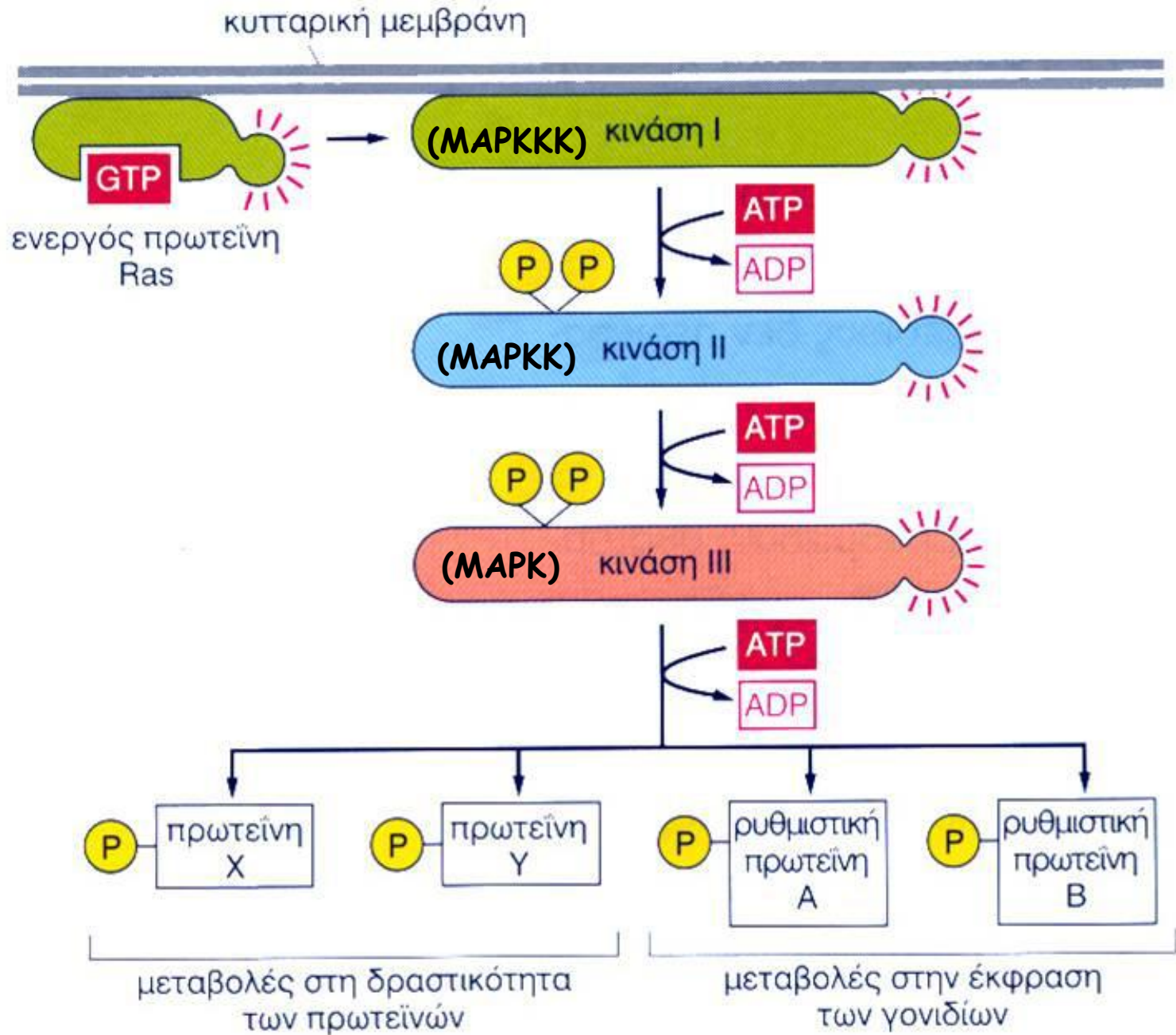


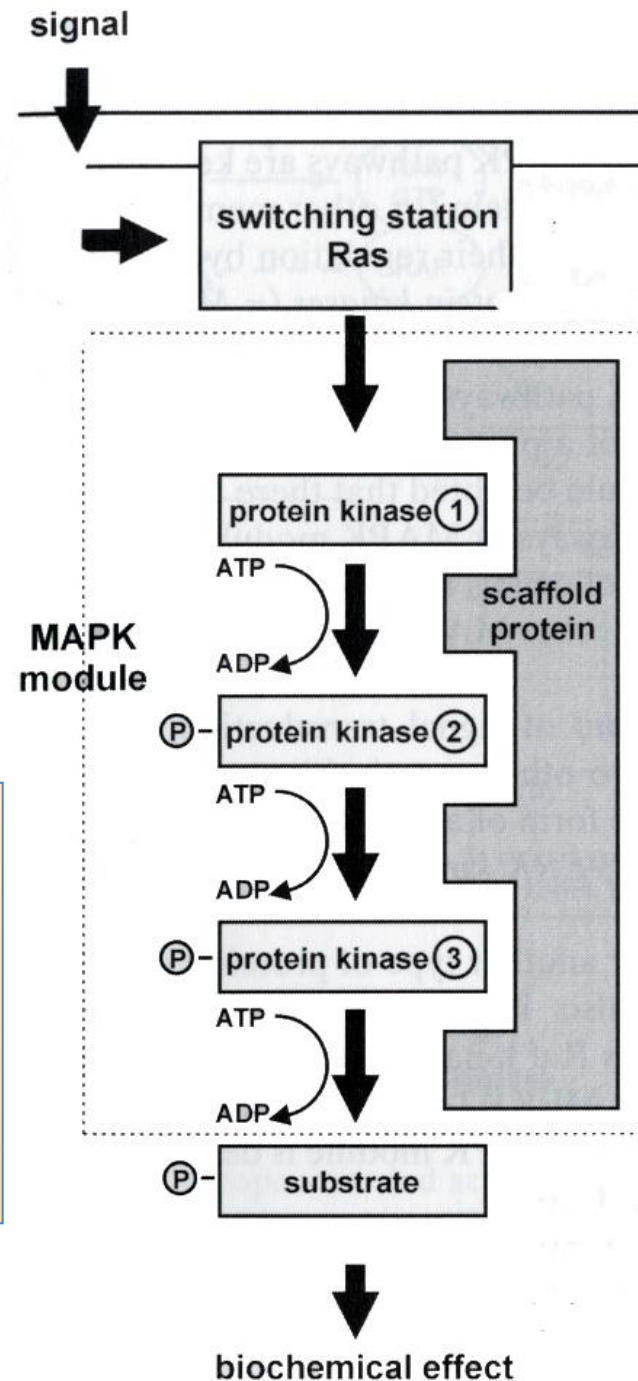
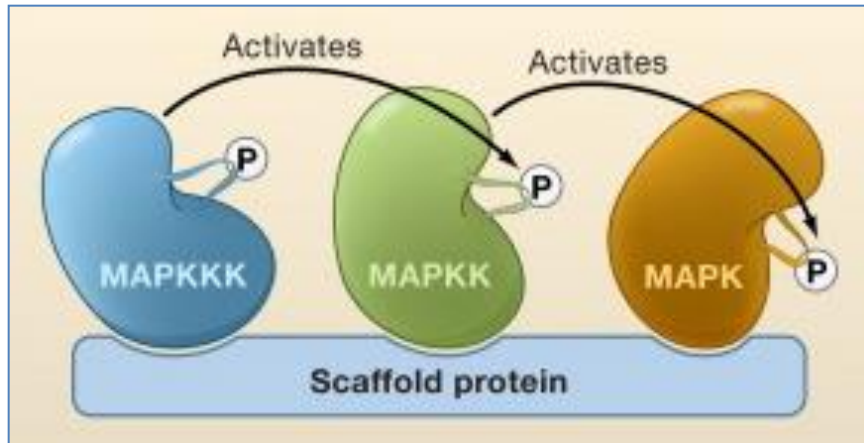
Σηματοδοτική οδός των MAP κινασών  
(Mitogenic Activated Protein Kinases)

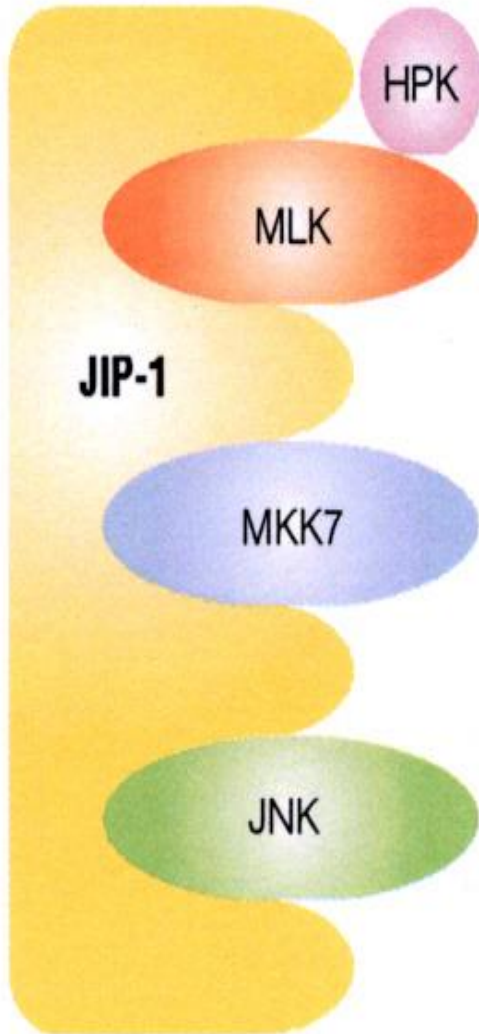
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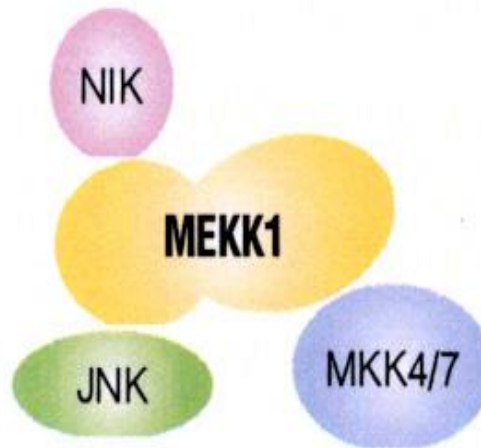
## Πολυπρωτεϊνικό σύμπλοκο

1. Διευκολύνει τη γρήγορη μεταφορά του σήματος
2. Πετυχαίνει μεγάλη εξειδίκευση

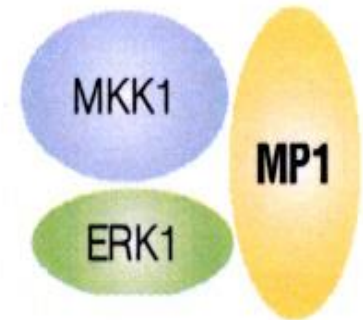




**A.** Ste5p-like scaffold complex



**B.** Pbs2p-like scaffold complex



**C.** MP1 scaffold complex

ligands and activators

ERK pathway

JNK/SAPK pathway

P38/HOG pathway

growth factors  
hormones

TNF- $\alpha$ , UV, IIs  
(stress)

TNF- $\alpha$ , UV, H<sub>2</sub>O<sub>2</sub>  
(stress)

exchange factor

Grb2/hSos

absent

possible role of TRAF2

GTP-binding protein

Ras

----->

Rac/Cdc42

protein kinases

Raf

MEKK1-3

TAK, TAO

MEK1,2

MEK4

MEK3, MEK6

ERK1,2

JNK/SAPKs

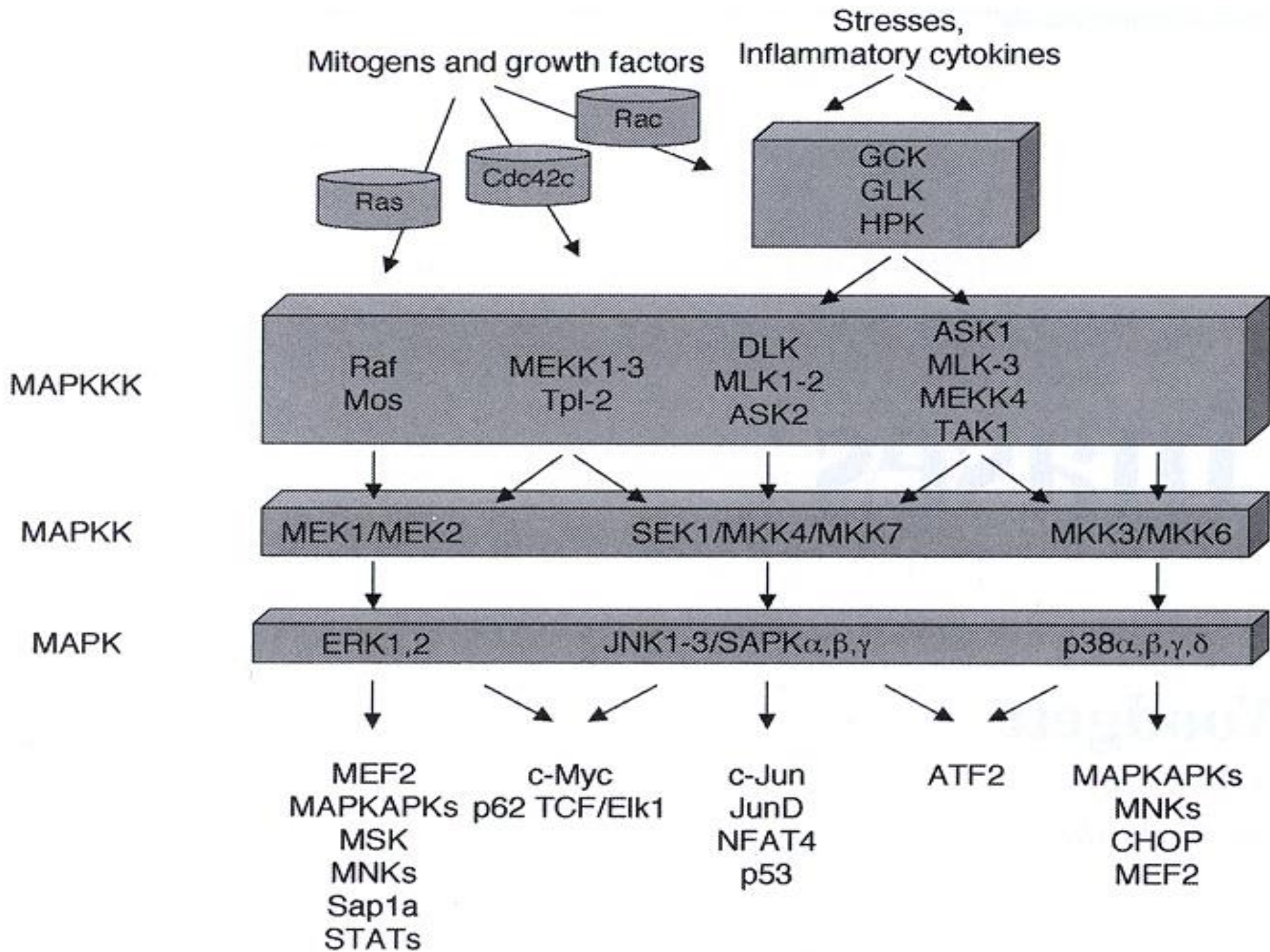
p38/HOG

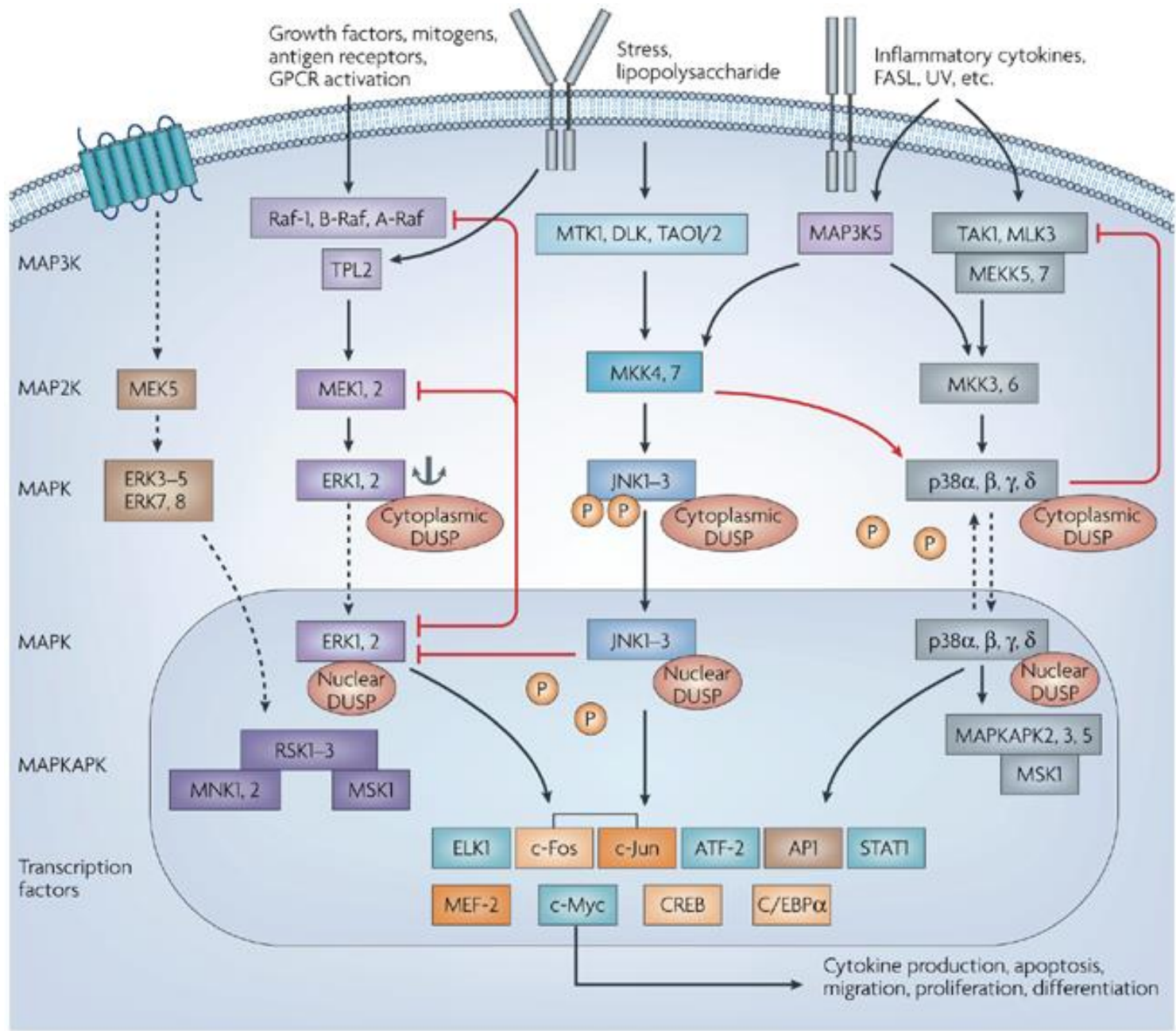
transcription factors

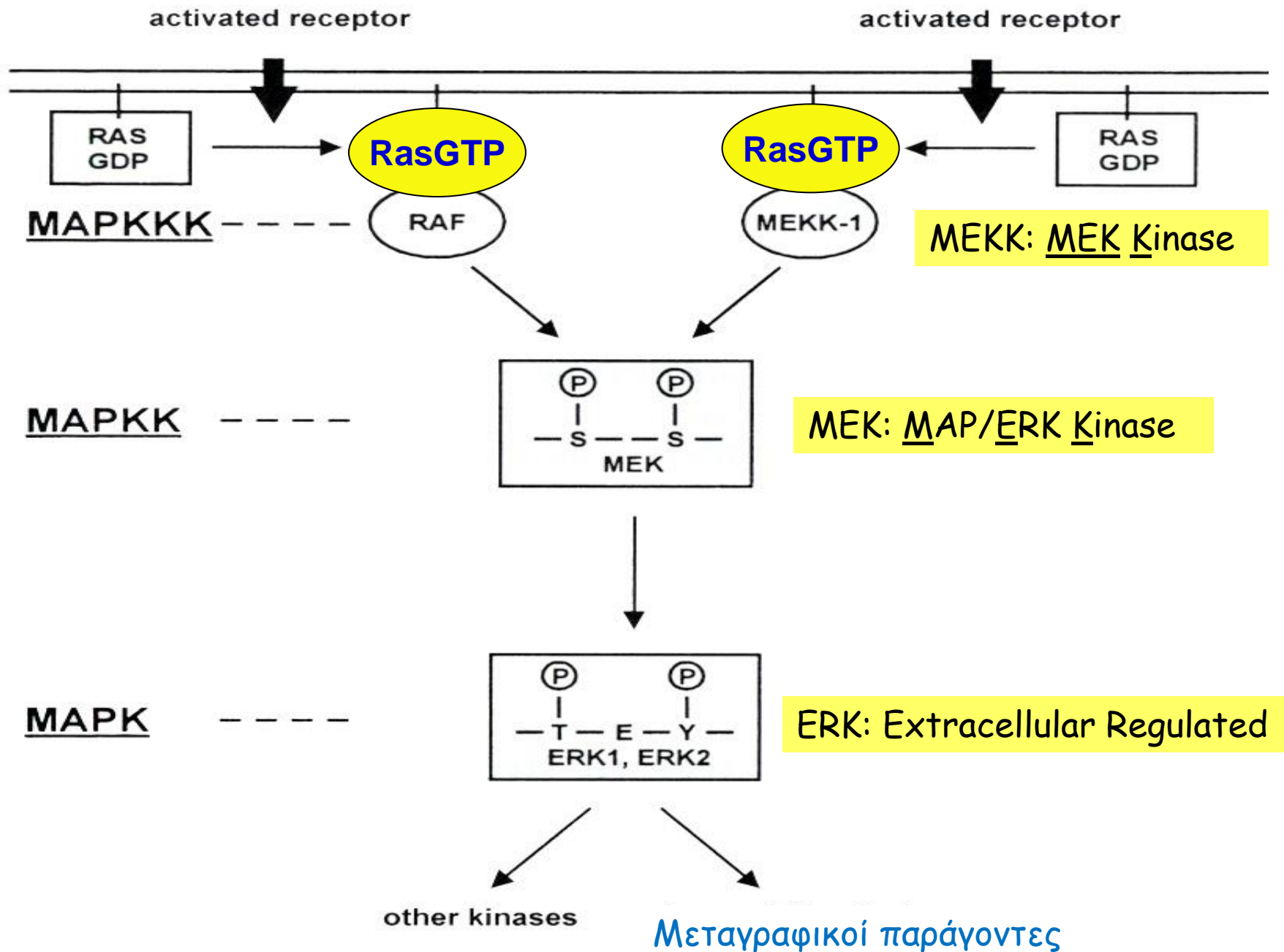
p62 TCF

c-Jun  
p62 TCF  
ATF2

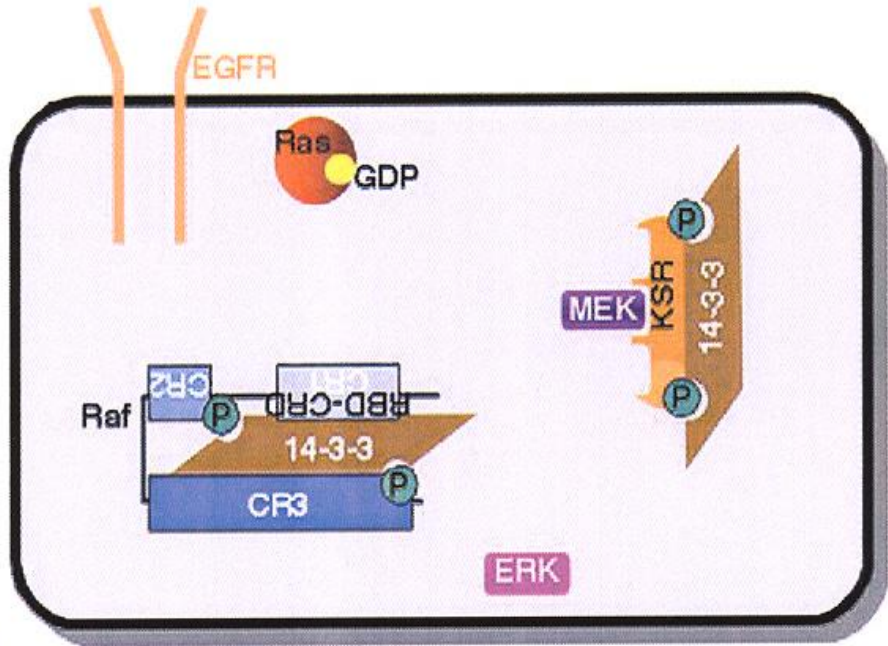
c-Jun  
CREB  
ATF2



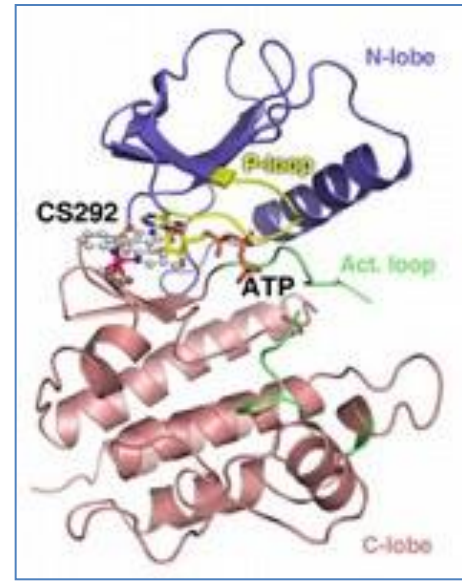




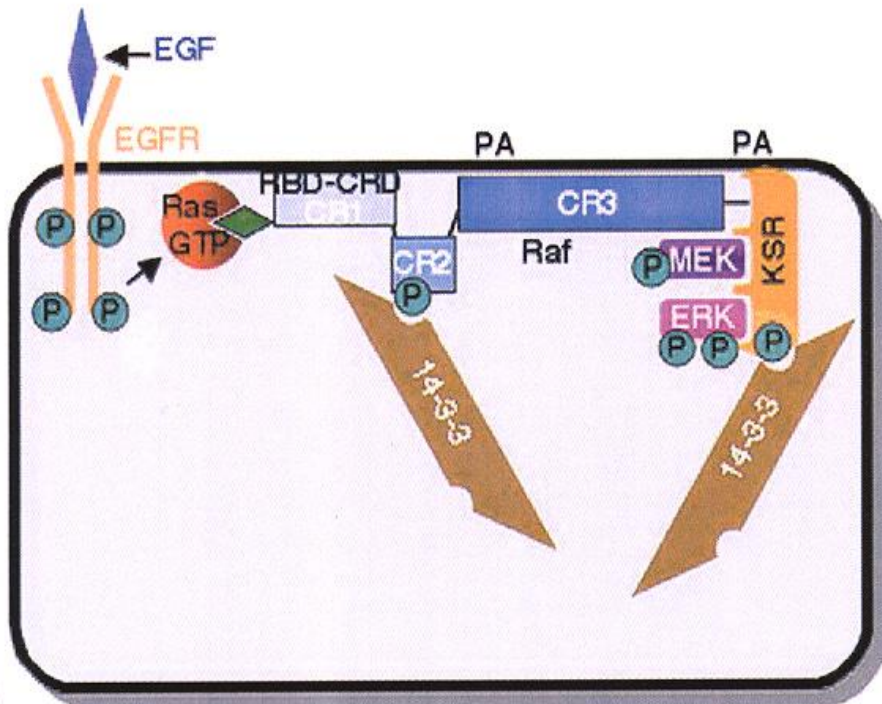




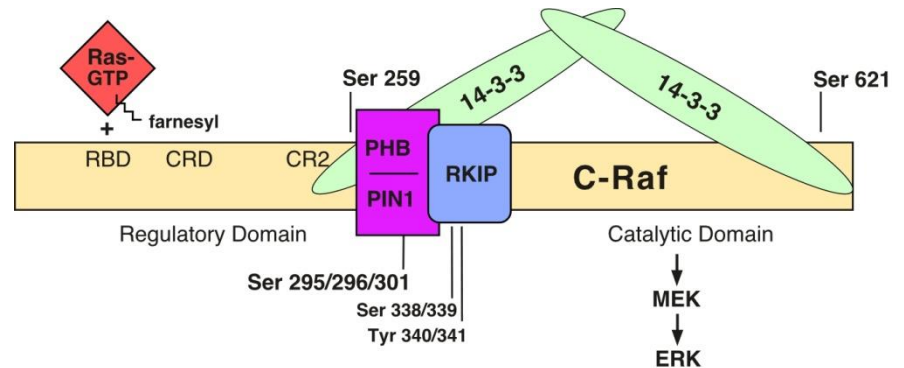
A



Raf kinase



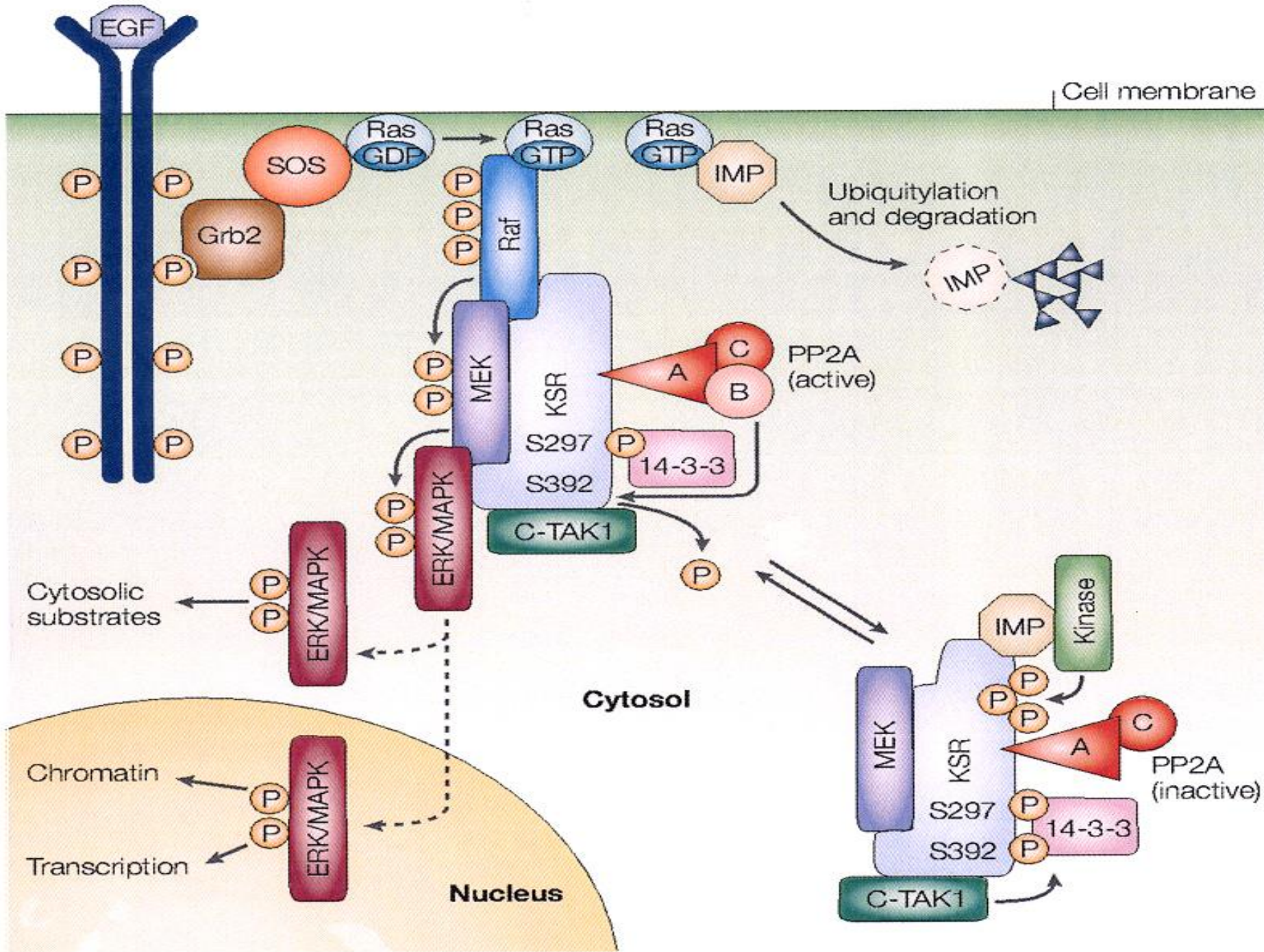
B



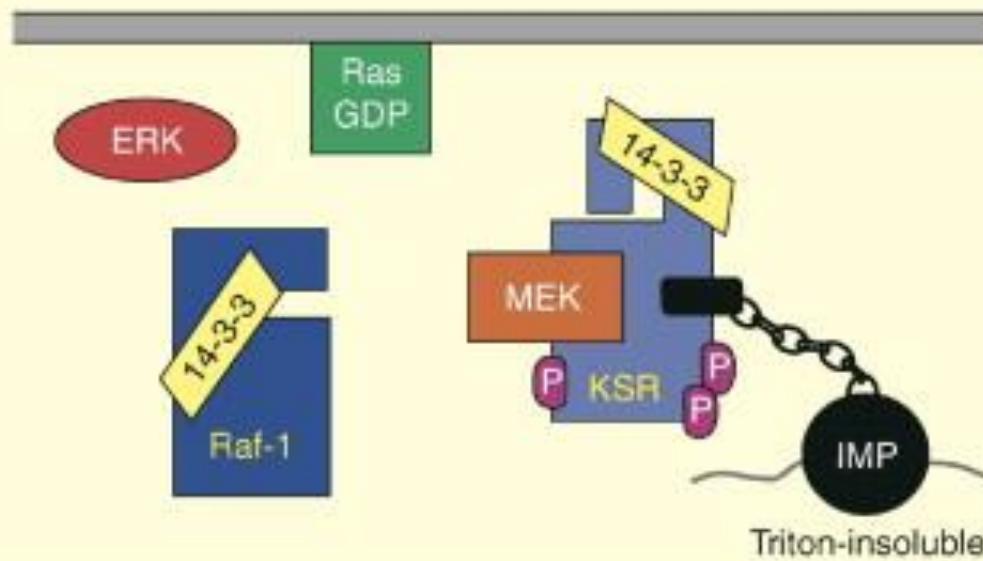
RBD: Ras binding domain

CRD: Cys-rich domain

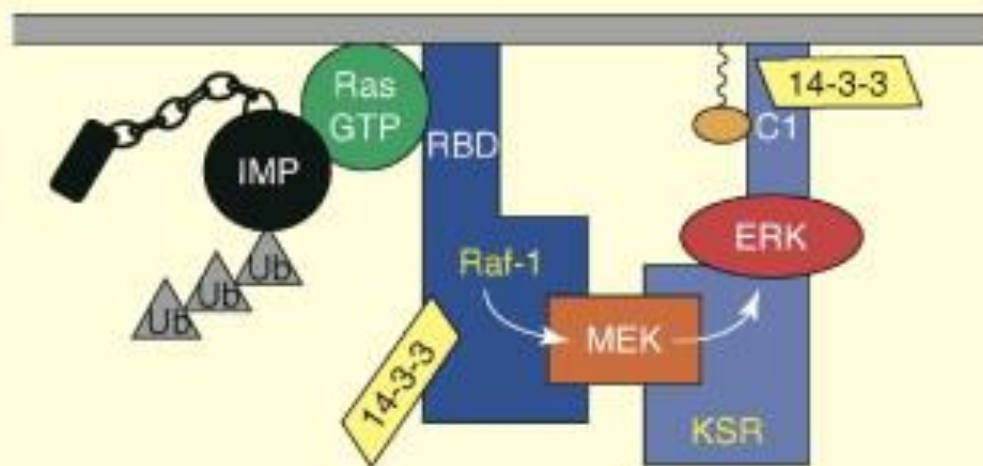
KD: kinase domain

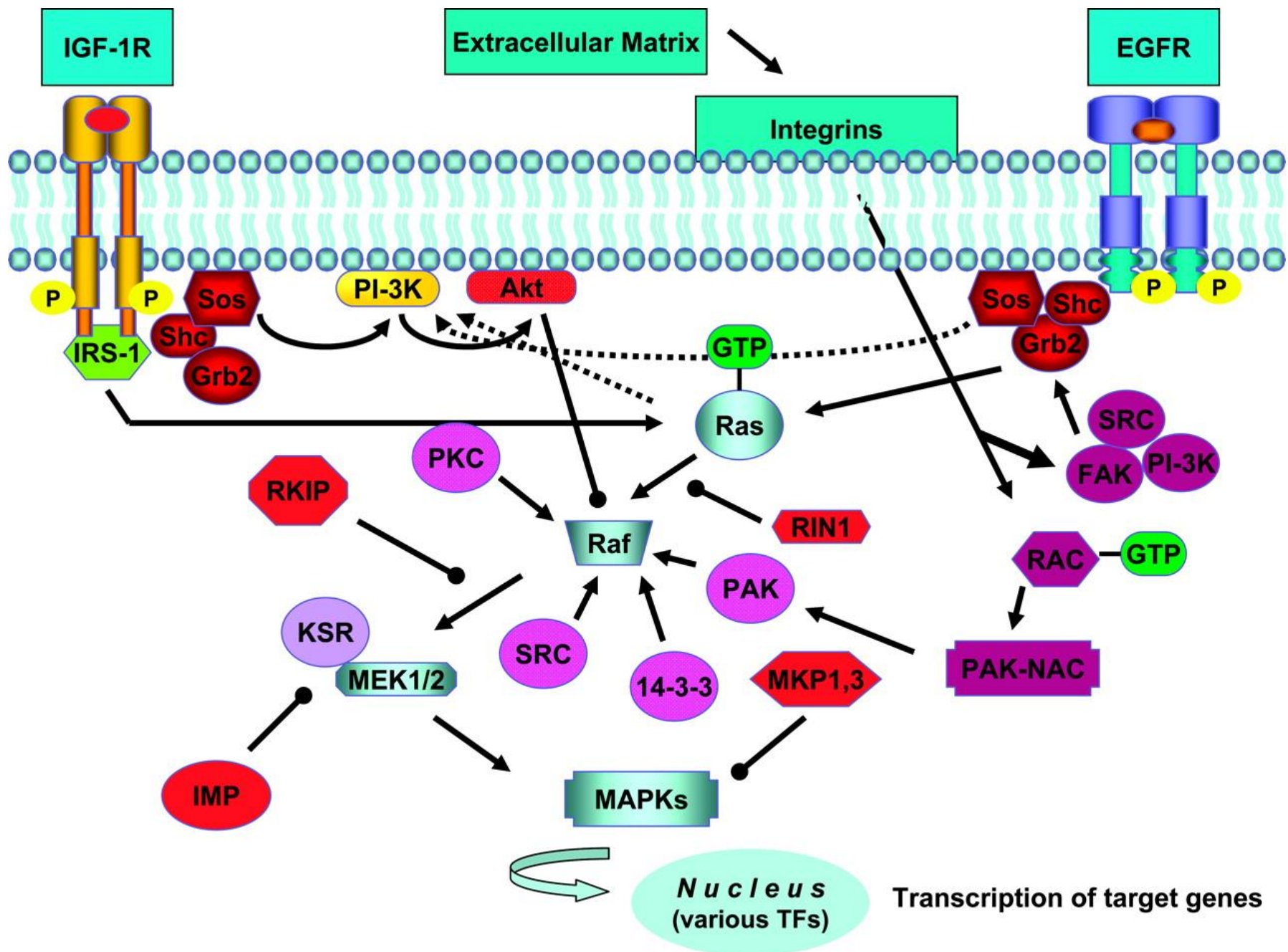


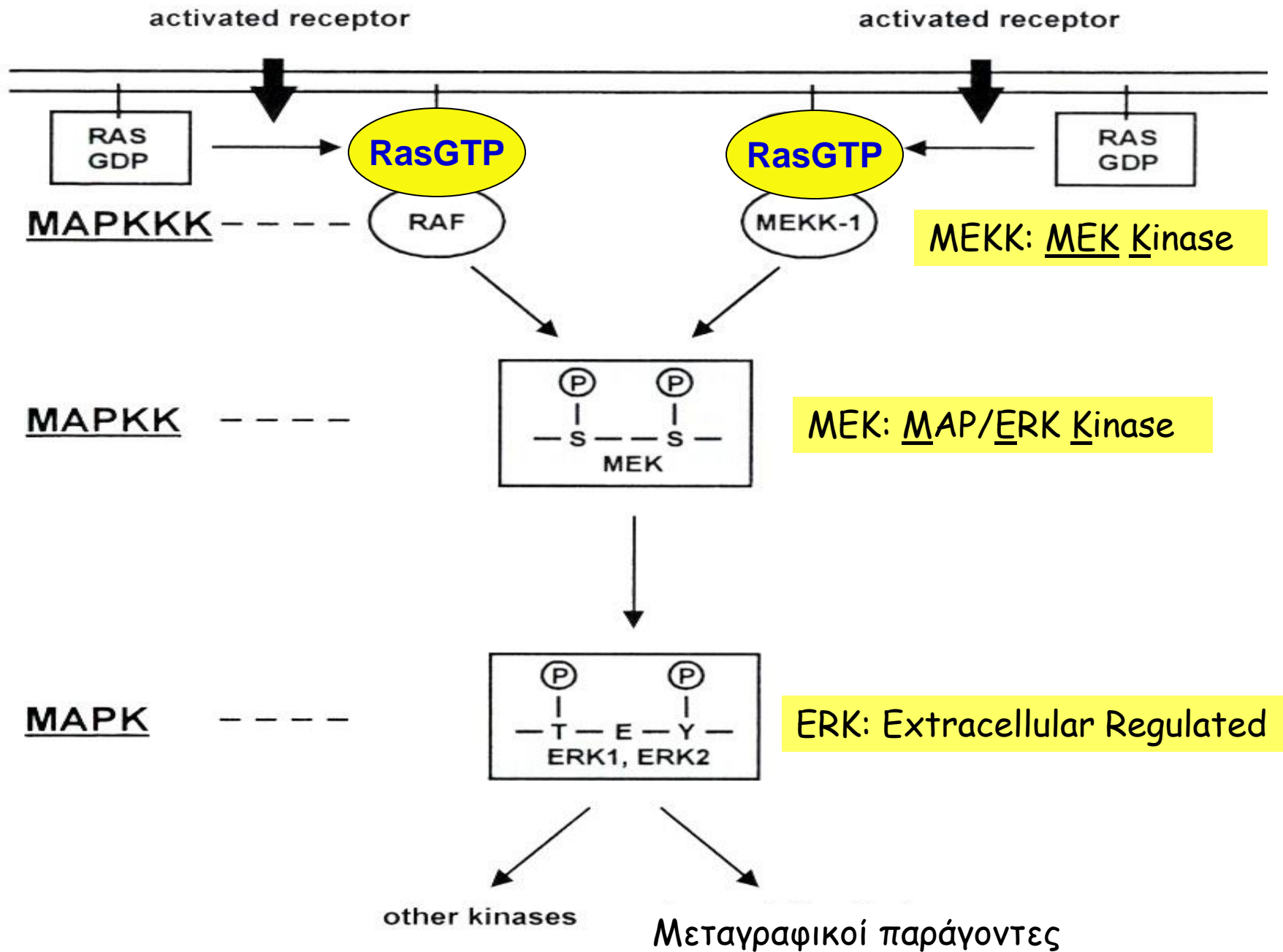
## A Quiescent cell



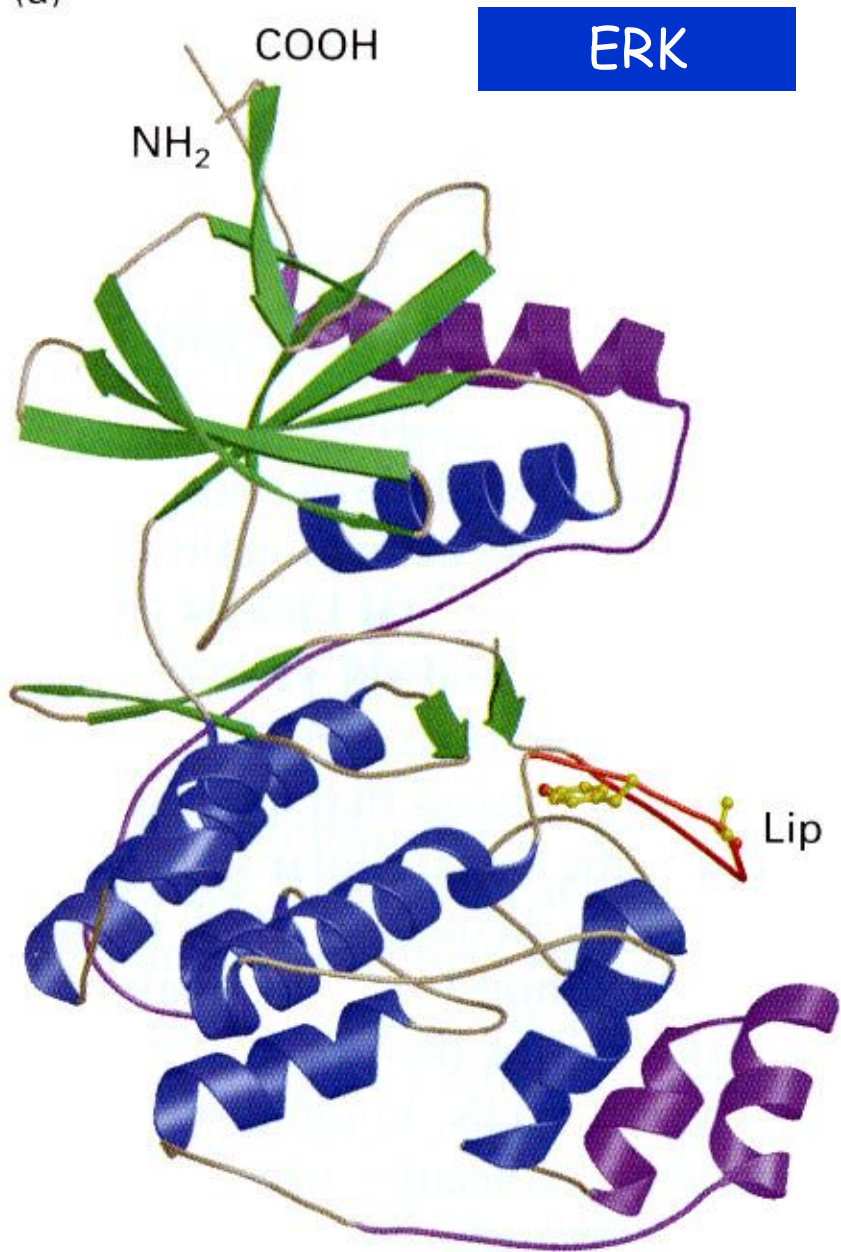
## B Stimulated cell



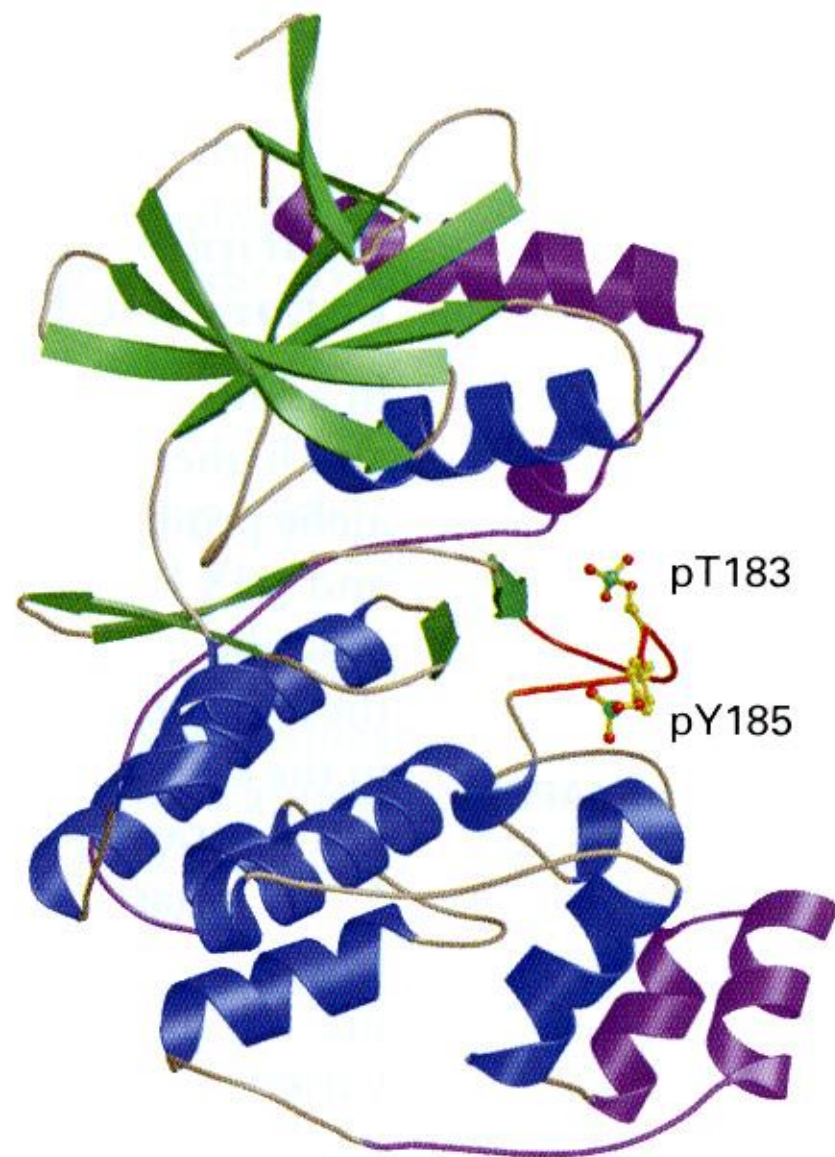




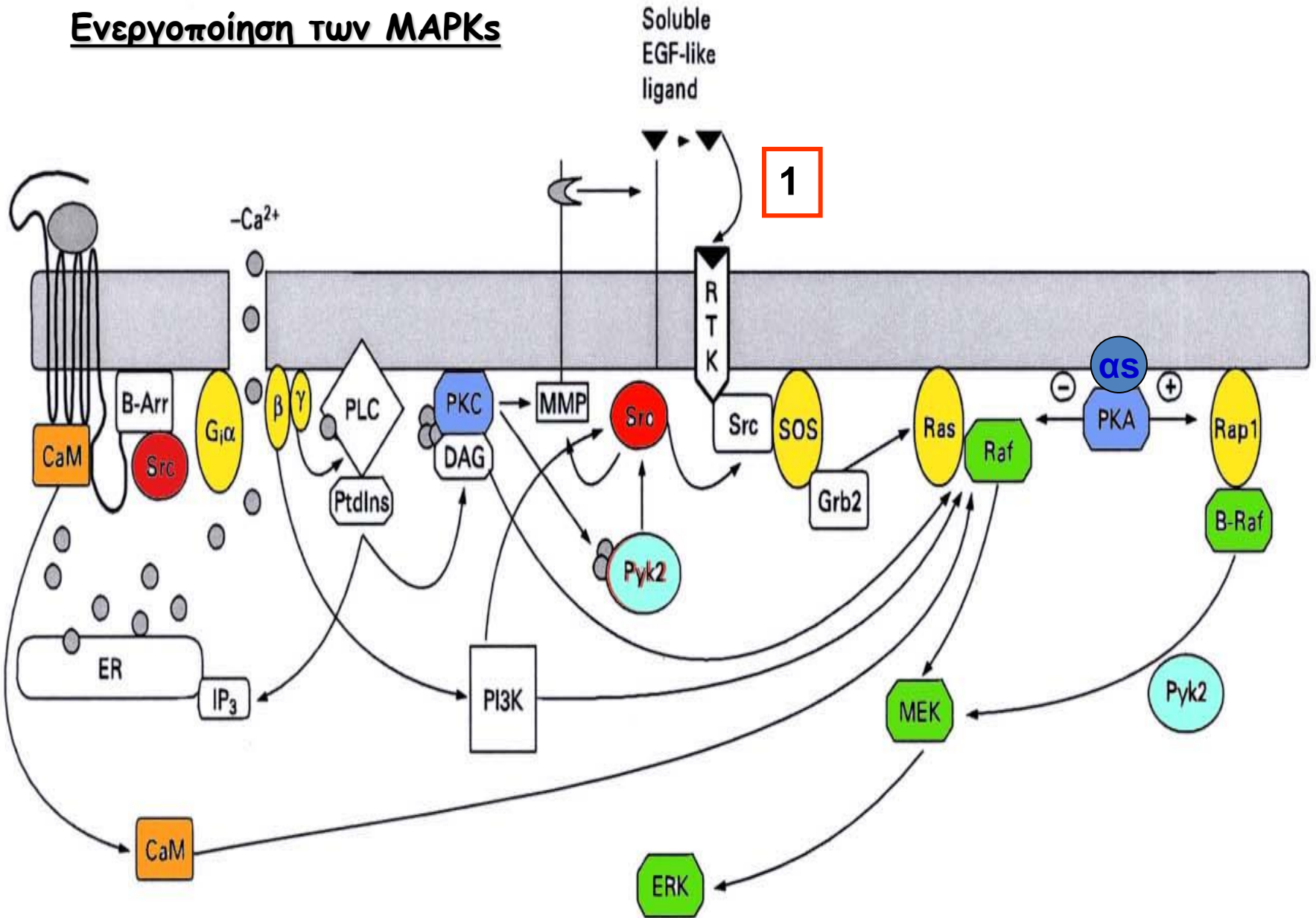
(a)

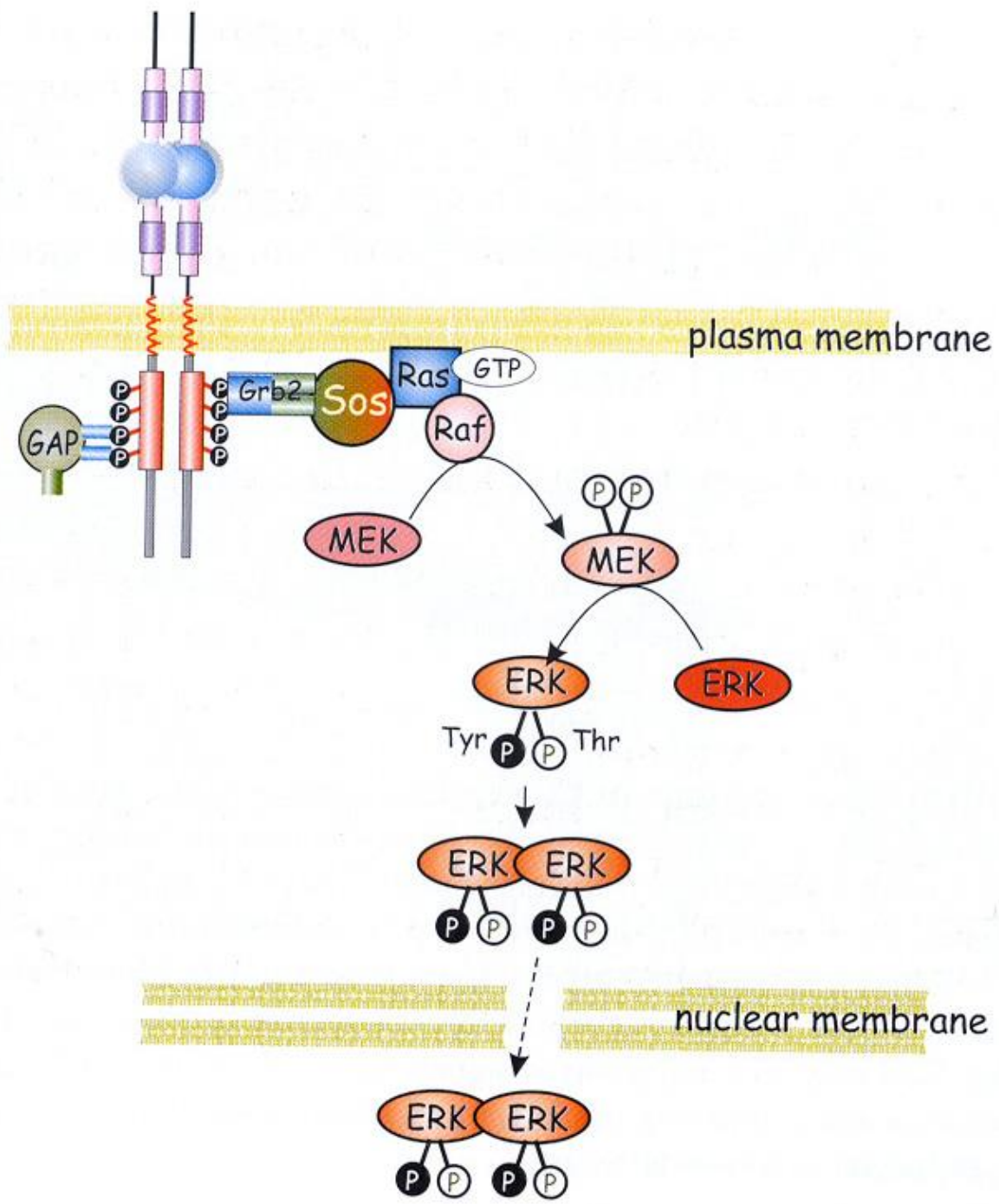


(b)

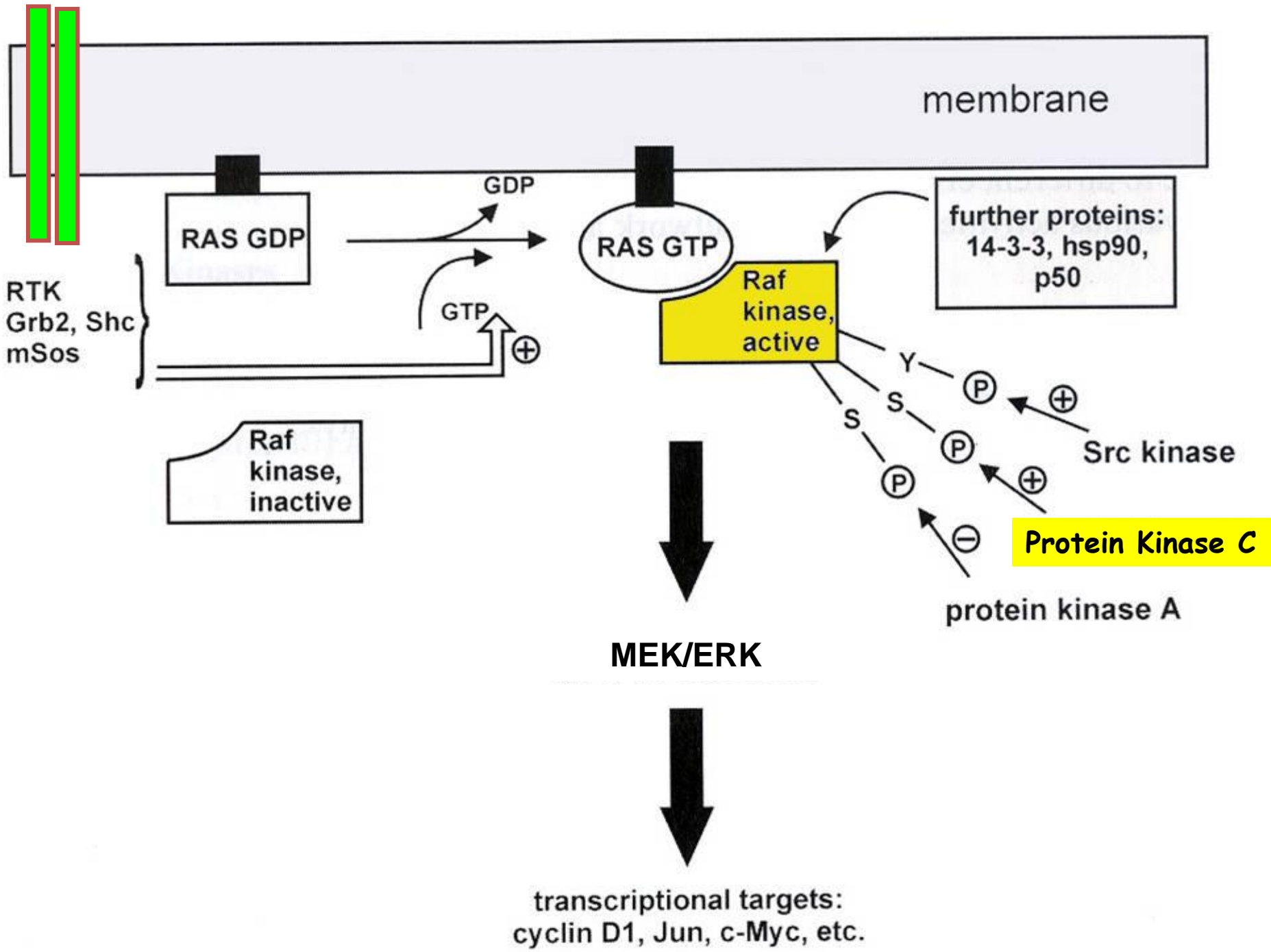


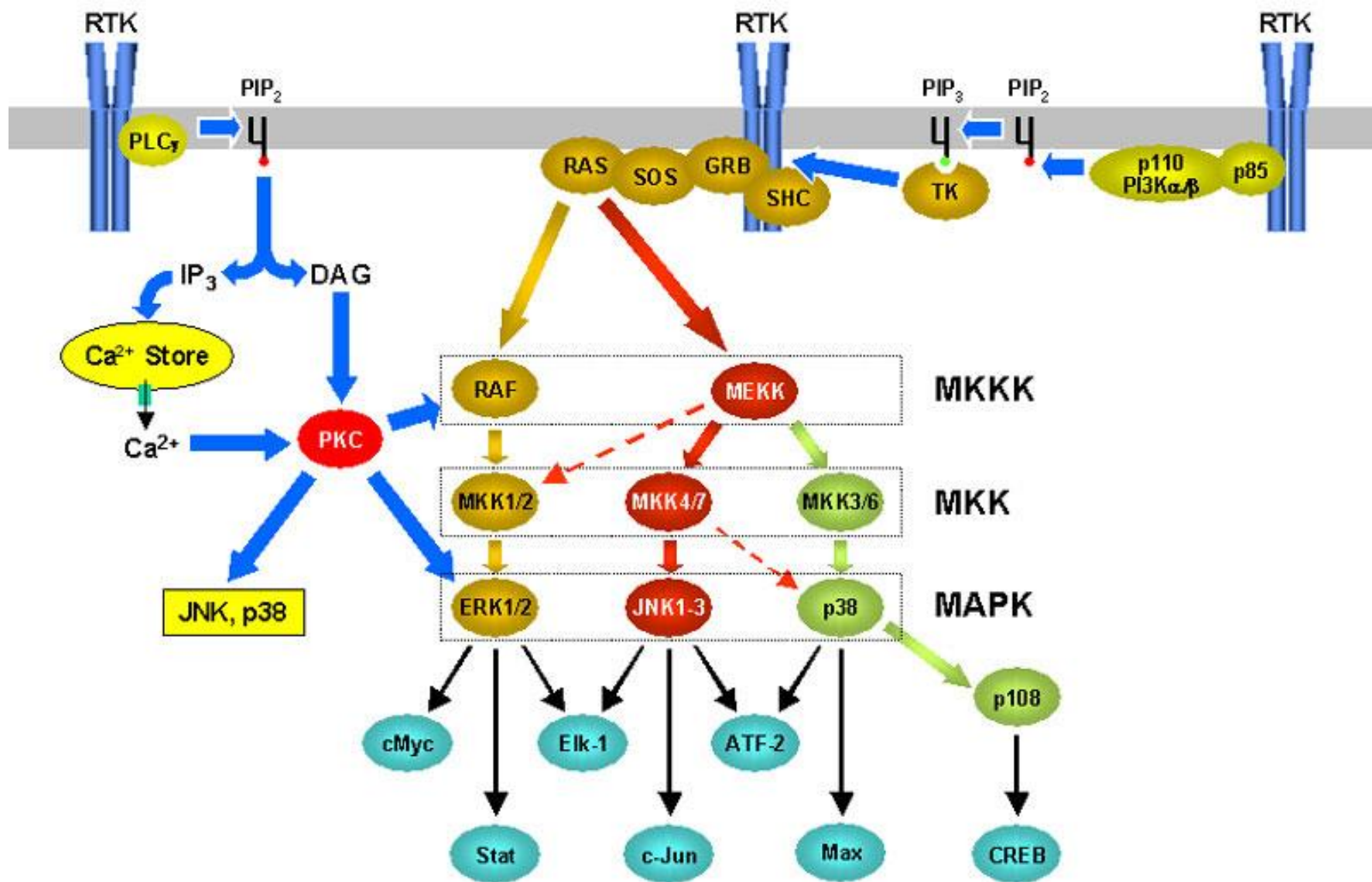
# Ενεργοποίηση των MAPKs



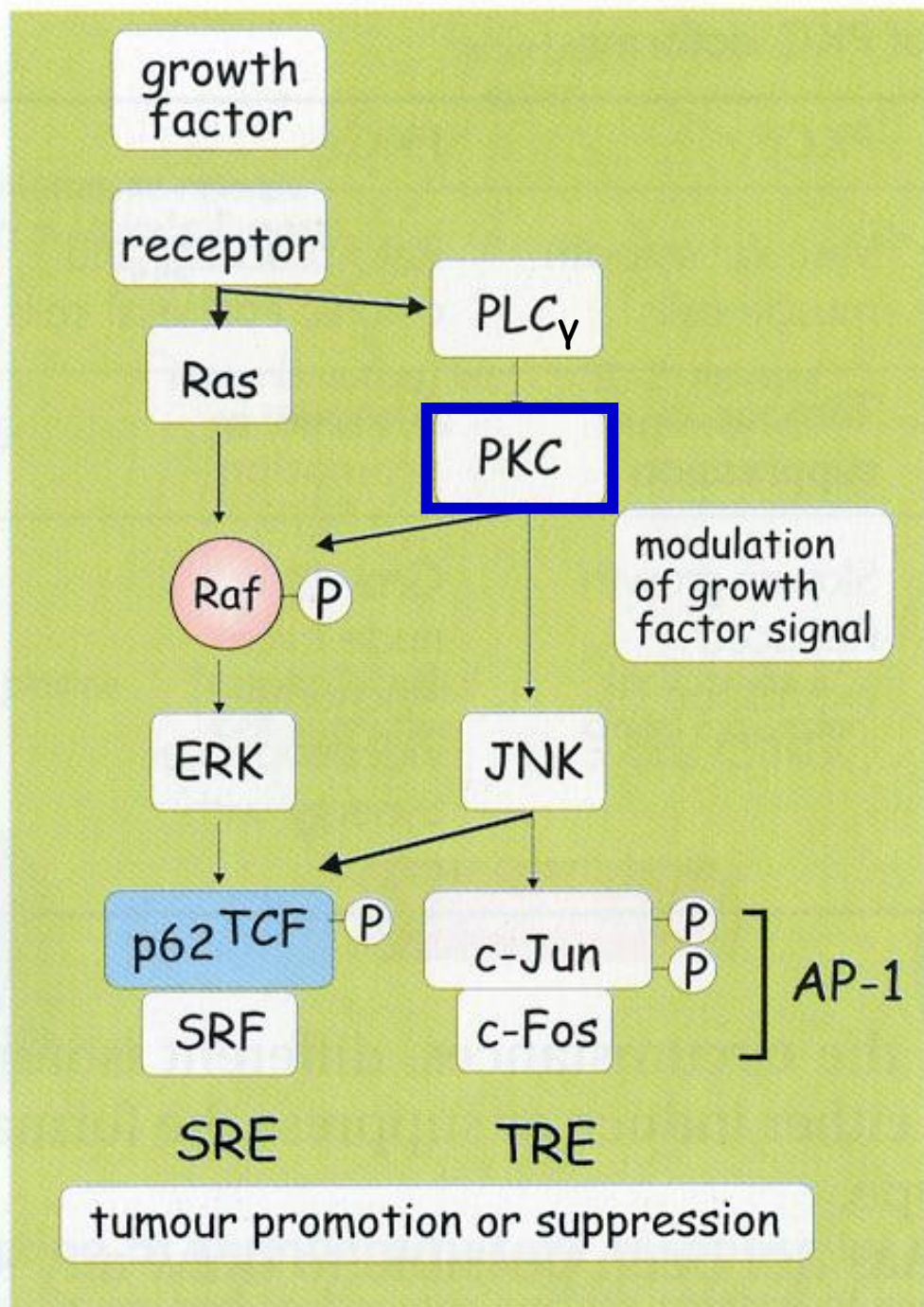




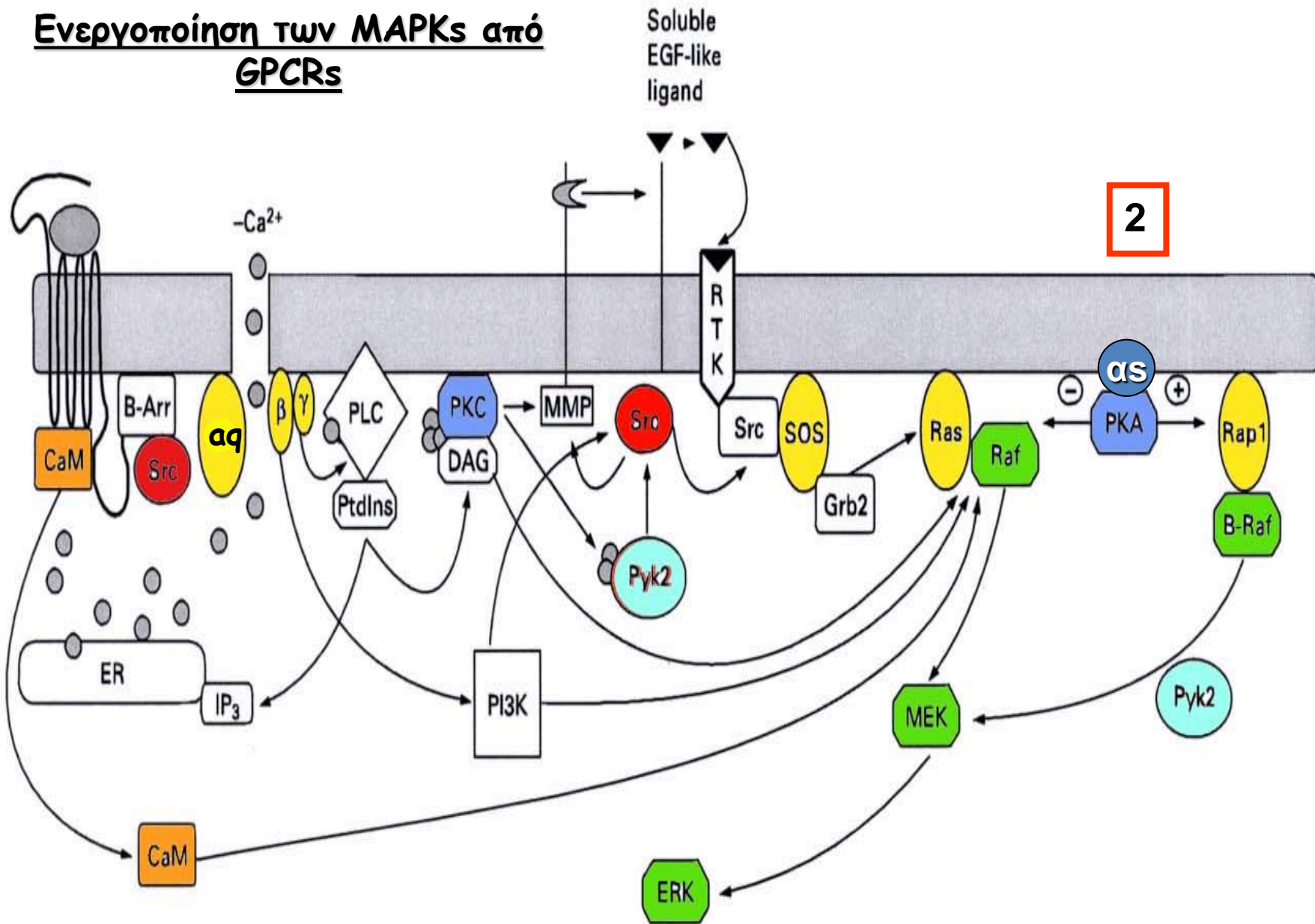




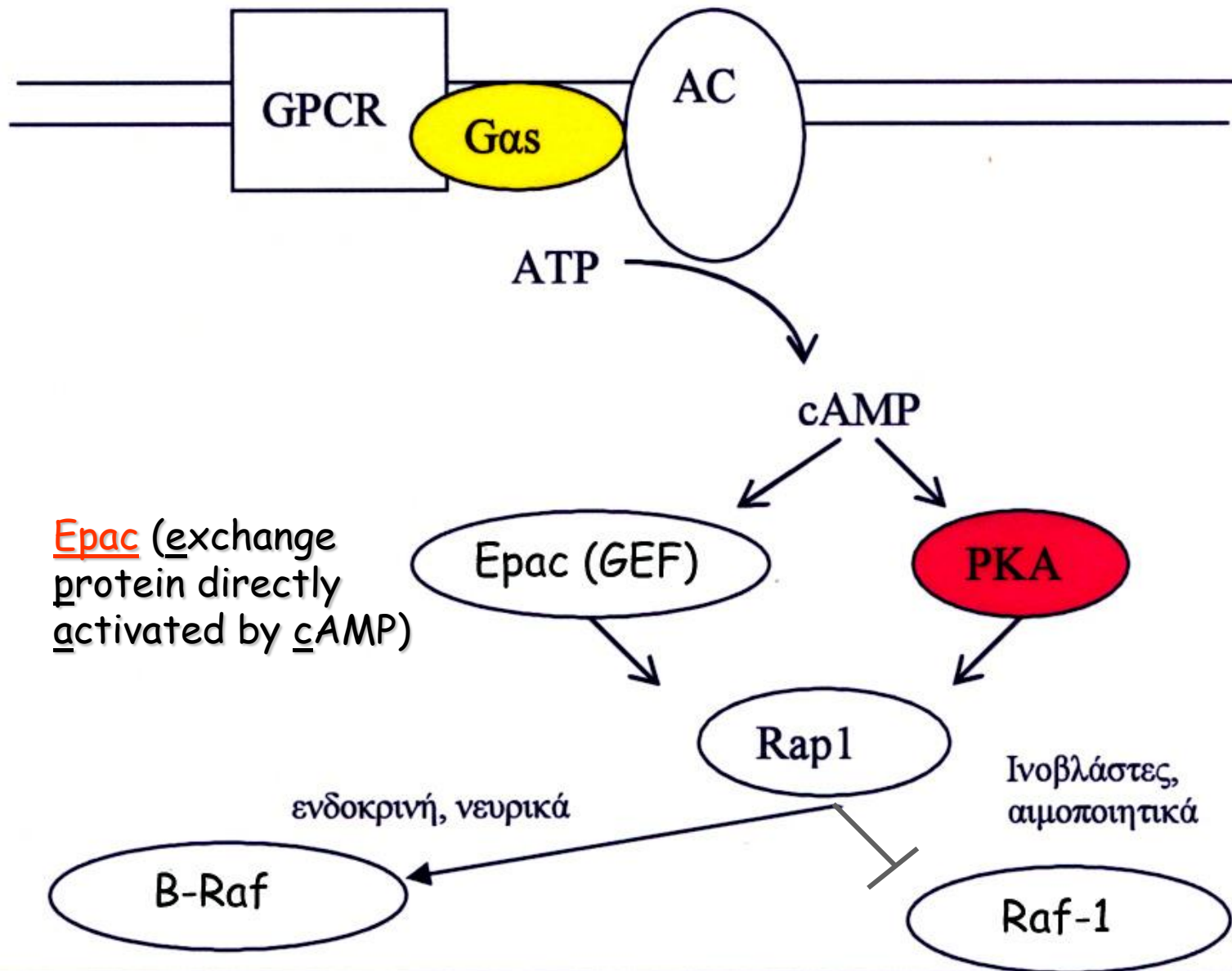
Μέσω της PKC  
ενισχύεται το  
σήμα του  
αυξητικού  
παράγοντα



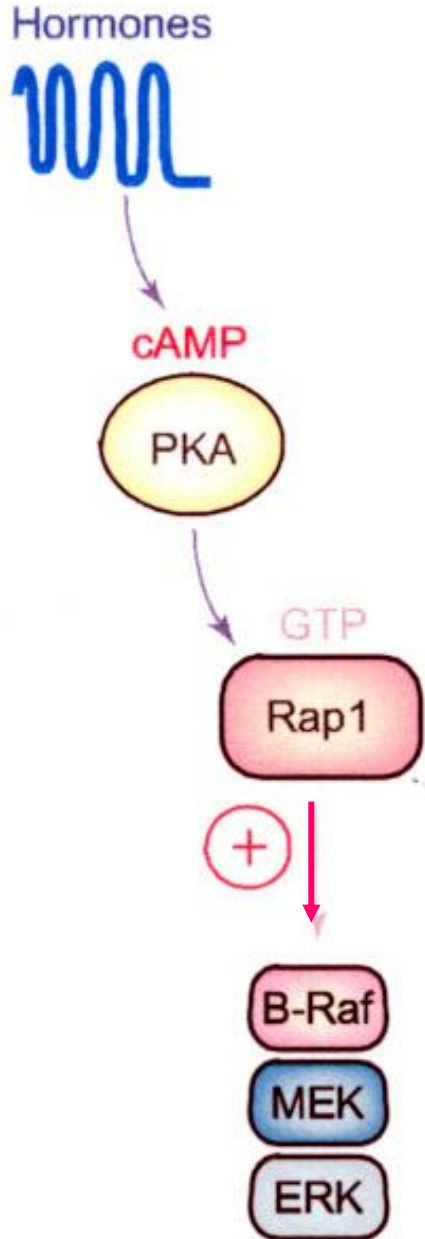
# Ενεργοποίηση των MAPKs από GPCRs



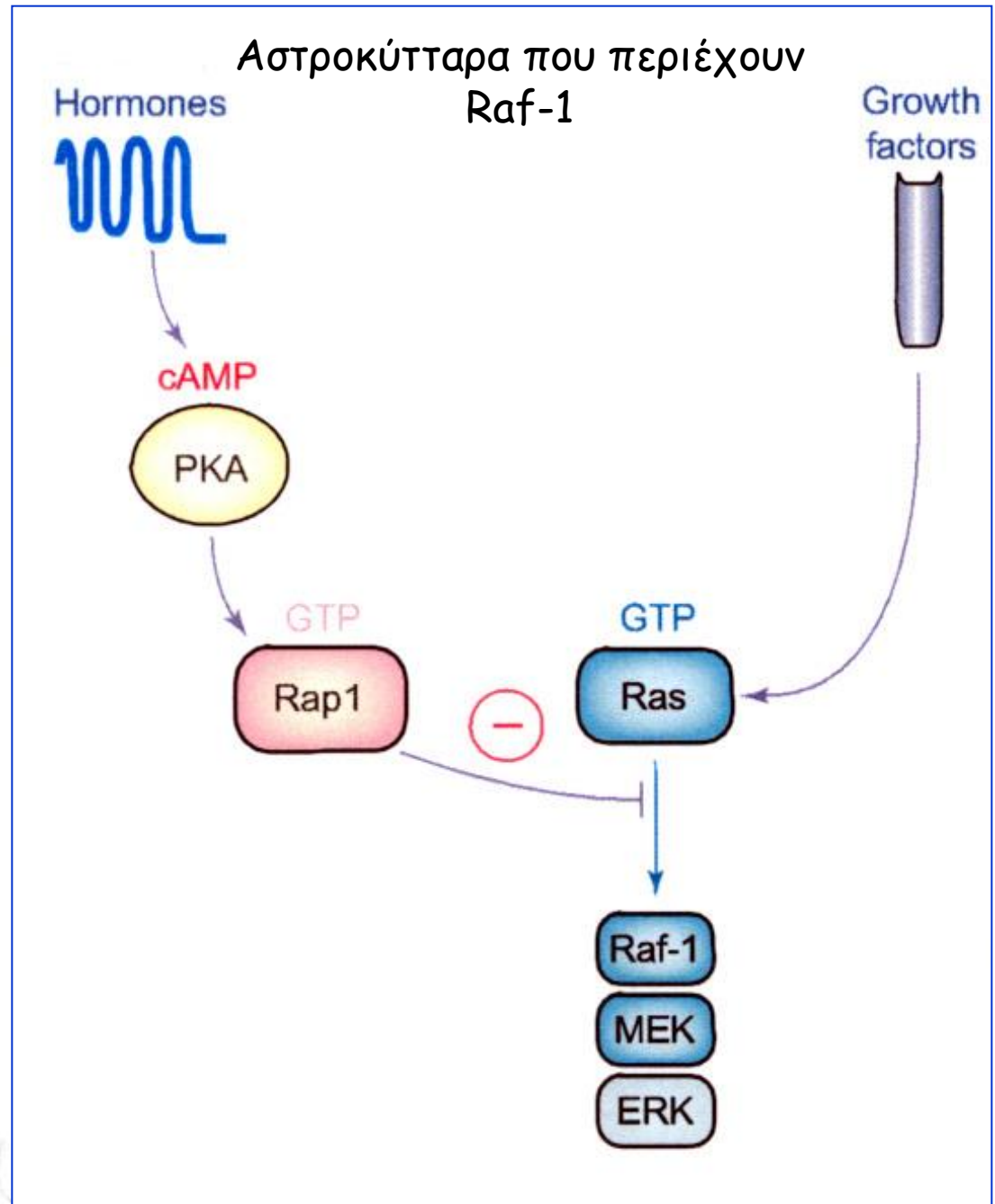
# Ενεργοποίηση του μονοπατιού των MAPKs μέσω της Gas



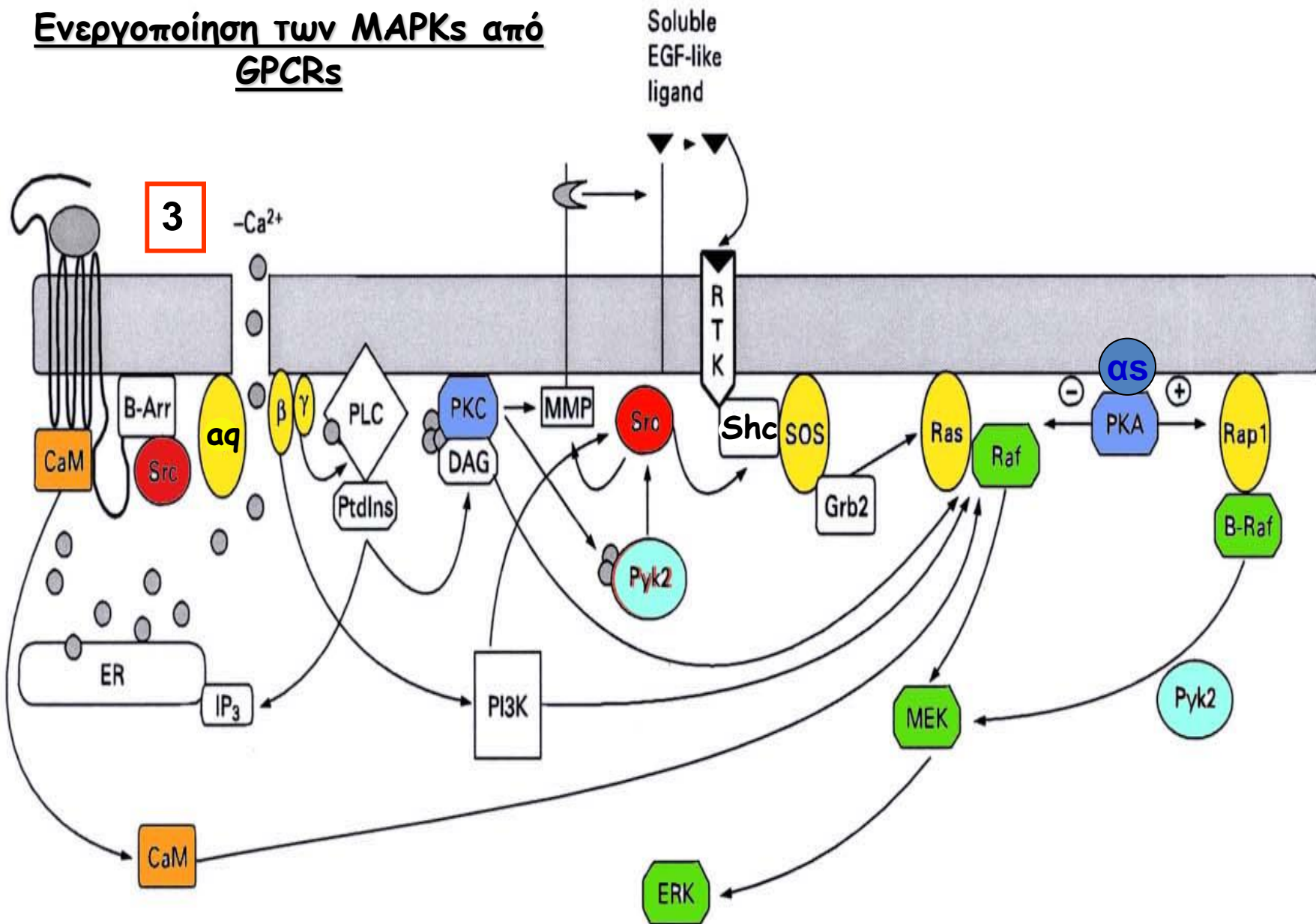
# Ενδοκρινή/νευρικά κύτταρα που περιέχουν B-Raf

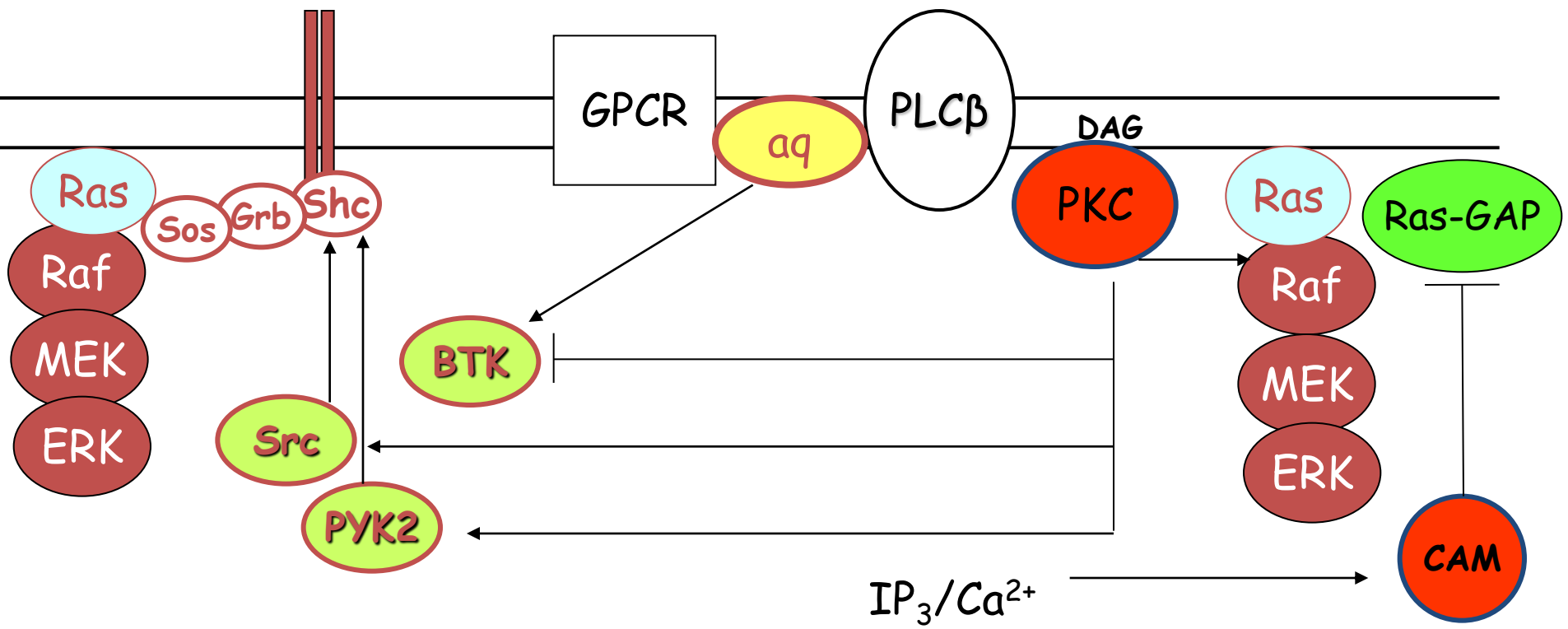


# Αστροκύτταρα που περιέχουν Raf-1



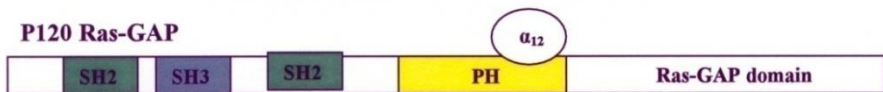
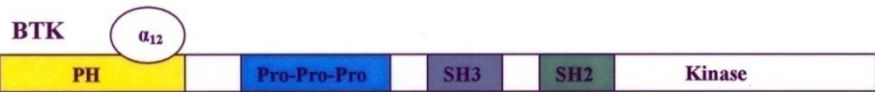
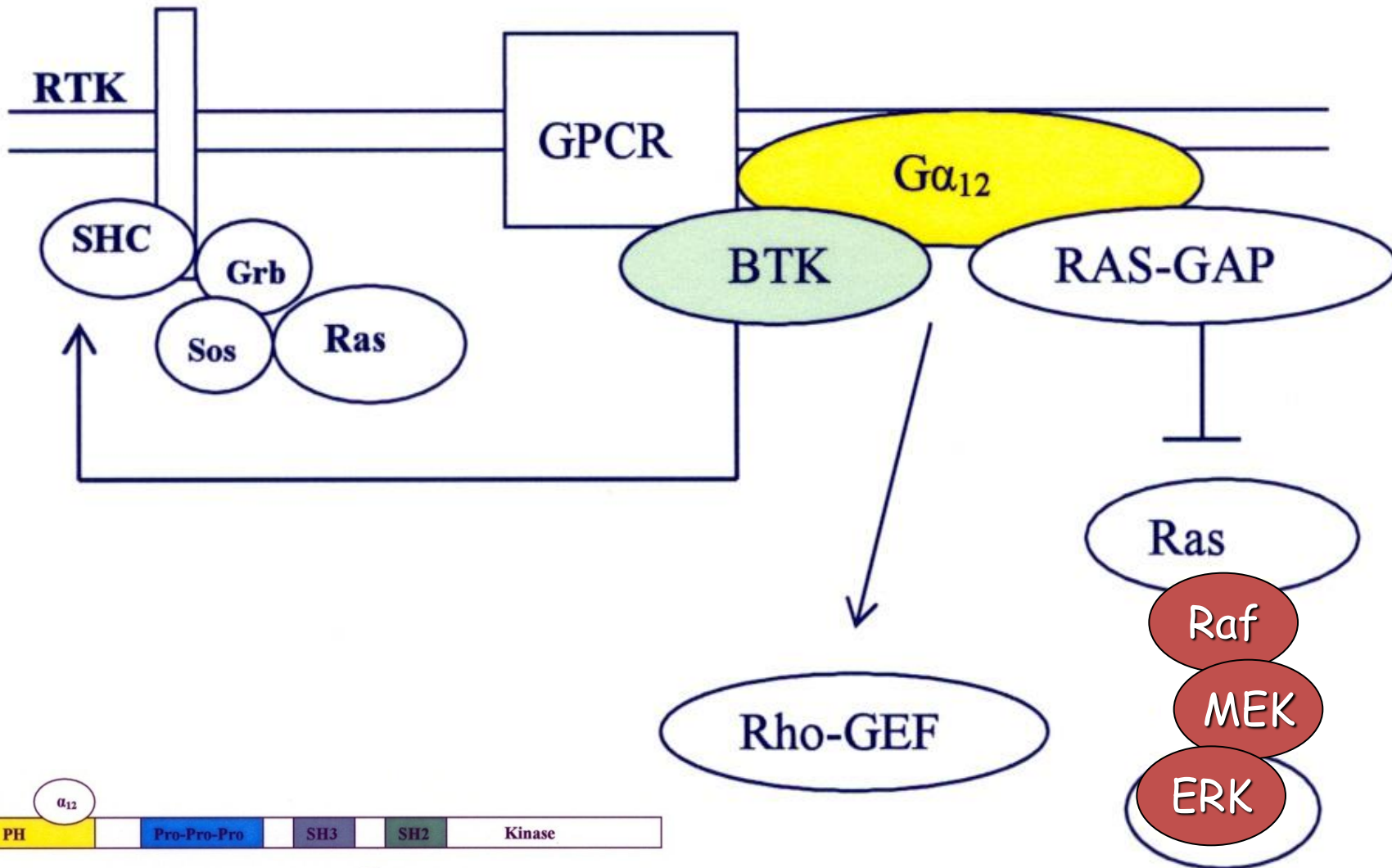
# Ενεργοποίηση των MAPKs από GPCRs





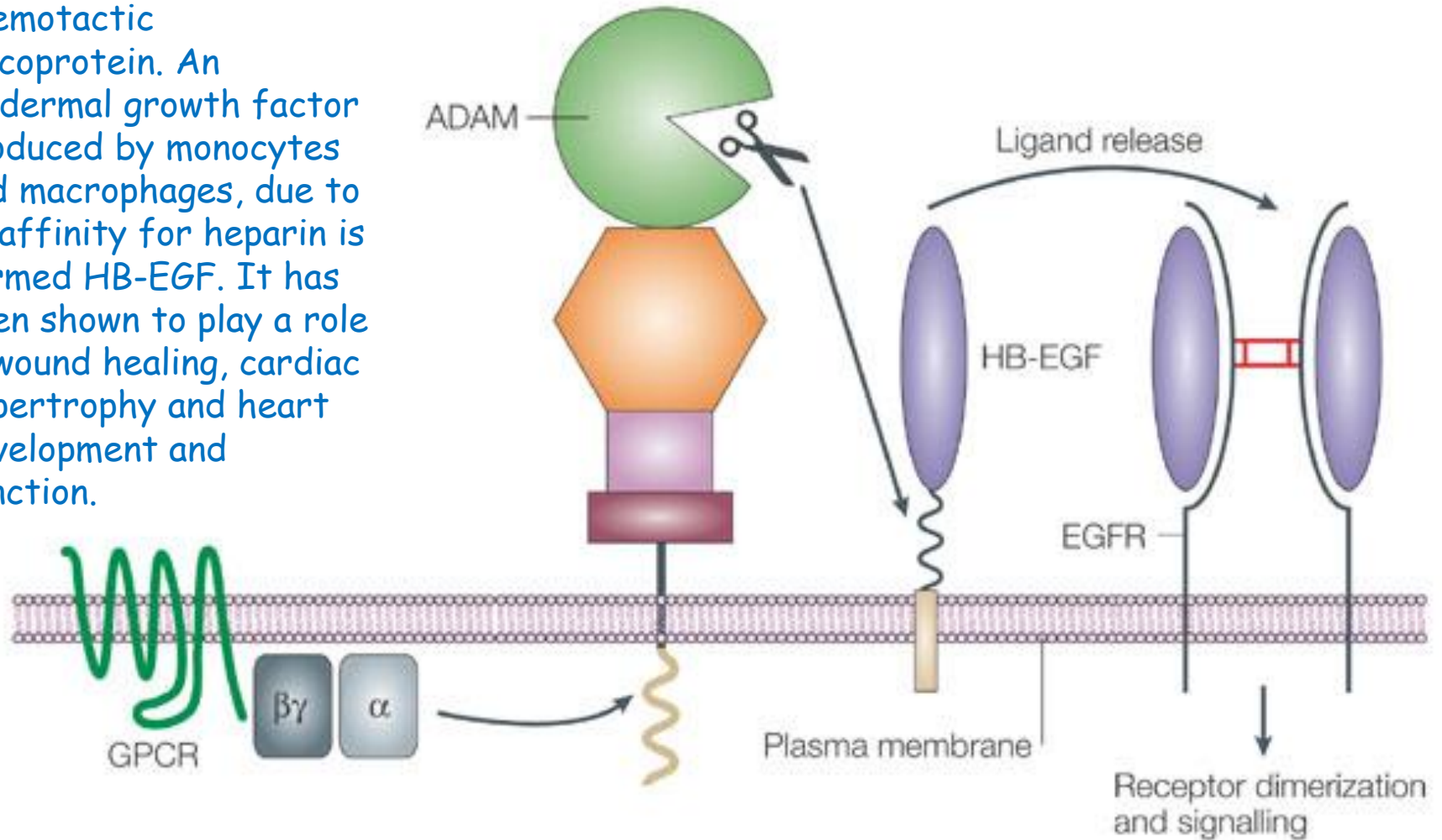


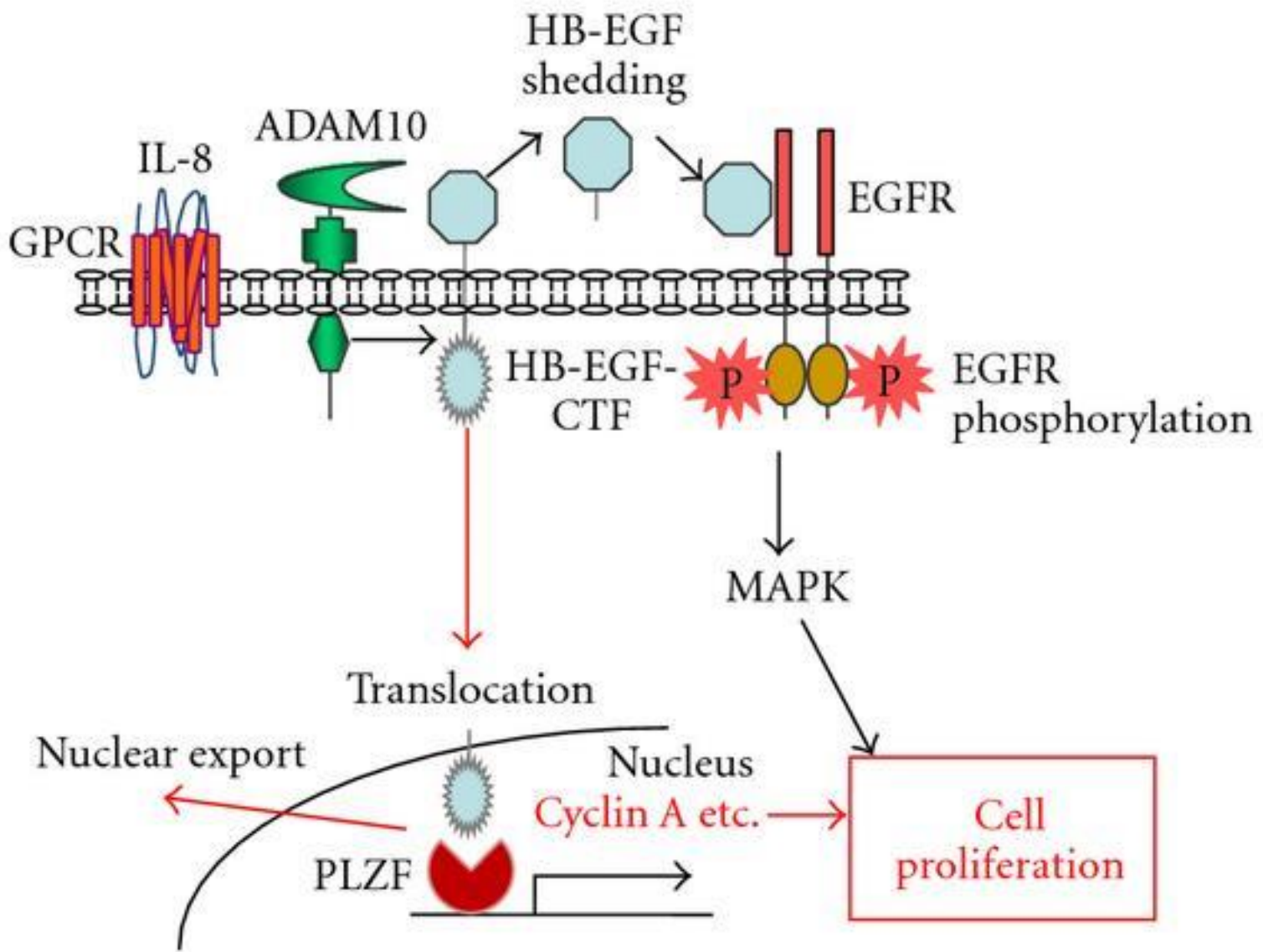
# Ενεργοποίηση του μονοπατιού των MAPKs μέσω της $G\alpha_{12}$

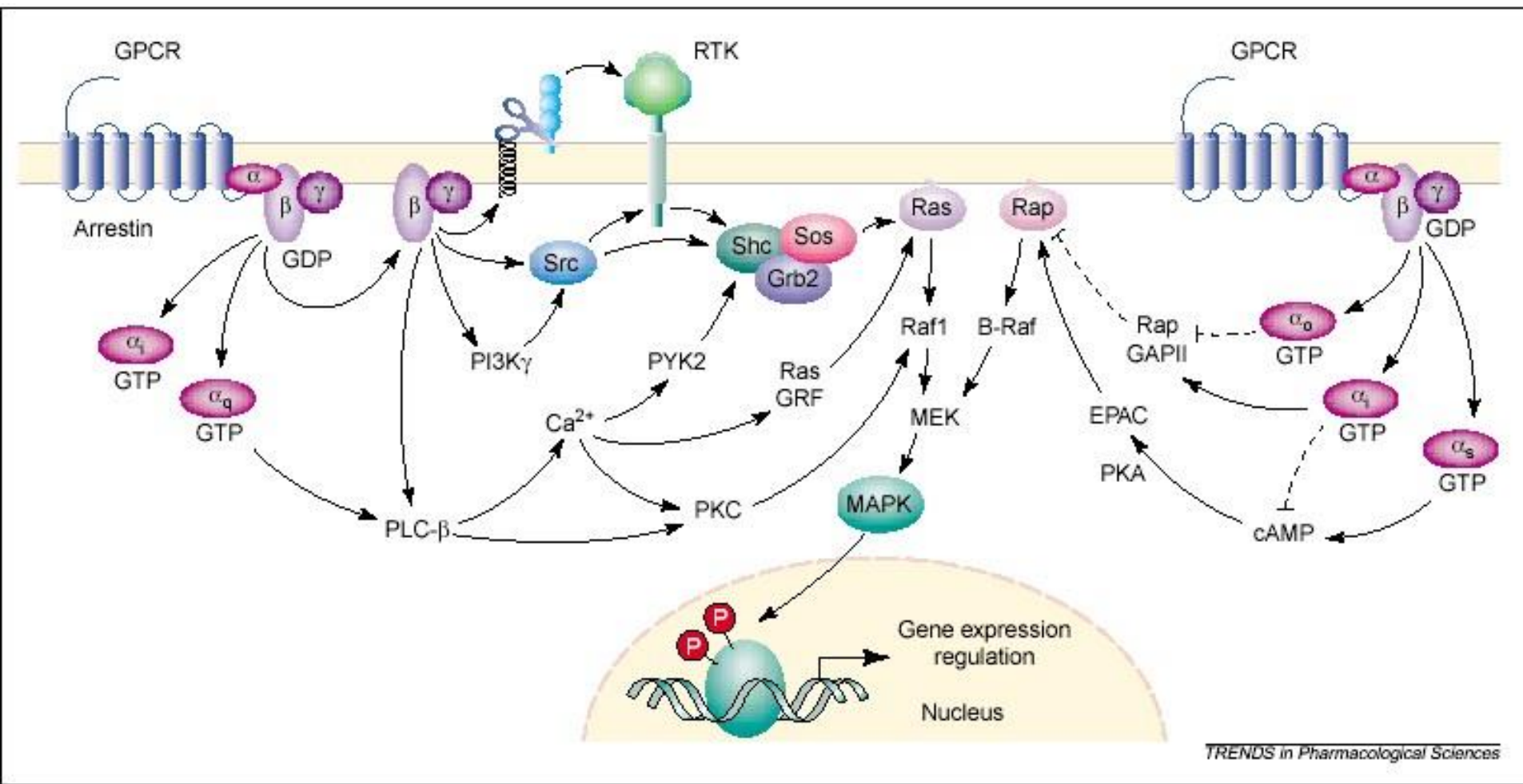




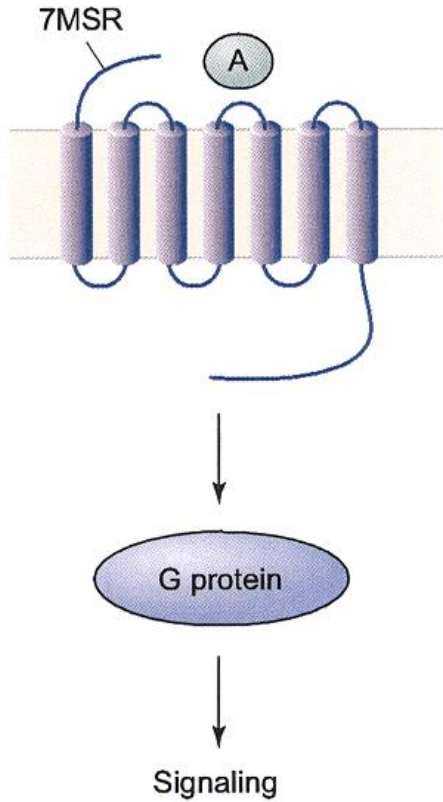
HB-EGF-like growth factor is synthesized as a membrane-anchored mitogenic and chemotactic glycoprotein. An epidermal growth factor produced by monocytes and macrophages, due to an affinity for heparin is termed HB-EGF. It has been shown to play a role in wound healing, cardiac hypertrophy and heart development and function.



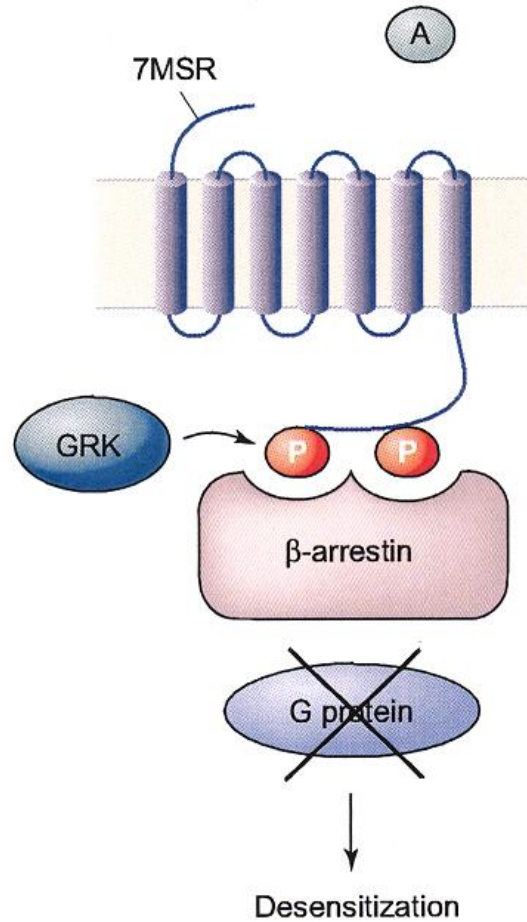




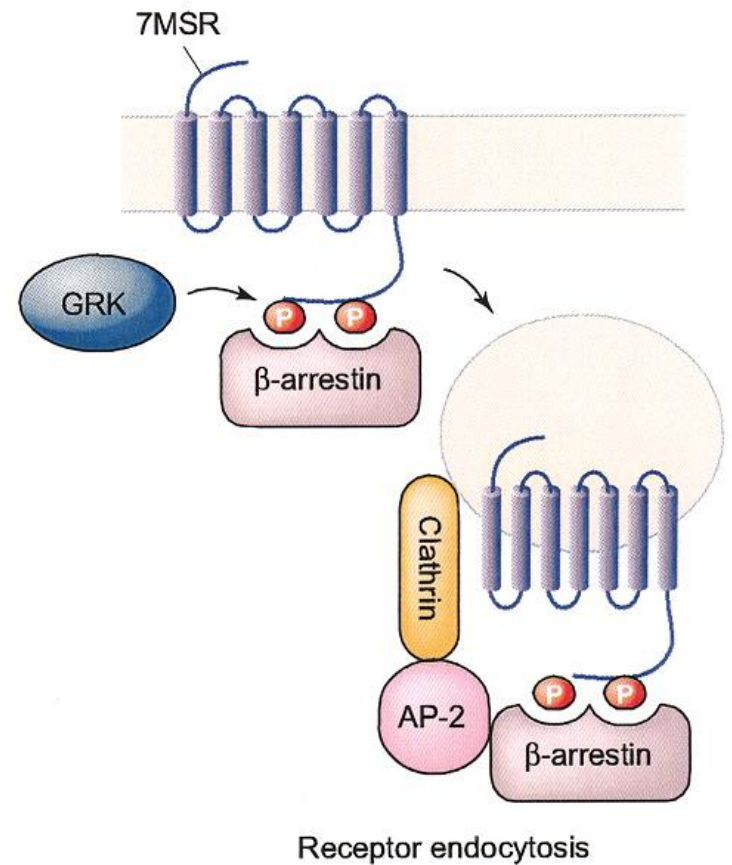
(a) Coupling to G protein

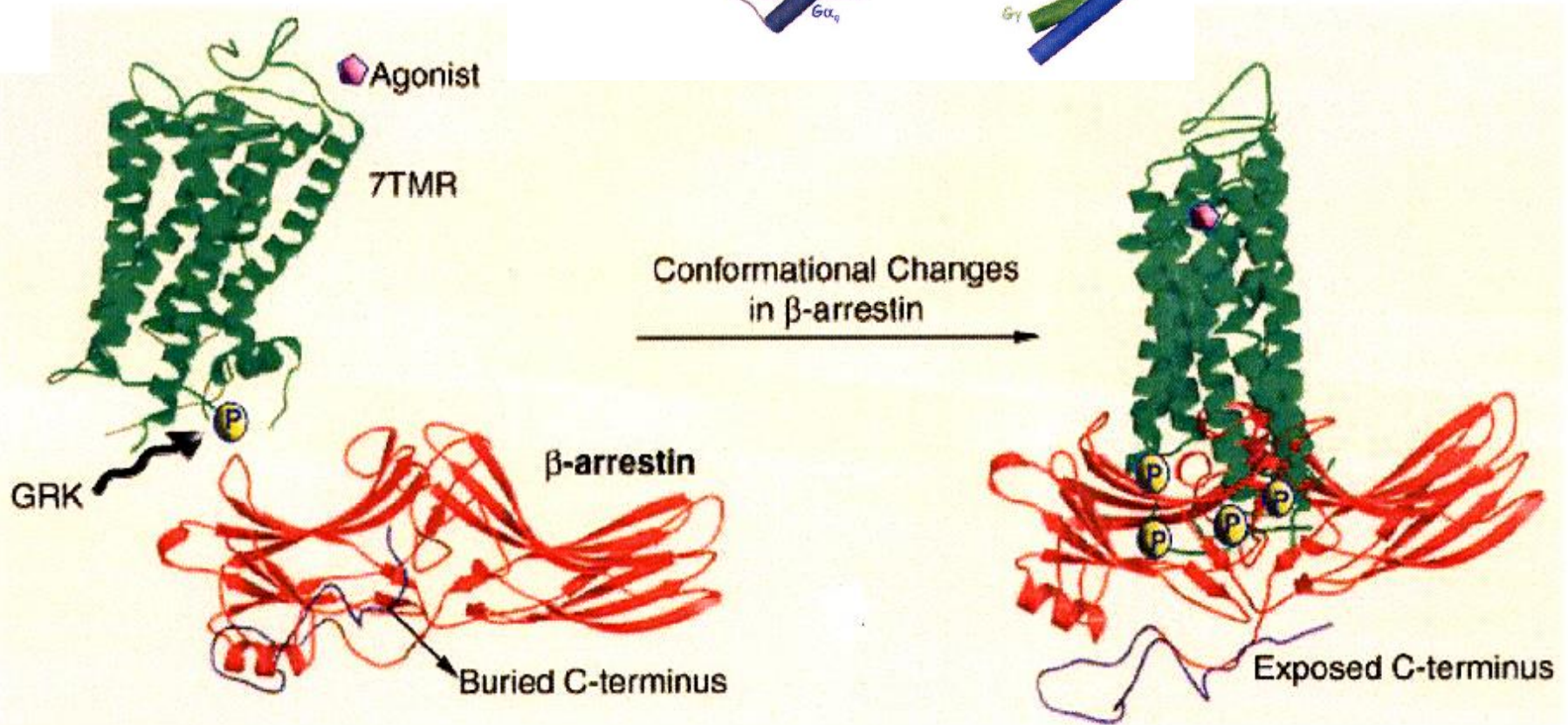
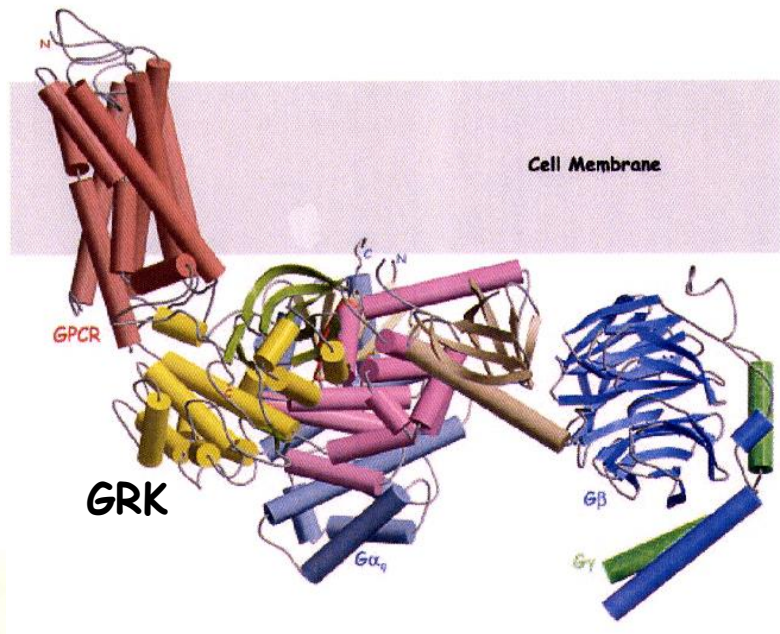


(b) Desensitization / inhibition of G-protein coupling

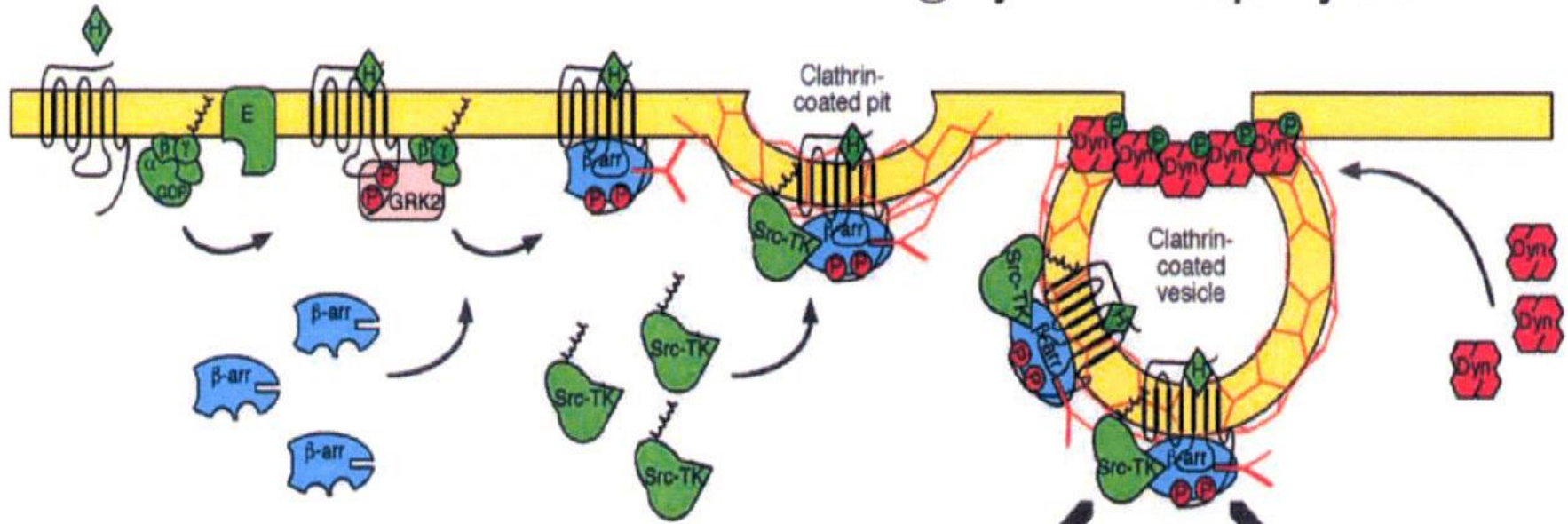


(c) Internalization

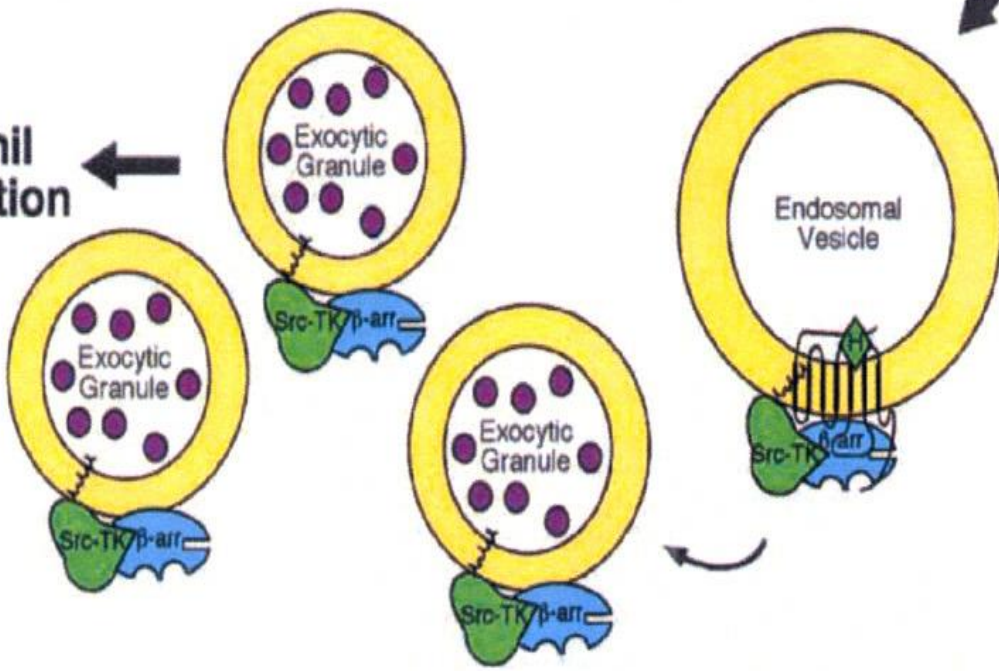




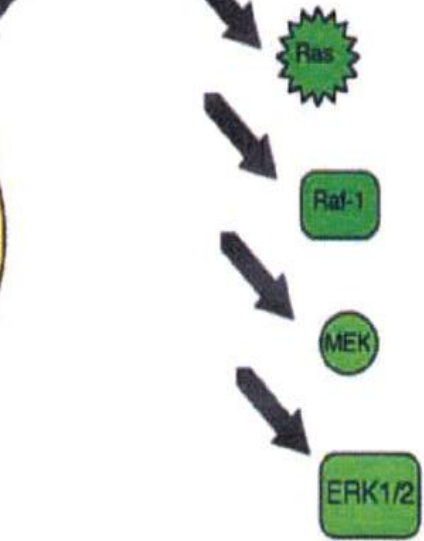
# ① Dynamin Phosphorylation



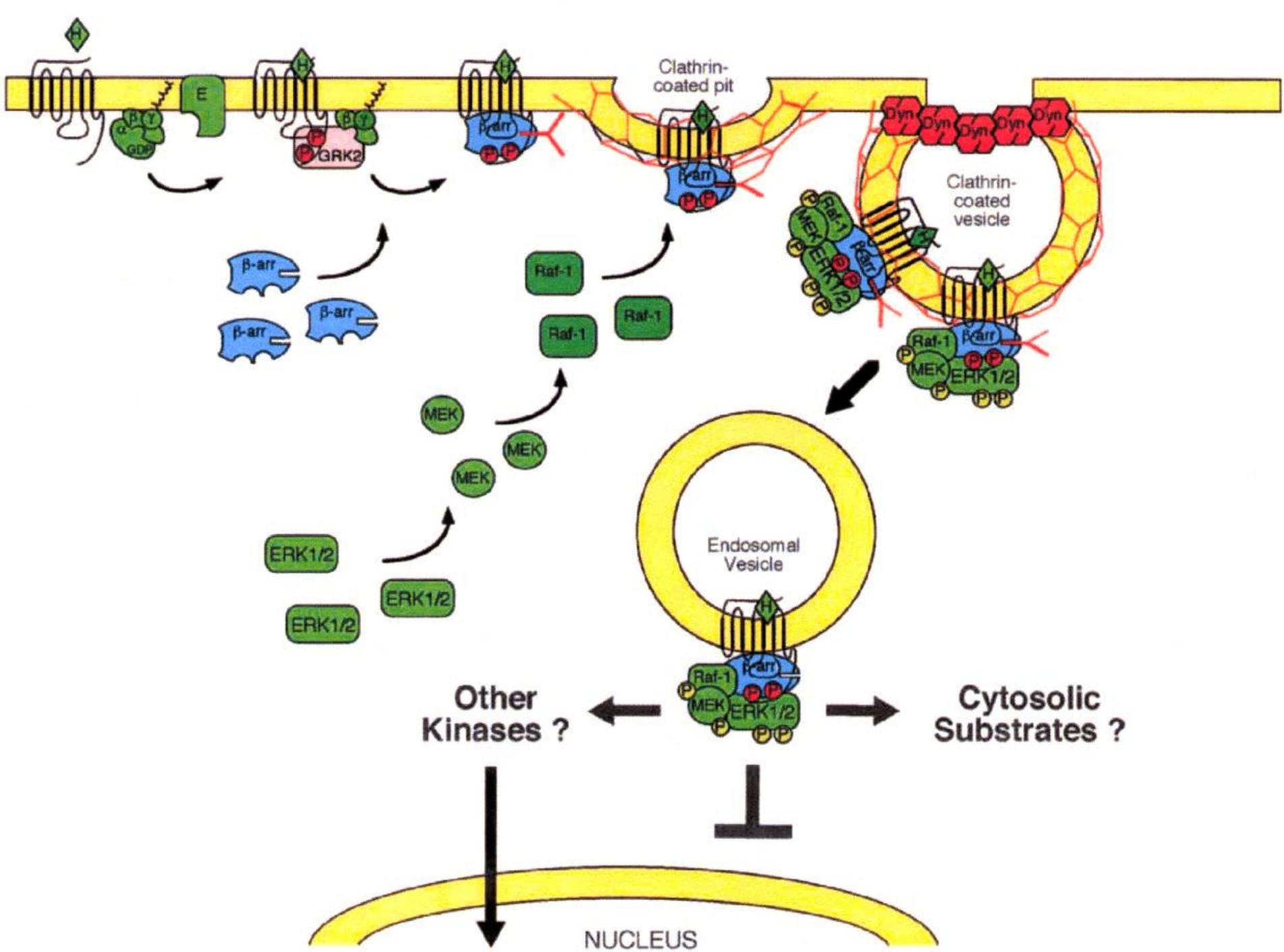
# ③ Neutrophil Degranulation

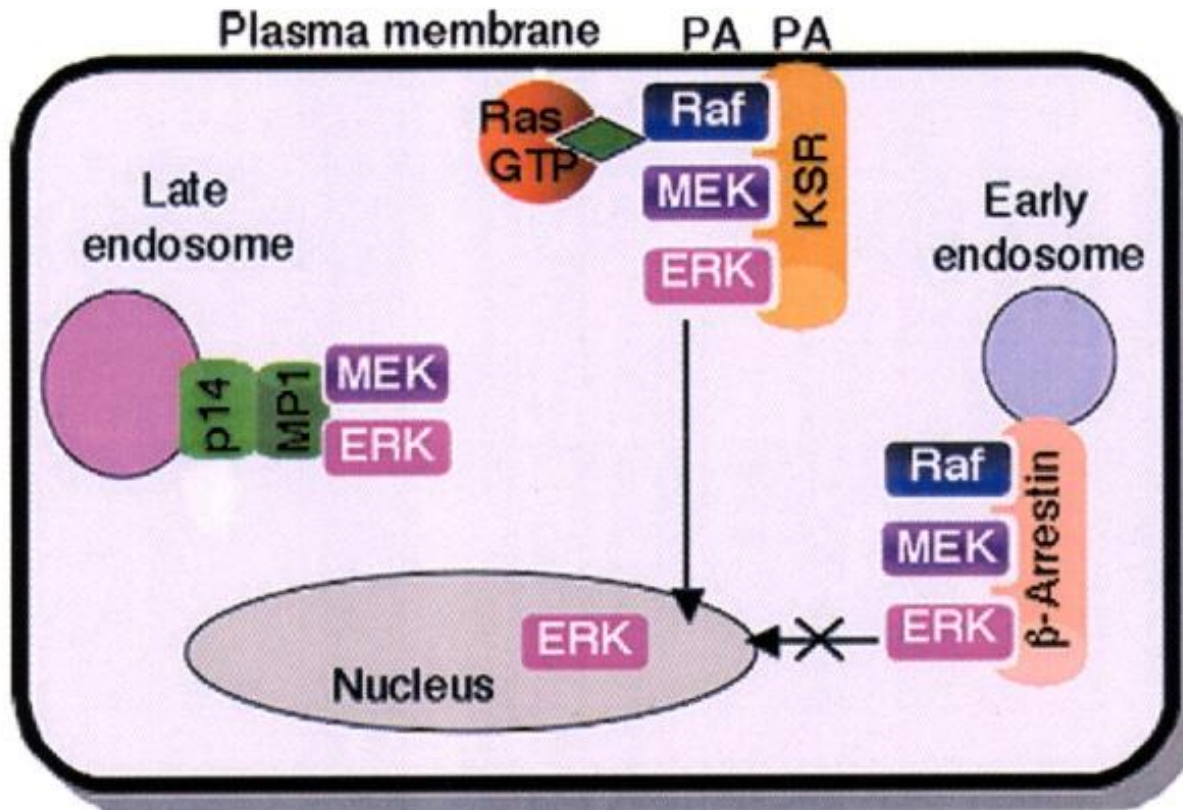


# ② ERK1/2 Activation Cell Proliferation



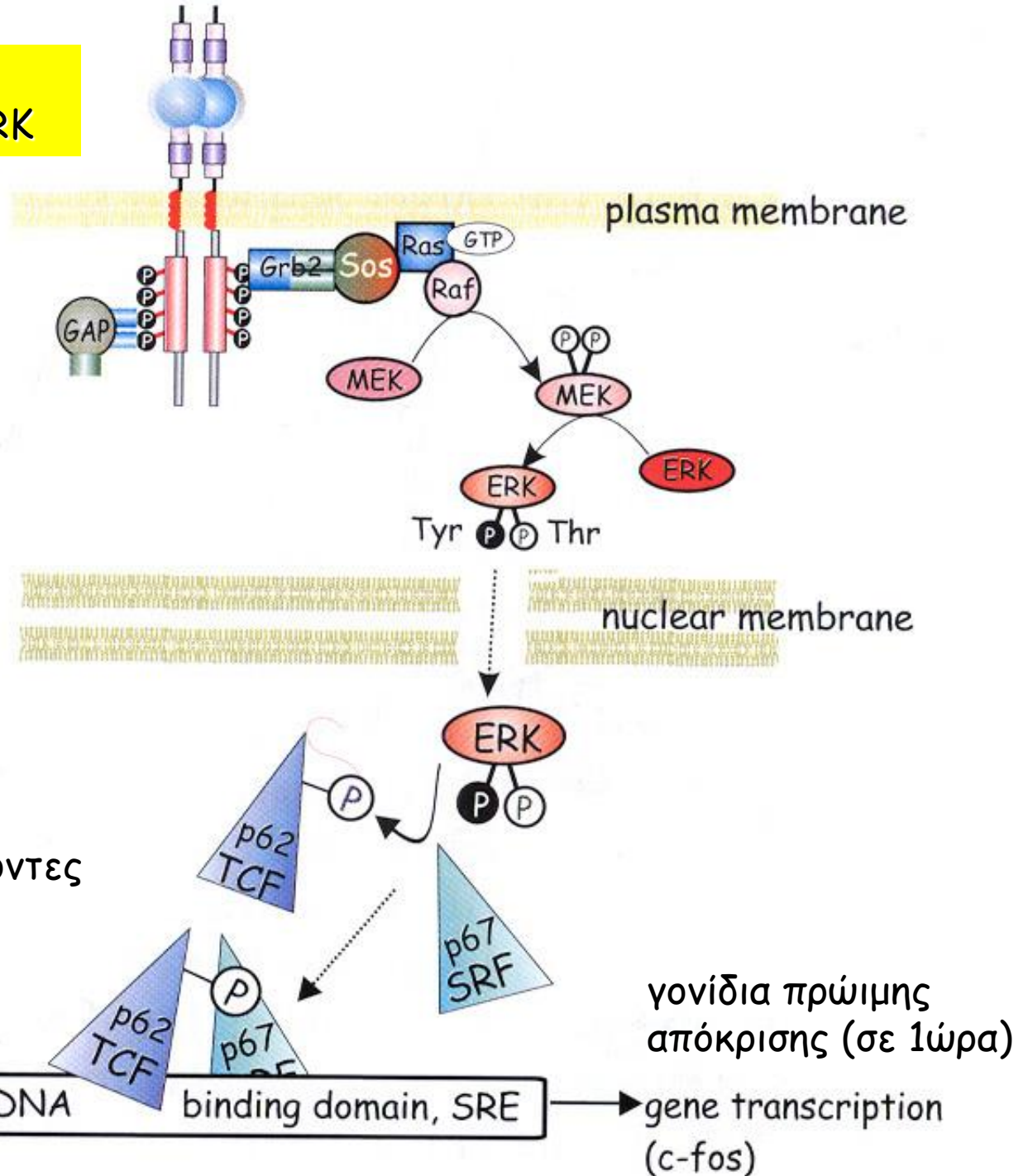






Διαφορετικές πρωτεΐνες σκαλωσιάς τοποθετούν τα στοιχεία του σηματοδοτικού συμπλέγματος των MAPK στην πλασματική μεμβράνη (KSR), στα πρώιμα ενδοσώματα (β-αρρεστίνη) ή στα όψιμα ενδοσώματα (MP1)

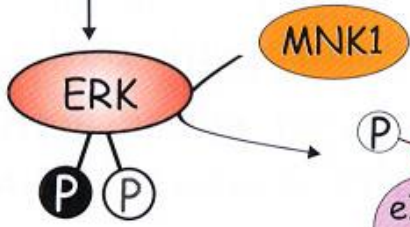
# 1. Ενεργοποίηση της μεταγραφής από την ERK



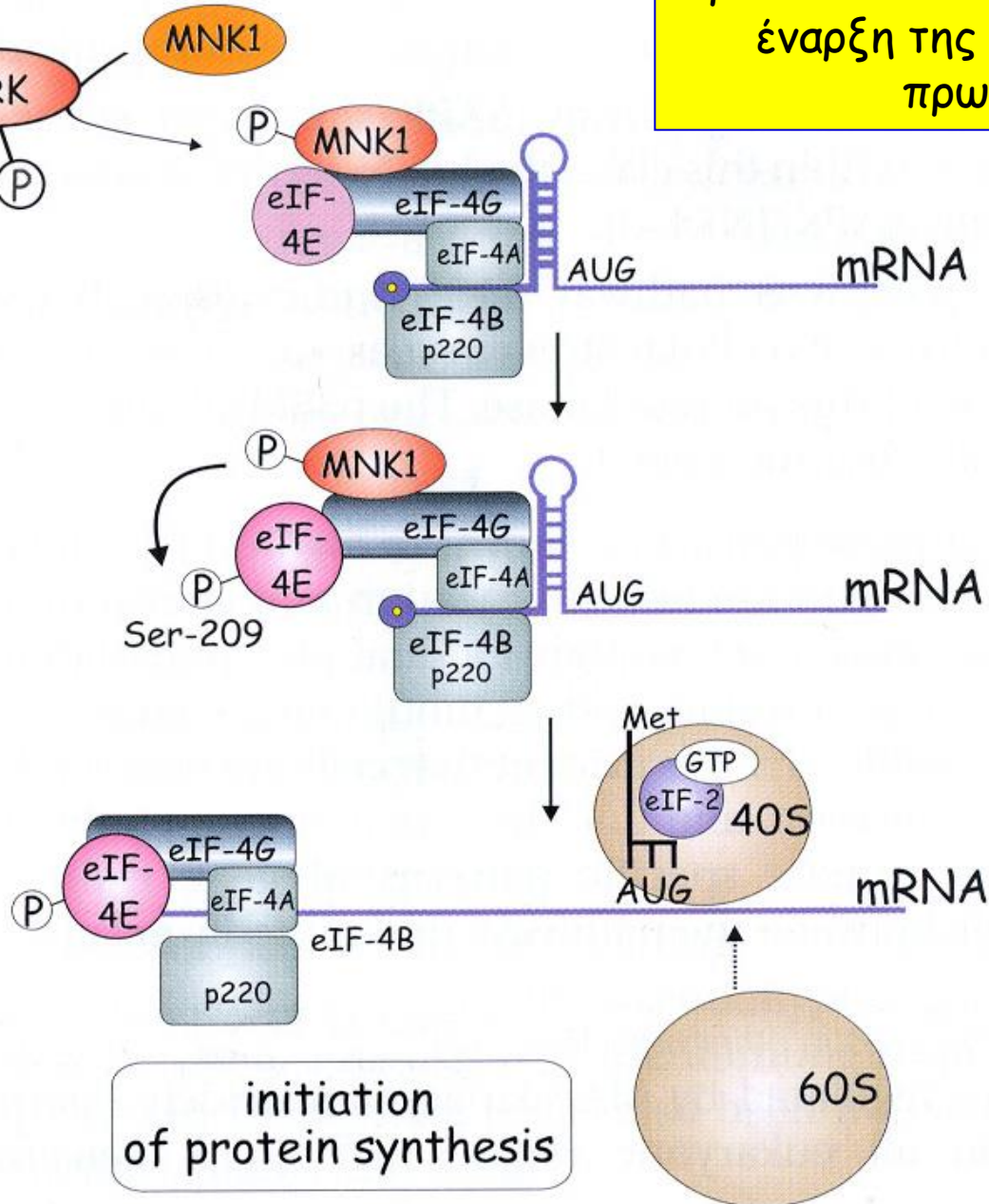
μεταγραφικοί παράγοντες

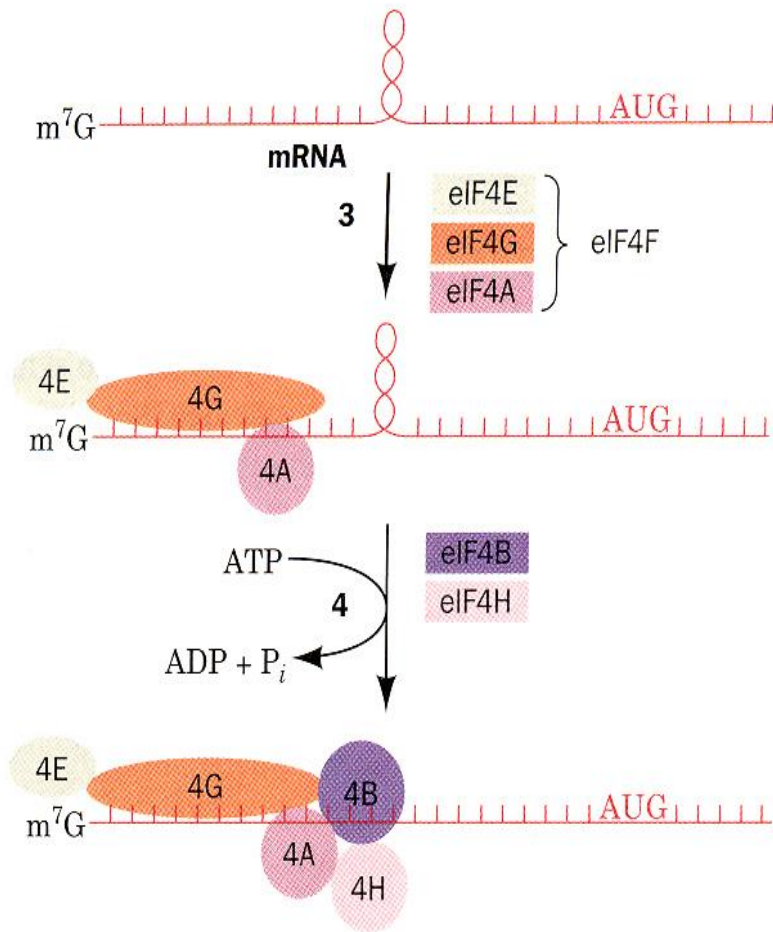
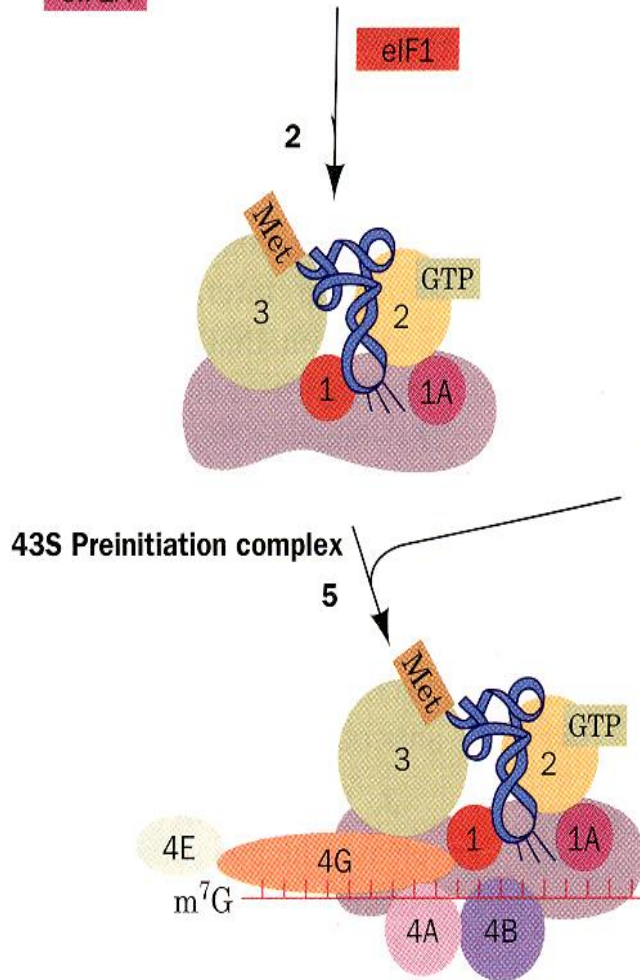
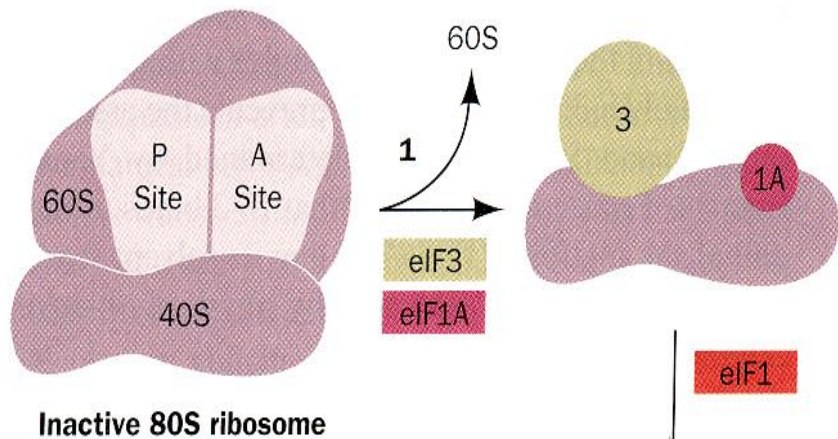
γονίδια πρώιμης απόκρισης (σε 1ώρα)

growth factors

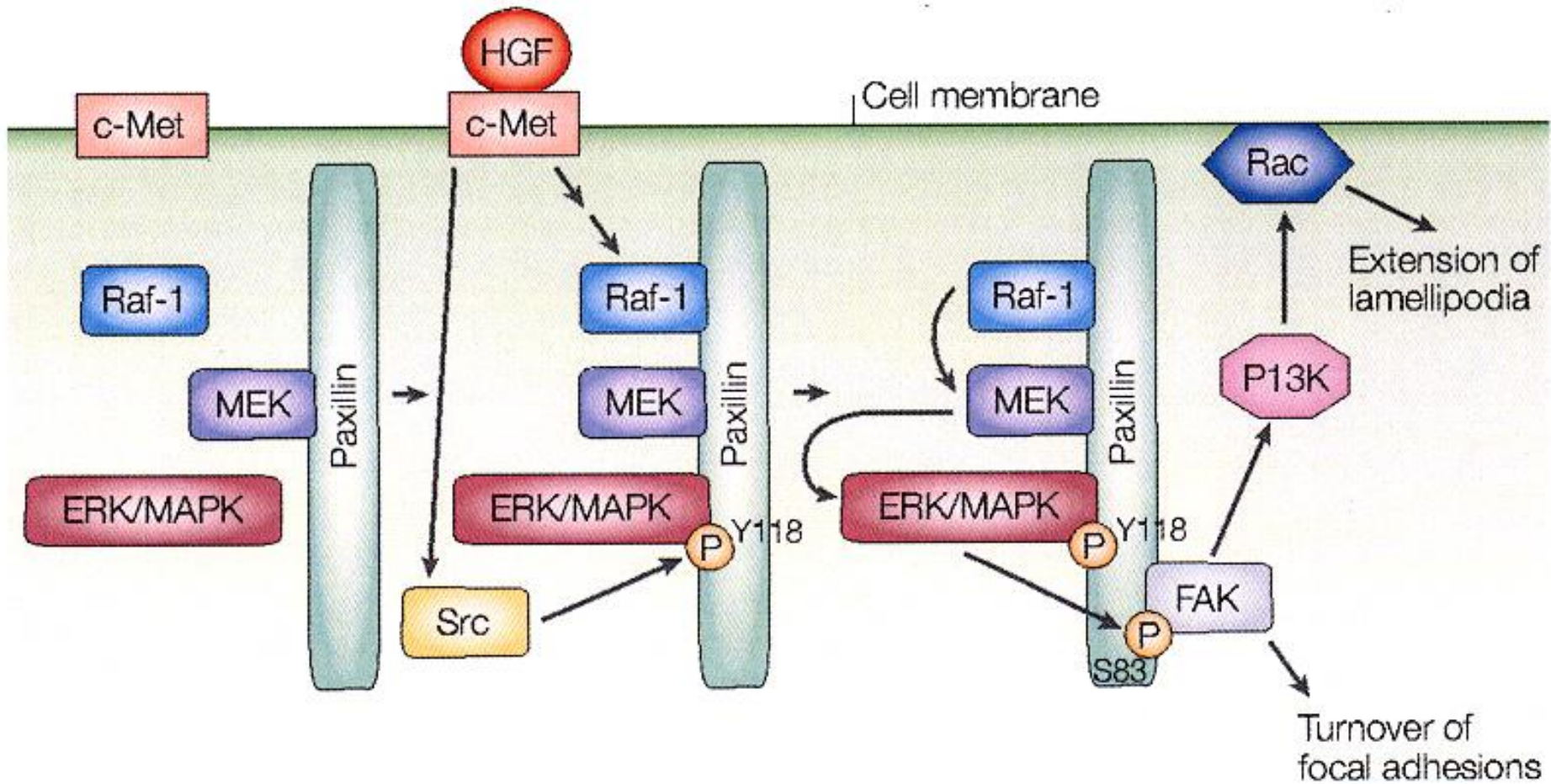


2. Ενεργοποίηση της πρωτεϊνοσύνθεσης από την ERK: έναρξη της σύνθεσης των πρωτεϊνών



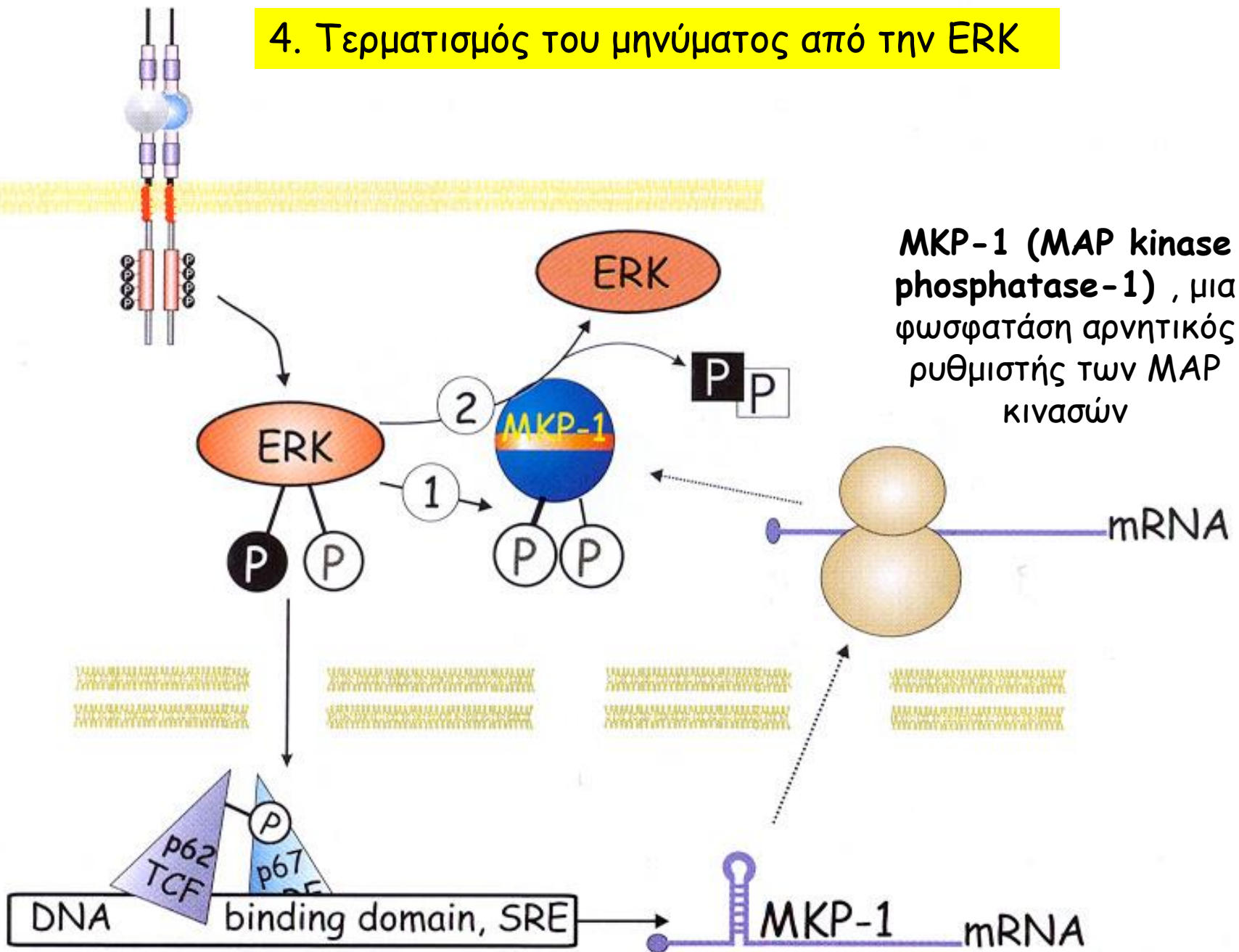


### 3. Ο ρόλος της ERK στην κυτταρική μετανάστευση

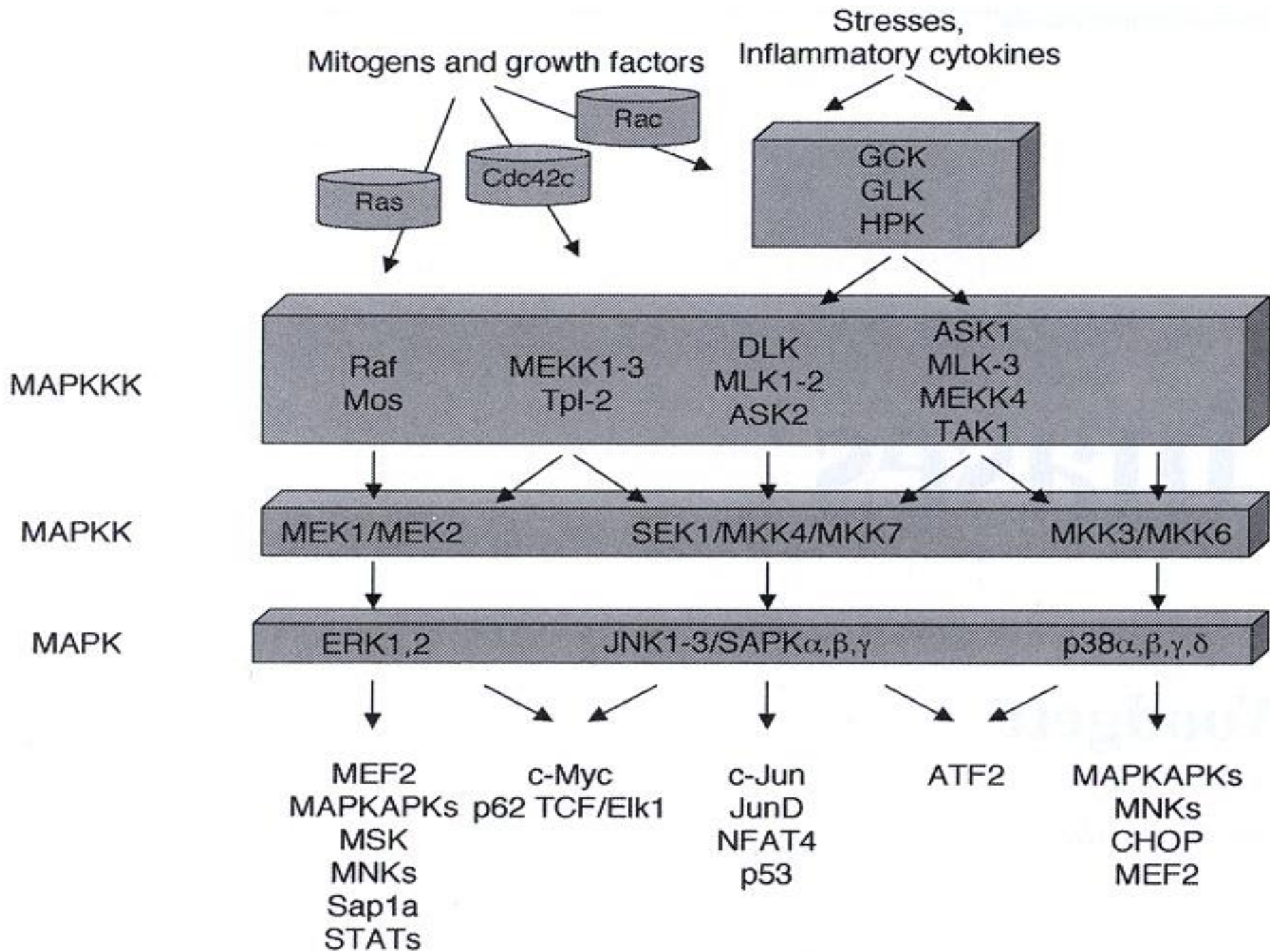


Η παξιλλίνη συνδέει το μονοπάτι της ERK και της FAK. Η παξιλλίνη είναι ένα εσωτερικό συστατικό των σημείων εστιακής προσκόλλησης. Είναι μόνιμα συνδεδεμένη με την MEK, και μετά τη σύνδεση του HGF στον υποδοχέα του c-Met και τη φωσφορυλίωσή της από τη Src συνδέει την Raf και την ERK. Σαν αποτέλεσμα, δημιουργούνται λαμελλιπόδια και καταστρέφονται τα σημεία εστιακής προσκόλλησης επιτρέποντας τη μετανάστευση του κυττάρου

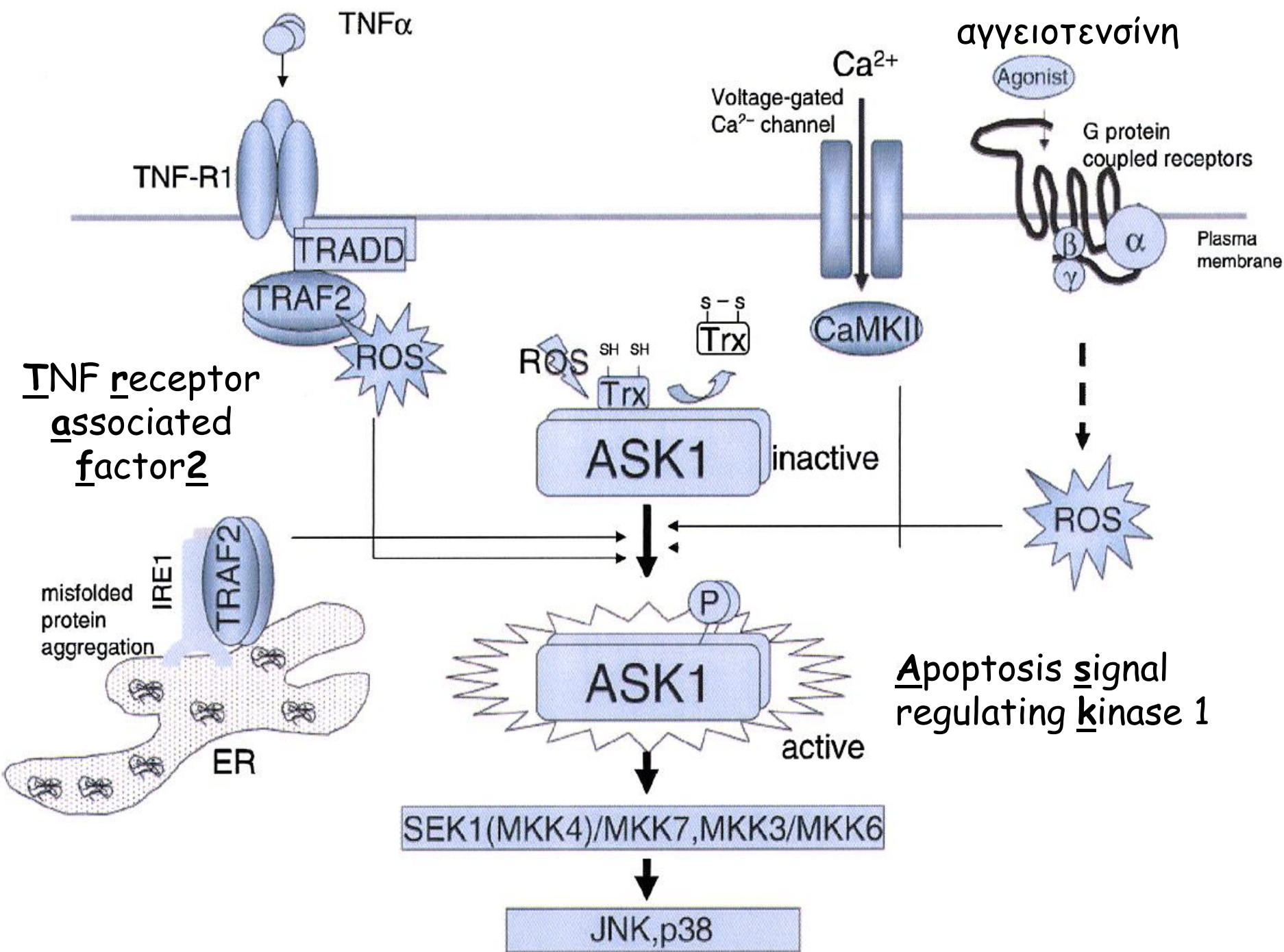
#### 4. Τερματισμός του μηνύματος από την ERK



**ΜΚΡ-1 (MAP kinase phosphatase-1)**, μια φωσφατάση αρνητικός ρυθμιστής των MAP κινασών





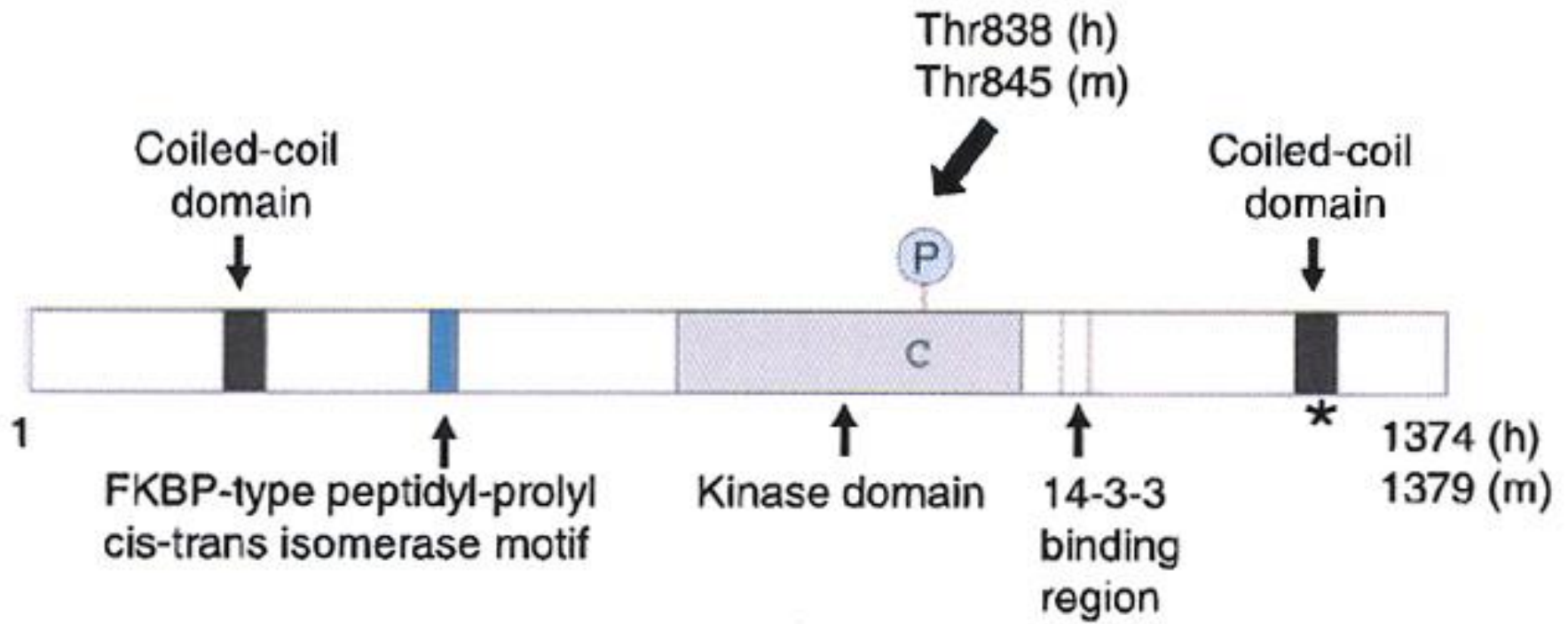


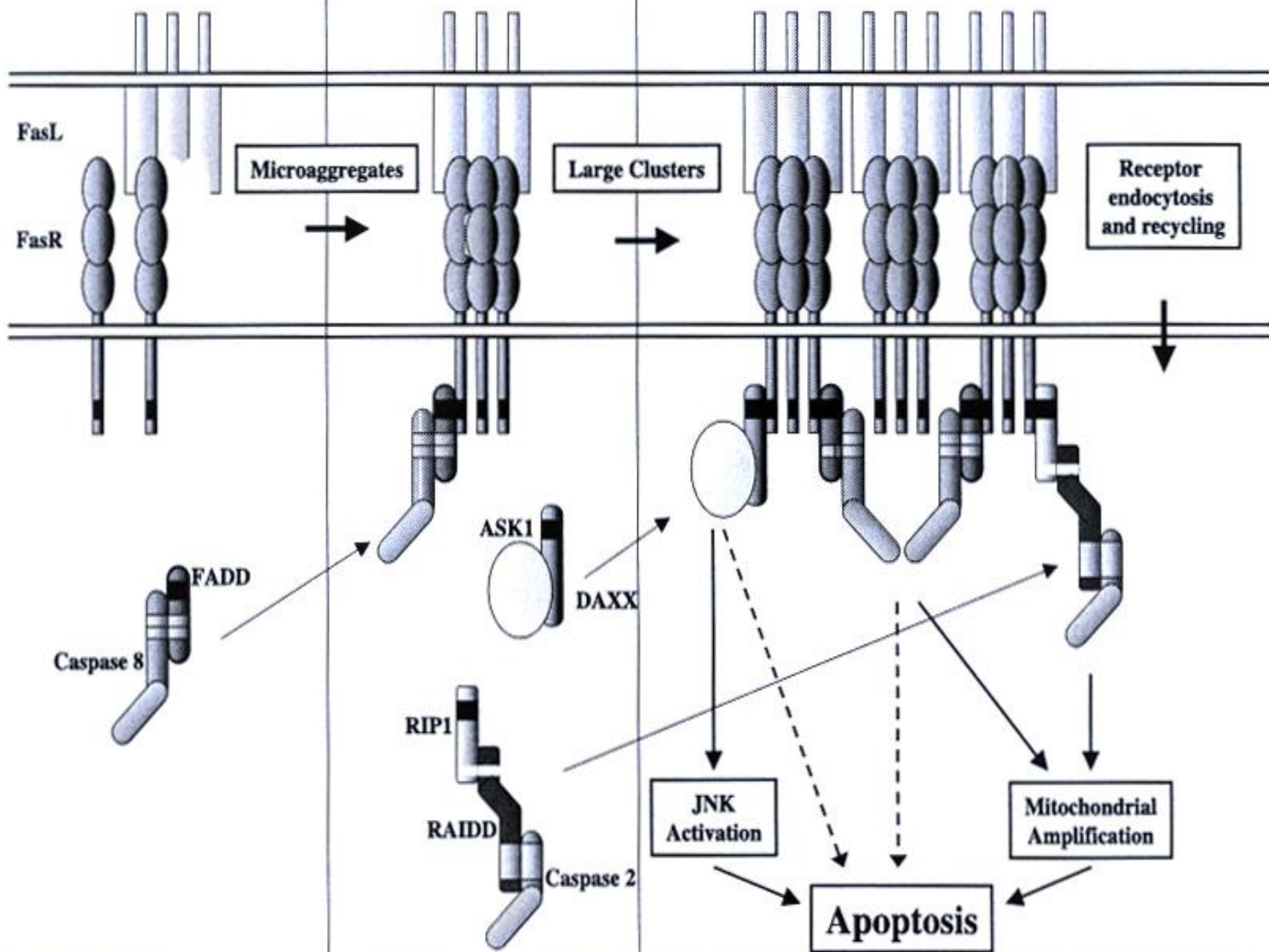
TNF receptor associated factor 2

αγγειοτενσίνη

Apoptosis signal regulating kinase 1

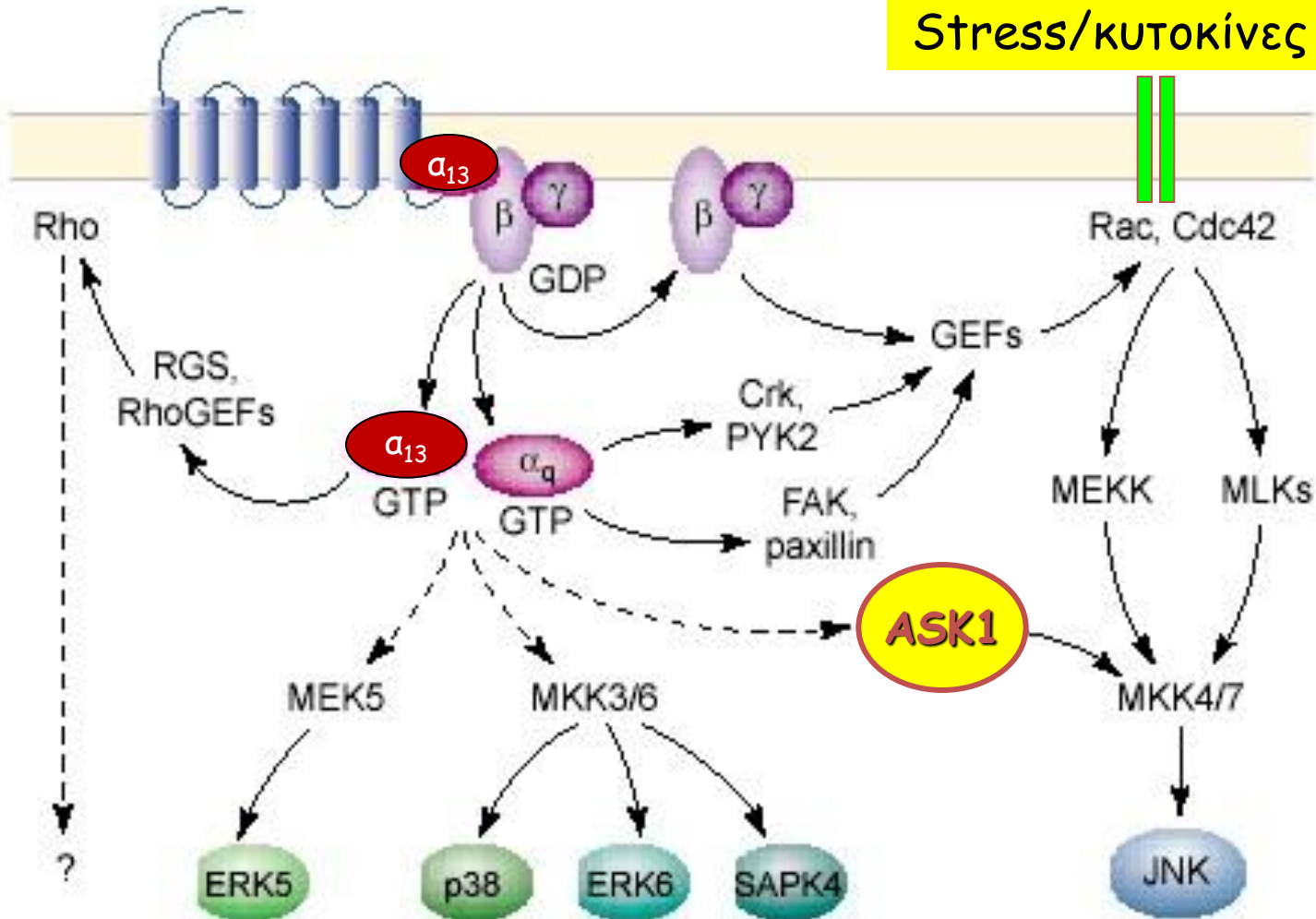
# ASK1



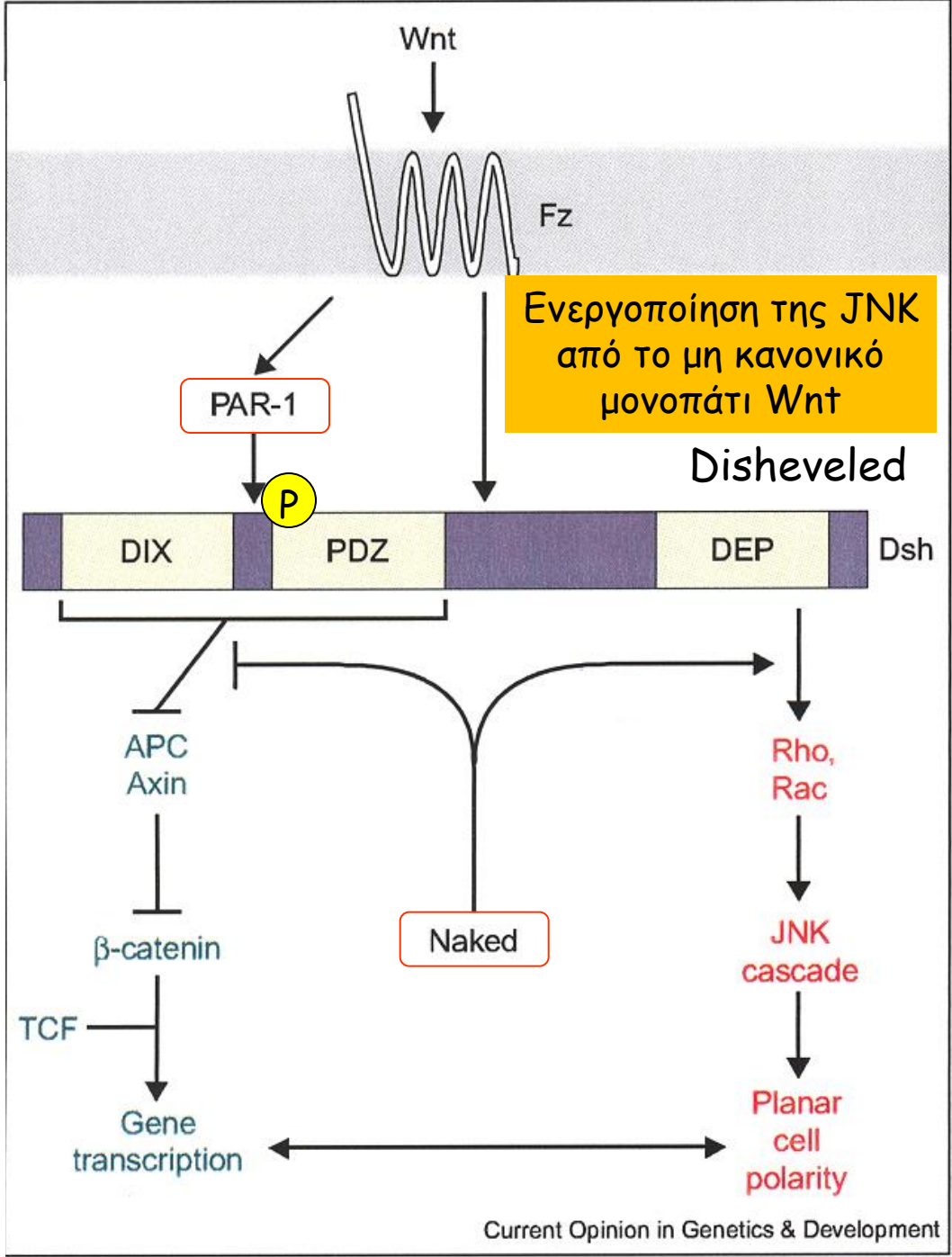
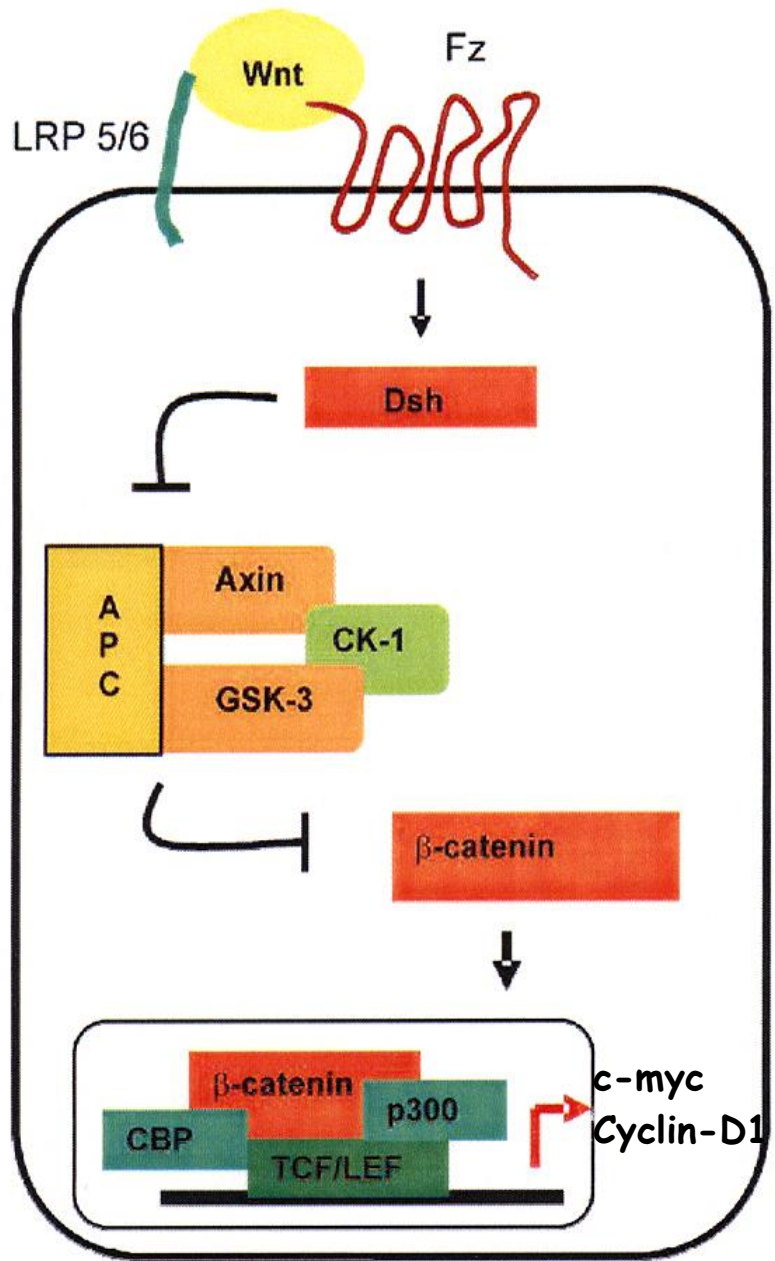


αγγειοτενσίνη

Stress/κυτοκίνες



**Κανονικό μονοπάτι Wnt**

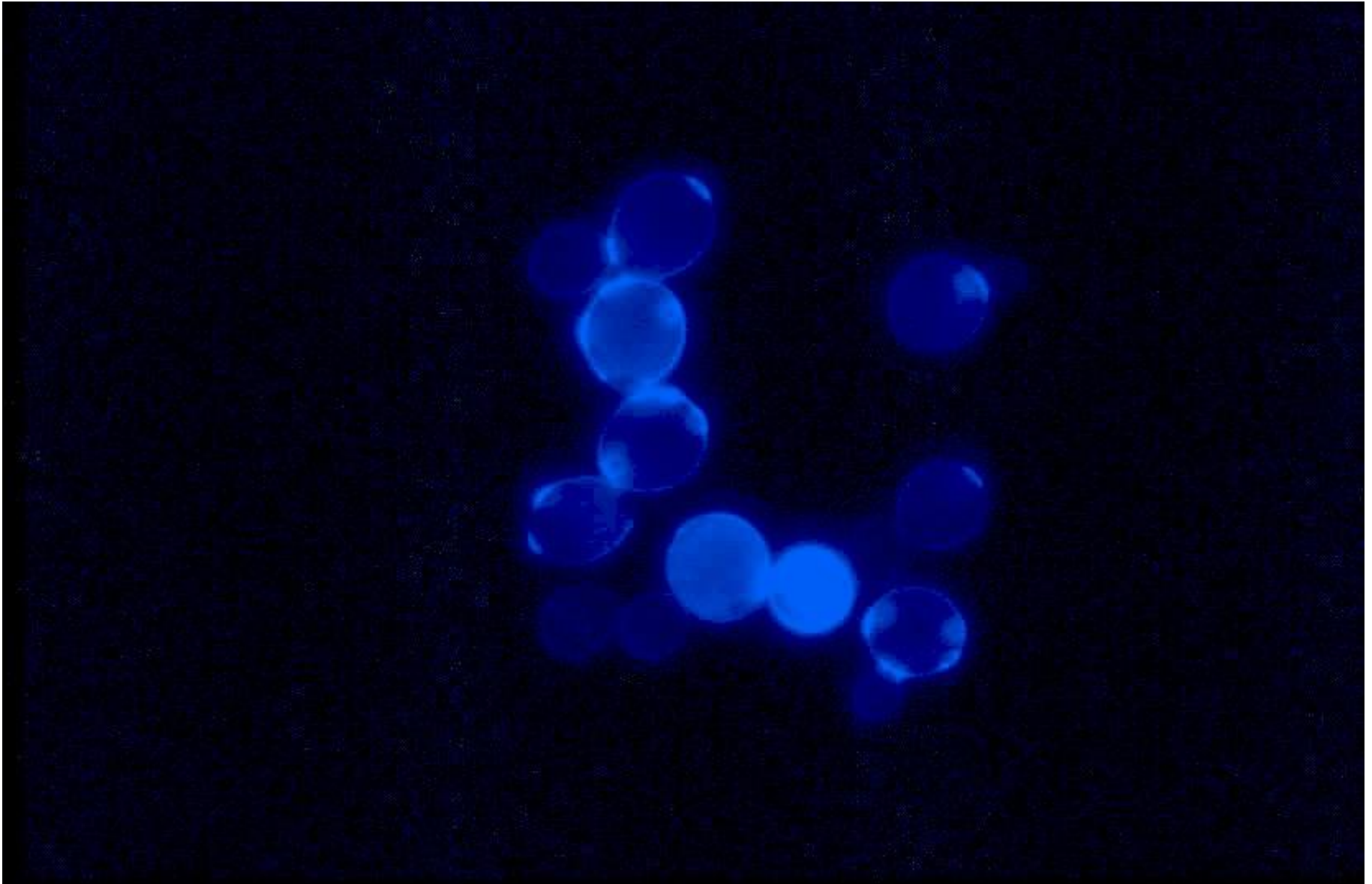




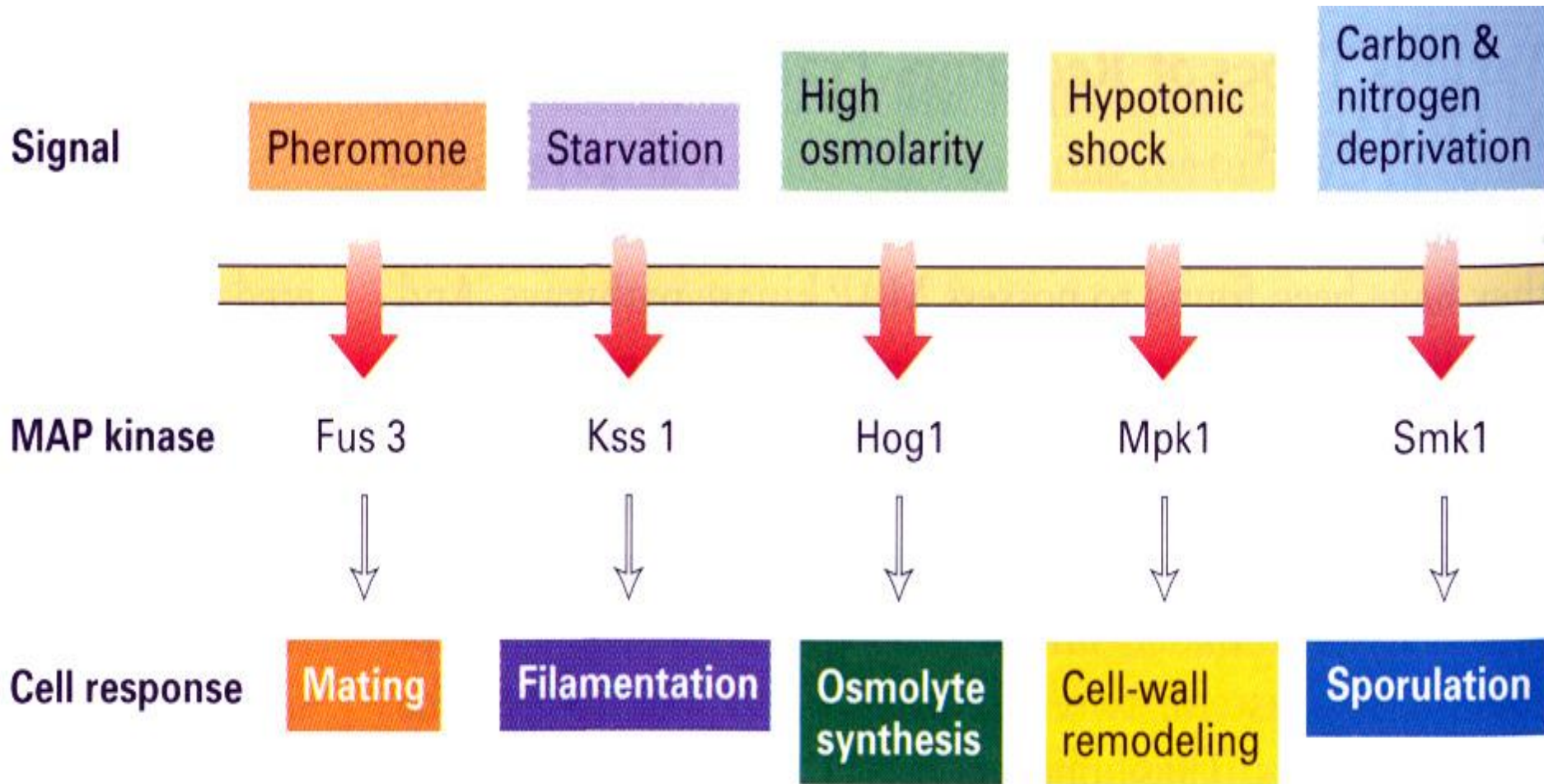
Απουσιάζουν δυο από τα τρία γονίδια JNK

Η εικόνα παρουσιάζει μία σπάνια περίπτωση ελαττώματος στον εγκέφαλο ανθρώπινου εμβρύου (exencephaly), όπου ο εγκέφαλος διαχέεται μέσα στο αμνιακό υγρό, λόγω μειωμένης απόπτωσης στον οπίσθιο μέρος του εγκεφάλου και αυξημένης στο πρόσθιο.

Η εξειδίκευση στη σηματοδότηση των MAPK στο ζυμομήκυτα *S. cerevisiae*

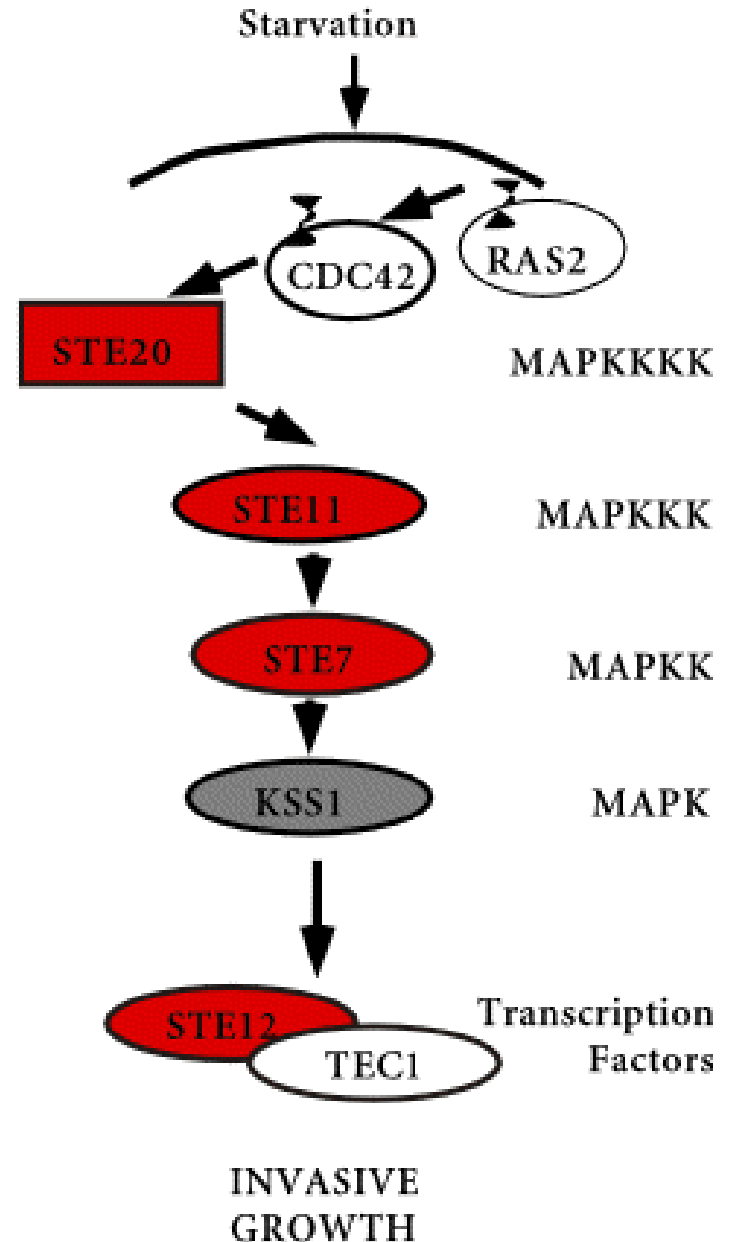
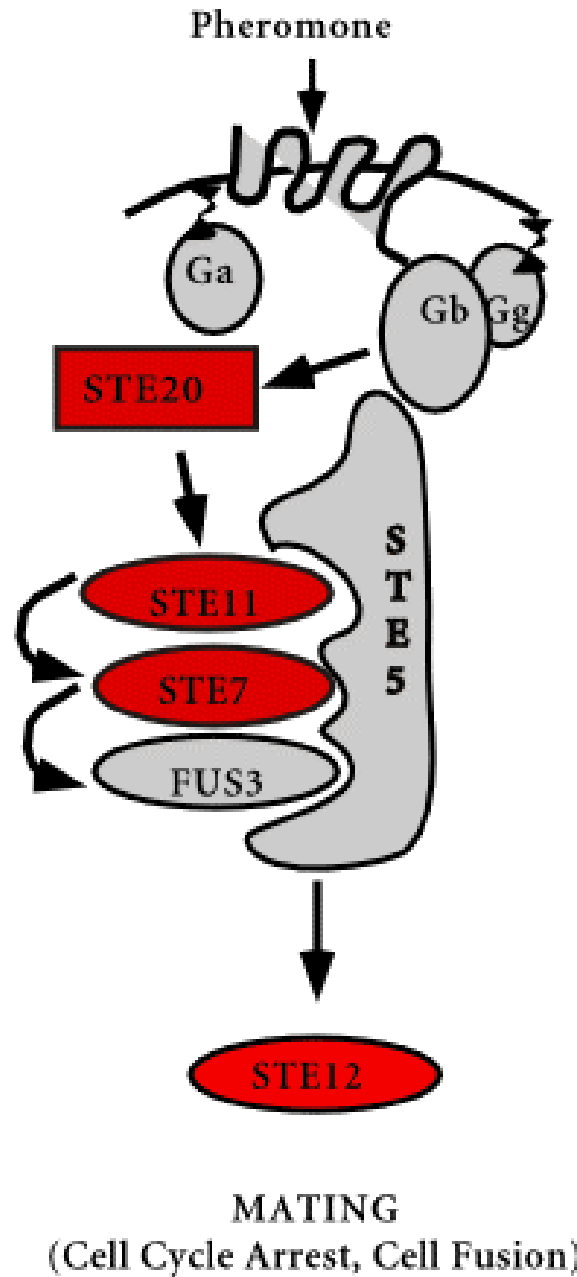
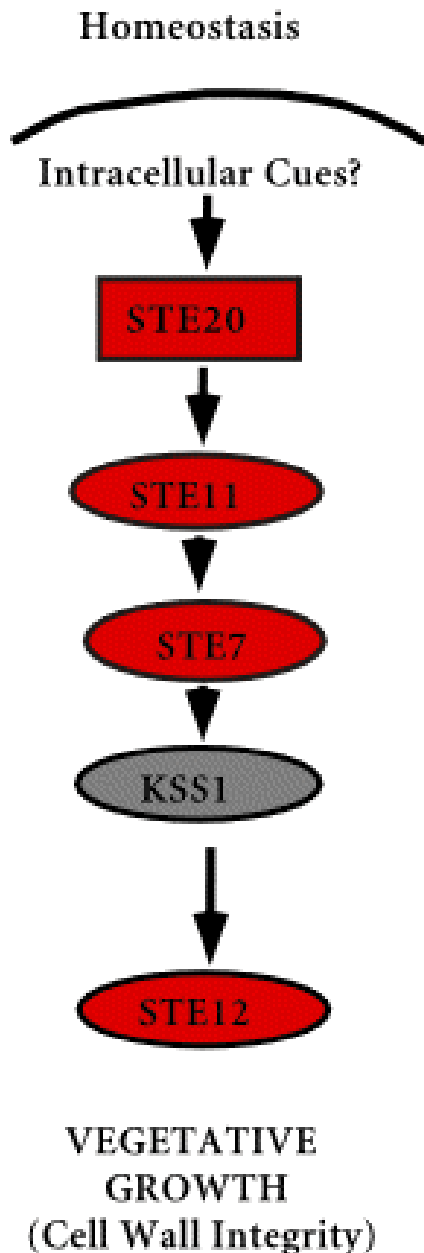


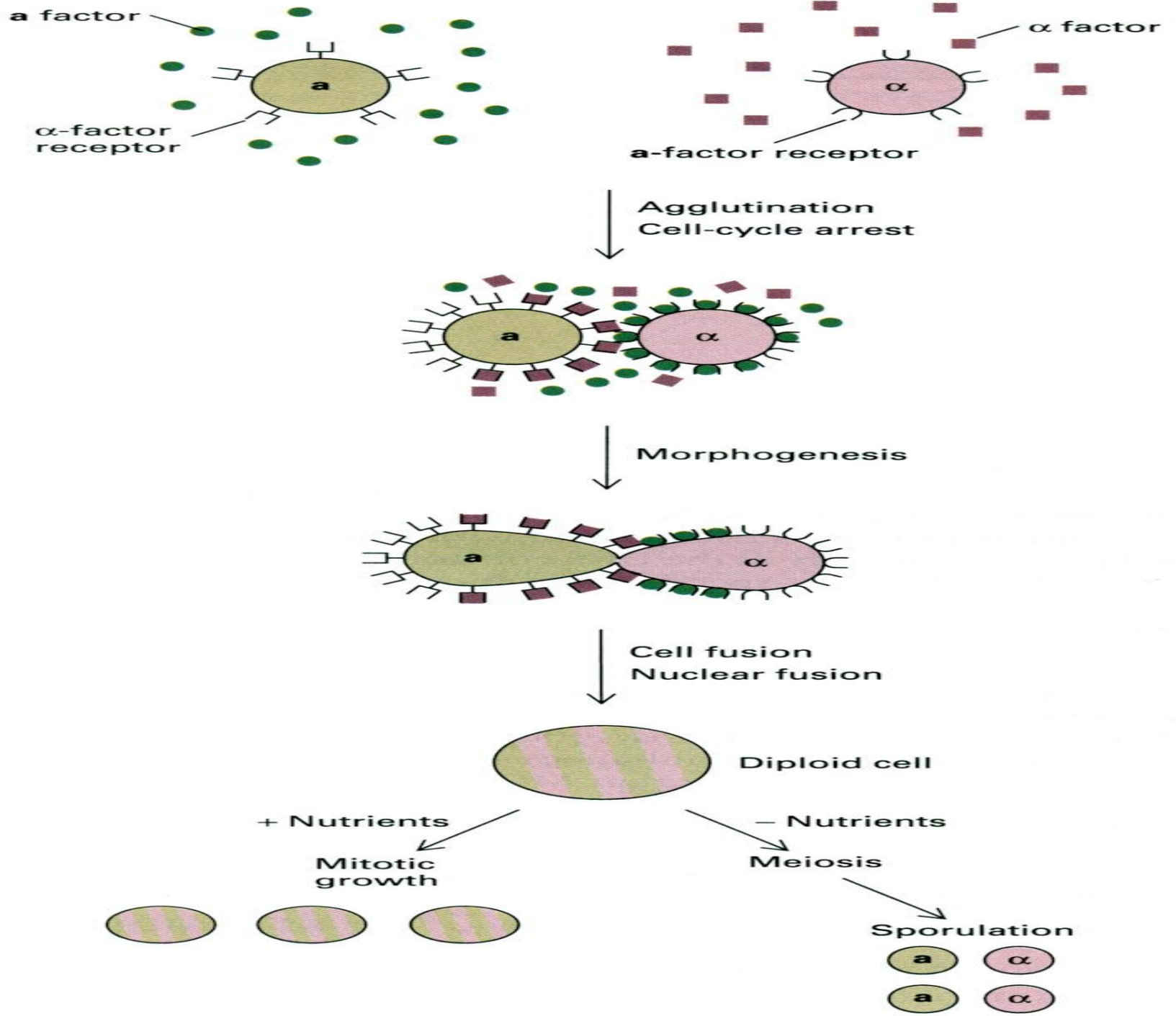
Στις ζύμες 5 διαφορετικά μονοπάτια MAPK ρυθμίζουν:

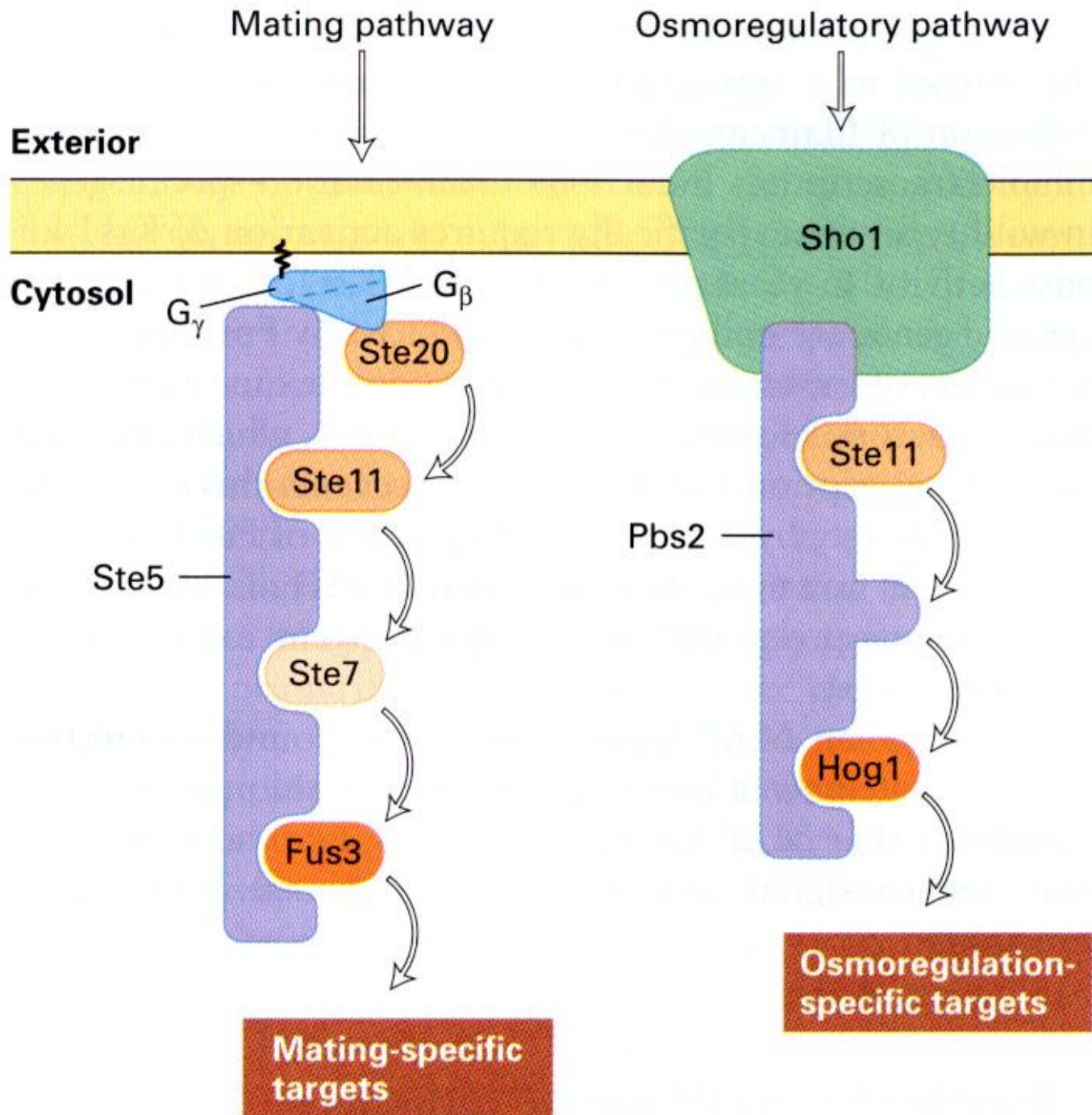




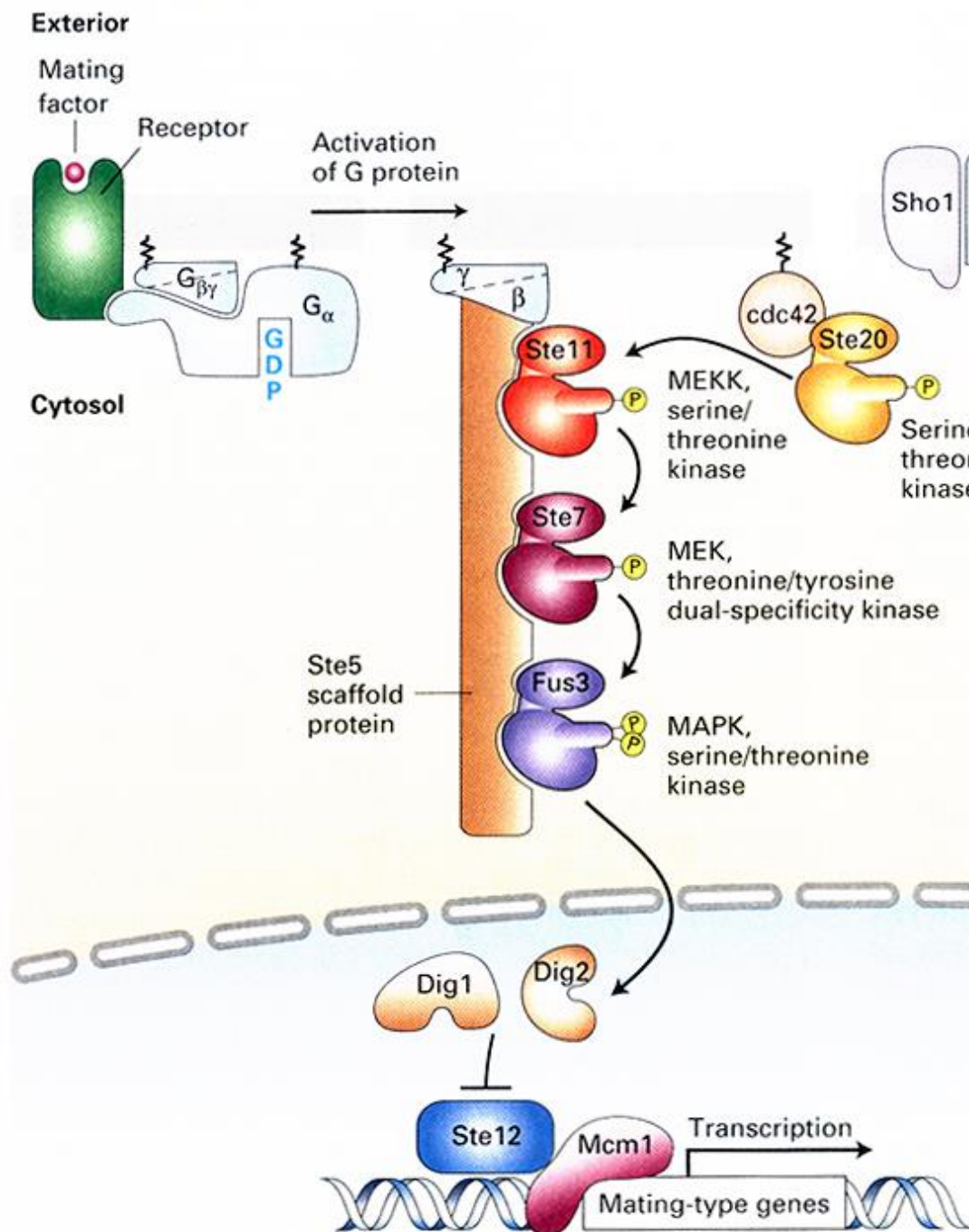
# A Multipurpose Signaling System



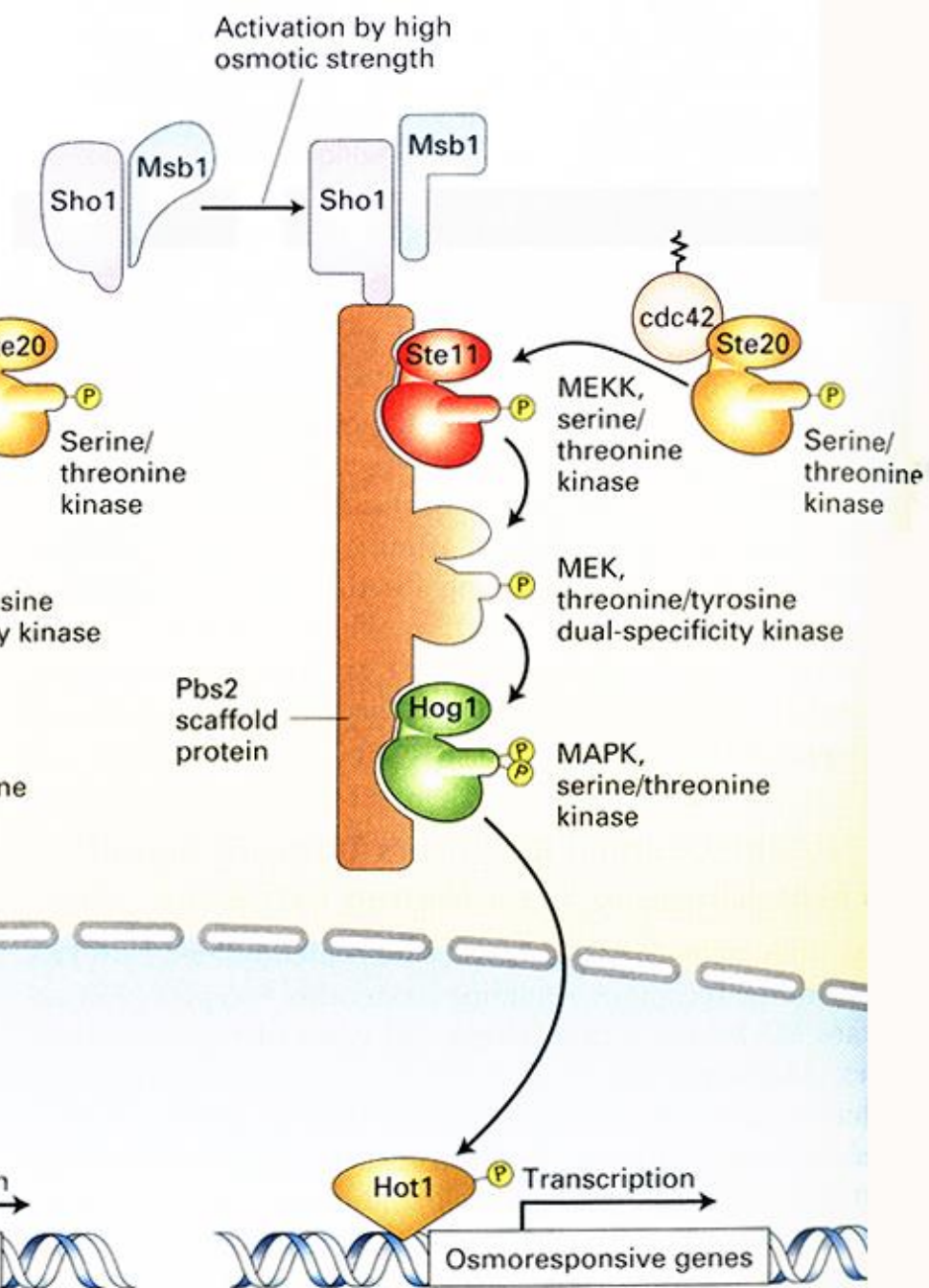




(a) Mating pathway



(b) Osmoregulatory pathway



Mating factor

Peptide pheromone  
Seven transmembrane domain receptor  
Heterotrimeric G protein

GEF  
GAP/small G protein/  
polarity establishment protein

Scaffold protein

MAPKKKK  
MAPKKK  
MAPKK  
MAPK/MAPK

CDK inhibitor/transcription factor

CDK

⊖(P) Phosphorylation



Gpa1

Ste18

Ste4

Cdc24

Bem1

Morphogenesis

Rga1

Cdc42

Ste20

Ste11

Ste7

Fus3

Kss1

P

Far1

P

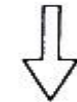
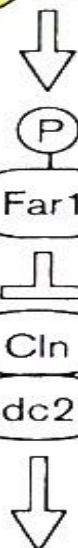
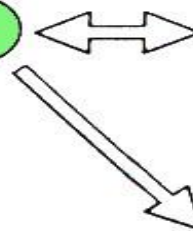
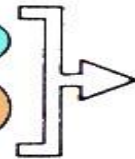
Ste12

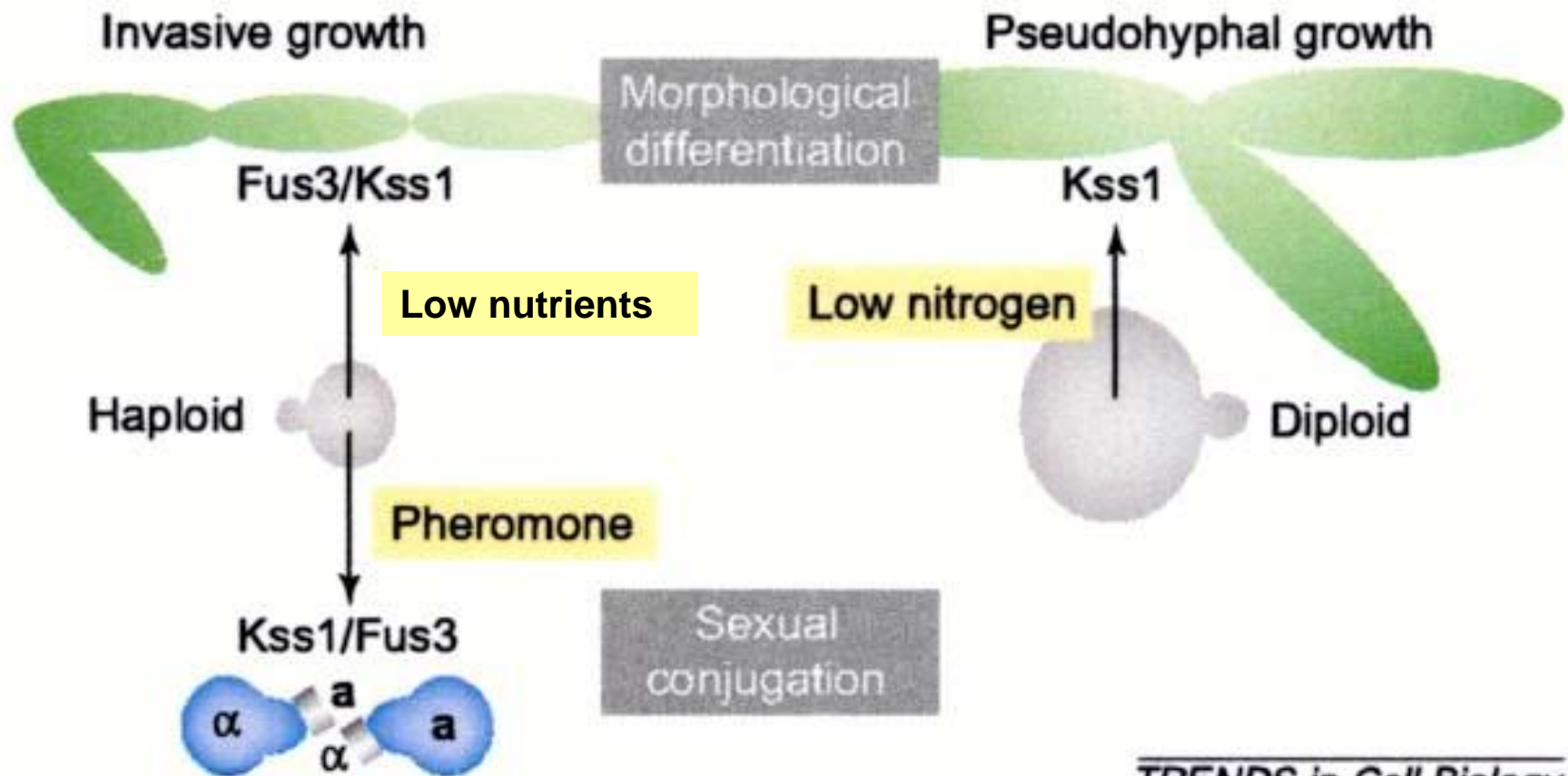
Cln

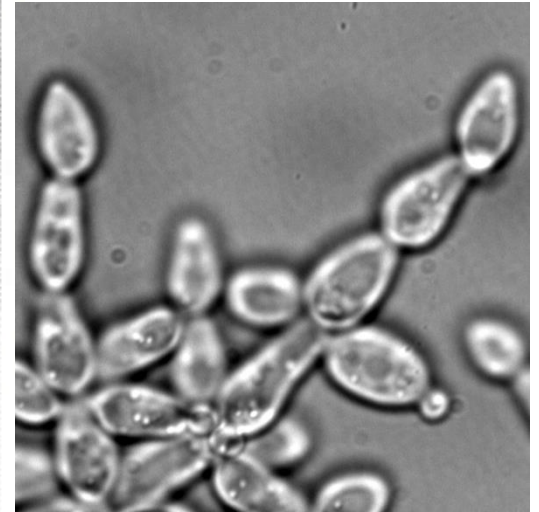
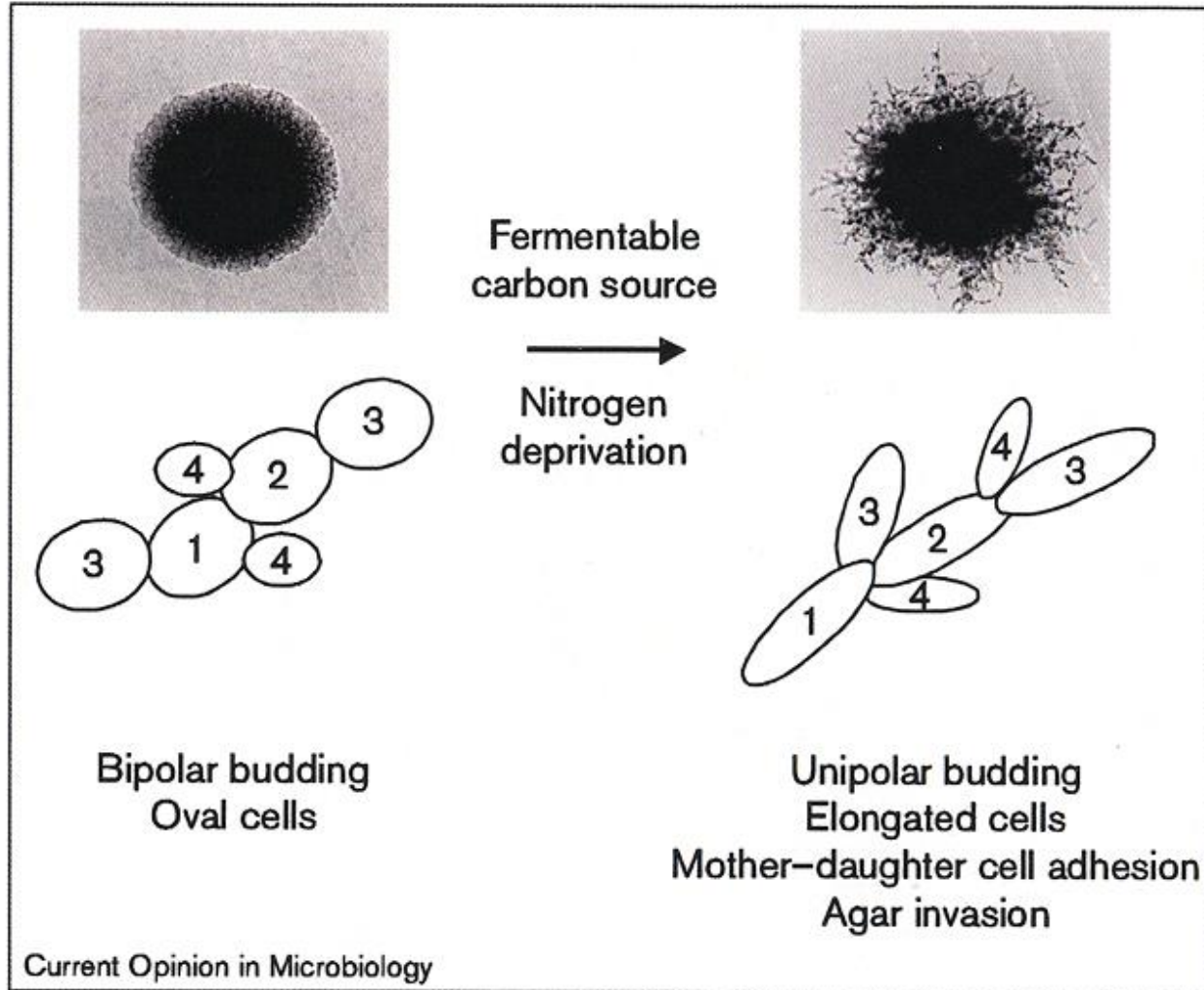
Cdc28

Mating-specific genes

Cell cycle arrest



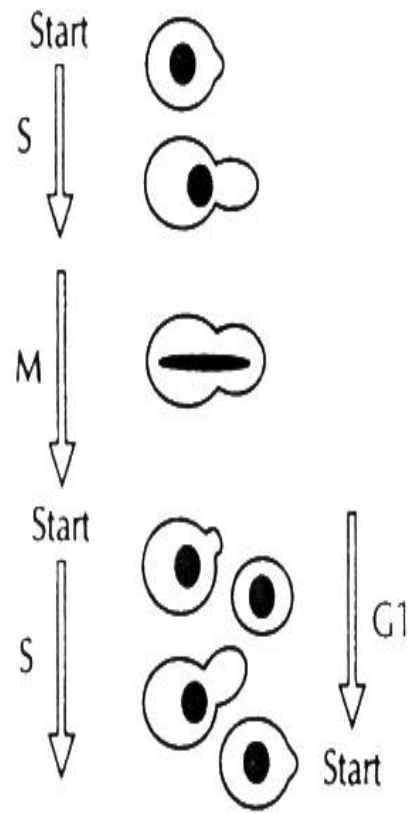




Diploid cells of the yeast *Saccharomyces cerevisiae* undergo pseudohyphal differentiation in response to nitrogen limitation. In response to nitrogen-limiting conditions, diploid cells of *S. cerevisiae* change their growth pattern: the cells elongate and switch from bipolar to unipolar budding, the mother and daughter cells remain physically attached, and the cells invade the growth substrate. As a result, filamentous pseudohyphal colonies are formed.

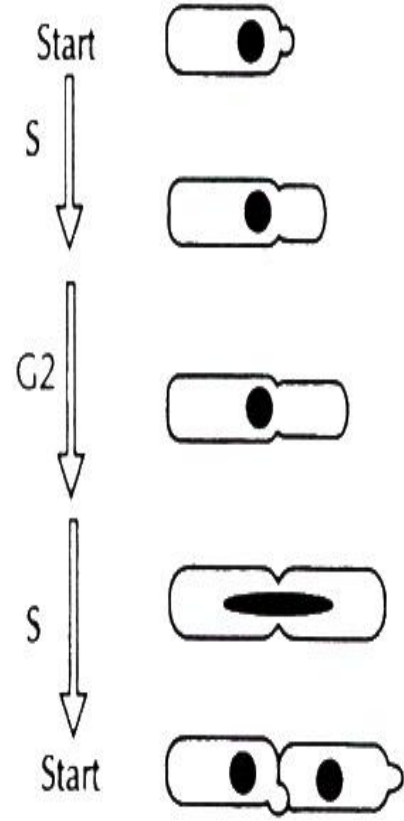
### Yeast-form growth

Asymmetric, asynchronous



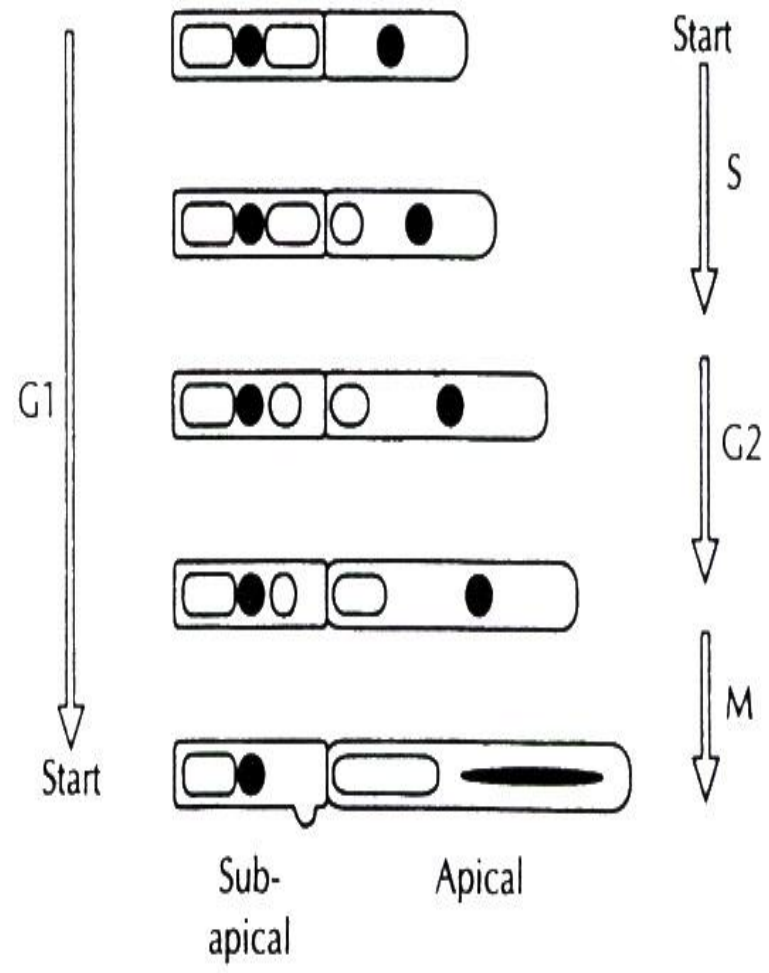
### Pseudohyphal growth

Symmetric, synchronous

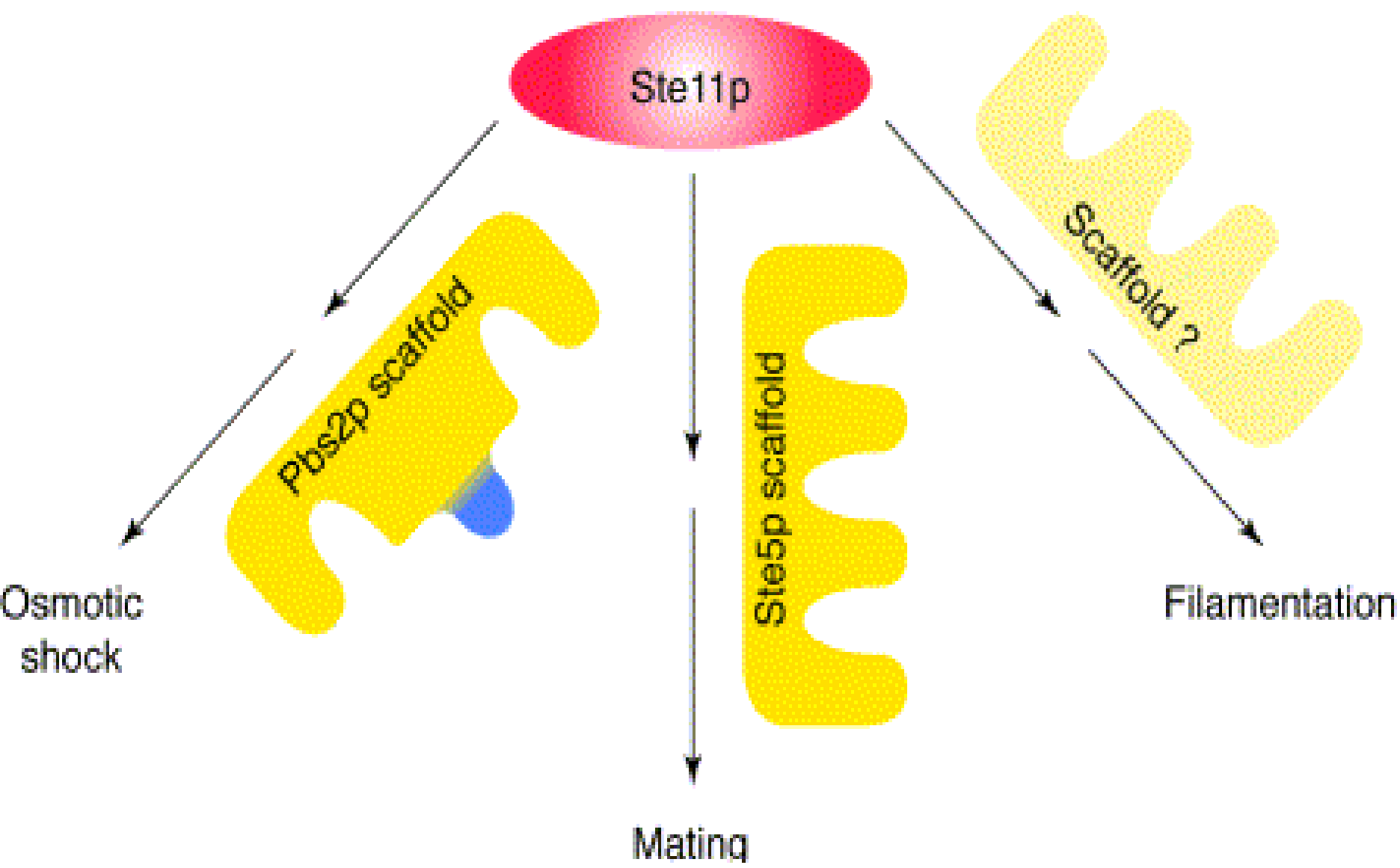


### Hyphal growth

Symmetric, asynchronous







## MAPKs

- ERK – Extracellular-signal regulated kinase (ERK1 = p44MAPK, ERK2 = p42 MAPK).
- Fus3 – MAPK in *S. cerevisiae* mating pathway.
- Hog1 – High osmolarity glycerol response MAPK in *S. cerevisiae* osmosensing response pathway.
- JNK – c-Jun amino-terminal kinase.
- p38 – MAPK involved in stress response in higher eukaryotes (p38 MAPK, p38/HOG1).

## MKKs

- MEK – MAPK/ERK kinase (MEK1 = MKK1, MEK2 = MKK2).
- PBS2 – MKK and scaffolding protein in *S. cerevisiae* osmosensing response pathway.
- SEK1 – SAPK/ERK kinase 1 (MKK4, JNKK).
- Ste7 – Sterile 7. MKK in *S. cerevisiae* mating pathway.

## MKKKs

- ASK1 – Apoptosis signal-regulating kinase 1 (MKKK5).
- DLK – dual leucine-zipper bearing kinase (MUK).
- MEKK – MAPK/ERK kinase kinase (MEKK1-3, MEKK4 = MTK1).
- MLK3 – mixed-lineage kinase 3 (SPRK).
- PAK – p21-activated kinase.
- Ste11 – Sterile 11. MKKK in *S. cerevisiae* mating and osmosensor response pathways.
- TAK1 – TGF $\beta$ -activated protein kinase.
- Tpl2 – tumor progression locus 2 (also known as Cot).

## MKKKKs

- GCK – germinal center kinase.
- GLK – GCK-like kinase.
- HPK1 – hematopoietic progenitor kinase 1.
- MST1 – mammalian Ste20-like protein kinase.
- NIK – Nck interacting kinase.
- Ste20 – Sterile 20. MKKKK in *S. cerevisiae* mating pathway.

## Scaffolding/anchoring proteins

- AKAP – A-kinase anchoring protein.
- IB1 – Islet-Brain 1.
- JIP-1 – JNK interacting protein-1.
- MP1 – MEK partner 1.
- PBS2 – A scaffolding protein for the yeast osmosensing response pathway (see above).
- RACK – receptor for activated C-kinase.
- Ste5 – Sterile 5. Scaffolding protein for *S. cerevisiae* mating pathway.