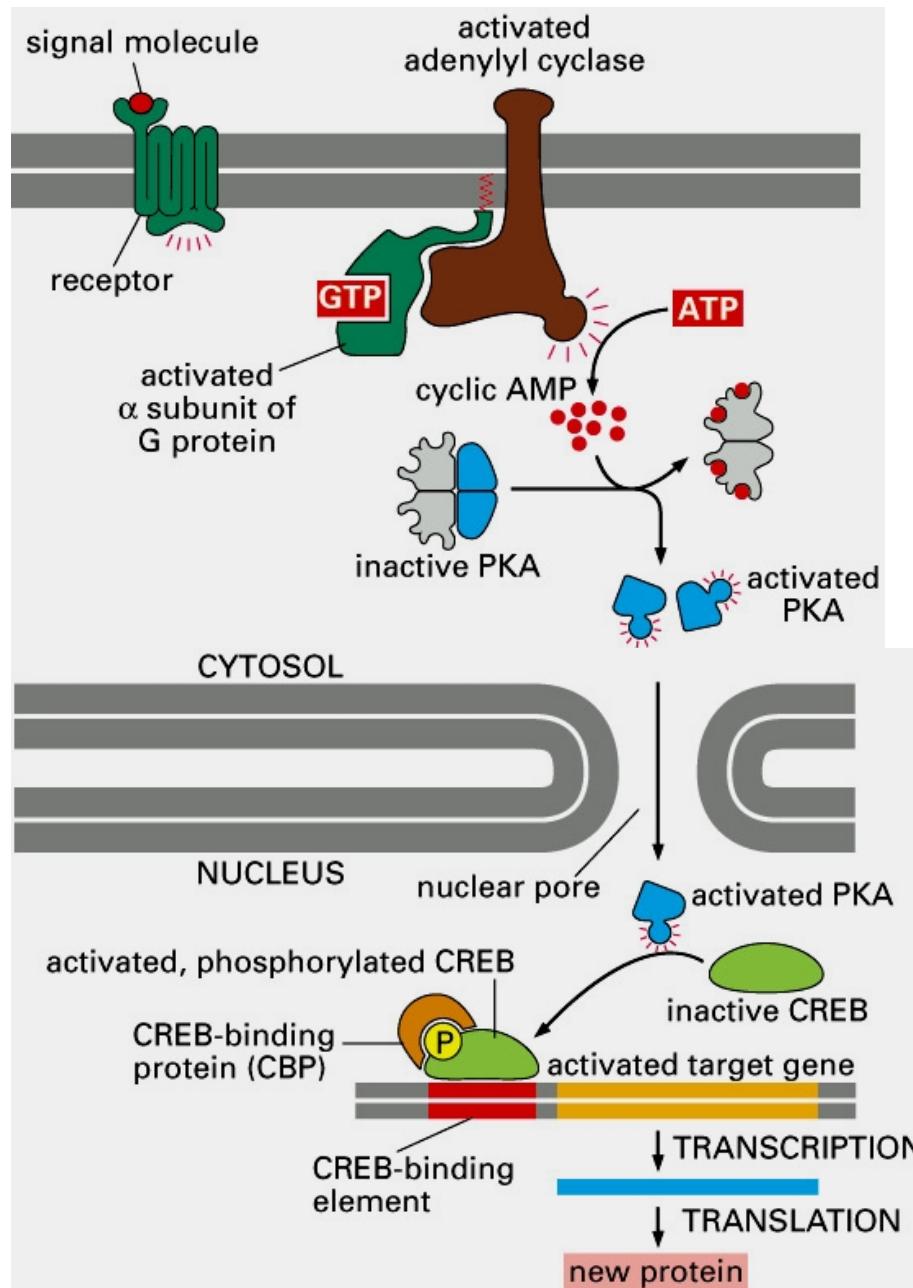
| TARGET TISSUE | HORMONE | MAJOR RESPONSE |
|----------------|------------------------------------|---|
| Thyroid gland | thyroid-stimulating hormone (TSH) | thyroid hormone synthesis and secretion |
| Adrenal cortex | adrenocorticotropic hormone (ACTH) | cortisol secretion |
| Ovary | luteinizing hormone (LH) | progesterone secretion |
| Muscle | adrenaline | glycogen breakdown |
| Bone | parathormone | bone resorption |
| Heart | adrenaline | increase in heart rate and force of contraction |
| Liver | glucagon | glycogen breakdown |
| Kidney | vasopressin | water resorption |
| Fat | adrenaline, ACTH, glucagon, TSH | triglyceride breakdown |

CYCLIC-AMP-DEPENDENT PROTEIN KINASE (PKA)

- Transfers P_i from ATP to Ser/Thr of target proteins
- PKA anchoring proteins => cytoskeleton
- Different speed:
 - in muscles very rapid in glycogen metabolism ~ seconds
 - somastatin very slow ~ hours



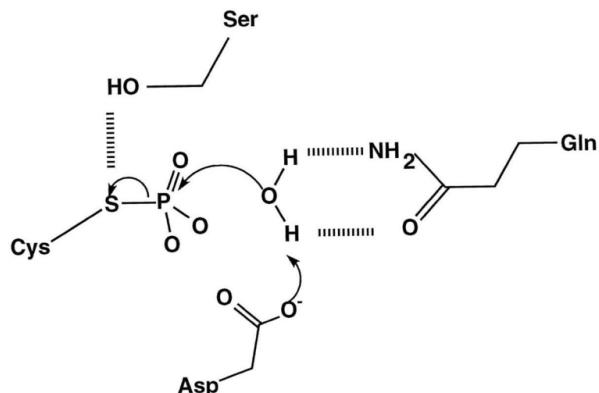
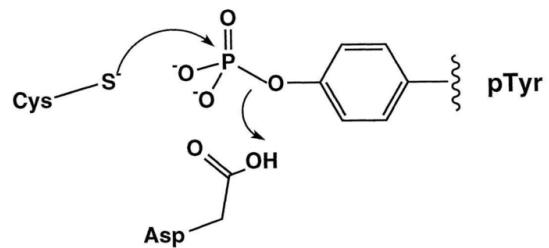
CYCLIC-AMP-DEPENDENT PROTEIN KINASE (PKA)



SERINE/THREONINE PHOSPHOPROTEIN PHOSPHATASES

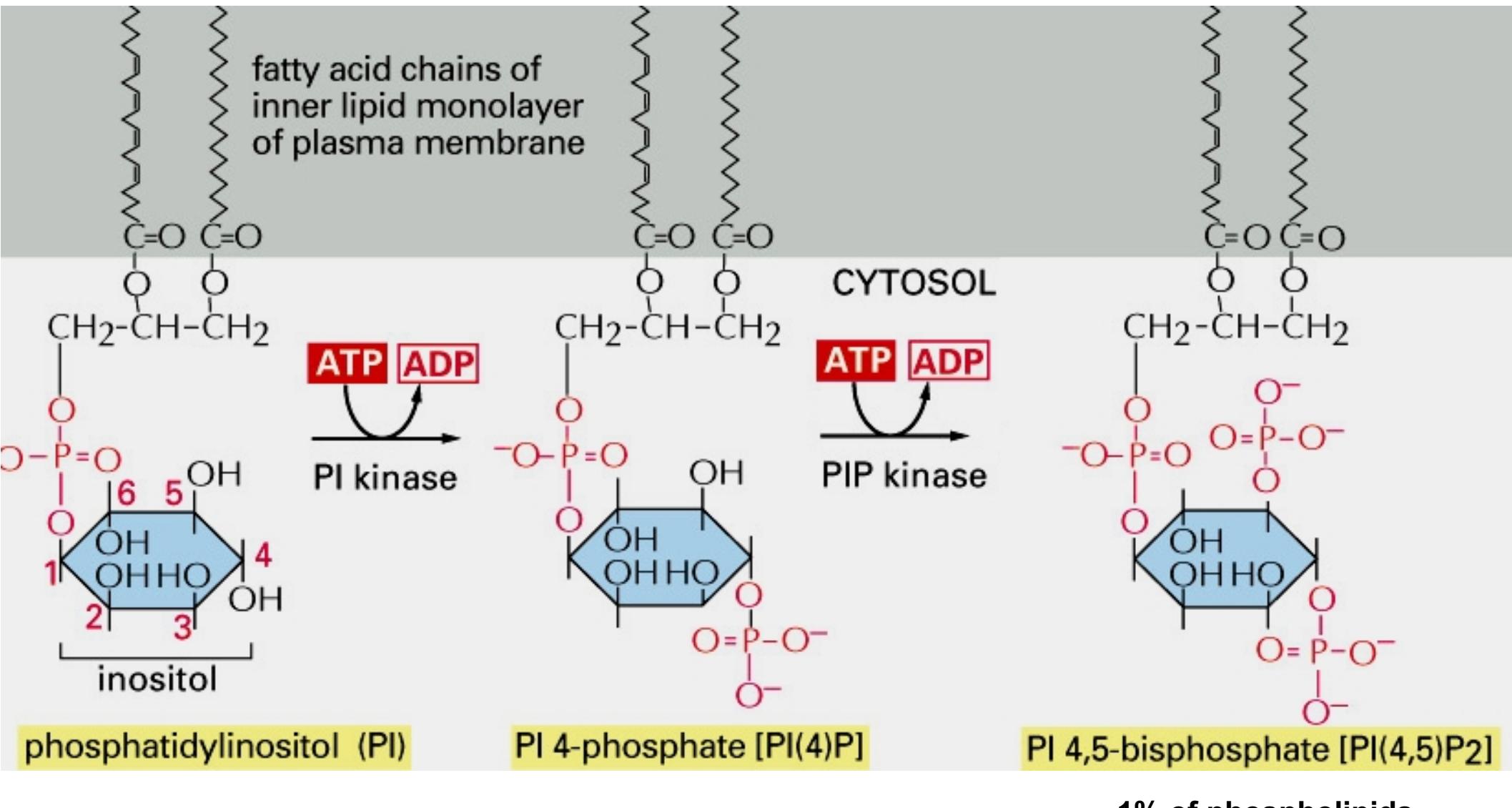
➤ Protein phosphatases \leftrightarrow kinases

- phosphatase I: dephosphorylation of PKA targets, f.i. inactivation of CREB
- phosphatase IIA: different Ser/Thr kinases
- phosphatase IIB (calcineruine): activation by Ca^{2+} , specific for brain
- phosphatase IIB: minor, structurally unrelated

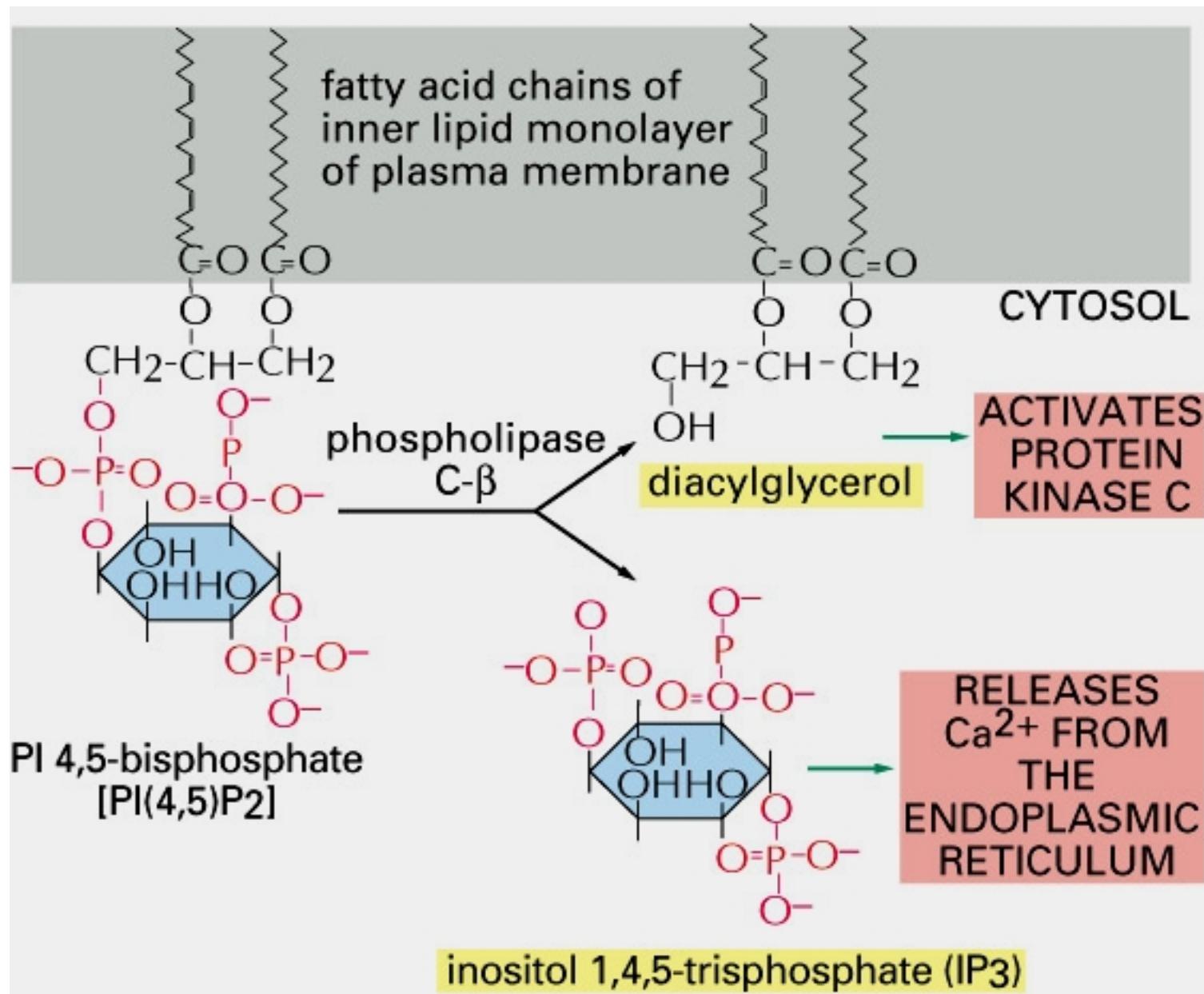


PHOSPHOLIPASE C- β

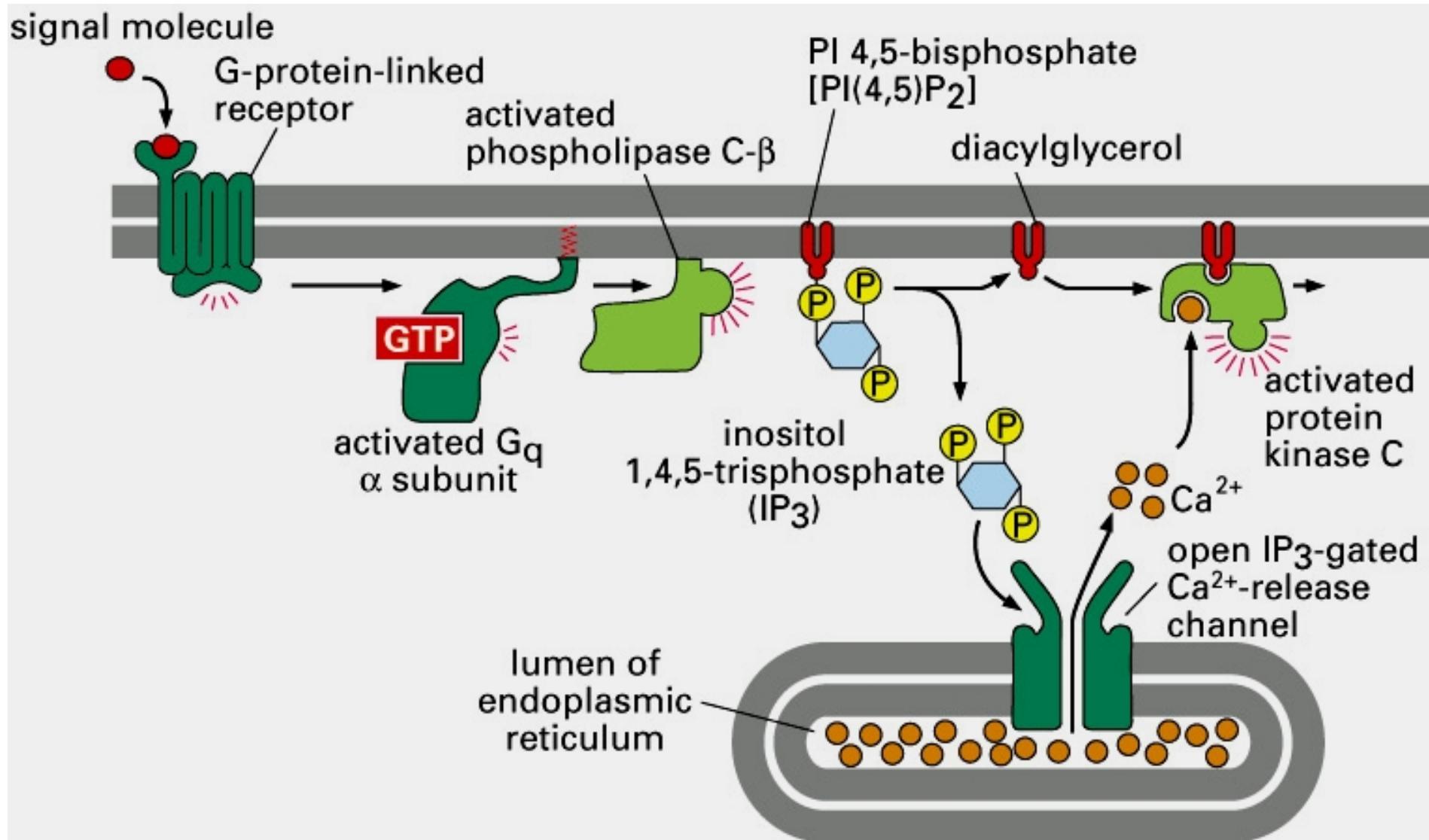
G-protein (G_q) activation \Rightarrow $[Ca^{2+}]$ increase



PHOSPHOLIPASE C- β



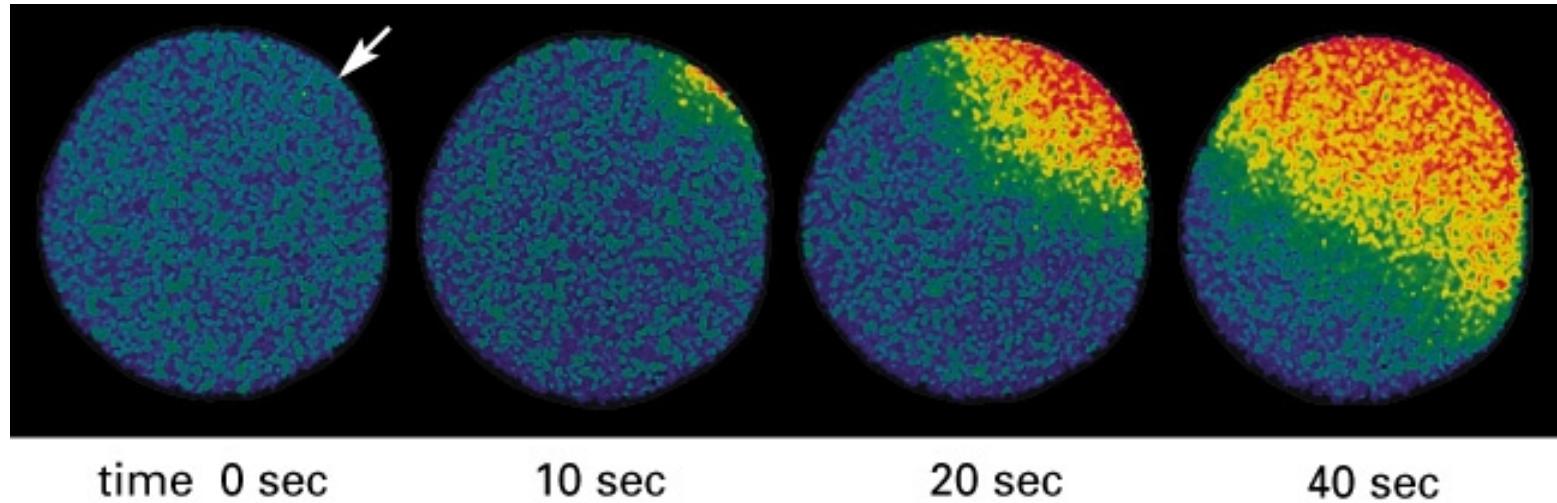
INOSITOL PHOSPHOLIPID PATHWAYS



INOSITOL PHOSPHOLIPID PATHWAYS

- IP₃-gated Ca²⁺ release in ER:
 - IP₃ => IP₂
 - IP₃ => IP₄ (another intracellular mediator)
 - Ca²⁺ is pumped out
- Diacylglycerol:
 - cleaved to arachidonic acid => synthesis lipids (eicosanoid)=> prostaglandins (inflammatory responses)
 - activation of protein kinase C (PKC) => target protein phosphorylation
- Mimicking components of two branches of signaling => drugs development

CA²⁺: UBIQUITOUS INTRACELLULAR MESSENGER

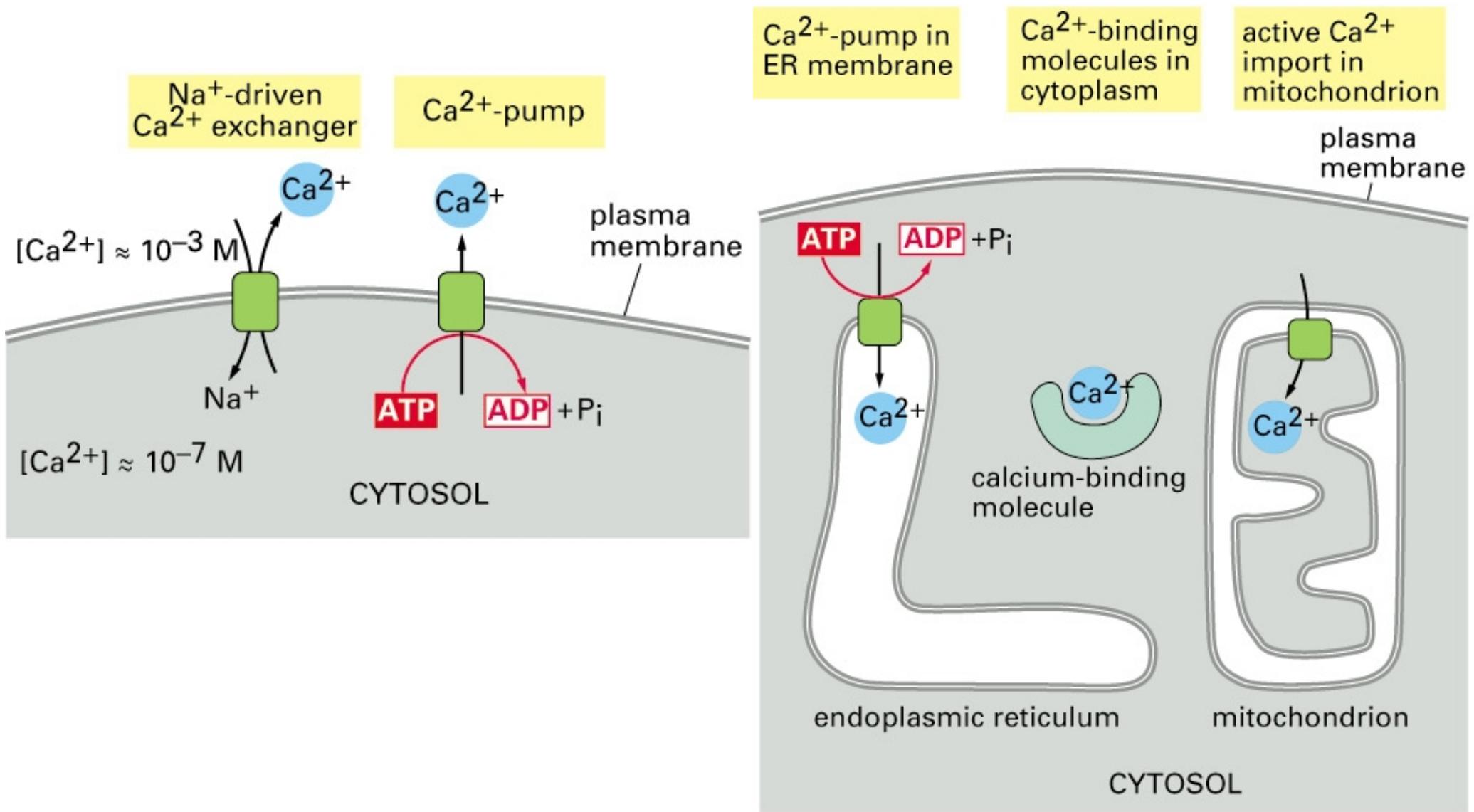


Starfish egg fertilization (Ca²⁺ sensitive fluorescent dye)

CA₂₊: UBIQUITOUS INTRACELLULAR MESSENGER

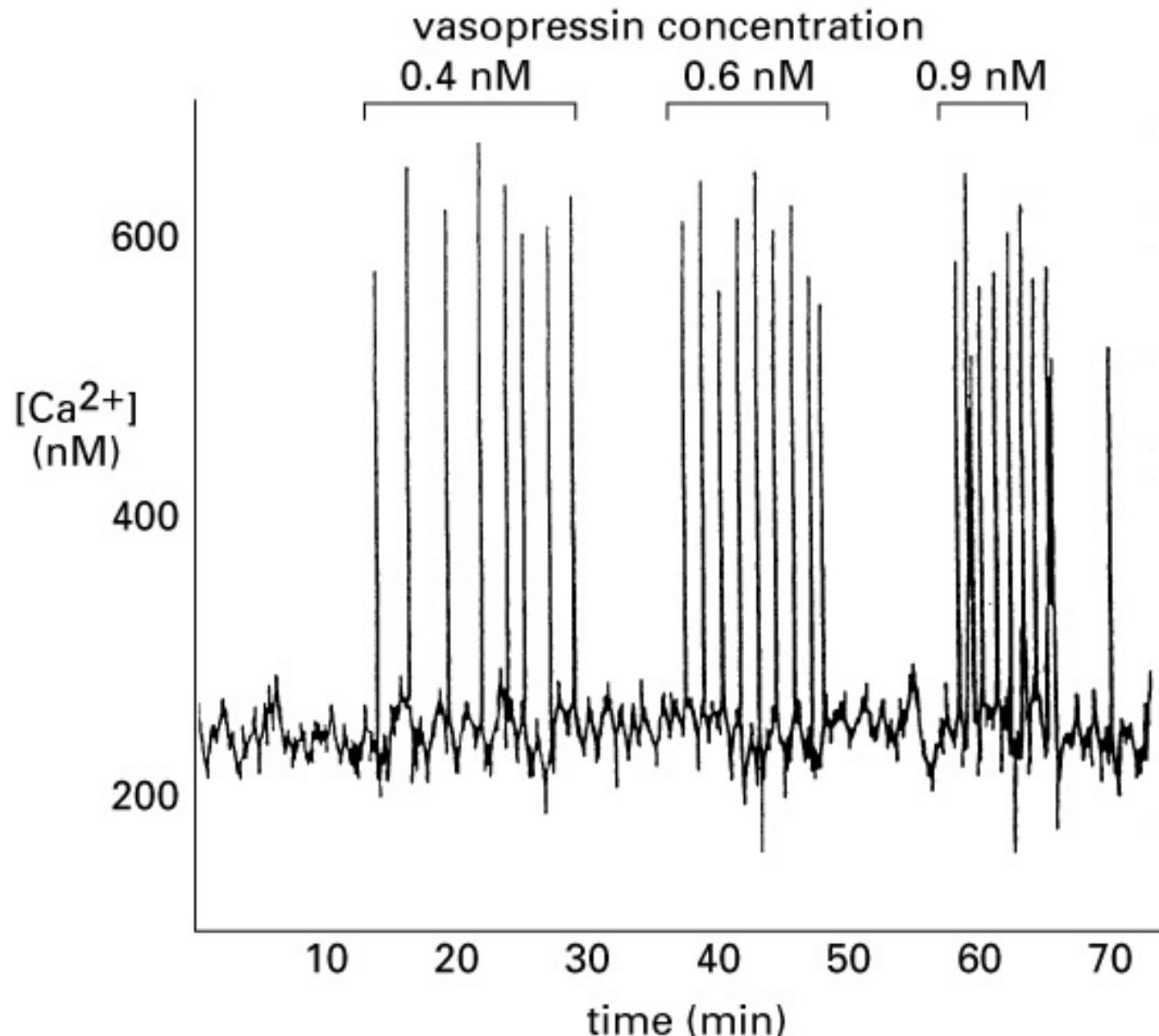
- **Mechanisms:**
 - voltage-dependent Ca²⁺ channels
 - IP₃-gated Ca²⁺-release channels
 - ryanodine receptors: PM potential change => Ca²⁺ release
- **Balance between compartments:**
 - PM Ca²⁺-pump
 - Na⁺/Ca²⁺ exchanger (neurons)
 - ER Ca²⁺-pump
 - mitochondrial Ca²⁺-pump (electrochemical gradient in oxydative phosphorylation)
- **Ca²⁺ oscillations**

CA₂₊: UBIQUITOUS INTRACELLULAR MESSENGER



CA₂₊ OSCILLATIONS IN THE CELL

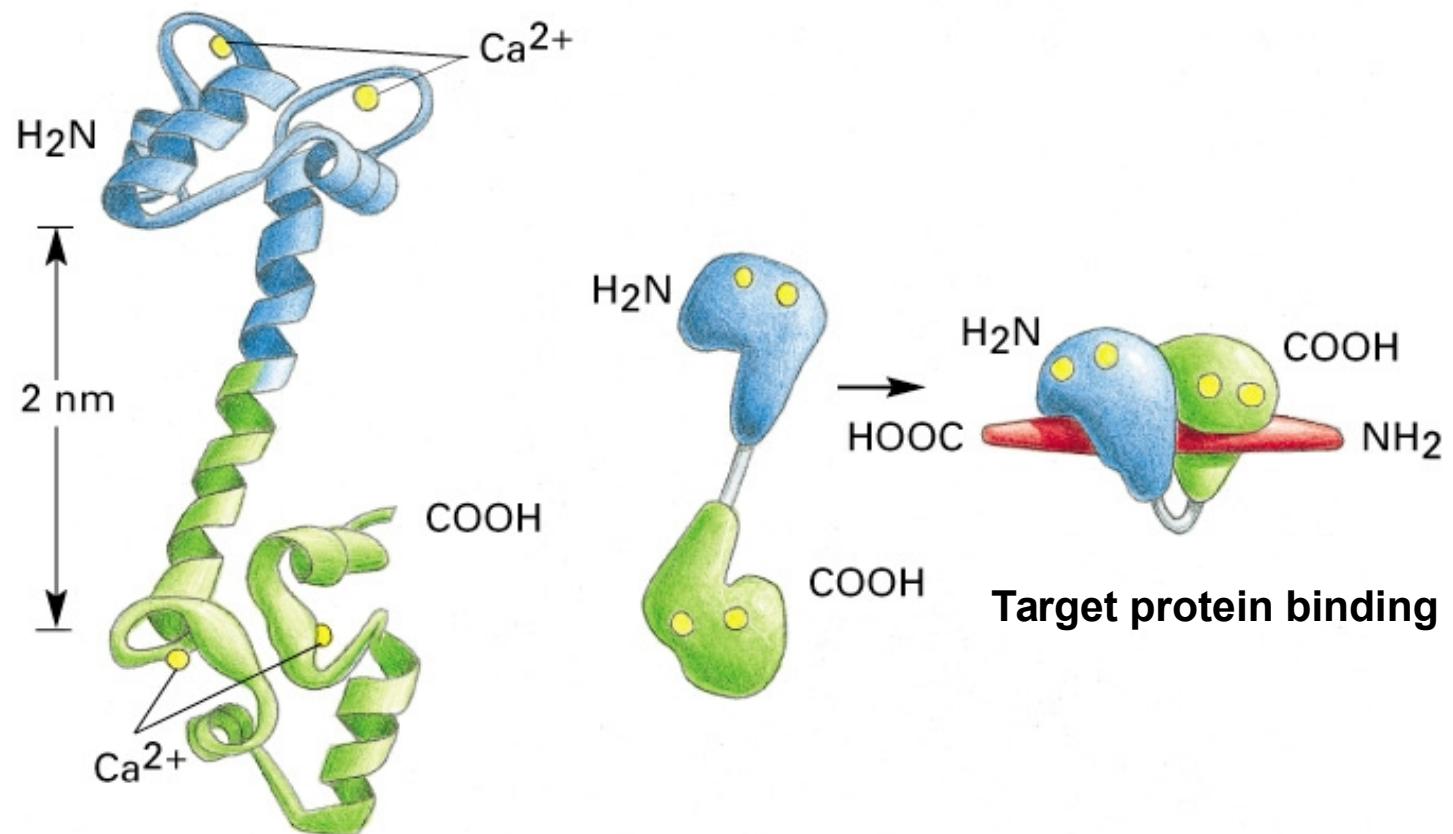
Frequency but not amplitude is affected by an inductor.



CA²⁺/CALMODULIN-DEPENDENT PROTEIN KINASES

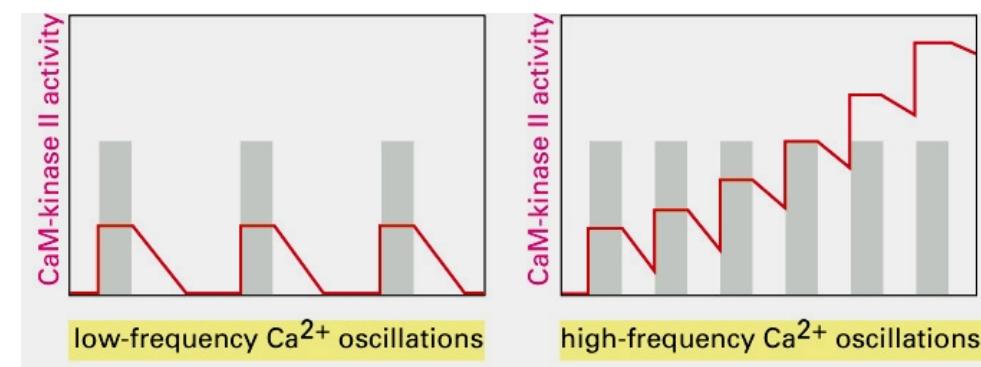
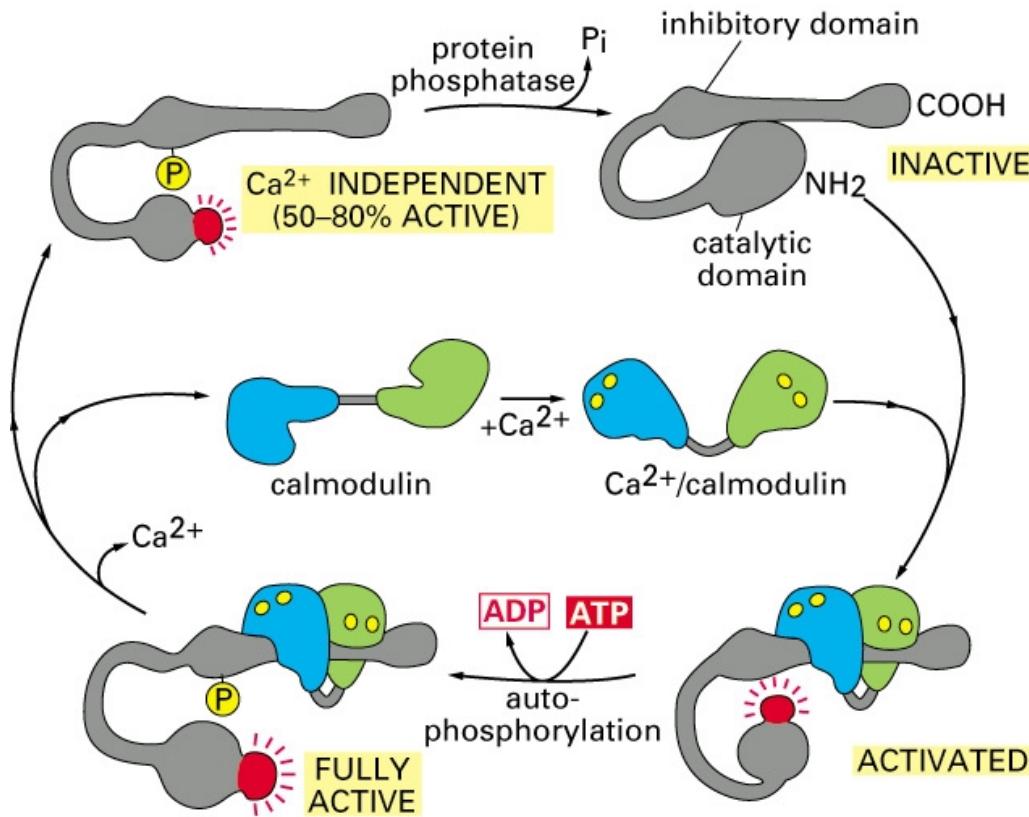
➤ Calmodulin:

- Ca²⁺-binding protein, ~1% of total protein mass
- Ca²⁺-binding => conformational change (allosteric activation)
- switch-like manner
- regulatory unit (f.i.: for Ca²⁺-pumps)



CA²⁺/CALMODULIN-DEPENDENT PROTEIN KINASES

- Action: Thr/Ser phosphorylation
- CaM-kinase II (~2% of total protein in some part of the brain)
 - molecular memory device (autophosphorylation)
 - frequency decoder of Ca²⁺ oscillations

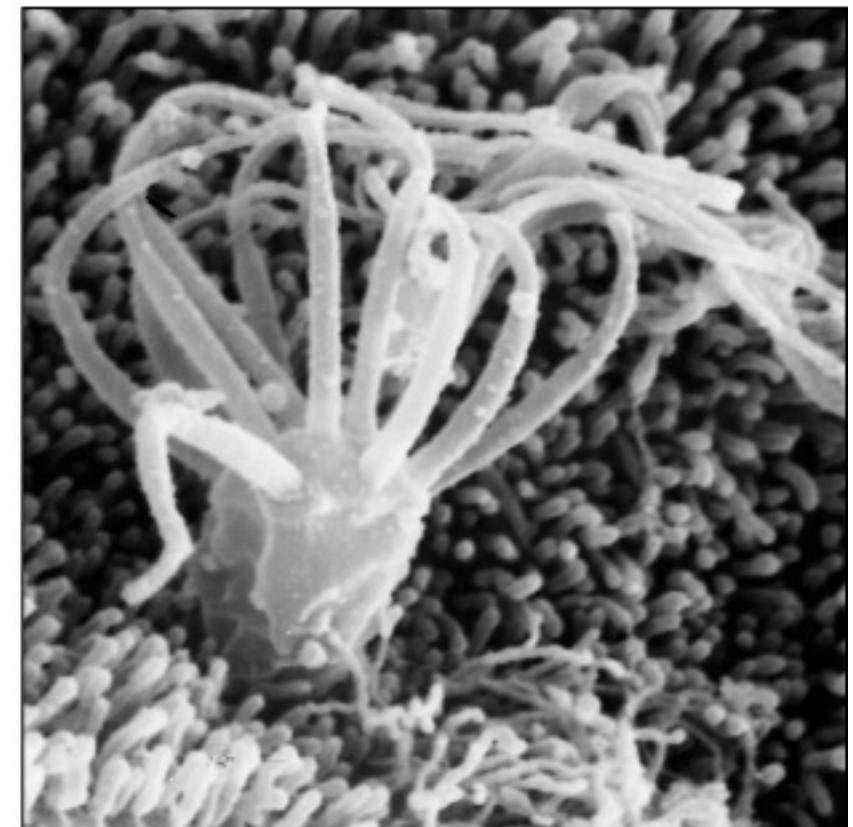
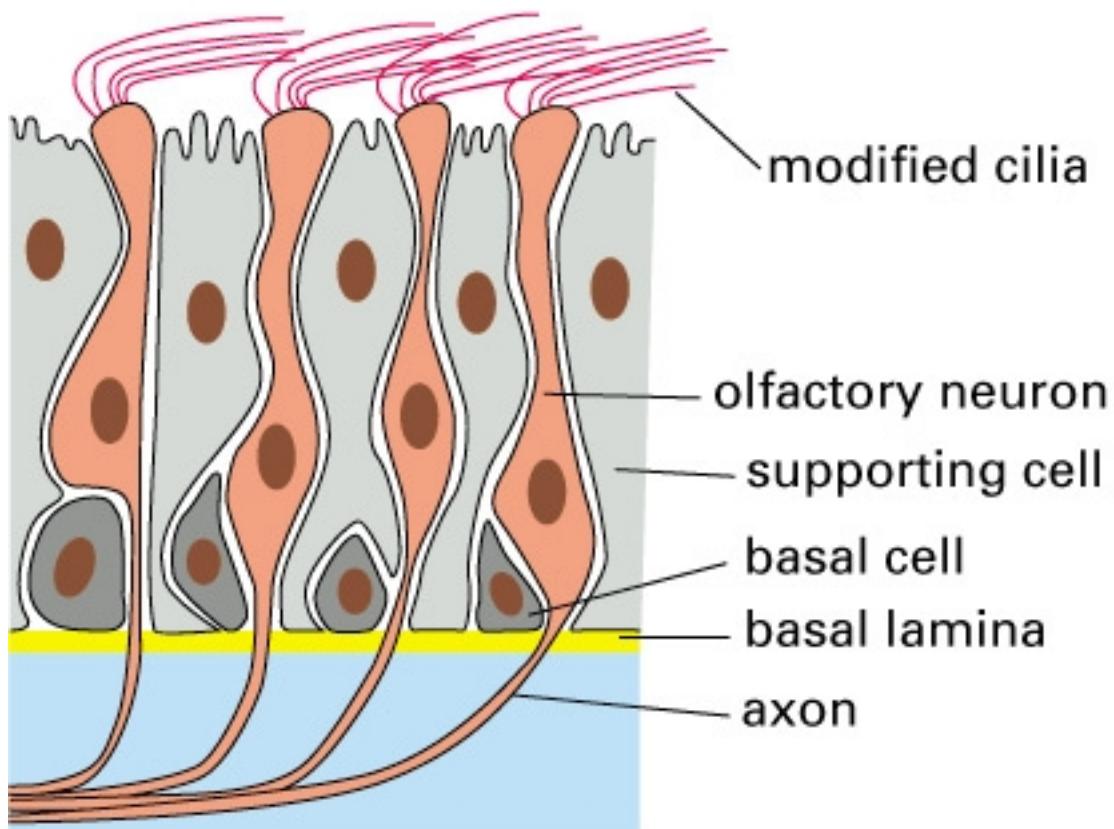


MORE ON G-PROTEINS MECHANISMS

- Activation membrane-bound enzymes => secondary messangers (cAMP, Ca²⁺)
- α-subunit => Rho-GTase => modifications of cytoskeleton
- Direct activation/inactivation of ionic channels:
 - acetylcholine receptors => K⁺-channels, called muscarinic receptors
- Indirect activation/inactivation of ionic channels: phosphorylation/production or destruction of nucleotides (cyclic-nucleotide-gated ion channels)

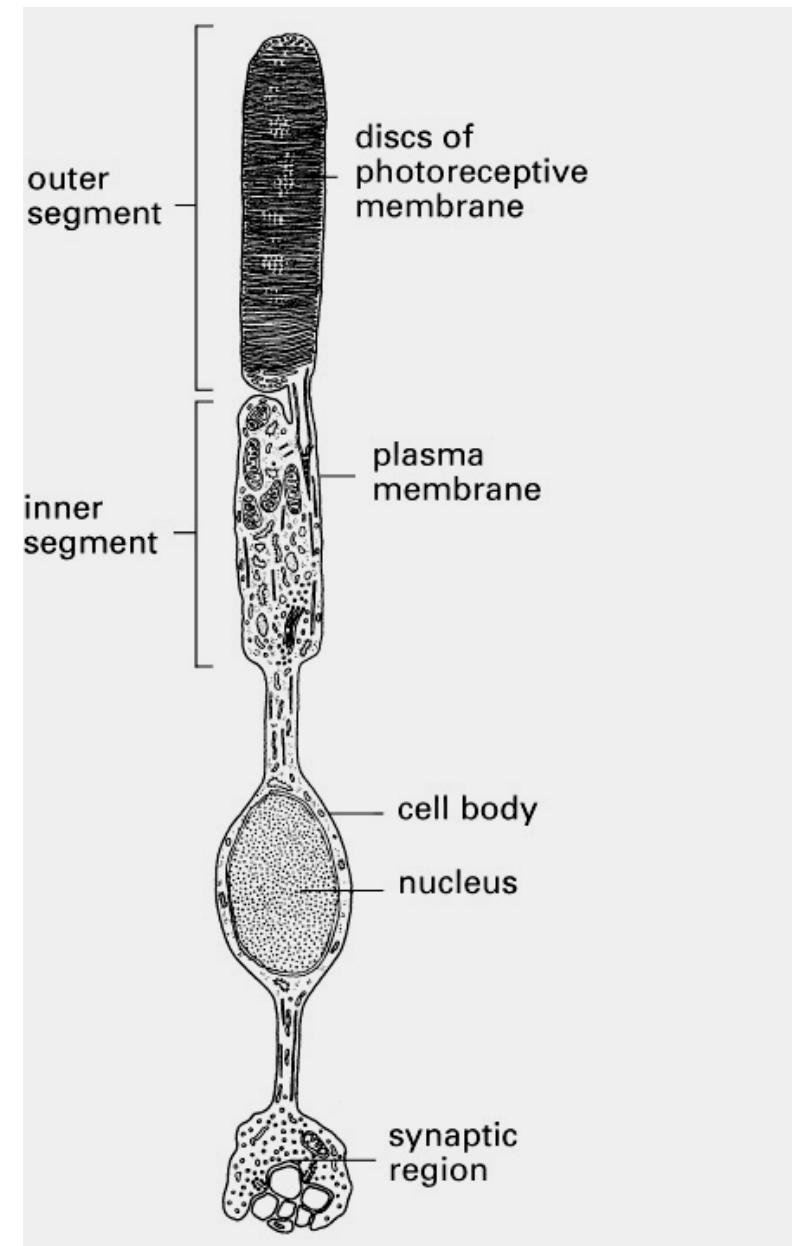
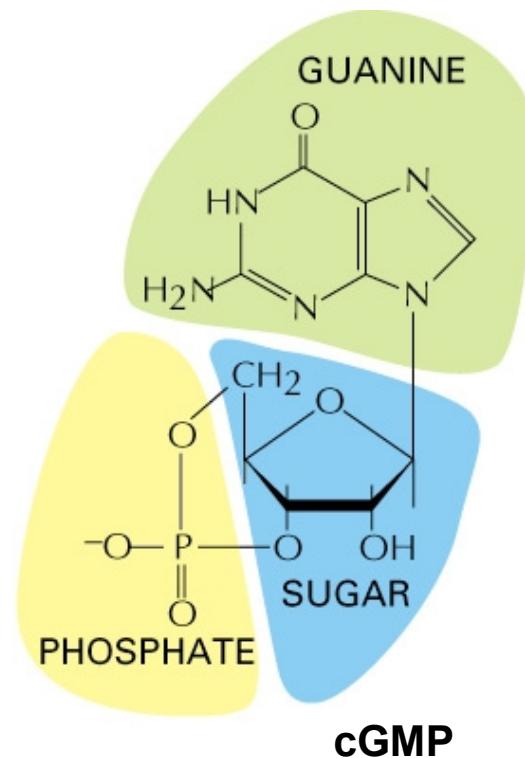
OLFACTORY RECEPTORS

- ~ 10000 smells
- cAMP pathway: adenylyl cyclase => cAMP-gated cation channels => depolarization => electric impulse
- G_{olf} , ~ 10^3 olfactory receptors



VISION

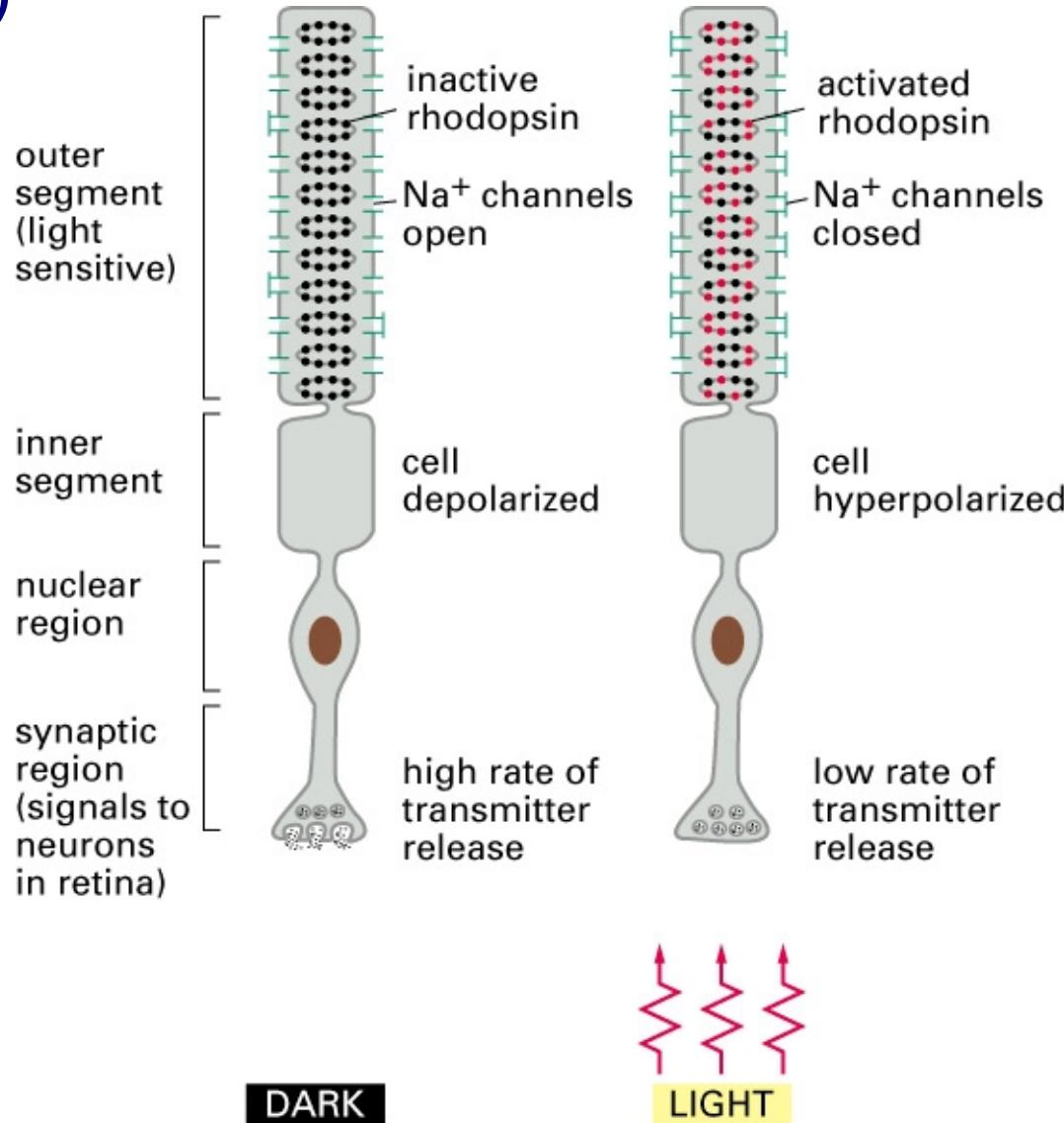
- cGMP pathway: guanylyl cyclase/phosphodiesterase
- The fastest G-protein-mediated response
- Rods/cones => BW/colours
- cGMP-dependent Na^+ -channels:
 - open in the dark
 - light => hyperpolarization => closed
- Rhodopsin: 7 TMD



Rod photoreceptor cell

VISION

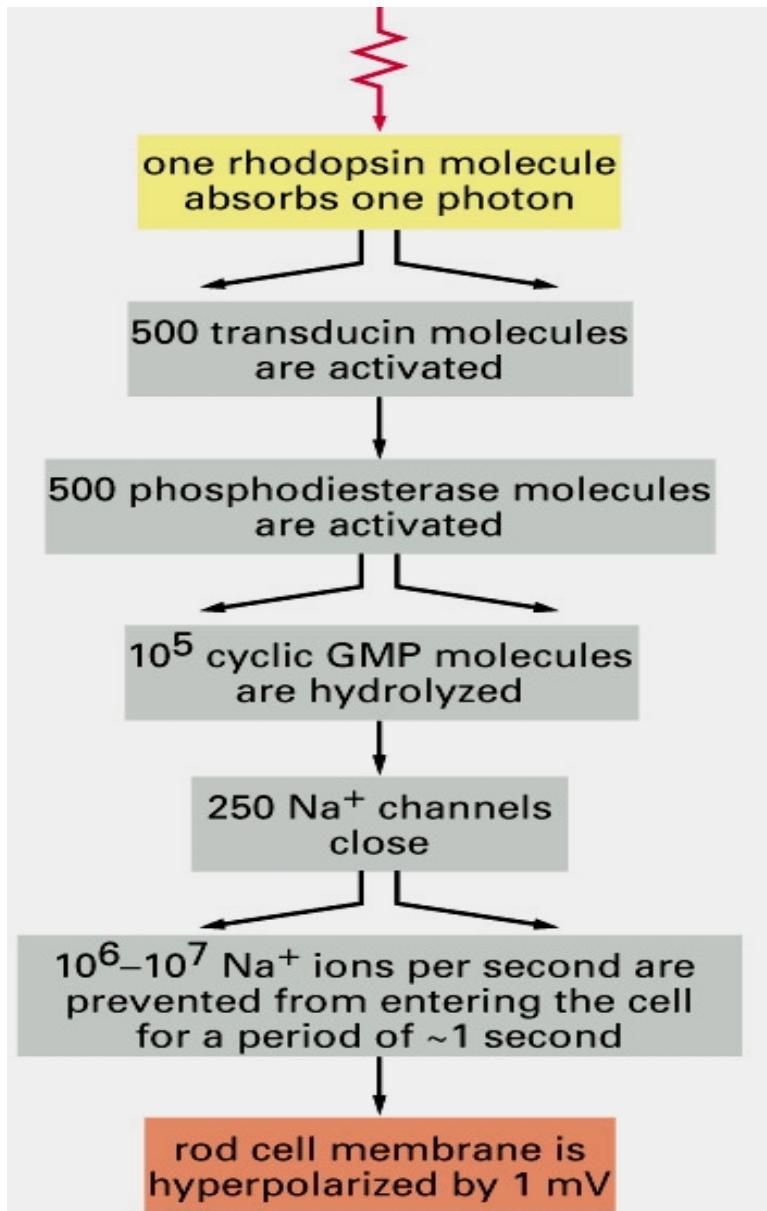
- Rhodopsin: 7 TMD
- => Trimeric G-protein (transducin, G_t)
- => cGMP-phosphodiesterase active
- => Decrease of [cGMP]
- => Channels close
- High speed:
 - rhodopsin-specific kinase
 - arrestin (inhibitor)
- Adaptation to continuous light:
 - RGS protein inactivates G_t
 - $\text{Ca}^{2+}/\text{Na}^+$ symports



TRIMERIC G-PROTEIN FAMILIES

| FAMILY | SOME FAMILY MEMBERS | ACTION MEDIATED BY | FUNCTIONS |
|--------|---------------------|----------------------------|--|
| I | G_s | α | activates adenylyl cyclase; activates Ca^{2+} channels |
| | G_{olf} | α | activates adenylyl cyclase in olfactory sensory neurons |
| II | G_i | α | inhibits adenylyl cyclase |
| | | $\beta\gamma$ | activates K^+ channels |
| | G_o | $\beta\gamma$ | activates K^+ channels; inactivates Ca^{2+} channels |
| | G_t (transducin) | α and $\beta\gamma$ | activates phospholipase C- β |
| III | G_q | α | activates cyclic GMP phosphodiesterase in vertebrate rod photoreceptors |
| | | | activates phospholipase C- β |

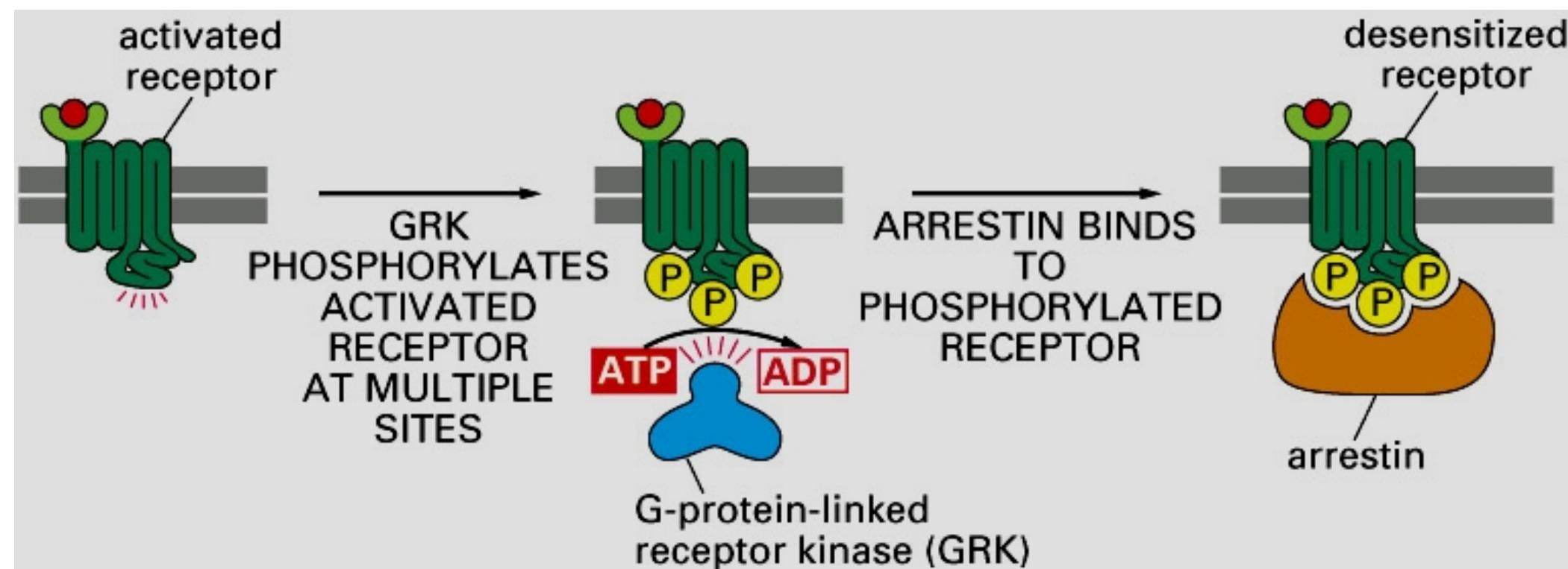
SIGNALS AMPLIFICATIONS: MESSANGERS AND CASCADES



vs. degrading/synthesizing cN, changing $[\text{Ca}^{2+}]$
in the cell

DESENSITIZATION: RECEPTOR PHOSPHORYLATION

- Mechanisms: inactivation, sequestration, down-regulation
- G-protein-linked receptor kinases
- Arrestin:
 - steric hindrance
 - adaptor to clathrin



SIGNALING THROUGH ENZYME-LINKED CELL-SURFACE RECEPTORS

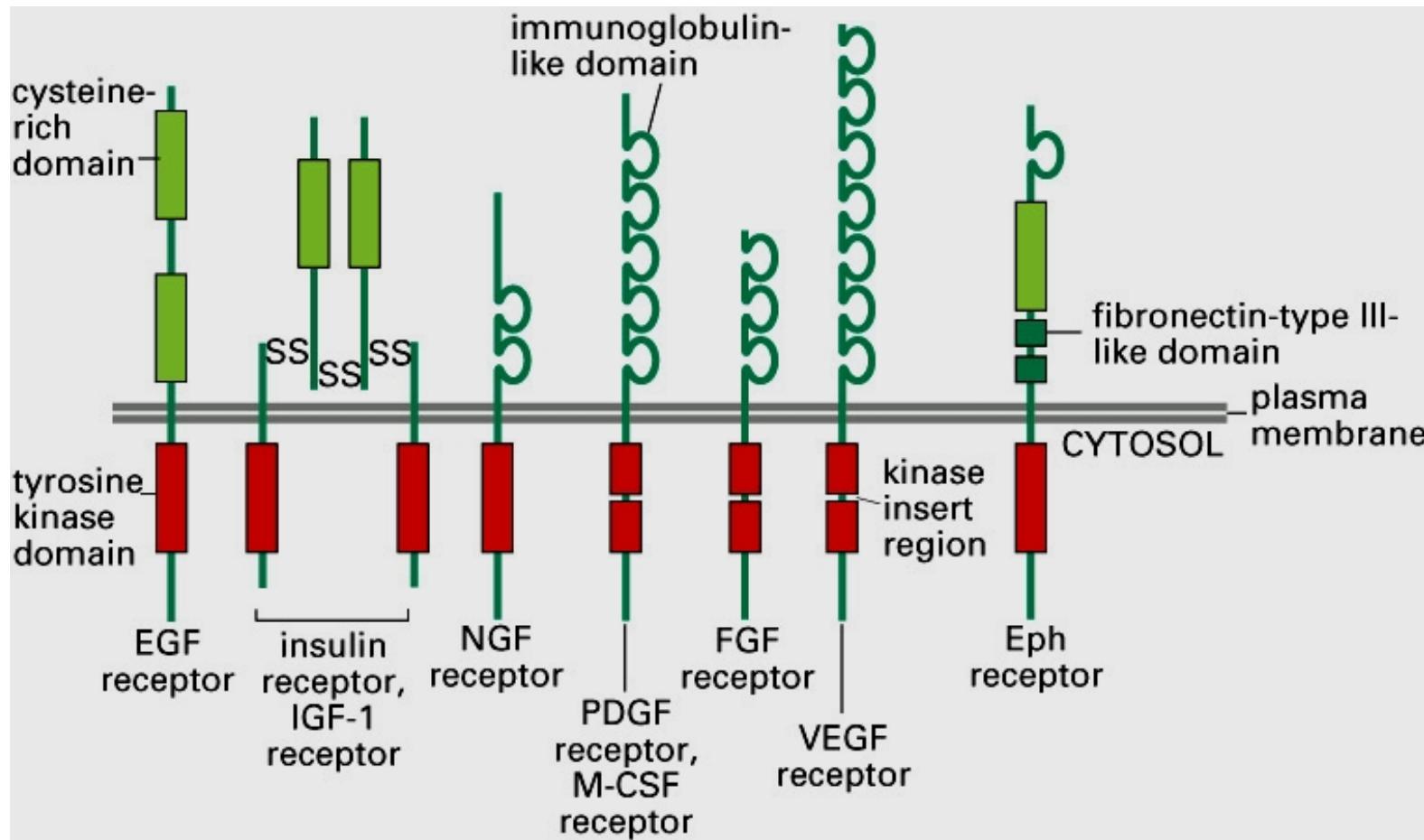
- Second major type of cell-surface receptors
- Act upon very low concentrations of ligands ($\sim 10^{-9}$ - 10^{-11} M)
- Slow response (\sim hours) => gene expression
- Rapid response => cytoskeleton structure
- TM proteins
- Direct enzyme activity
- Classes:
 - Receptor tyrosine kinases
 - Tyrosine kinase-associated receptors
 - Receptor-like tyrosine phosphatases
 - Receptor serine/threonine kinases
 - Receptor guanylyl cyclases
 - Histidine-kinase-associated receptors

SIGNALING PROTEINS FOR RECEPTOR TYROSINE KINASES

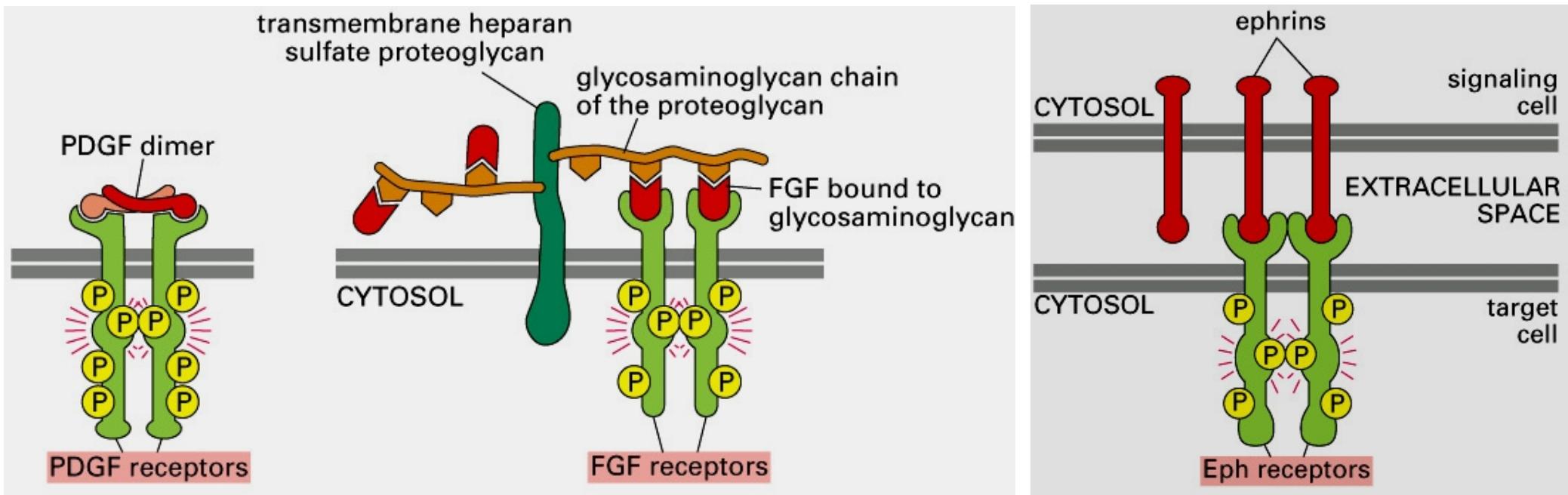
| SIGNALING LIGAND | RECEPTORS | SOME RESPONSES |
|--|--|--|
| Epidermal growth factor (EGF) | EGF receptor | stimulates proliferation of various cell types |
| Insulin | insulin receptor | stimulates carbohydrate utilization and protein synthesis |
| Insulin-like growth factors (IGF-1 and IGF-2) | IGF receptor-1 | stimulate cell growth and survival |
| Nerve growth factor (NGF) | Trk A | stimulates survival and growth of some neurons |
| Platelet-derived growth factors (PDGF AA, BB, α , β , AB) | PDGF receptors (α and β) | stimulate survival, growth, and proliferation of various cell types |
| Macrophage-colony-stimulating (M-CSF) | M-CSF receptor factor | stimulates monocyte/macrophage proliferation and differentiation |
| Fibroblast growth factors (FGF-1 to FGF-24) | FGF receptors (FGF-R1-FGF- R4, plus multiple isoforms of each) | stimulate proliferation of various cell types; inhibit differentiation of some precursor cells; inductive signals in development |
| Vascular endothelial growth factor (VEGF) | VEGF receptor | stimulates angiogenesis |
| Ephrins (A and B types) | Eph receptors (A and B types) | stimulate angiogenesis; guide cell and axon migration |

RECEPTOR TYROSINE KINASES

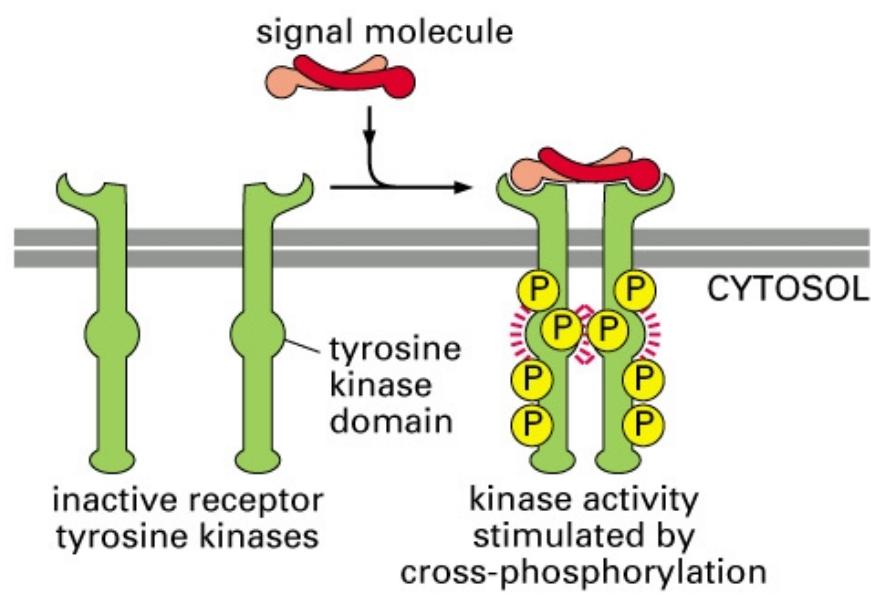
- Secreted growth factors and hormones
- Ephrins <=> ephrin receptors: bidirectional signaling
- Ligand binding => autophosphorylation, target protein phosphorylation
- Often oligomerization is involved



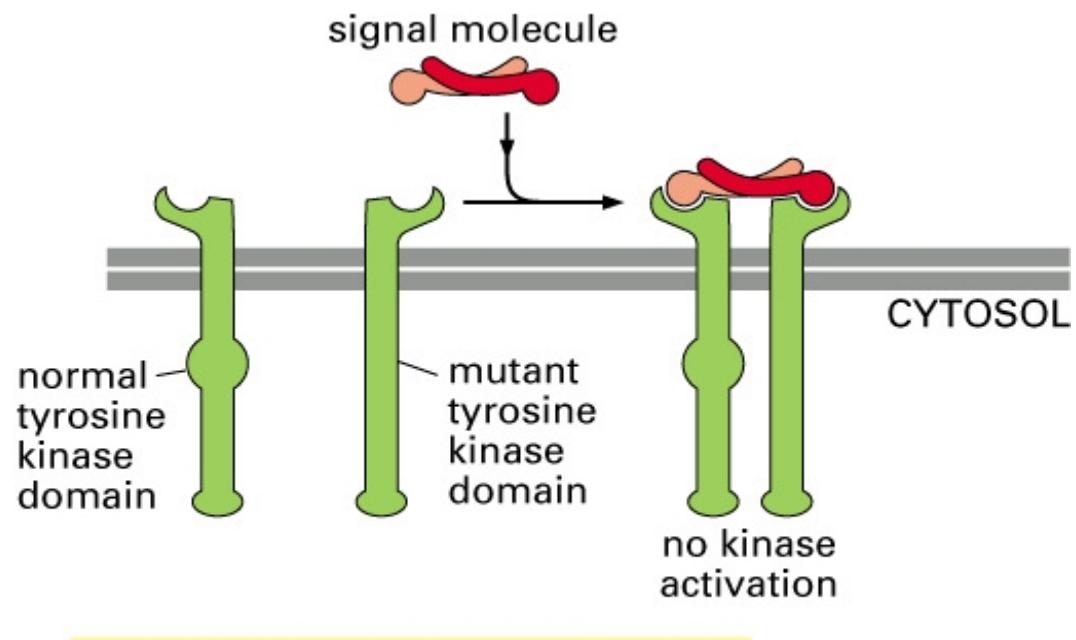
RECEPTOR TYROSINE KINASES: CROSSLINKING CHAINS



RECEPTOR TYROSINE KINASES: INHIBITION BY MUTAGENESIS

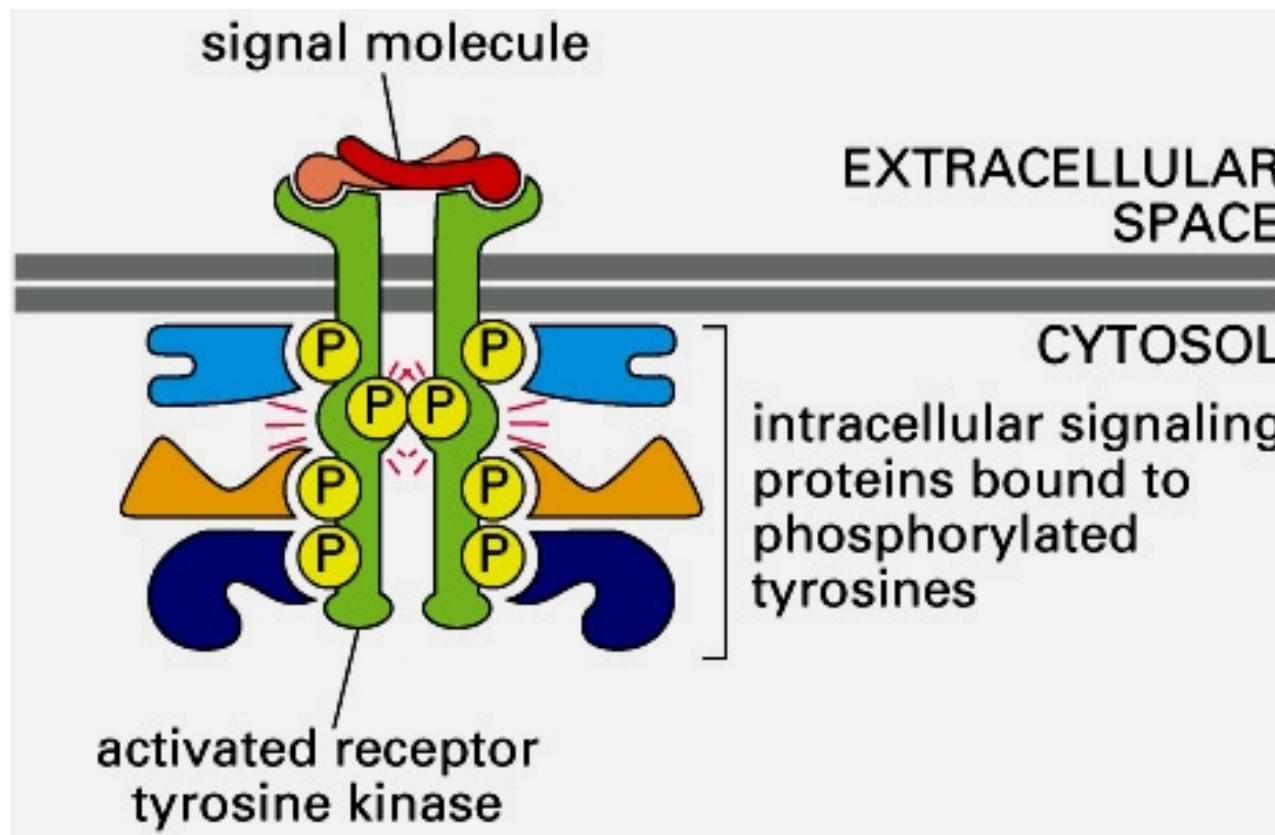


NORMAL RECEPTOR ACTIVATION



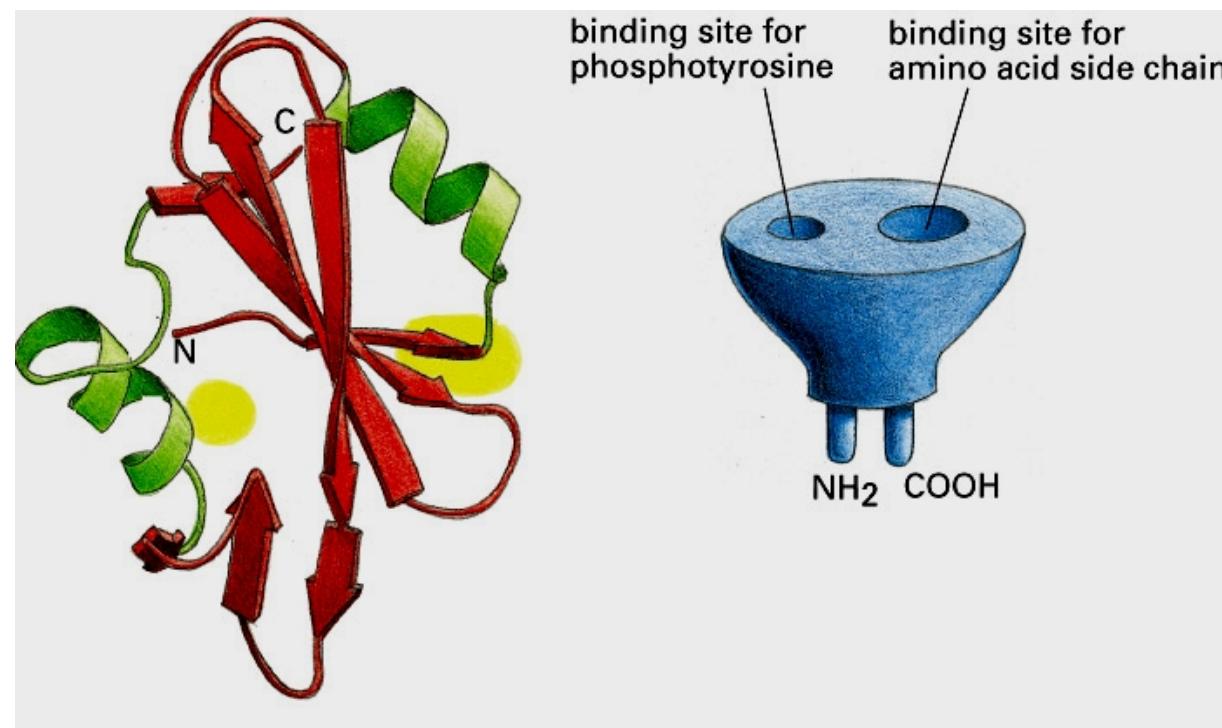
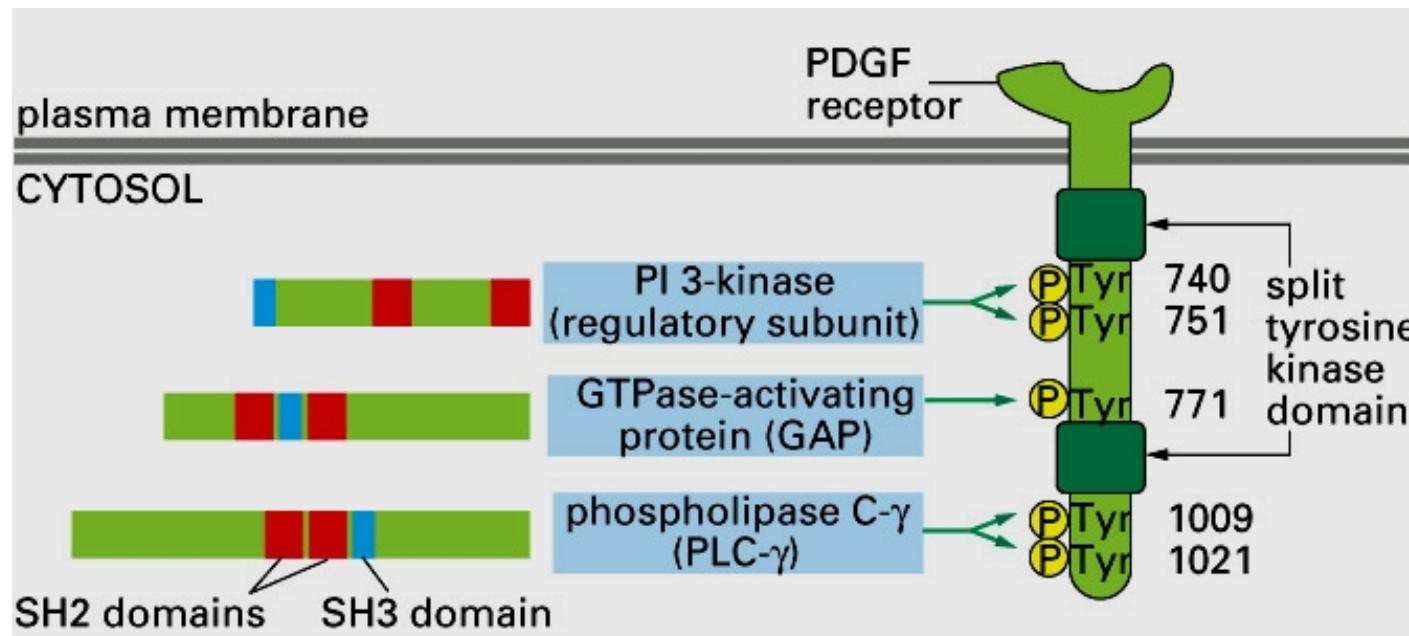
DOMINANT-NEGATIVE INHIBITION
BY MUTANT RECEPTOR

RECEPTOR TYROSINE KINASES: BINDING INTRACELLULAR SIGNALING PROTEINS



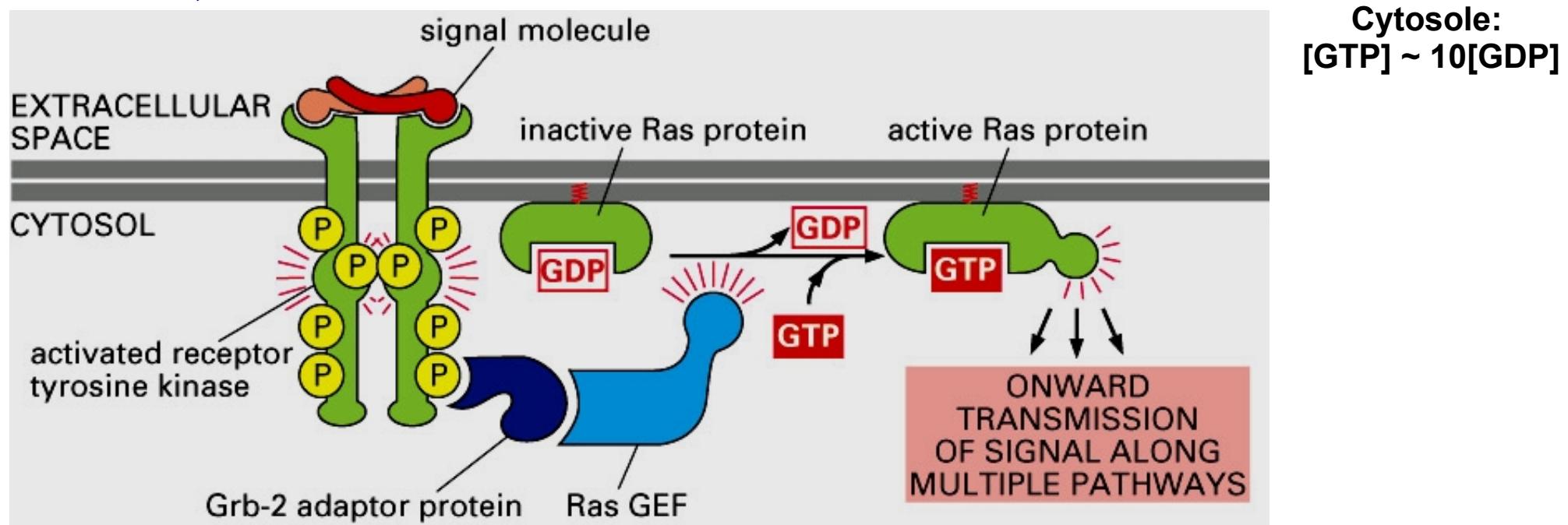
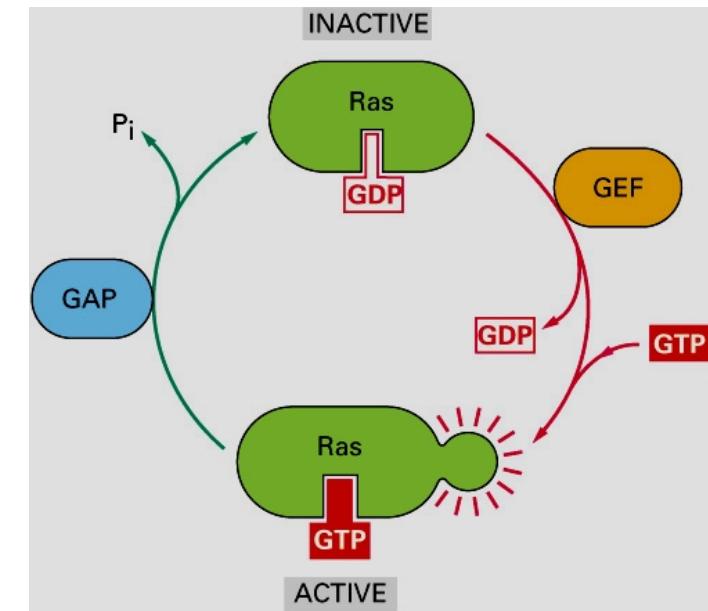
- Directly to the enzyme
- To adaptors (phosphotyrosine-binding domains: SH2, PTB)

BINDING TO SH2-DOMAIN



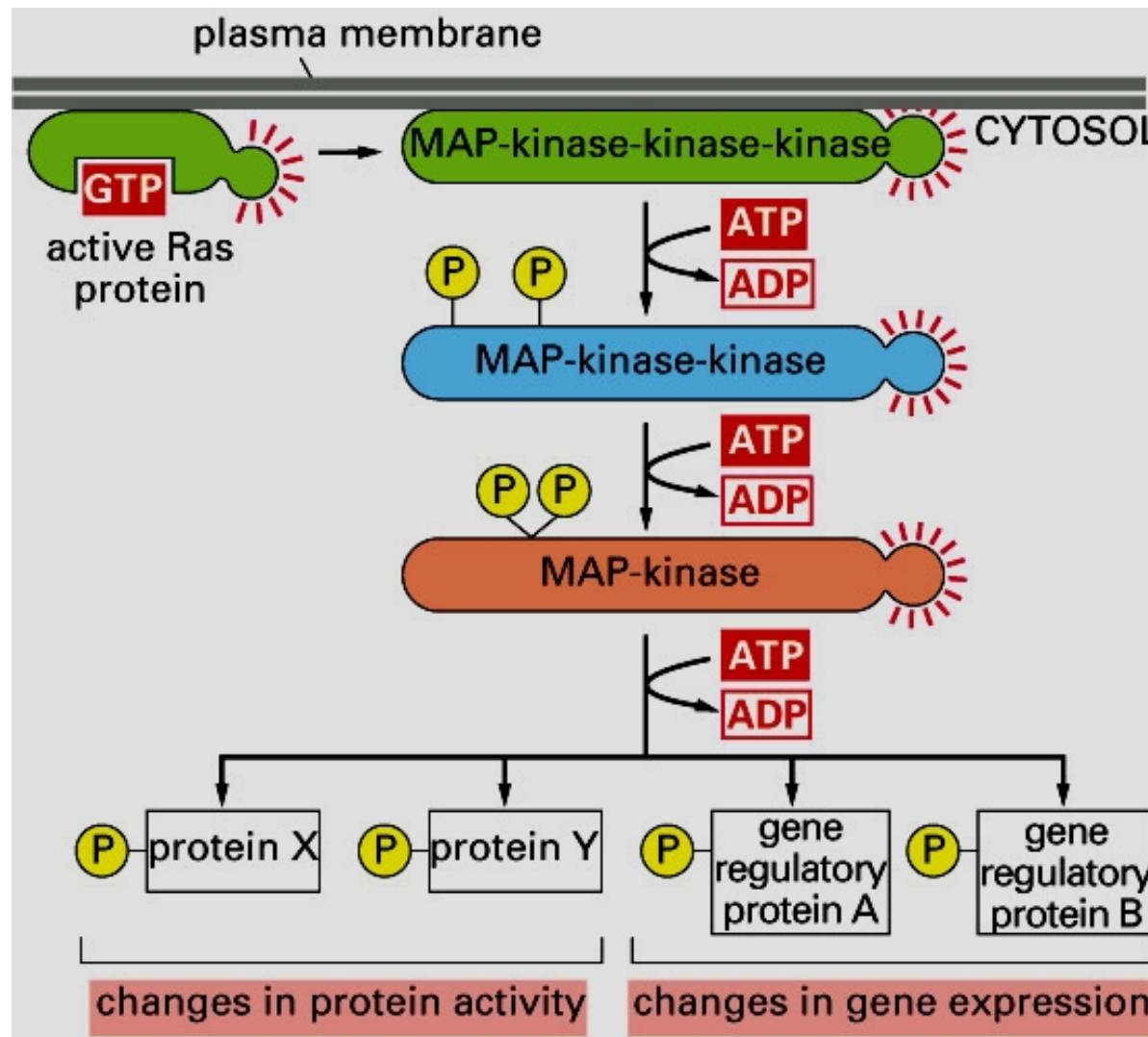
RAS PROTEINS

- Ras superfamily of monomeric GTPases, peripheral proteins
 - Rho subfamily
 - Rab subfamily
- Transferring signal to other parts of the cell
- Switch: GEFs and GAPs
- Linked to RTK through adaptors:
 - Grb-2, Sos

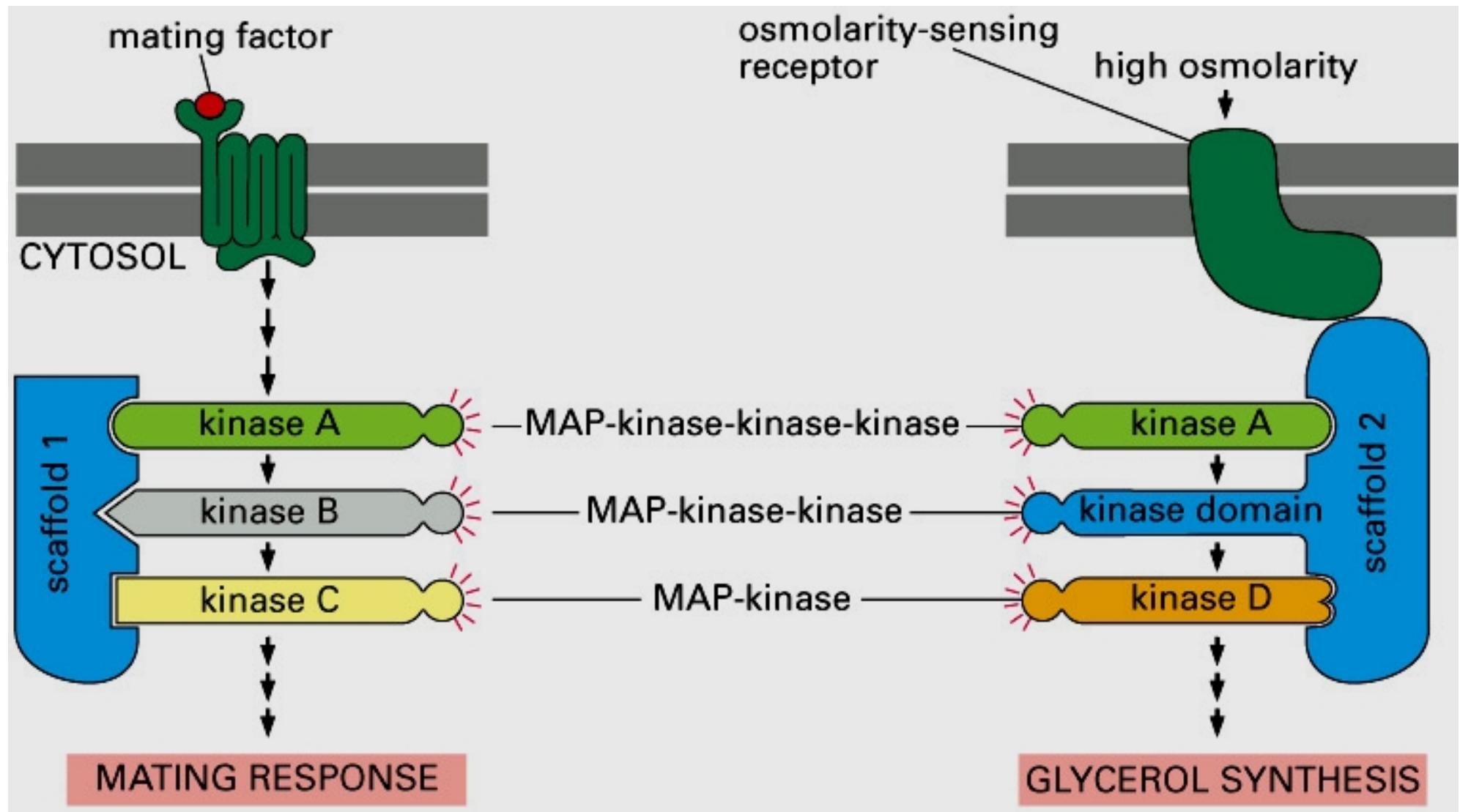


RAS => MAP KINASE CASCADES

- The need for longer living signals (~hours)
- Mitogen-activated protein kinase: active/inactive when both Tyr and Thr are phosphorylated/dephosphorylated



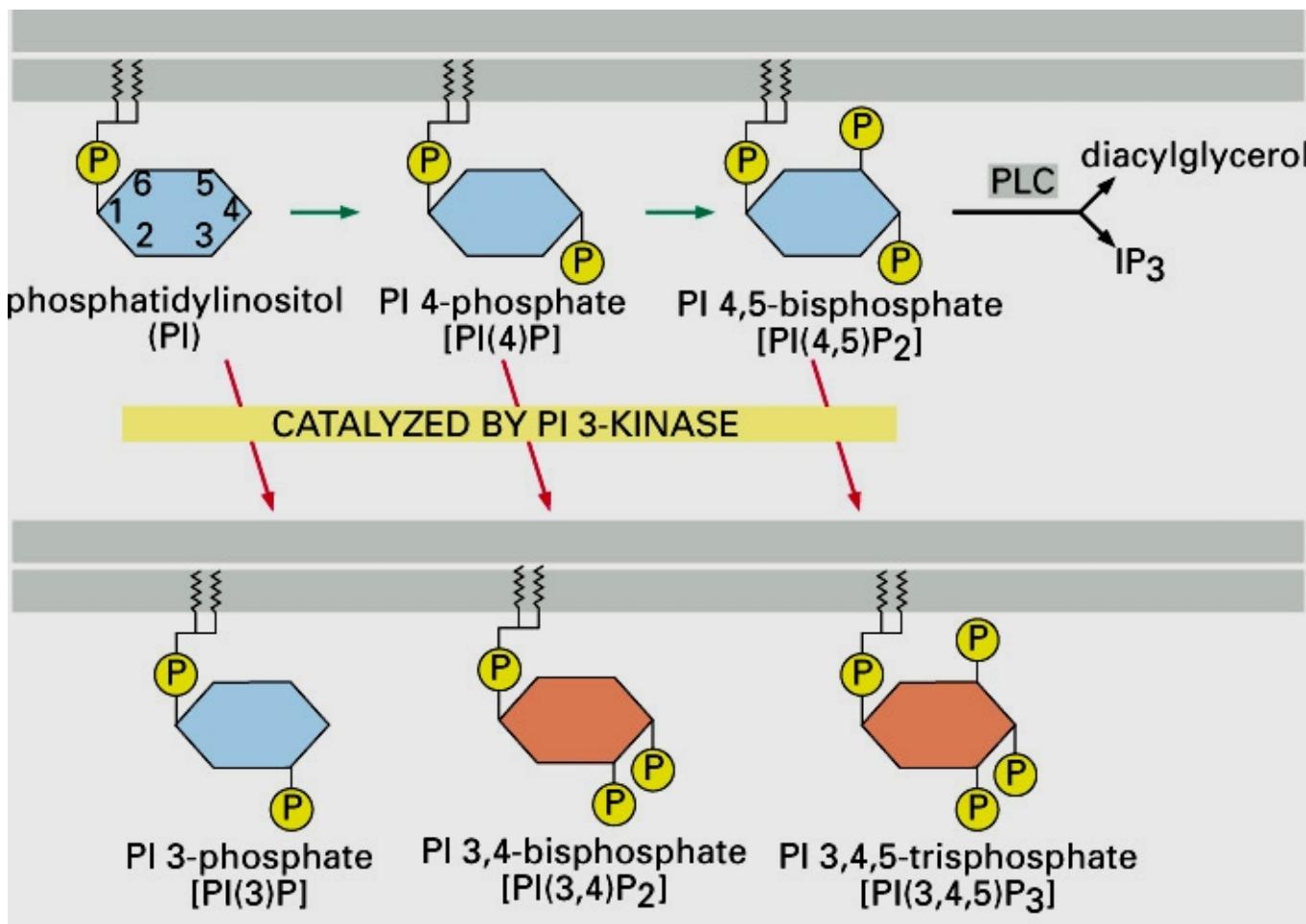
MAP KINASE CASCADES DEPEND ON SCAFFOLDS



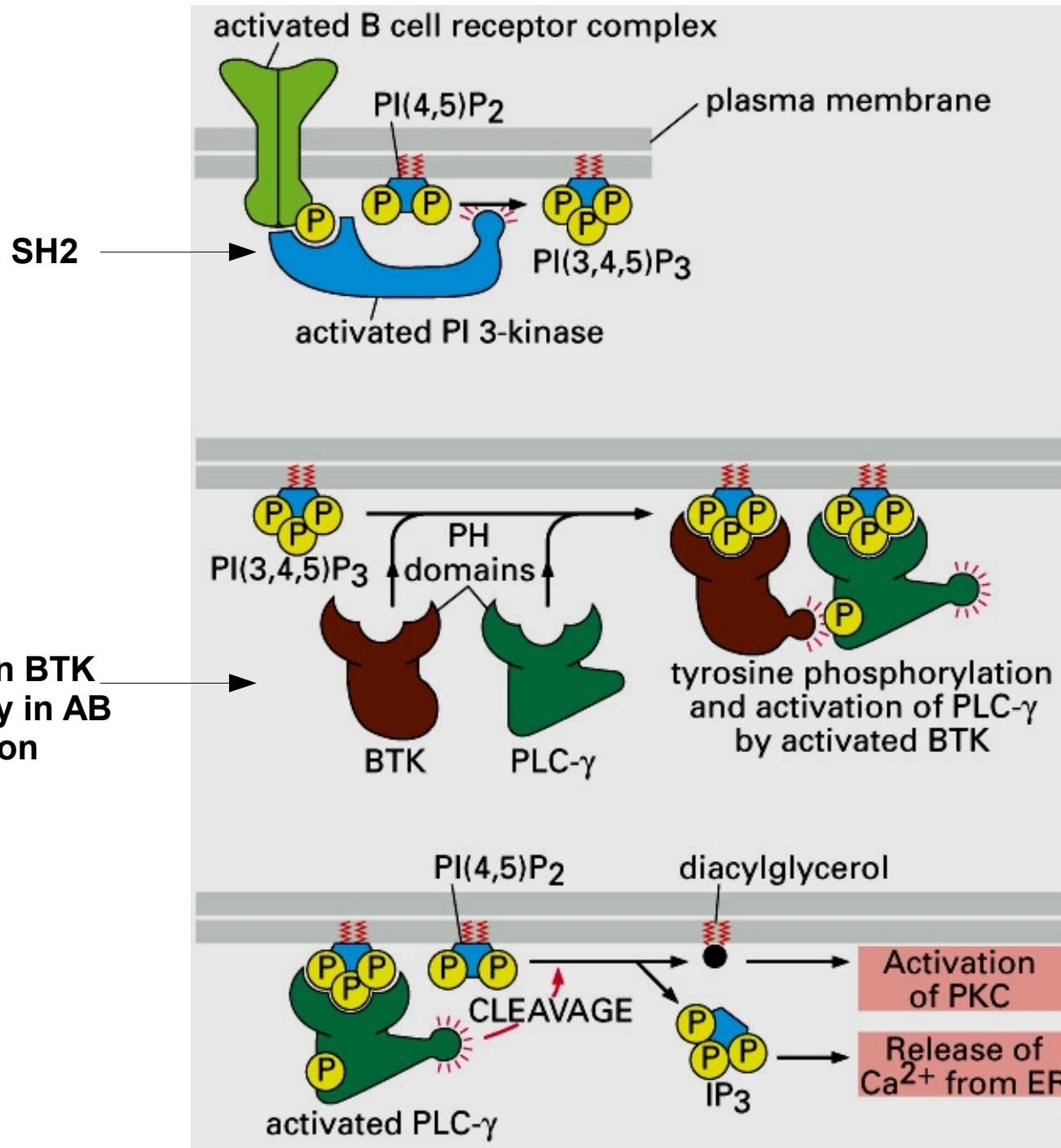
➤ In human: 5 MAP-kinase modules, 12 MAP-kinases, 7 MAP-KK, 7 MAP-KKK

RAS => PI3 KINASE

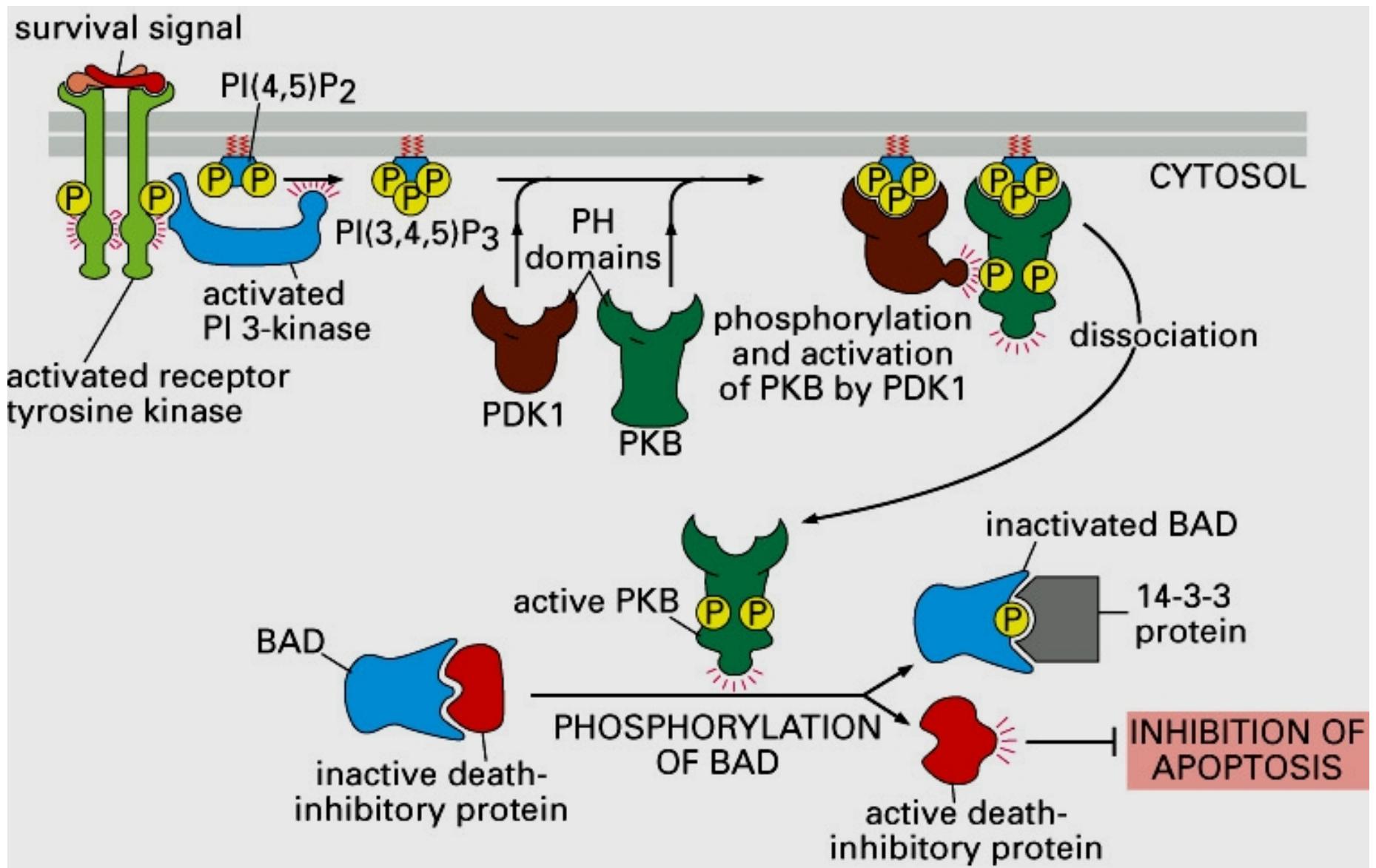
- Phosphatidylinositol 3-kinase
- Signal for survival and growth
- PI (3,4)P₂ and PI(3,4,5)P₃ are not cleaved by PLC, form rafts



PI3 KINASE SIGNALING MECHANISM: B-CELLS

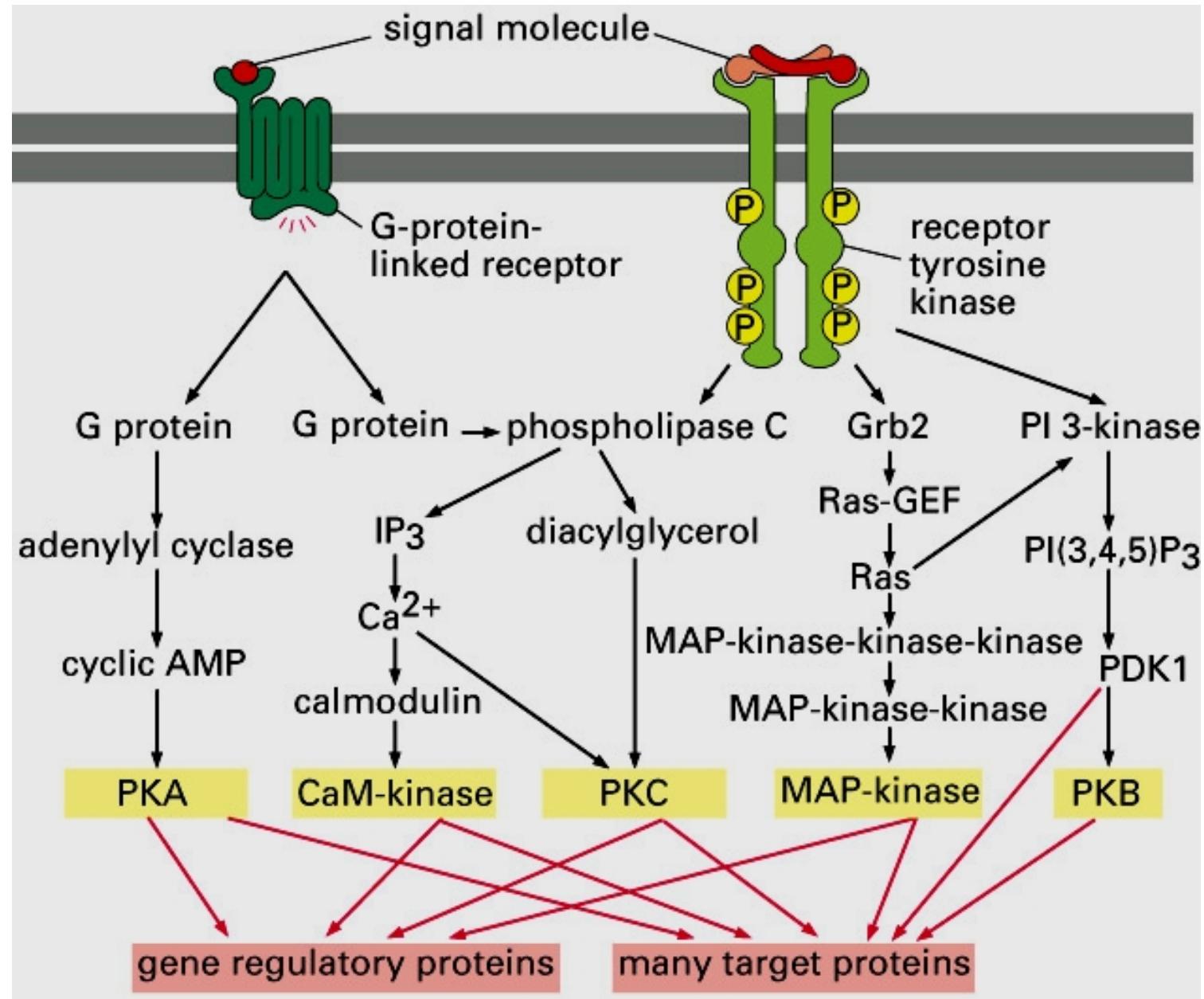


PI3 KINASE SIGNALING MECHANISM: CELL SURVIVAL



G-PROTEIN-LINKED AND RTK SIGNALING INTERCONNECTION

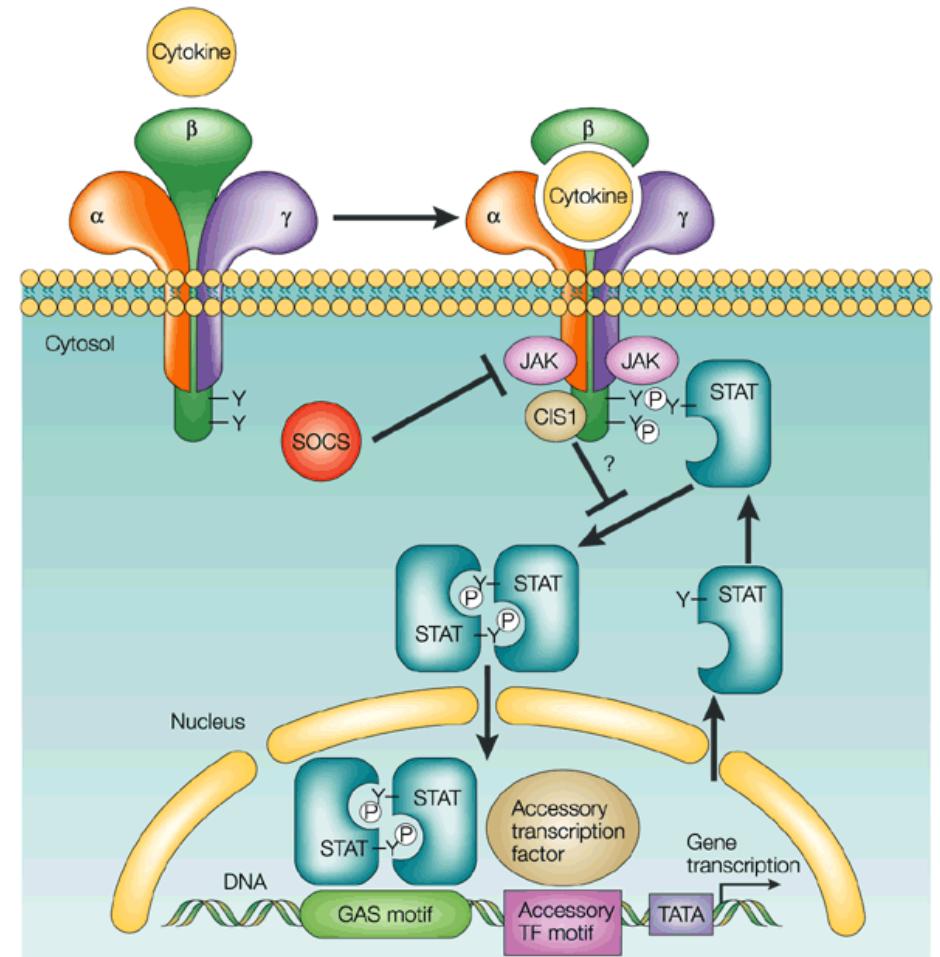
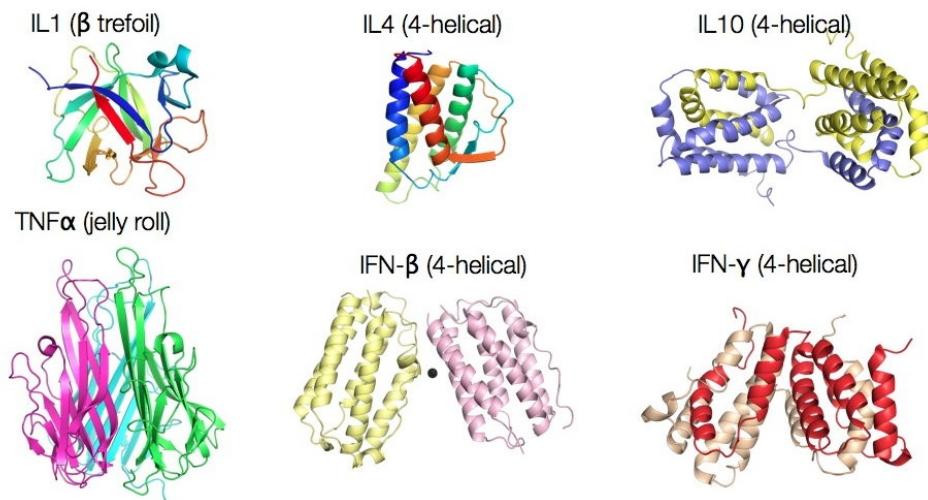
+
Kinases
vs.
Phosphatases



CYTOSOLIC TYROSINE KINASES

- Phosphorylate/activate other proteins, interact with other receptors
 - Src family: SH2, SH3, kinase domain
 - Focal adhesion kinase (FAK): integrin-associated cytosolic TK (in adhesion)
 - Janus kinases (Jaks): cytokine receptors-associated

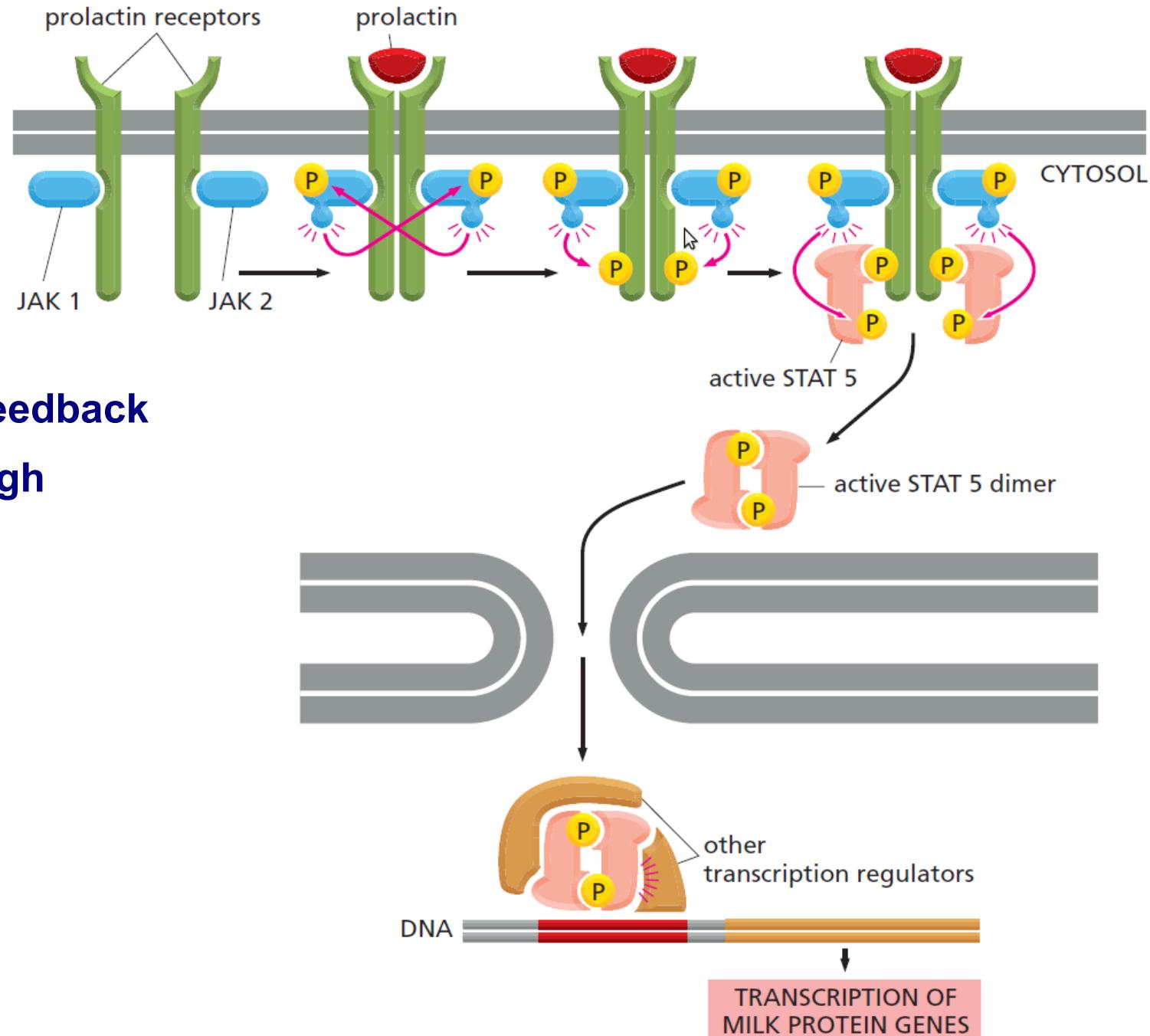
Diversity of the cytokine folds. I.



CYTOKINE RECEPTOR SIGNALING

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

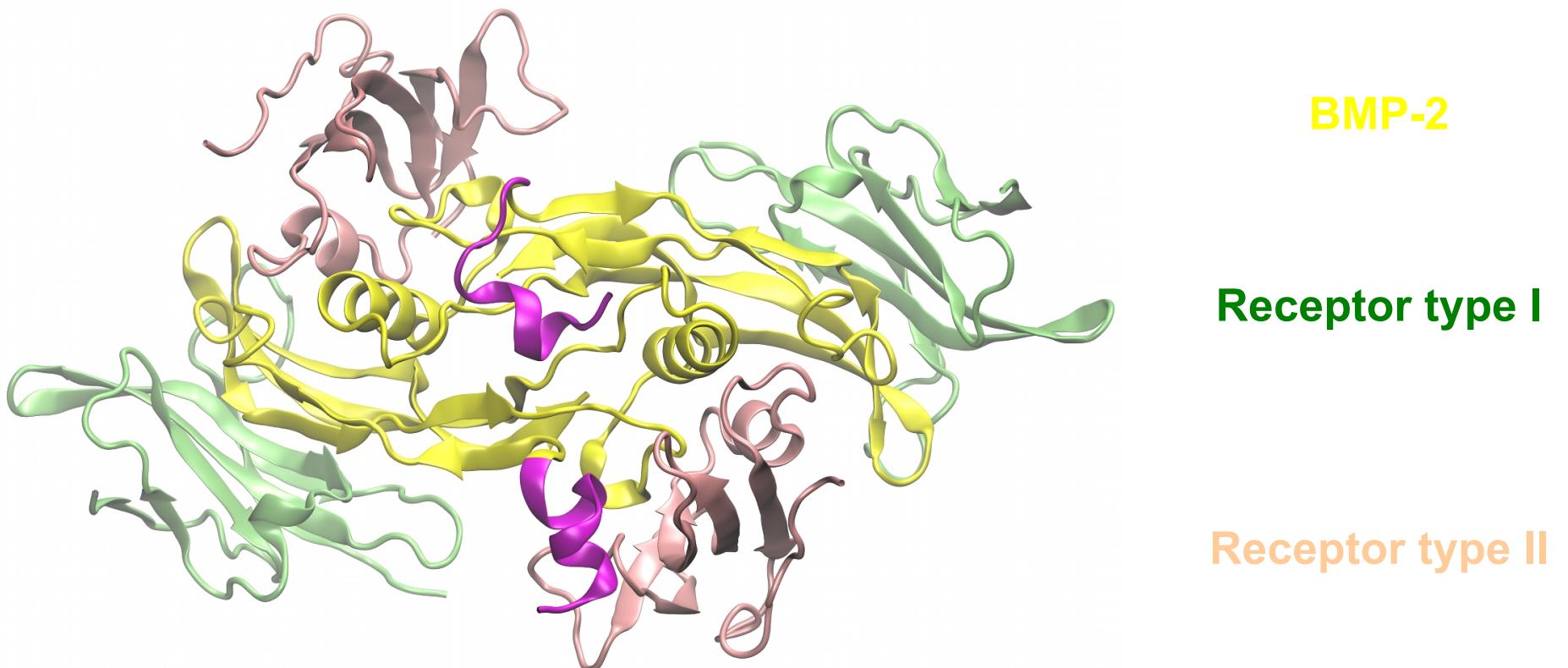
JAK-STAT SIGNALING: MILK PRODUCTION



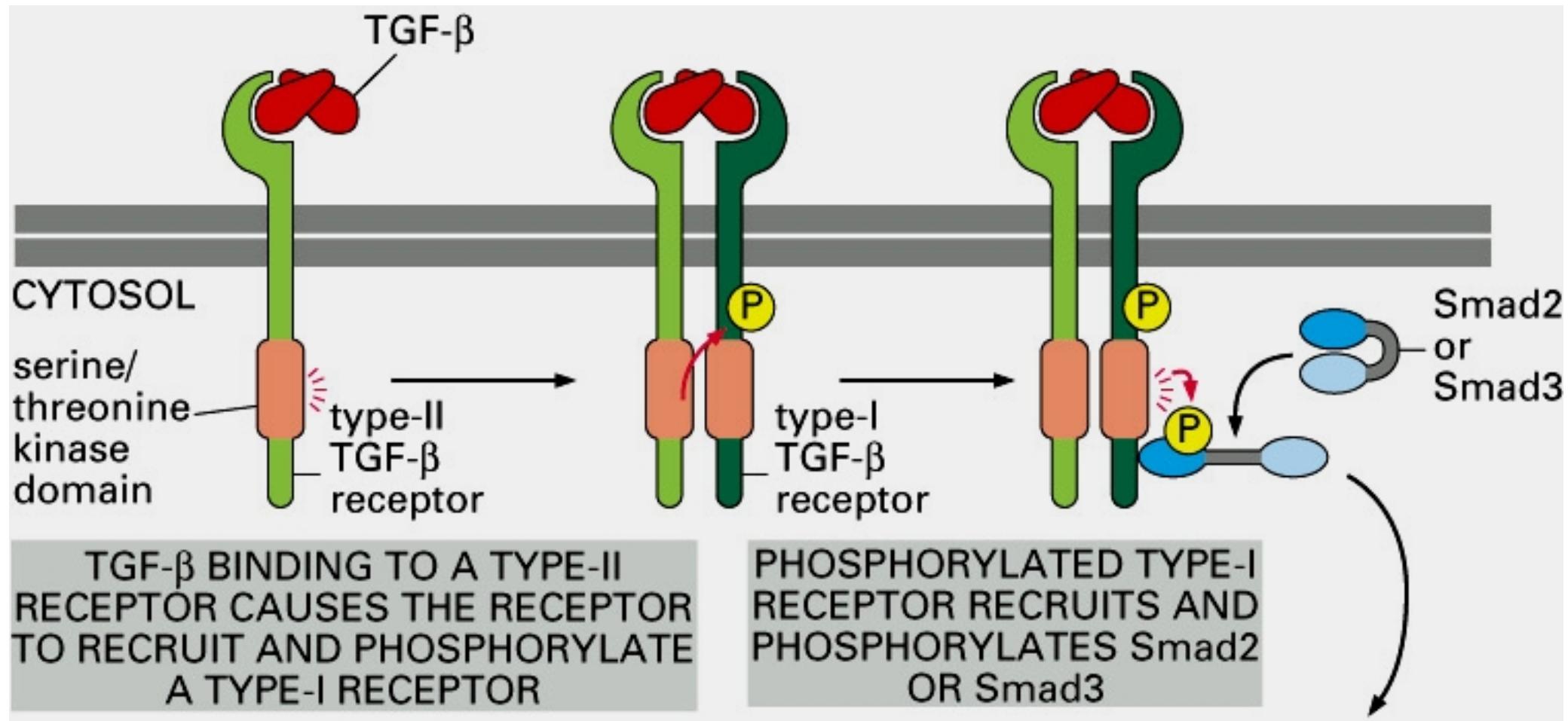
- Often negative feedback mechanisms through dephosphorylation

TGF- β SIGNALING

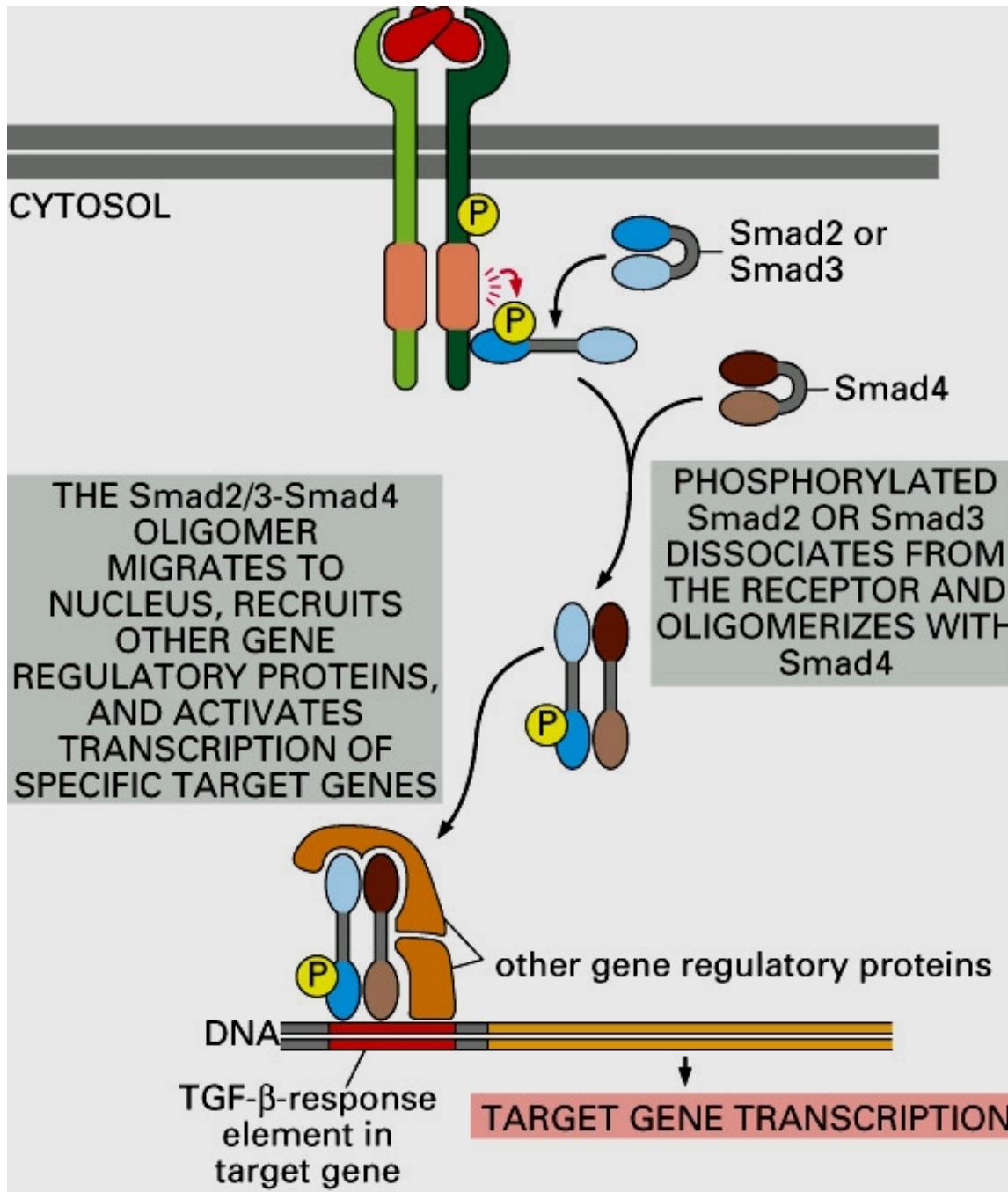
- Proliferation, differentiation, EM production, cell death
- Classes: TGF- β s, BMPs, activins
- Two classes of receptors
- Target proteins: Smads => nuclear factors
- Negative feedback including Jak-STAT pathway



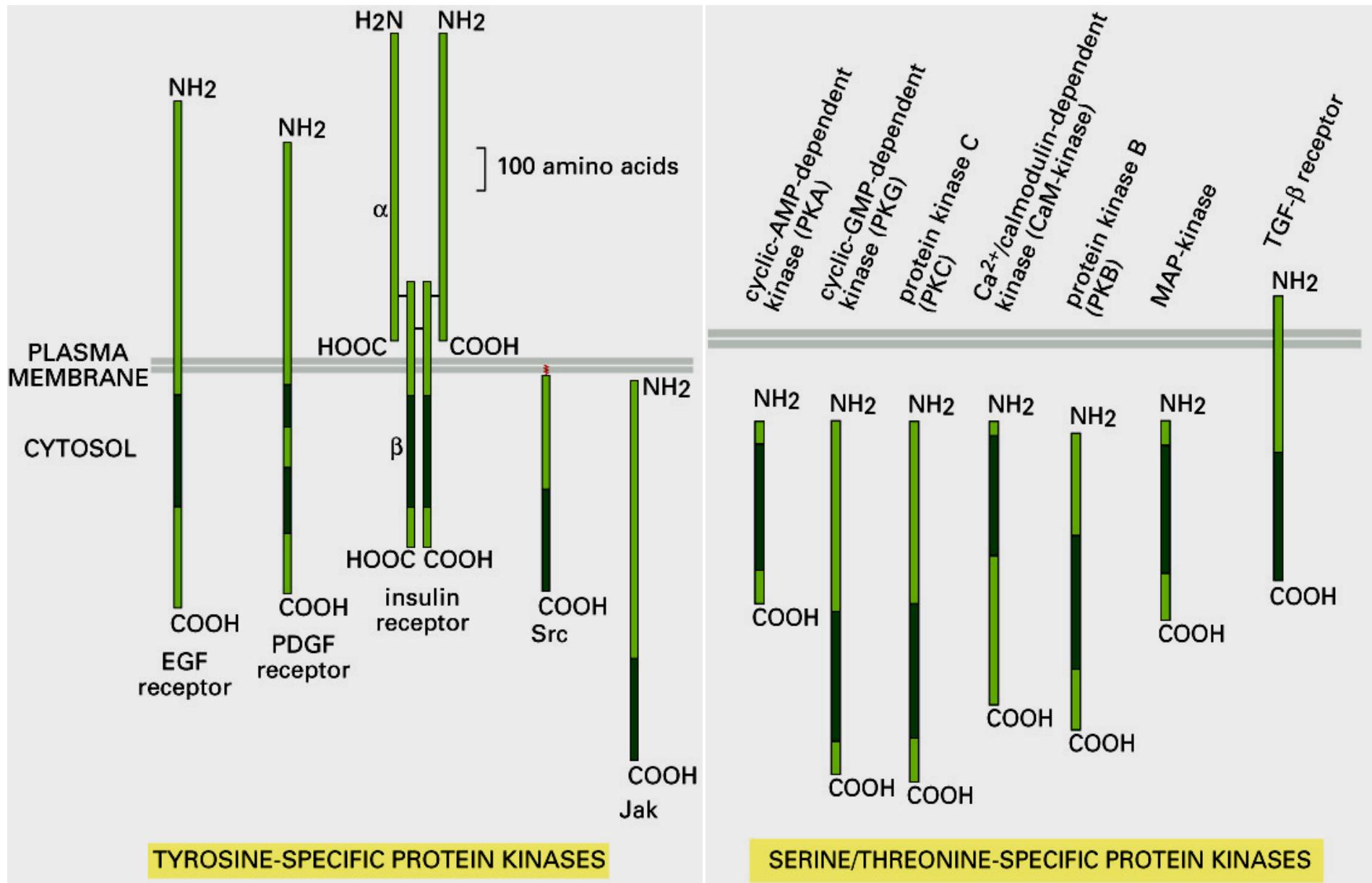
TGF- β SIGNALING



TGF- β SIGNALING



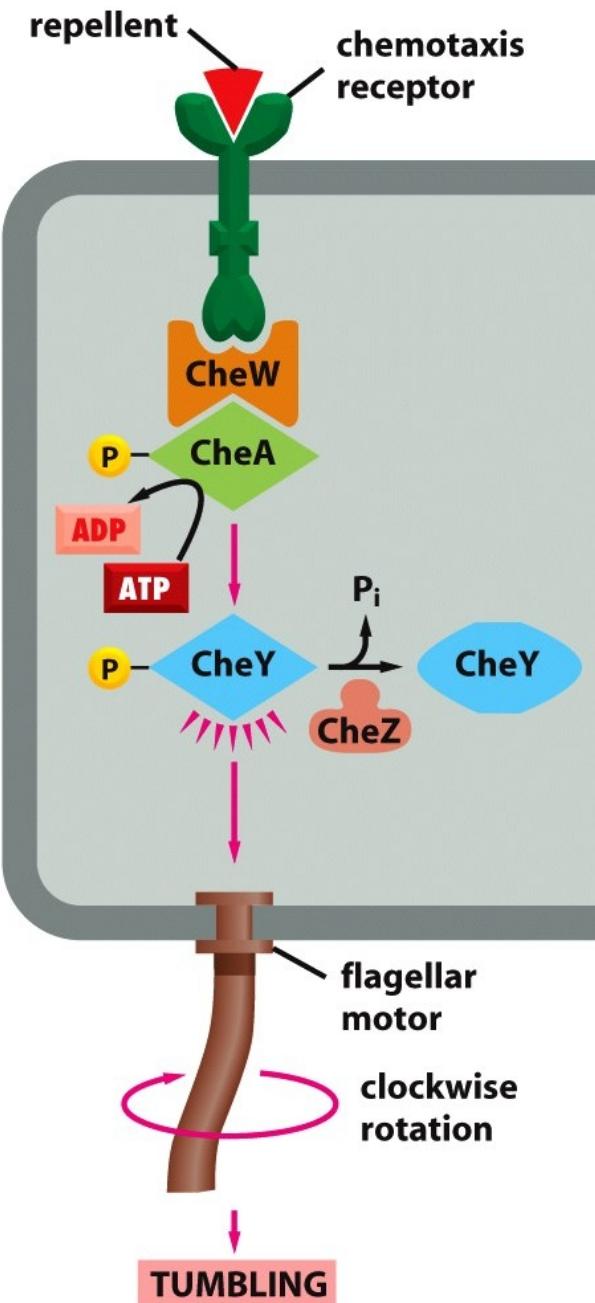
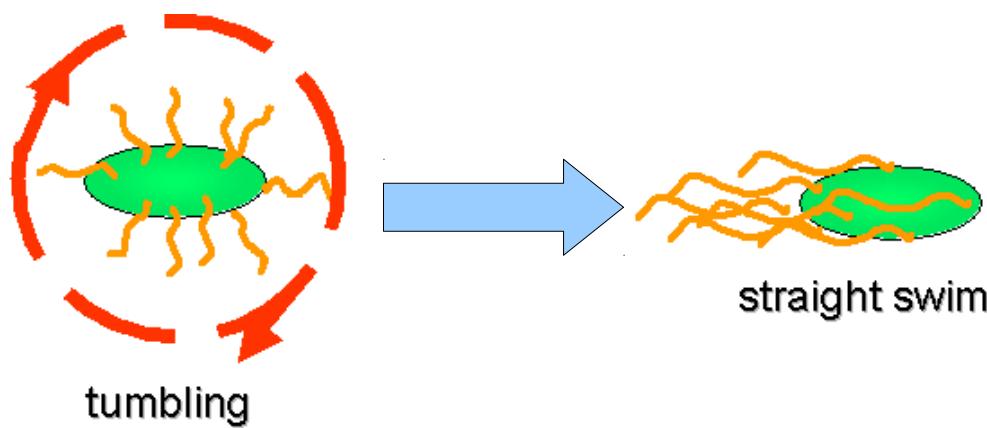
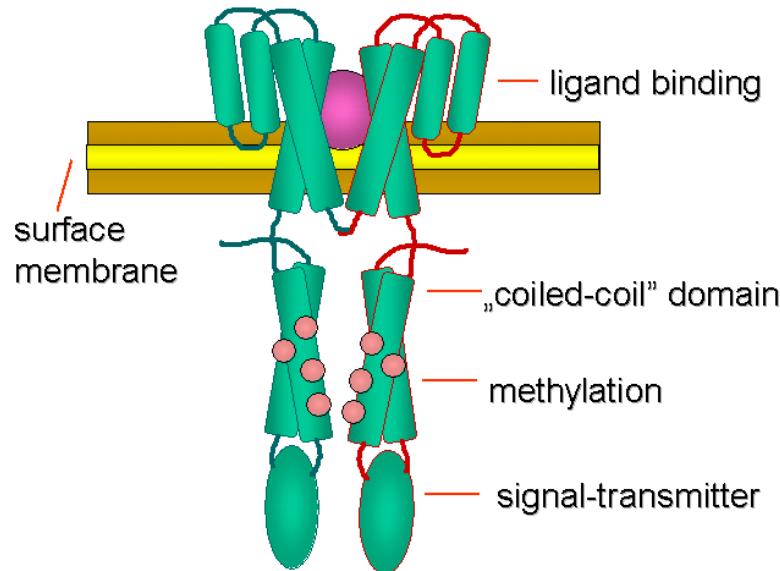
PROTEIN KINASES: SUMMARY



Catalytic domain ~ 250aa

HISTIDINE-KINASE-ASSOCIATED RECEPTORS AND CHEMOTAXIS: MOST UNDERSTOOD

Aspartate receptor dimer



REGULATED PROTEOLYSIS IN SIGNALING PATHWAYS

➤ Classes:

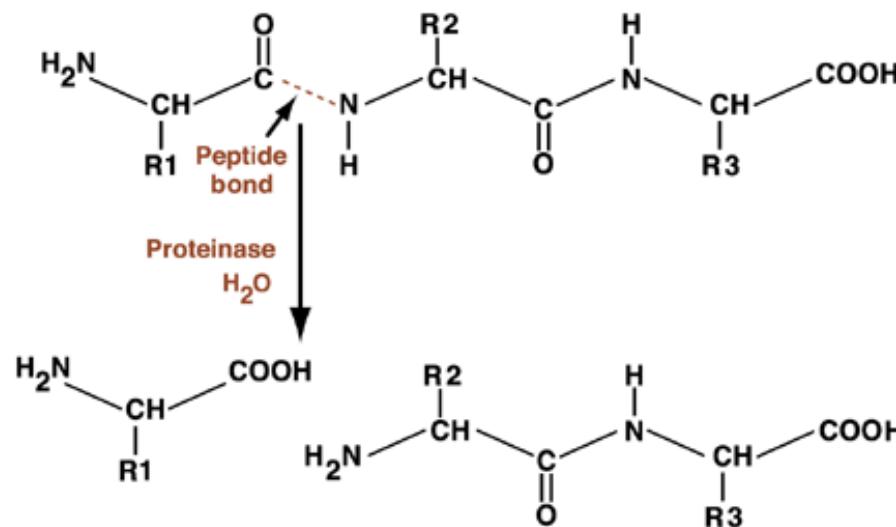
- Notch

- Wnt

- Hedgehog

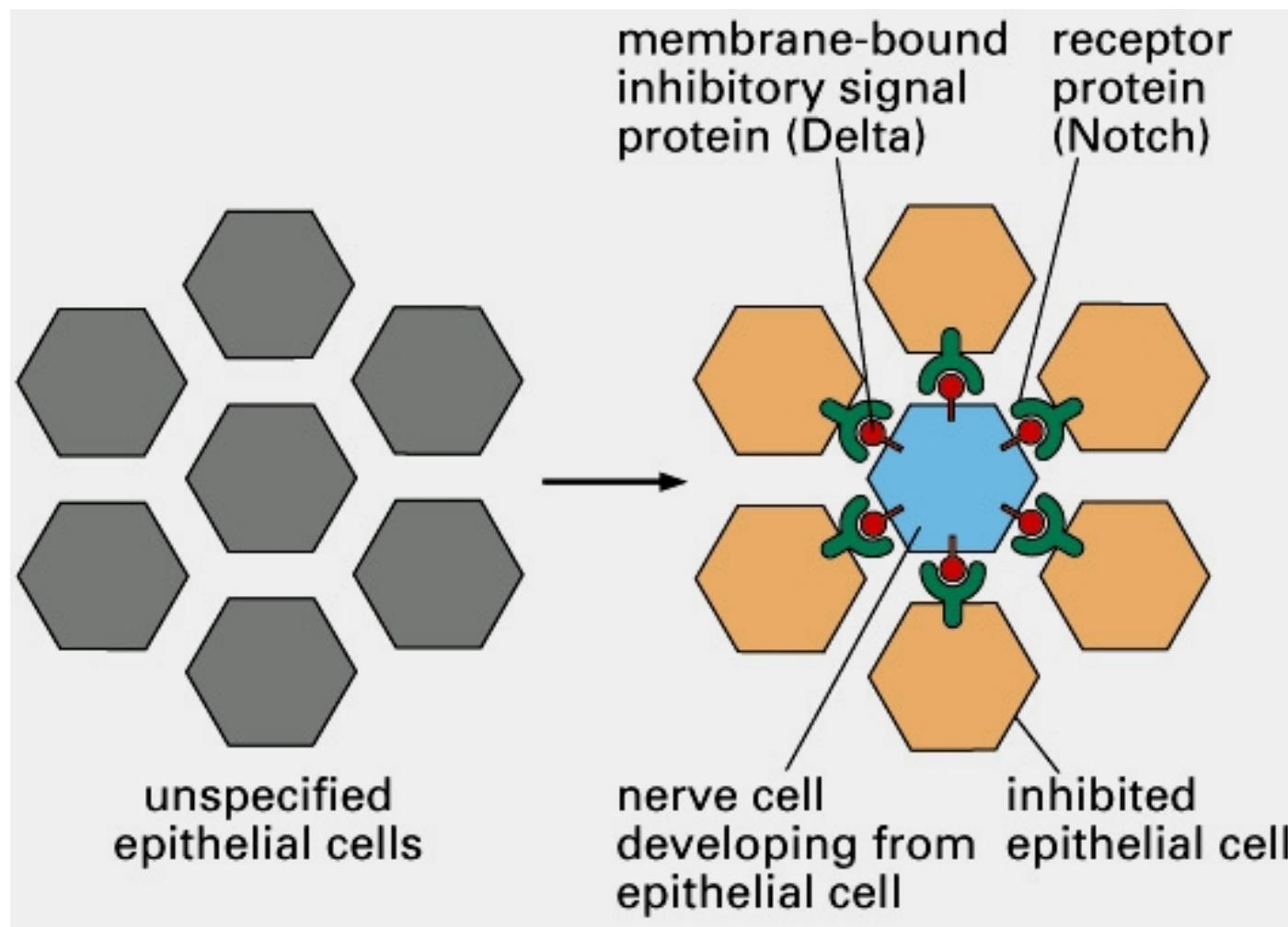
- NF-kB

➤ Function: crucial role in animal development

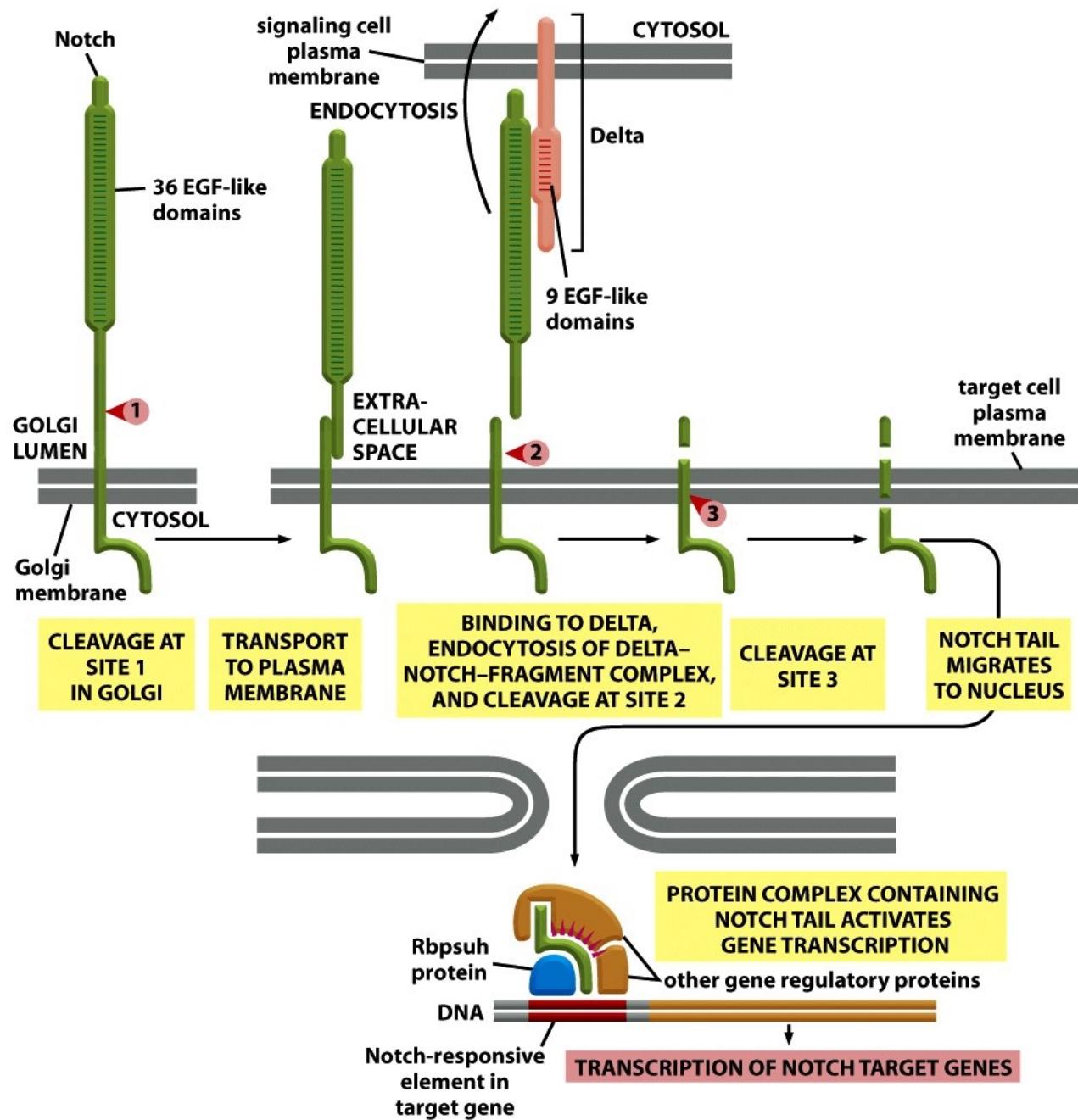


NOTCH PATHWAY

- Development of most tissues
- Best studied in nerve cells of Drosophila
- Delta: inhibitory signal => epithelial cells around the neuron
- Regulation by glycosylation

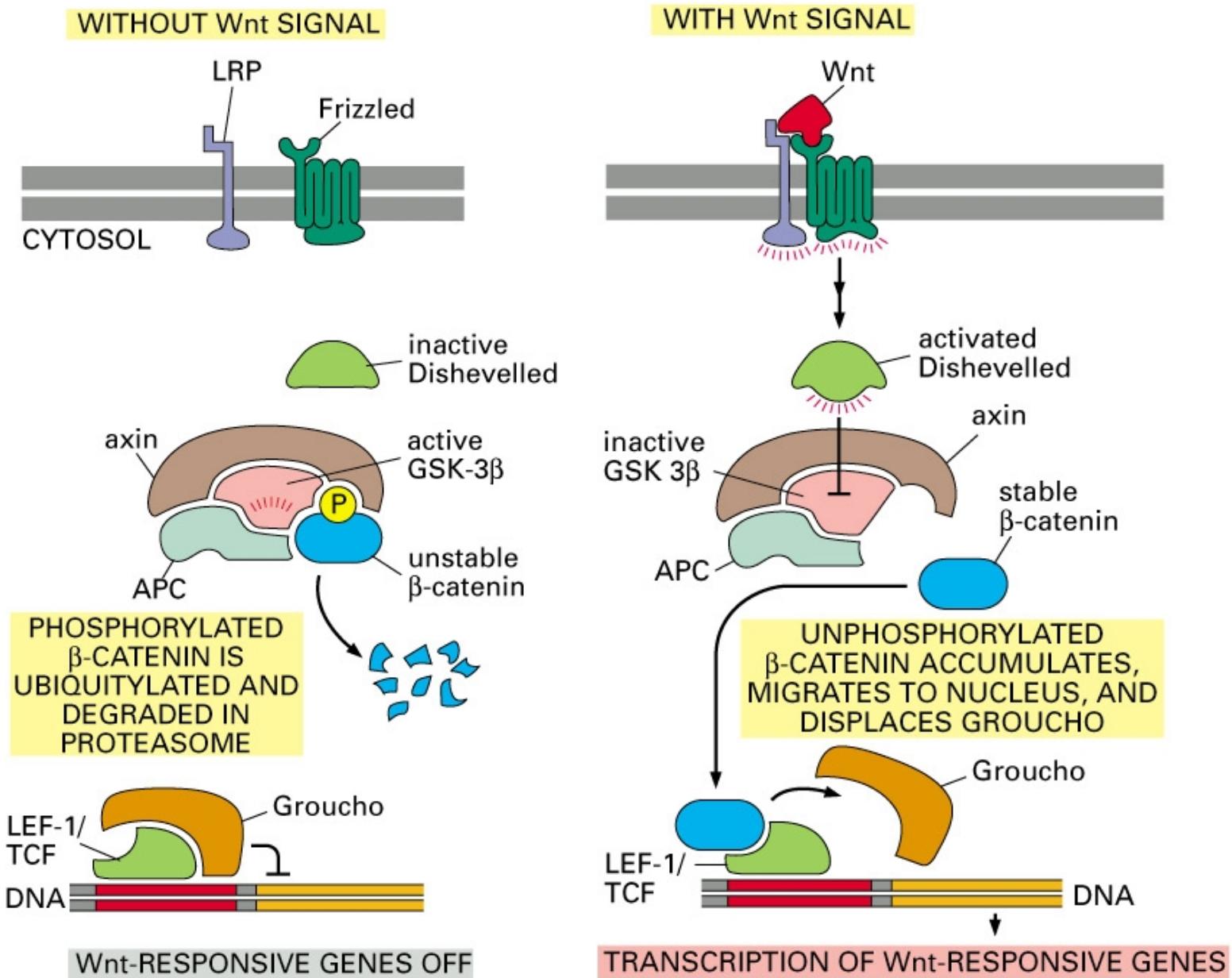


NOTCH PATHWAY



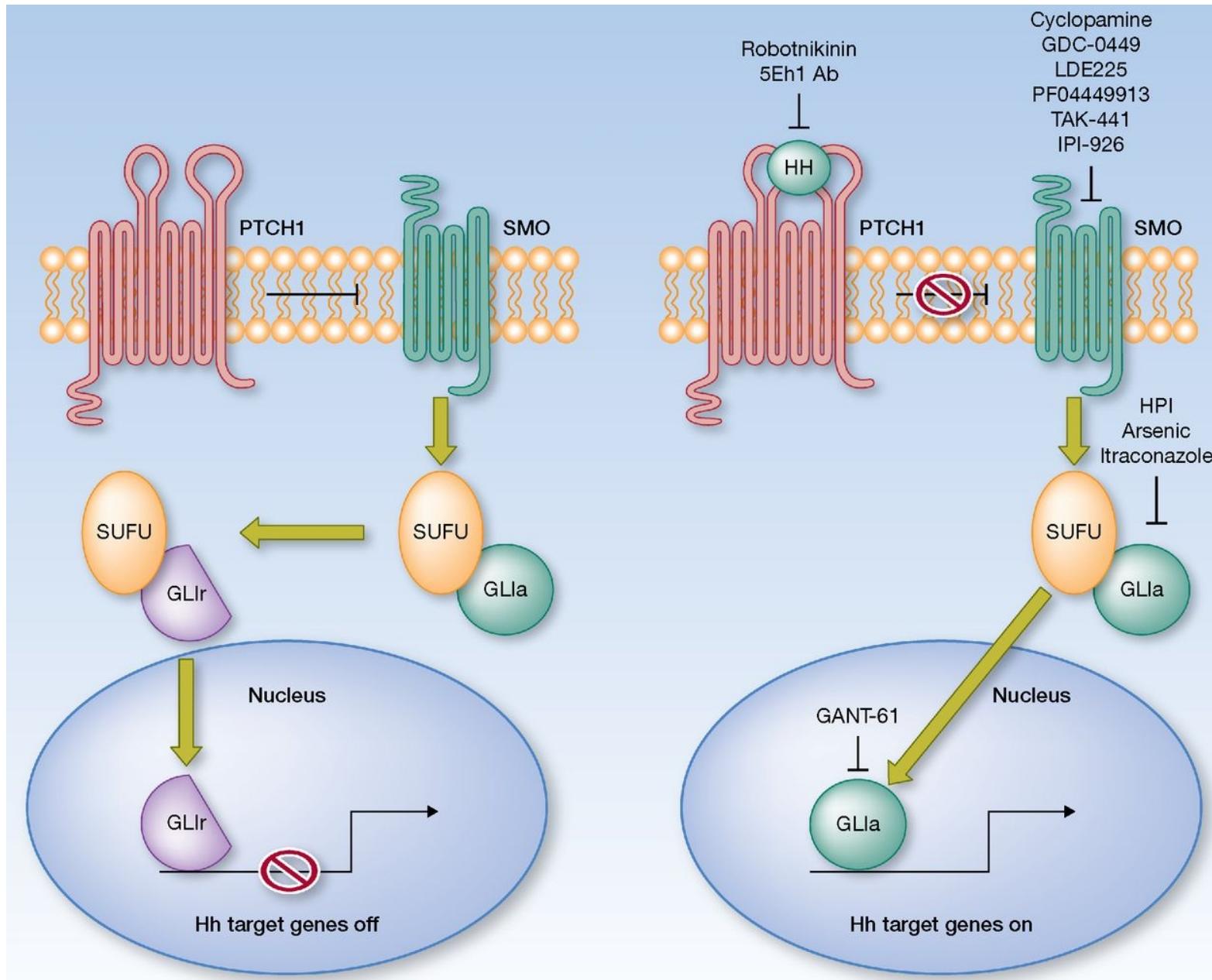
WNT PATHWAY

➤ Abnormality => cancer



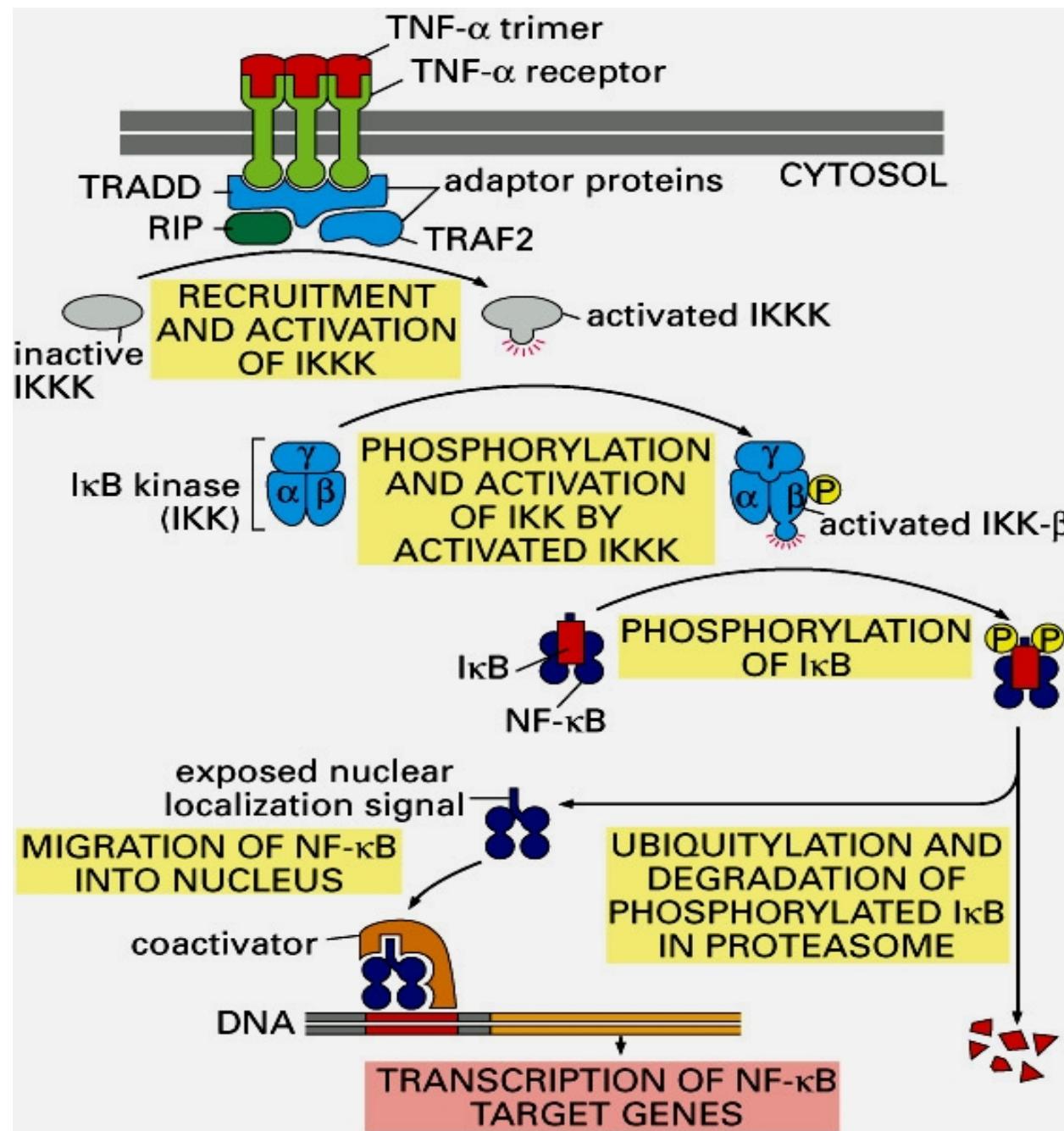
HEDGEHOG PATHWAY

➤ Abnormality => cancer



NF-κB PATHWAY

- Inflammatory responses, switch of ~60 genes



LECTURES 19-20: CELLULAR SIGNALING

- Basic principles
- Nuclear receptors
- Signaling through G-protein, secondary messengers
- Signaling through enzyme-linked cell receptors:
 - key role of phosphorylation/dephosphorylation
- Signaling pathways depending on regulated proteolysis:
 - Notch, Wnt, Hedgehog, NF-κB

