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PROGRAM	**FOR PhD STUDENTS**
SUBTOPIC NAME	**Signalling by Enzyme-Linked Cell-Surface Receptors**
CONTENT TYPE	**PDF**
SEARCH KEYWORD	**Enzyme-Linked Cell-Surface Receptors, Receptor Tyrosine Kinases**

Enzyme Linked Cell Surface Receptors

Objectives:

To acquaint the students about:

i) Enzyme linked receptors: General structure and their types

ii) Signal transduction by Receptor Tyrosine Kinases

iii) Mitogen Activated Protein (MAP) Kinase signaling via Ras

iv) Phosphatidyl Inositol -3 Kinase Signaling for cell survial

v) JAK-STAT signaling.

vi) NF-kB dependent signaling

vii) Ethylene signaling

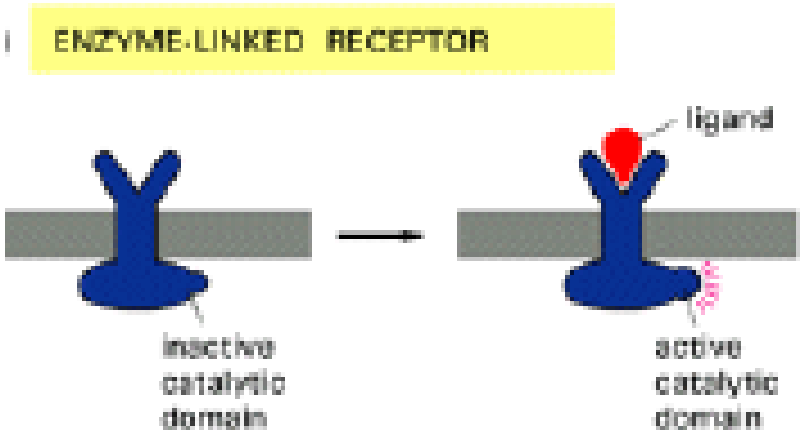
- Enzyme-linked receptors are **second major type of cell-surface receptors**. Respond to extracellular signal proteins that ***promote the growth, proliferation, differentiation or survival of cells in animal tissues***. These signal proteins - collectively called as *growth factors* *& usually act as local mediators at very low* concentrations (10^{-9}-10^{-11} M).

- The responses to them are typically slow (on the order of hours) and usually require many intracellular signaling steps that eventually lead to changes in gene expression.

- Enzyme-linked receptors also mediate direct, rapid effects on cytoskeleton, controlling the way a cell moves and changes its shape. The extracellular signals that induce these rapid responses are often not diffusible but instead attached to surfaces over which cell is crawling.

- Disorders of cell proliferation, differentiation, survival, and migration are fundamental events giving rise to cancer, and abnormalities of signaling through enzyme linked receptors have major roles in this class of disease.

- Enzyme-linked receptors are also *transmembrane proteins* with their ligand-binding domain on outer surface of PM.
- Their cytosolic domain either has an intrinsic enzyme activity or associates directly with an enzyme.
- For enzyme-linked receptors, 2 or more receptor chains come together in PM, forming a dimer or higher oligomer.



Six classes of enzyme-linked receptors identified:

1. ***Receptor tyrosine kinases (RTK)*** *phosphorylate specific tyrosine on a small set of* intracellular signalling proteins.

2. ***Tyrosine-kinase-associated receptors*** *associate with intracellular proteins* that have tyrosine kinase activity.

3. ***Receptor like tyrosine phosphatases*** *remove phosphate groups from tyrosine* of specific intracellular signalling proteins. (They are called "receptor like“ because the presumptive ligands have not yet been identified, and so their receptor function has not been directly demonstrated.)

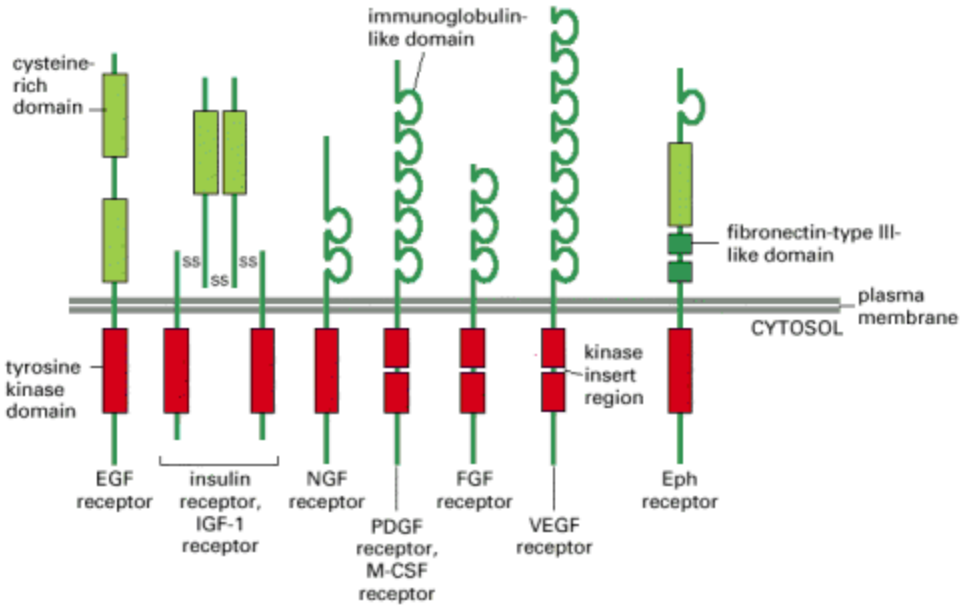
4. ***Receptor serine/threonine kinases*** *phosphorylate specific serines or threonine* on associated latent gene regulatory proteins.

5. ***Receptor guanylyl cyclases*** *directly catalyze the production of cyclic GMP* in the cytosol.

6. ***Histidine-kinase-associated receptors*** *activate a "two-component" signalling pathway* in which the kinase phosphorylates itself on histidine and then immediately transfers the phosphate to a second intracellular signalling protein.

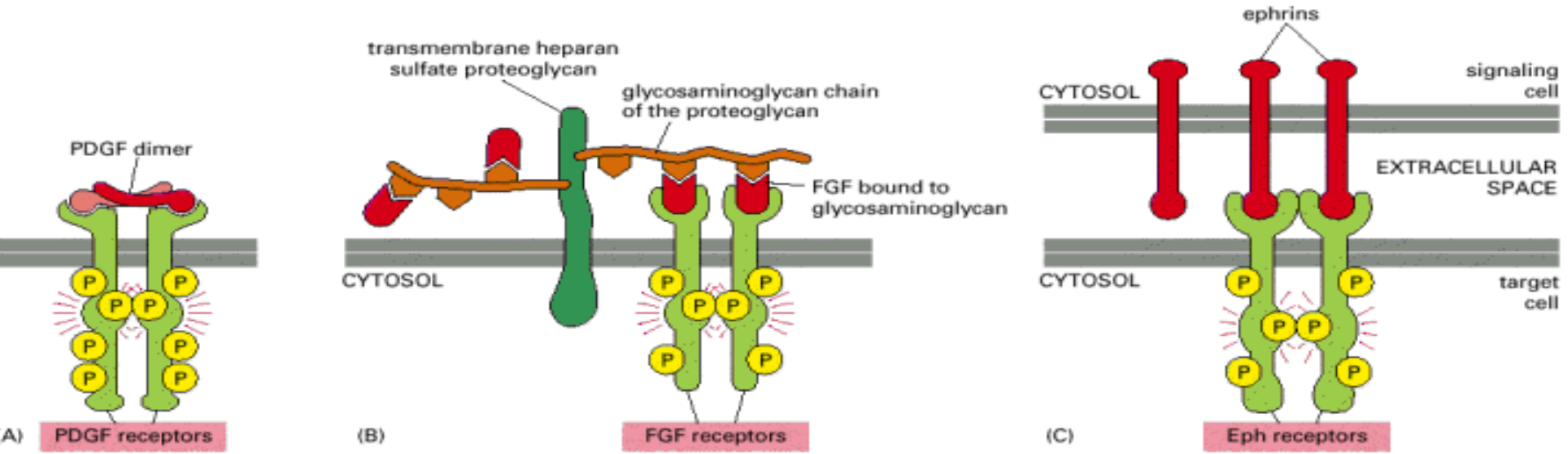
Receptor Tyrosine Kinases

- Extracellular signal proteins that act through **receptor tyrosine kinases** consist of a large variety of secreted growth factors and hormones e.g. *epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs) etc.*
- Receptor tyrosine kinases can be classified into more than 16 structural subfamilies, each dedicated to its complementary family of protein ligands.



Activated Receptor Tyrosine Kinases (RTKs) phosphorylate themselves

- The binding of a signal protein to ligand-binding domain on extracellular side activates the intracellular tyrosine kinase domain. Once activated, the kinase domain transfers a phosphate group from ATP to selected tyrosine side chains, on receptor proteins themselves and on intracellular signalling proteins that subsequently bind to phosphorylated receptors.
- The rearrangement induced in cytosolic tails of the receptors initiates the intracellular signalling process. For RTKs, the rearrangement enables the neighbouring kinase domains of the receptor chains to cross-phosphorylate each other on multiple tyrosine, a process referred to as ***auto-phosphorylation***.
- Receptor activation leads to stimulation of various pathway as cell proliferation, differentiation, promotion of cell survival, modulation of cellular mechanism.
- To activate a RTK, the ligand usually has to bind simultaneously to 2 adjacent receptor chains. E.g. PDGF is a dimer, which cross-links 2 receptors together. Even some monomeric ligands, as EGF, bind to 2 receptors simultaneously and cross-link them directly.



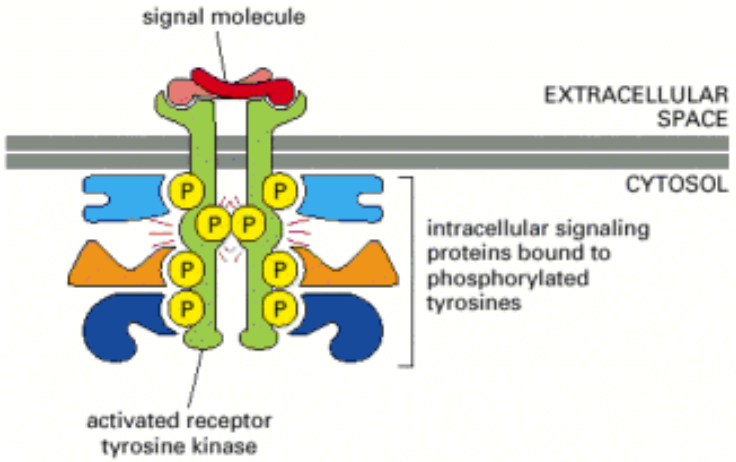
Three ways in which signaling proteins can cross-link receptor chains

❖ **Auto phosphorylation of cytosolic tail of RTKs contributes to activation** process in 2 ways.

1. Phosphorylation of tyrosine within kinase domain **increases the kinase activity** of the enzyme.
2. phosphorylation of tyrosine outside the kinase domain **creates high affinity docking sites for the binding of a number of intracellular signalling proteins in the target cell**. Each type of signalling protein binds to a different phosphorylated site on activated receptor because it contains a specific phosphotyrosine-binding domain that recognizes surrounding features of polypeptide chain in addition to phosphotyrosine.

Once bound to activated kinase, the **signalling protein itself becomes phosphorylated on tyrosine and thus activated**; alternatively, binding alone may be sufficient to activate docked signalling protein.

In summary, auto-phosphorylation serves as a switch to trigger the transient assembly of a large intracellular signalling complex, which then broadcasts signals along multiple routes to many destinations in the cell. Because different receptor tyrosine kinases bind different combinations of these signalling proteins, they activate different responses.



The docking of intracellular signaling proteins on an activated RTK. The activated receptor and bound signaling proteins form a signaling complex that broadcasts signals along multiple signaling pathways.

- Although the **intracellular signalling proteins** that bind to phosphotyrosine on activated RTKs and docking proteins have varied structures and functions, they usually share highly conserved **phosphotyrosine-binding domains**. These can be either **SH2** domains (for *Src homology region, because* it was first found in the Src protein) or, less commonly, ***PTB*** *domains (for phosphotyrosine-binding).*

- *By recognizing specific phosphorylated tyrosine,* these small domains serve as modules that enable the proteins that contain them to bind to activated receptor tyrosine kinases, as well as to many other intracellular signalling proteins that have been transiently phosphorylated on tyrosine.

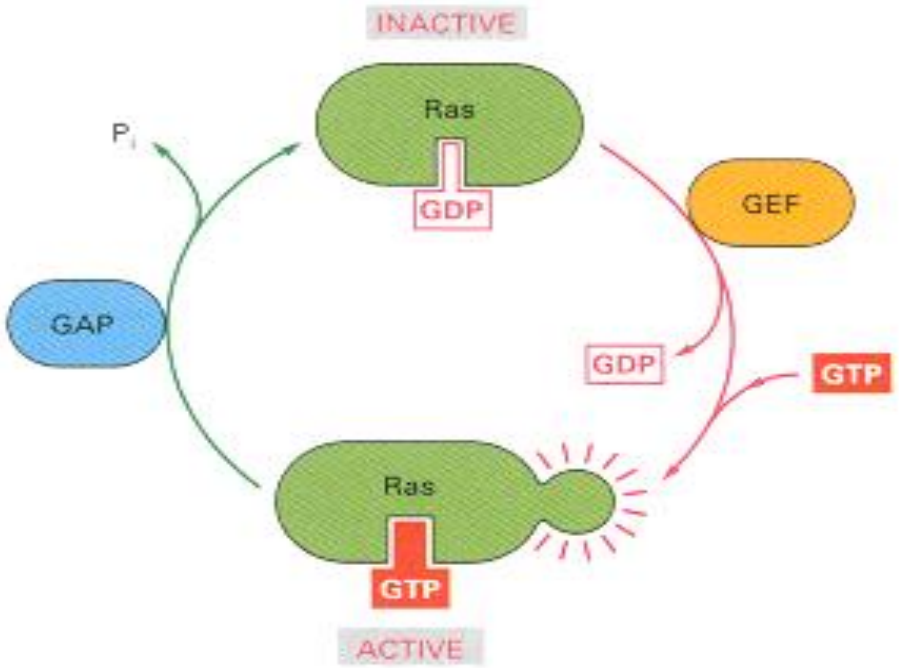
- Many signalling proteins also contain other protein modules that allow them to interact specifically with other proteins as part of the signalling process. These include the ***SH3*** *domain (again, so named because* it was first discovered in Src), which binds to proline-rich motifs in intracellular proteins.

❖ Ras Is Activated by a Guanine Nucleotide Exchange Factor.

Ras proteins belong to the large Ras superfamily of monomeric GTPase that includes 2 other subfamilies: the Rho family, involved in relaying signals from cell-surface receptors to the actin cytoskeleton, and the Rab family, involved in regulating the traffic of intracellular transport vesicles.

❖ Ras proteins contain a covalently attached lipid group that helps to anchor the protein to a membrane in this case, to the cytoplasmic face of PM where the protein functions.

Ras helps to broadcast signals from the cell surface to other parts of the cell.



Regulation of Ras activity. Like other GTP-binding proteins, Ras functions as a switch, cycling between 2 conformational states: *active* when GTP is bound and *inactive* when GDP is bound.

Two classes of signalling proteins regulate Ras activity by influencing its transition between active and inactive states.

-**Guanine nucleotide exchange factors (GEFs)** promote the exchange of bound nucleotide by stimulating the dissociation of GDP and the subsequent uptake of GTP from the cytosol, thereby activating Ras.

-**GTPase-activating proteins (GAPs)** increase the rate of hydrolysis of bound GTP by Ras, thereby inactivating Ras.

- If Ras function is inhibited by microinjection of neutralizing anti-Ras antibodies or dominant-negative mutant form of Ras, the cell proliferation or differentiation responses normally induced by the activated RTKs do not occur. Conversely, if a hyperactive mutant Ras protein is introduced into some cell lines, the effect on cell proliferation or differentiation is sometimes the same as that induced by the binding of ligands to cell-surface receptors. In fact, Ras was first discovered as the hyperactive product of a mutant ras gene that promoted the development of cancer; we now know that about 30% of human tumors have a hyperactive ras mutation.

- Hyperactive mutant forms of Ras are resistant to GAP-mediated GTPase stimulation and are locked permanently in the GTP bound active state, which is why they promote the development of cancer.

- In principle, receptor tyrosine kinases could activate Ras either by activating a GEF or by inhibiting a GAP. Even though some GAPs bind directly (via their SH2 domains) to activated RTKs, whereas GEFs bind only indirectly, it is the indirect coupling of the receptor to a GEF that is responsible for driving Ras into its active state.

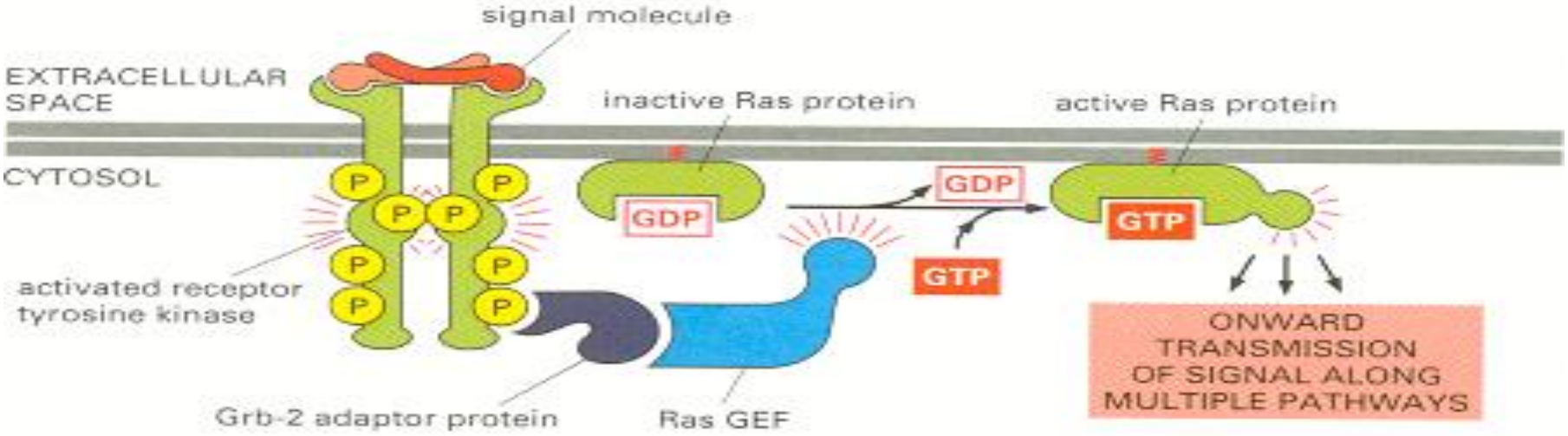
- In fact, the loss of function of a Ras-specific GEF has a similar effect to the loss of function of that Ras.

❖ **Adaptor proteins link receptor tyrosine kinases to Ras**.

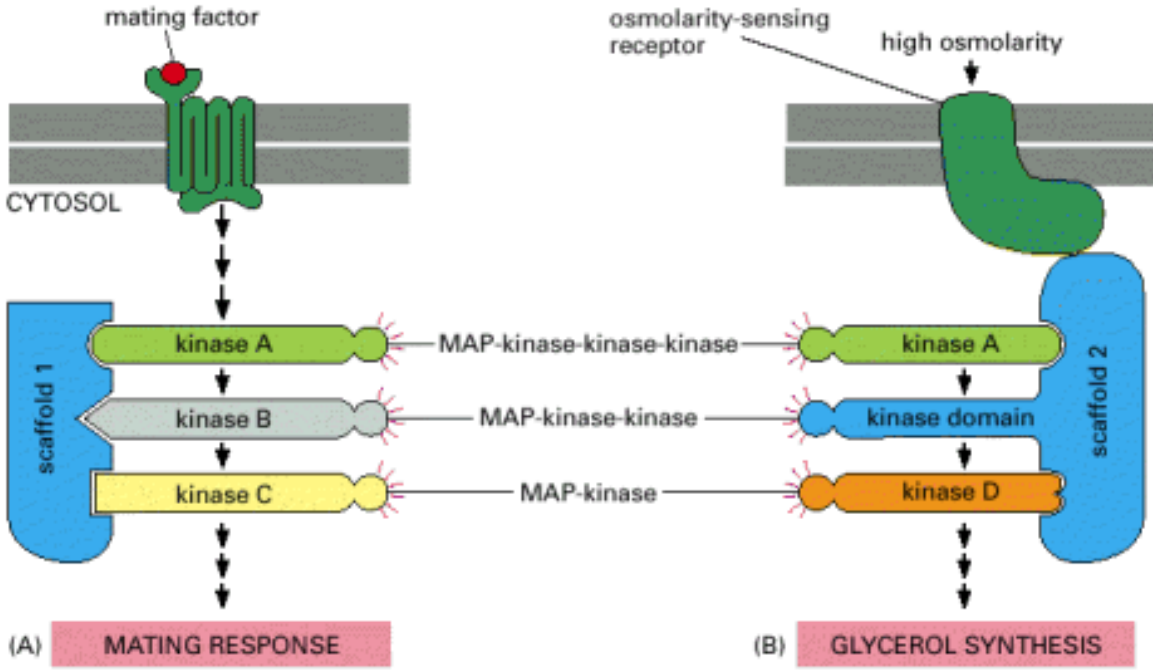
The **Grb-2 protein in mammalian cells**, for example, binds through its SH2 domain to specific phosphotyrosine on activated receptor tyrosine kinases and through its SH3 domains to proline-rich motifs on a GEF called **Sos.**

❖ This pathway from receptor tyrosine kinases is not the only means of activating Ras. Other Ras GEFs are activated independently of Sos.

❖ Once activated, Ras in turn activates various other signalling proteins to relay the signal downstream along several pathways. One of the signalling pathways Ras activates is a serine/threonine phosphorylation cascade that is highly conserved in eukaryotic cells from yeasts to humans. A crucial component in this cascade is a novel type of protein kinase called *MAP kinase.*



The activation of Ras by an activated receptor tyrosine kinase. The Grb-2 adaptor protein binds to a specific phosphotyrosine on the receptor and to the Ras guanine nucleotide exchange factor (GEF), which stimulates Ras to exchange its bound GDP for GTP. The activated Ras then activates several downstream signalling pathways, one of which is shown on next slide.



The organization of MAP-kinase pathways by scaffold proteins in budding yeast. Budding yeast have at least 6 three-component MAP-kinase modules involved in a variety of biological processes, (A) The mating response is triggered when a mating factor secreted by a yeast of opposite mating type binds to a GPCR. This activates a G protein, and the βγ complex of the G protein indirectly activates the MAP-kinase-kinase-kinase (kinase A), which then relays the response onward. Once activated, the MAP-kinase (kinase C) phosphorylates and thereby activates several proteins that mediate the mating response, in which the yeast cell stops dividing and prepares for fusion. The 3 kinases in this module are bound to scaffold protein 1. (B) In a second response, a yeast cell exposed to a high-osmolarity environment is induced to synthesize glycerol to increase its internal osmolarity. This response is mediated by a transmembrane, osmolarity-sensing, receptor protein and a different MAP-kinase module bound to a second scaffold protein. (the kinase domain of scaffold 2 provides the MAP-kinase-kinase activity of this module)

• Although both pathways use the same MAP-kinase-kinase-kinase*, there is no cross talk between them, because the kinases in each module are* tightly bound to different scaffold proteins, and the osmosensor is bound to the same scaffold protein as the particular kinase it activates.

- **Ras Activates a Downstream Serine/Threonine Phosphorylation Cascade That Includes a MAP-Kinase**

- Both the tyrosine phosphorylation and the activation of Ras triggered by activated RTK are short-lived.
- Tyrosine-specific protein phosphatases quickly reverse the phosphorylation, and GAPs induce activated Ras to inactivate itself by hydrolyzing its bound GTP to GDP.

  To stimulate cells to proliferate or differentiate, these short-lived signalling events must be converted into longer-lasting ones that can sustain the signal and relay it downstream to the nucleus to alter the pattern of gene expression.
- Activated Ras triggers this conversion by initiating a series of downstream serine/threonine phosphorylation, which are much longer-lived than tyrosine phosphorylation. Many serine/threonine kinases participate in this phosphorylation cascade, but three of them constitute the core module of the cascade. The last of the three is called a **mitogen-activated protein kinase (MAP-kinase).**
- An unusual feature of a MAP-kinase is that its full activation requires the phosphorylation of both a threonine and a tyrosine, which are separated in the protein by a single amino acid. The protein kinase that catalyzes both of these phosphorylation is called a *MAP-kinase-kinase, which in the mammalian Ras* signalling pathway is called MEK. The requirement for both a tyrosine and a threonine phosphorylation ensures that the MAP-kinase is kept inactive unless specifically activated by a MAP-kinase-kinase, whose only known substrate is a MAP-kinase. MAP-kinase-kinase is itself activated by phosphorylation catalyzed by the first kinase in the three-component module, *MAP-kinase kinase-kinase, which in the mammalian Ras signalling pathway is called* ***Raf.*** The Raf kinase is activated by activated Ras.

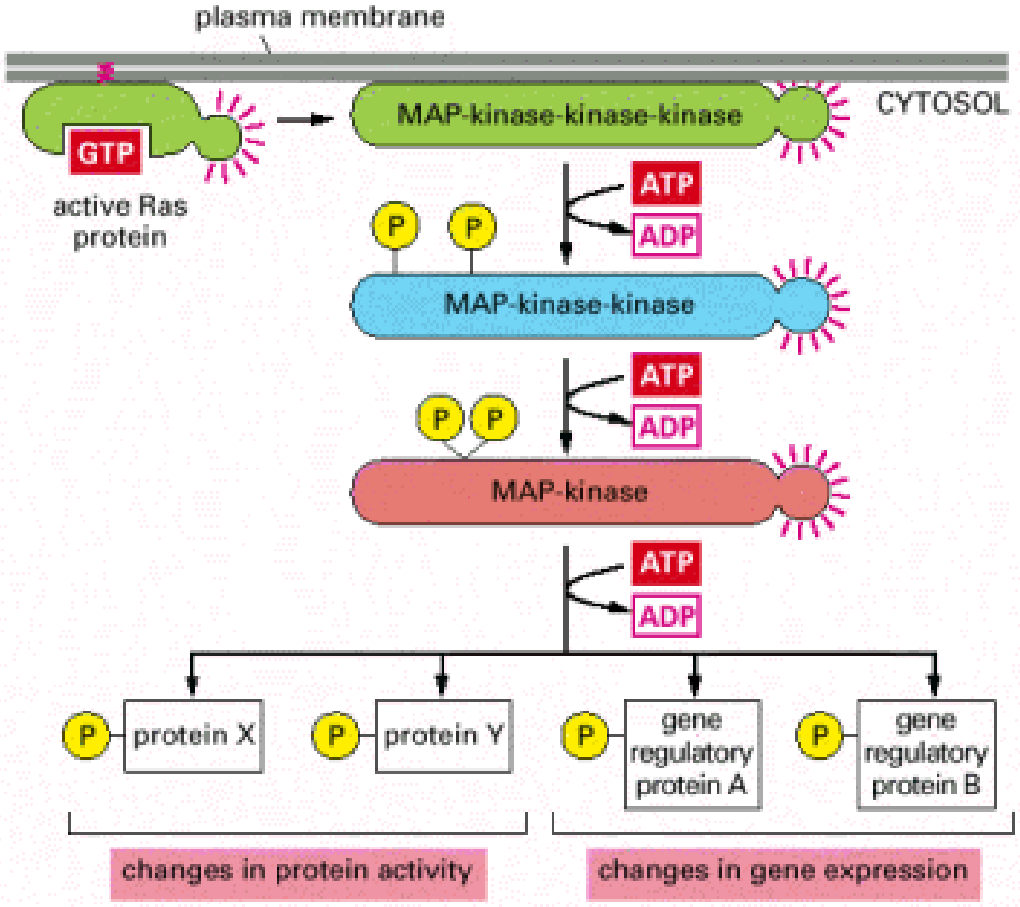
- Once activated, the MAP-kinase relays the signal downstream by phosphorylating various proteins in the cell, including gene regulatory proteins and other protein kinases. It enters the nucleus, for example, and phosphorylates one or more components of a gene regulatory complex. This activates the transcription of a set of *immediate early genes,* that turn on within minutes of the time that cells are stimulated by an extracellular signal, even if protein synthesis is experimentally blocked with drugs. Some of these genes encode other gene regulatory proteins that turn on other genes, a process that requires both protein synthesis and more time.

- In this way the Ras-MAP-kinase signalling pathway conveys signals from the cell surface to the nucleus and **alters the pattern of gene expression** in significant ways e.g . Among the genes activated by this pathway are those required for cell proliferation, such as the genes encoding *G1 cyclins.*

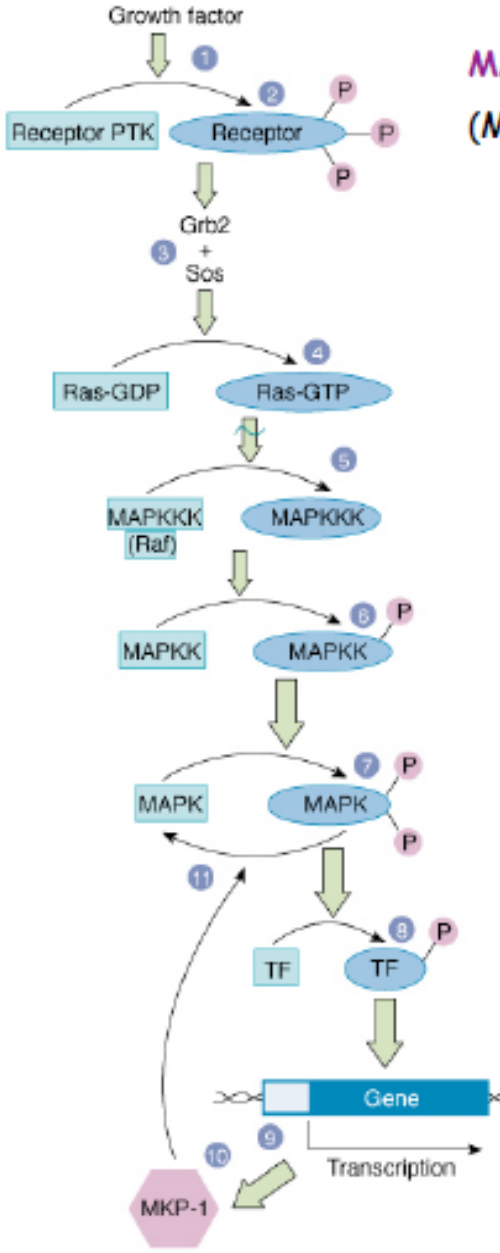
- MAP-kinases are usually activated only transiently in response to extracellular signals, and the period of time they remain active can profoundly influence the nature of the response. When EGF activates its receptors on a neural precursor cell line, ex., MAP-kinase activity peaks at 5 min and rapidly declines, and cells later go on to divide. By contrast, when NGF activates its receptors on same cells, MAP-kinase activity remains high for many hours, and the cells stop proliferating and differentiate into neurons.

- MAP-kinases are inactivated by dephosphorylation, and the specific removal of phosphate from either tyrosine or threonine is enough to inactivate the enzyme.

Ras Activates a Downstream Serine/Threonine Phosphorylation Cascade That Includes a MAP-Kinase



The pathway activated by Ras begins with a **MAP-kinase-kinase-kinase called *Raf***, *which activates the* **MAP-kinase-kinase *Mek***, *which then activates* ***MAP-kinase called Erk***. *Erk* in turn phosphorylates a variety of downstream proteins, including other kinases, as well as gene regulatory proteins in the nucleus. The resulting changes in gene expression and protein activity cause complex changes in cell behaviour.



MAP kinase cascade

(Mitogen-Activated Protein: activated by a mitosis-stimulating growth factor)

Recruitment of Raf by activated Ras to the plasma membrane activates it as a kinase (MAPKKK)

Raf phosphorylates MAPKK

MAPKK phosphorylates MAPK

MAPK phosphorylates transcription factors like Elk-1

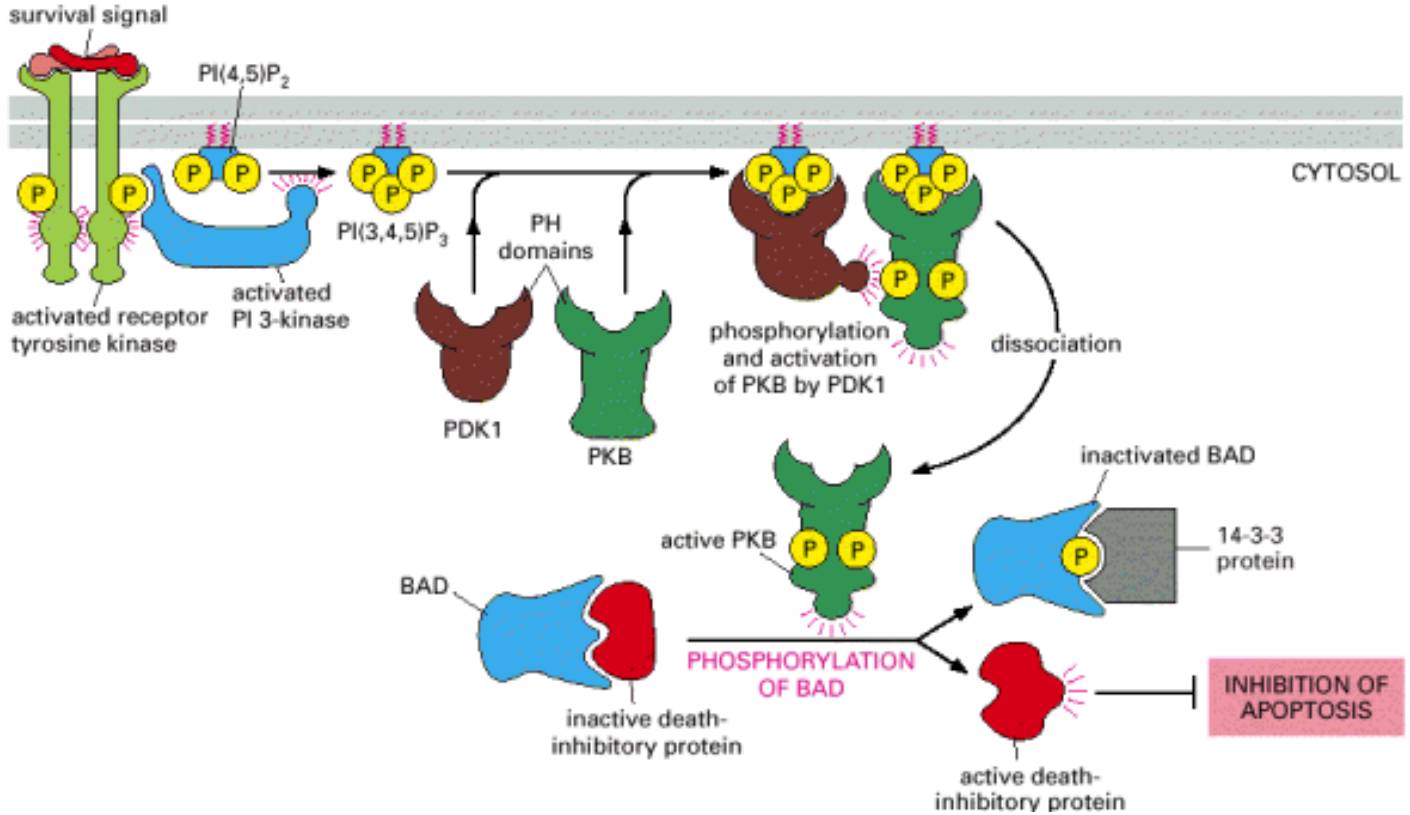
Elk-1 activates the transcription of Fos and June. These proteins then make a dimer that activates the transcription of cell proliferating genes

The transcription of MAPK phosphatase (MKP-1) is also activated. MKP-1 dephosphorylates MAPK and stop signalling

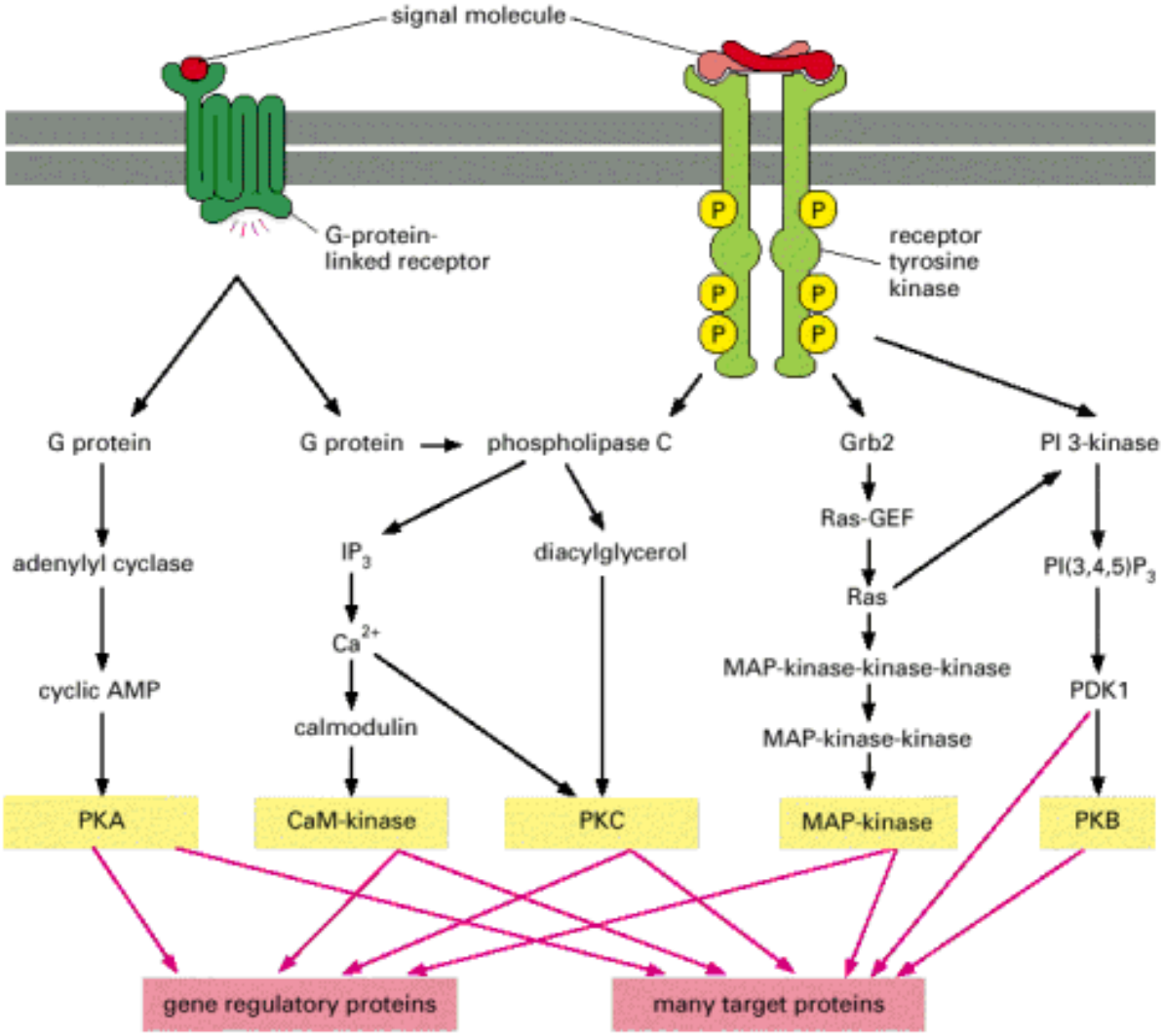
This pathway is generally used in eukaryotes for many different functions. Different types of information are transmitted thanks to the existence of different isoforms for each of the cascade proteins.

The human genome encodes for 2000 kinases and 1000 phosphatases

Signaling through PI 3-kinase promotes cell survival



An extracellular survival signal activates a RTK, which recruits and activates PI 3-kinase. The PI 3-kinase produces PI(3,4,5)P3 and PI(3,4)P2 (not shown), both serve as docking sites for 2 serine/threonine kinases with PH domains protein kinase B (PKB) and the phosphoinositol dependent kinase PDK1. The binding of PKB to inositol lipids alters its conformation so that the protein can be phosphorylated and activated by PDK1. The activated PKB now dissociates from PM and phosphorylates BAD protein, which, when unphosphorylated, holds 1 or more death-inhibitory proteins in an inactive state. Once phosphorylated, BAD releases the inhibitory proteins, which now can block apoptosis and thereby promote cell survival. Once phosphorylated, BAD binds to a ubiquitous cytosolic protein called *14-3-3, which keeps* BAD out of action. The activation of other signaling pathways can also lead to BAD phosphorylation and the promotion of cell survival.



Five parallel intracellular signaling pathways activated by GPLRs, RTKs, or both. The 5 kinases (*yellow) at the end of each pathway phosphorylate* target proteins (*red), some of which are phosphorylated by more than one of* the kinases. The specific phospholipase C activated by the two types of receptors is different: G-protein-linked receptors activate PLC-β, whereas receptor tyrosine kinases activate PLC-γ.

How quickly do you need your message to arrive?

- VERY FAST (milliseconds)
  Nerve conduction, vision
  – Ion channels
- FAST (seconds)
  Vision, metabolism, cardiovascular
  – G protein-coupled receptors
- SLOW (minutes to hours)
  Cell division, proliferation, developmental processes
  – Growth factor receptors
  – Steroid hormones

Cytokine Receptors Activate the Jak-STAT Signaling Pathway, Providing a Fast Track to the Nucleus

- The Jak-STAT signaling pathway directly leads from cell-surface receptors to the nucleus, where they alter gene transcription. It was initially discovered in studies on *interferons (cytokines secreted by cells* in response to viral infection).
- When activated, interferon receptors activate the cytoplasmic tyrosine kinases called **Janus kinases (Jaks)** (after the two-faced Roman god)**.** The Jaks then phosphorylate and activate a set of latent gene regulatory proteins called **STATs (signal transducers and activators of transcription)**, which move into the nucleus and stimulate the transcription of specific genes.
- More than 30 cytokines and hormones activate the Jak-STAT pathway by binding to cytokine receptors. All STATs also have an SH2 domain that enables them to dock onto specific phosphotyrosines on activated tyrosine kinase receptors.
- Cytokine receptors are composed of two or more polypeptide chains. All cytokine receptors, are associated with one or more Jaks. There are 4 known Jaks Jak1, Jak2, Jak3, and Tyk2 and each is associated with particular cytokine receptors. The receptors for α-interferon, for example, are associated with Jak1 and Tyk2, whereas the receptors for γ-interferon are associated with Jak1 and Jak2.
- Cytokine binding either induces the receptor chains to oligomerize or reorients the chains in a preformed oligomer. In either case, the binding brings the associated Jaks close enough together for them to cross-phosphorylate each other, thereby increasing the activity of their tyrosine kinase domains. The Jaks then phosphorylate tyrosines on the cytokine receptors, creating phosphotyrosine docking sites for STATs and other signaling proteins.

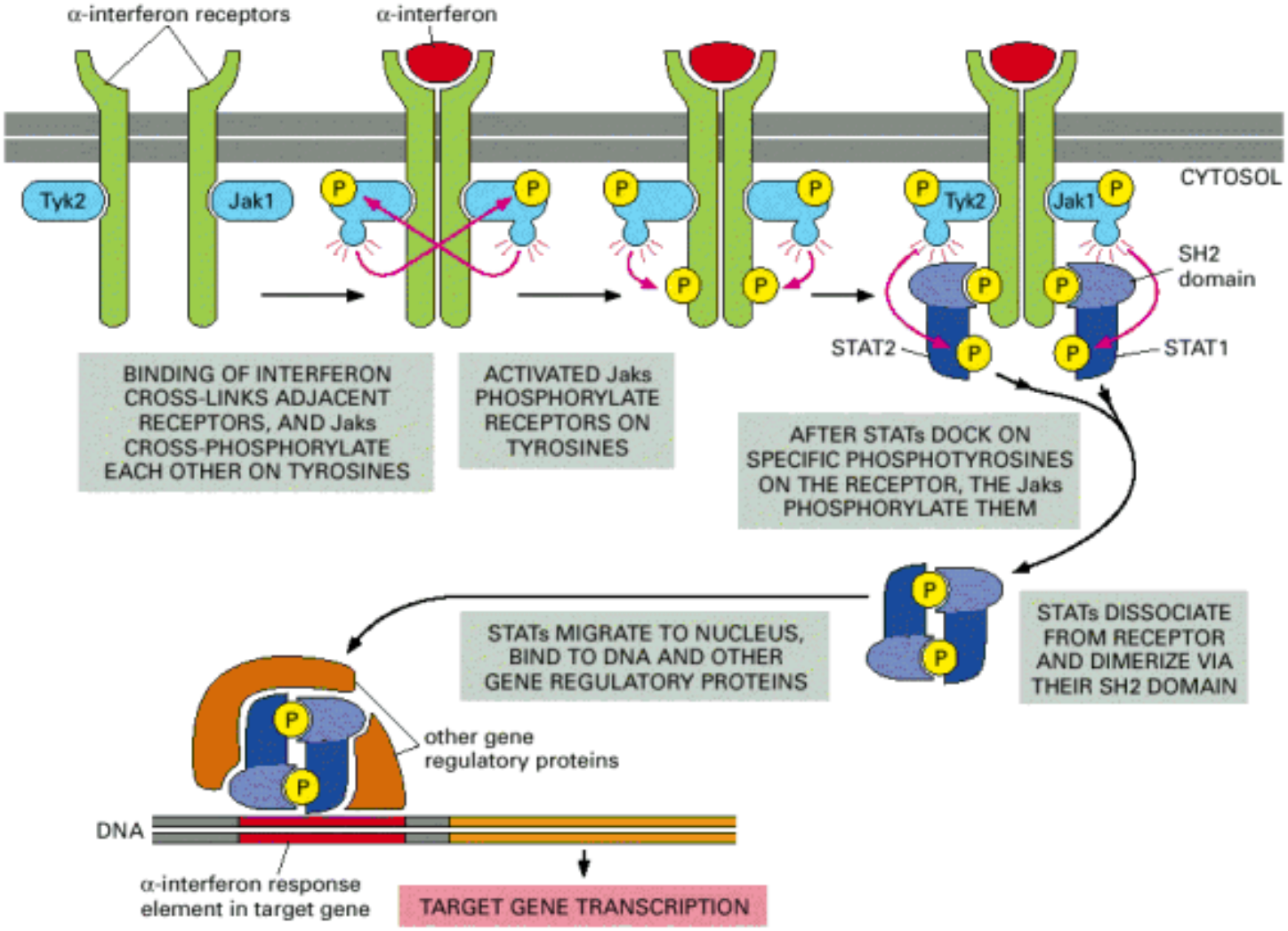
There are 7 known STATs, each with an SH2 domain that performs 2 functions. First, it mediates the binding of the STAT protein to a phosphotyrosine docking site on an activated cytokine receptor (or receptor tyrosine kinase); once bound, the Jaks phosphorylate the STAT on tyrosines, causing it to dissociate from the receptor. Second, the SH2 domain on the released STAT now mediates its binding to a phosphotyrosine on another STAT molecule, forming either a STAT homodimer or heterodimer.

The STAT dimer then moves into the nucleus, where, in combination with other gene regulatory proteins, it binds to a specific DNA response element in various genes and stimulates their transcription. In response to the hormone prolactin, for example, which stimulates breast cells to produce milk, activated STAT5 stimulates the transcription of genes that encode milk proteins.

The responses mediated by STATs are often regulated by negative feedback. In addition to activating genes that encode proteins mediating the cytokine induced response, the STAT dimers may also activate genes that encode inhibitory proteins.

Such negative feedback mechanisms, however, are not enough on their own to turn off the response. The activated Jaks and STATs also have to be inactivated by dephosphorylation of their phosphotyrosines. As in all signaling pathways that use tyrosine phosphorylation, the dephosphorylation is performed by *protein tyrosine phosphatases,*

The Jak-STAT signaling pathway activated by α-interferon



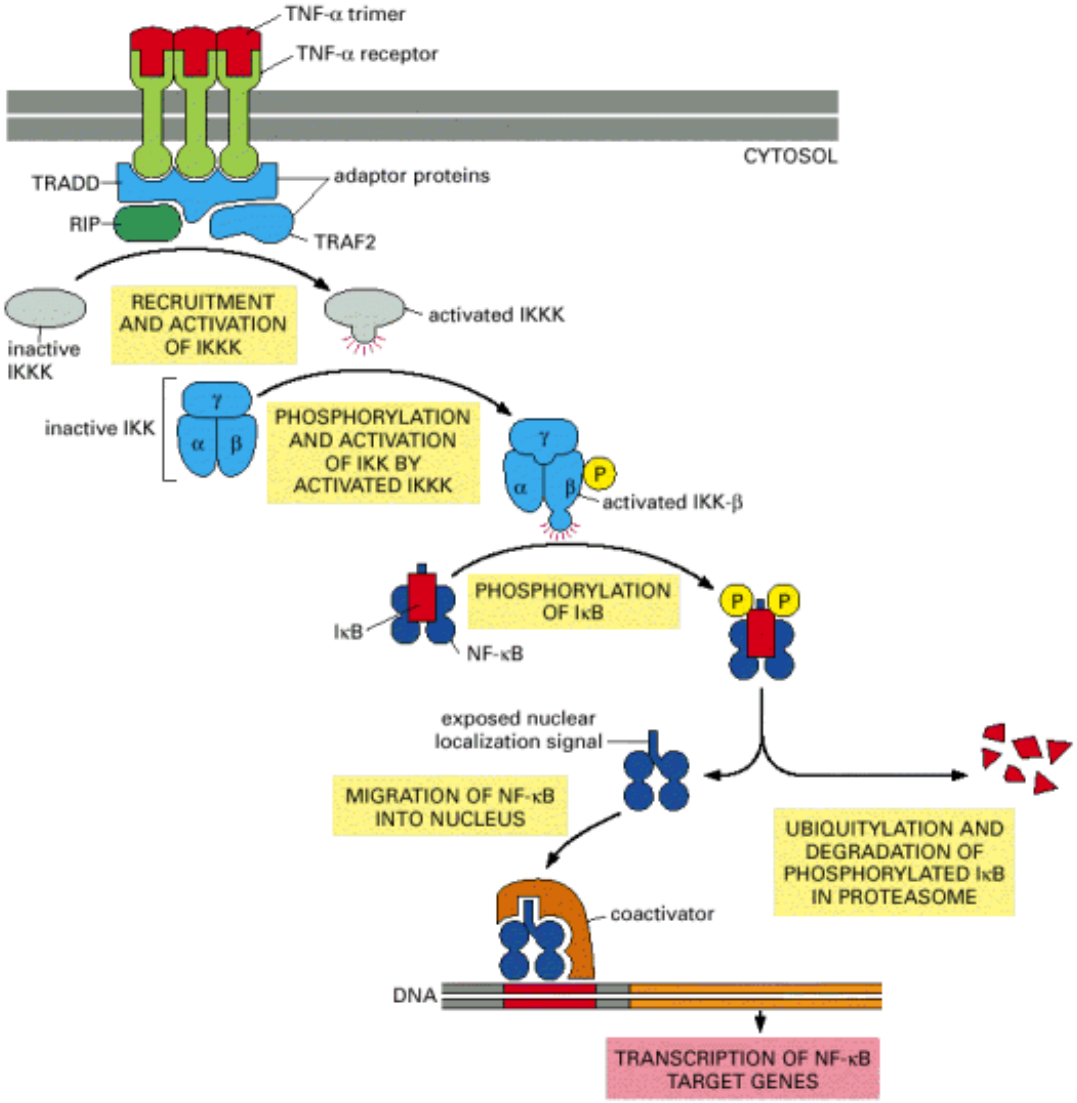
Interferon binding either causes two separate receptor polypeptide chains to dimerize or reorients receptor chains in a preformed dimer. In either case, associated Jaks are brought together so that they can cross-phosphorylate each other on tyrosines, starting signaling process. Two different receptor chains are associated with different Jaks (Tyk2 and Jak1), and they recruit different STATs (STAT1 and STAT2). The STATs dissociate from the receptors and form heterodimers when activated by phosphorylation, and they bind to specific DNA sequences in the cell nucleus, where, together with other gene regulatory proteins, they induce transcription of adjacent genes

Multiple Stressful and Proinflammatory Stimuli Act Through an NF-kB-Dependent Signalling Pathway

NF-kB proteins are latent gene regulatory proteins that lie at the heart of most inflammatory responses. These responses occur as a reaction to infection or injury and help protect the animal and its cells from these stresses. Excessive, inflammatory responses can damage tissue and cause severe pain, as in joints in rheumatoid arthritis.

T*umor necrosis factor-α (TNF-α) and interleukin-1 (IL-1)* vertebrate cytokines are especially important in inducing inflammatory responses. These proinflammatory cytokines bind to cell-surface receptors and activate NF-kB, which is normally sequestered in an inactive form in the cytoplasm of almost all of our cells.

5 NF-kB proteins in mammals (RelA, RelB, c-Rel, NF-kB1, and NF-kB2), form a variety of homodimers and heterodimers, each of which activates its own characteristic set of genes. Inhibitory proteins called **IkB** bind tightly to the dimers and hold them in an inactive state within large protein complexes in the cytoplasm.



The activation of NF-kB by TNF-α.

Both TNF-α and its receptors are trimers. TNF-α binding causes a rearrangement of the clustered cytosolic tails of the receptors, which recruit a no. of intracellular signalling proteins, including the *receptor interacting protein kinase (RIP) and two adaptor proteins, TNF-associated death-domain protein (TRADD) and TNF-receptor-associated factor 2 (TRAF2).*

These then recruit and activate an unidentified kinase, IkB kinase kinase kinase (IKKK), which phosphorylates and activates IkB kinase kinase (IKK).

IKK is a heterotrimer composed of 2 kinase subunits (IKK-α and IKK-β) and a regulatory adaptor subunit called IKK-γ.

The IKK-β then phosphorylates IkB on 2 serines, which marks the protein for ubiquitylation and degradation in proteasomes. The nuclear localization signal on the free NF-kB now directs the transport of this protein into the nucleus where, in collaboration with co-activator proteins, it stimulates the transcription of its target genes. In addition to target genes involved in inflammatory response, NF-kB also activates the *IkB gene, providing negative feedback.*

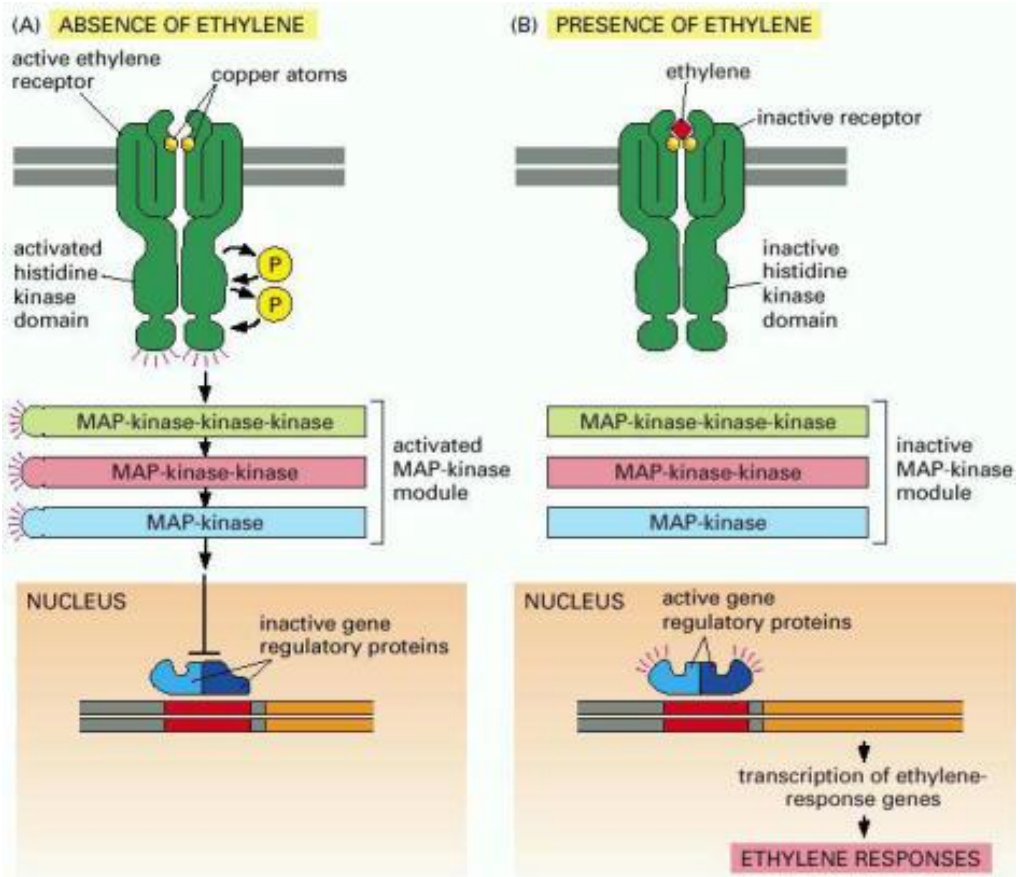
Ethylene Activates a Two-Component Signalling Pathway

- Ethylene, a gas molecule can influence plant development in various ways, including the promotion of fruit ripening, leaf abscission, and plant senescence.

- It also functions as a stress signal in response to wounding, infection, flooding, and so on.

- When the shoot of a germinating seedling, for ex. encounters an obstacle in the soil, the seedling responds to the encounter in 3 ways, controlled by ethylene.
  -Ist, it thickens its stem, which can then exert more force on the obstacle.
  -2nd, it shields the tip of the shoot by increasing the curvature of a specialized hook structure.
  -3rd, it reduces the shoot's tendency to grow away from the direction of gravity to avoid the obstacle.

- Ethylene receptors are dimeric transmembrane proteins, that function as *histidine kinases*



Extracellular domain has a Cu atom that binds ethylene, and an intracellular histidine kinase-like domain.

The kinase domain, when active, phosphorylates itself on histidine and then is believed to transfer the phosphate to an aspartic acid in another domain of the receptor.

The binding of ethylene inactivates ethylene receptors, inhibiting the kinase domain and the downstream signalling pathway emanating from it. In its unbound, active state, the receptor activates the first component of a MAP kinase signalling module.

The activation of this MAP-kinase cascade leads to the *inactivation of gene regulatory proteins in the nucleus that* are responsible for stimulating the transcription of ethylene-responsive genes. Ethylene binding to the receptors inactivates this signaling pathway, thereby turning these genes on.

A) In the absence of ethylene, the receptors and the MAPK module are active, leading to inhibition of the gene regulatory proteins in nucleus that are responsible for transcription of ethylene-responsive genes. (B) In the presence of ethylene, the receptors and the MAPK module are inactive, so the ethylene-responsive genes are transcribed.

Two-component signaling systems operate in bacteria and fungi, as well as in plants, but apparently not in animals.

(Note: All the original contributors of the concept and findings published elsewhere are gratefully acknowledged while preparing the E-content for the purpose of student reading material in convenient form for biochemistry and allied discipline).

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