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PHARMACOLOGY 838801

CELL COMMUNICATION

MAP KINASE

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Mitogen:-is a chemical substance that encourages a cell to commence cell division, triggering mitosis. A mitogen is usually some form of a protein.

- **Signal transduction pathway** → MAPK → mitosis.
- Mitogens act primarily by influencing a set of proteins which are involved in the restriction of progression through the cell cycle.
- Only the G1 checkpoint is controlled most directly by mitogens:
- The point where mitogens are no longer needed to move the cell cycle forward is called the **"restriction point"** and depends on **cyclins** to be passed.

Ubiquitin:- is a small (8.5 kDa) regulatory protein found in most tissues of eukaryotic organisms.

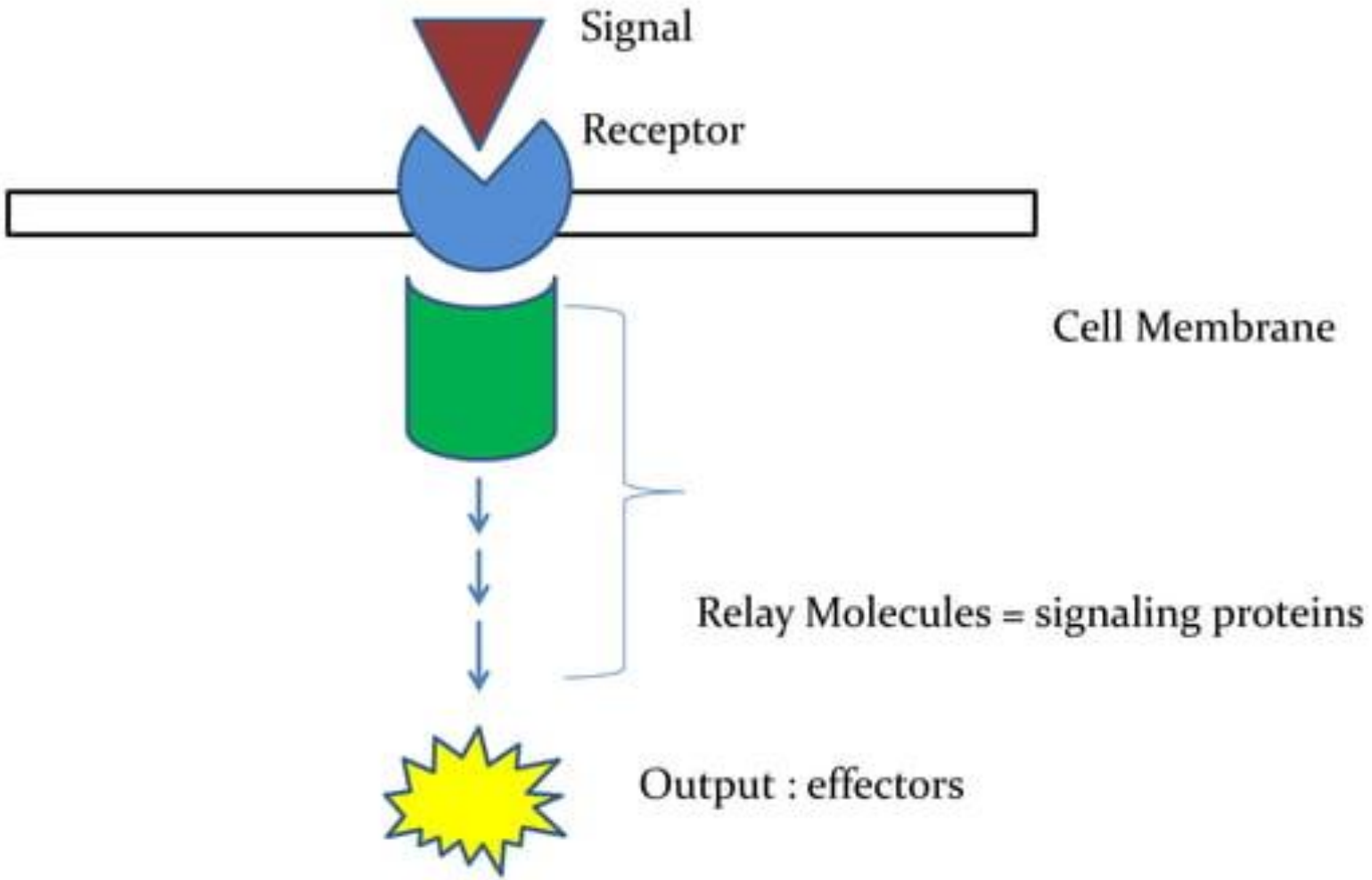
- The addition of ubiquitin to a substrate protein is called **ubiquitination** or less frequently **ubiquitylation**.

- Ubiquitination affects proteins in many ways: it can mark them for degradation via the **proteasome**, alter their cellular location, affect their activity, and promote or prevent protein interactions.

- **Kinase:-** is an enzyme that catalyzes phosphorylation reaction.

And kinase helps in inhibiting the ubiquitination.

Signaling: An overview



Slide adapted from NESI 2012

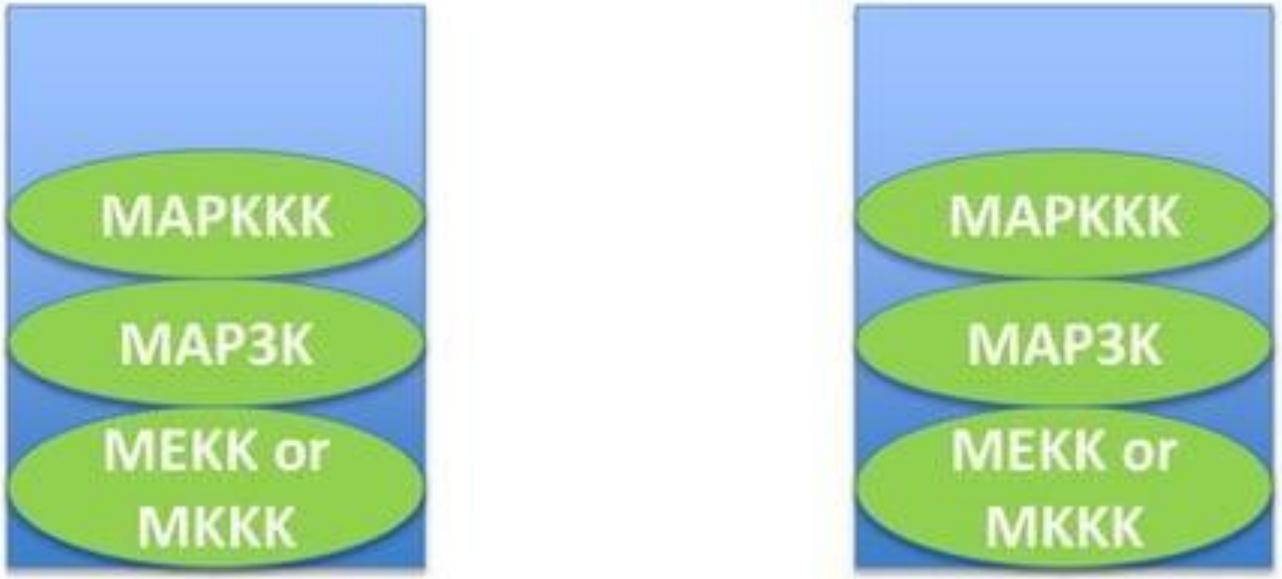
MAP kinases are intermediates in signal transduction pathways that are initiated by many types of surface receptors

The targets of MAPK are located within many cellular compartments

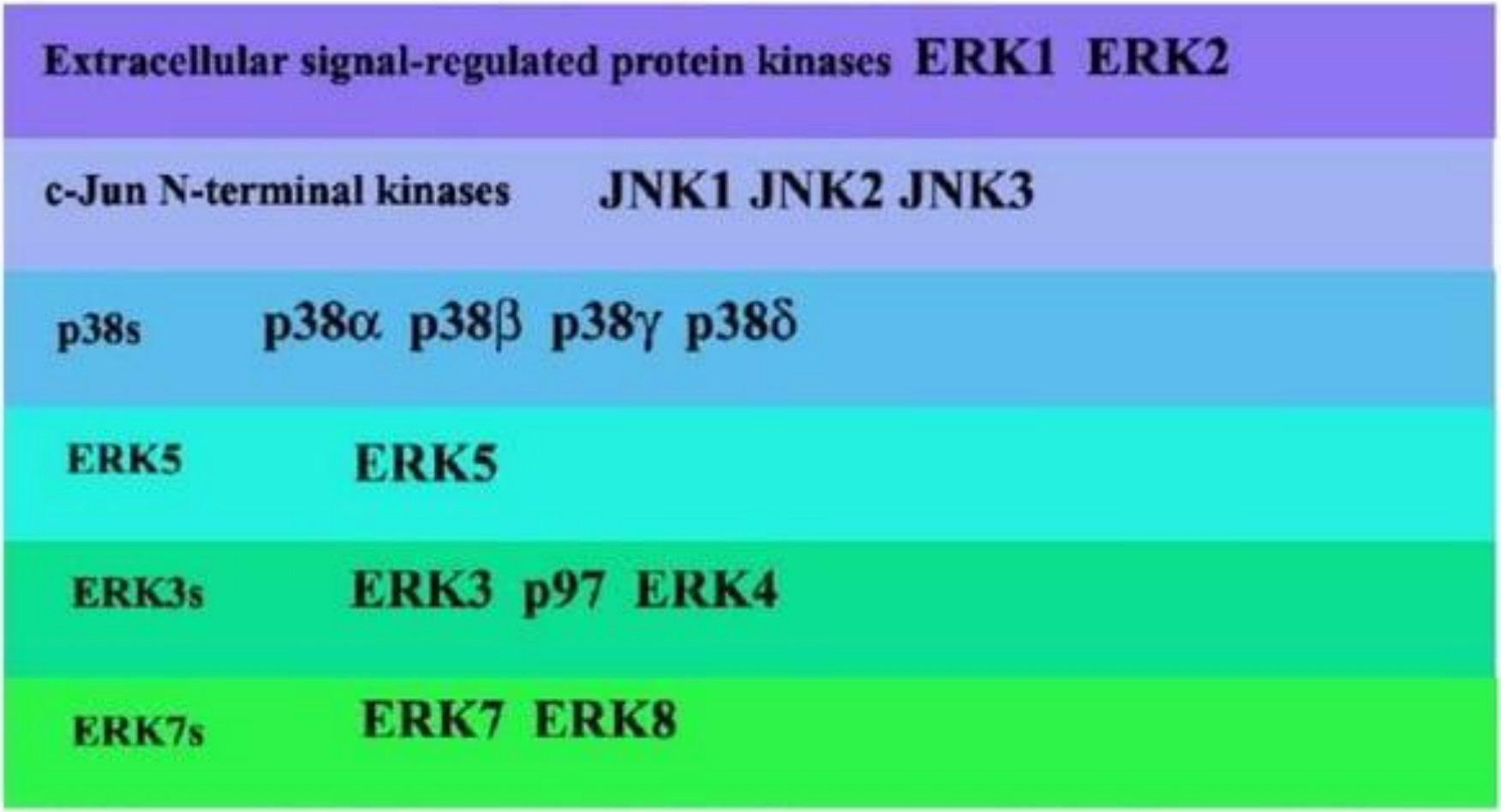
MAPK provide a physical link in the signal transduction pathway from the cytoplasm to the nucleus

Each MAPK pathway contains a three tiered kinase cascade comprising a MAP kinase kinase kinase (MAPKKK, MAP3K, MEKK or MKKK), a MAP kinase kinase (MAPKK, MAP2K, MEK or MKK) and the MAPK

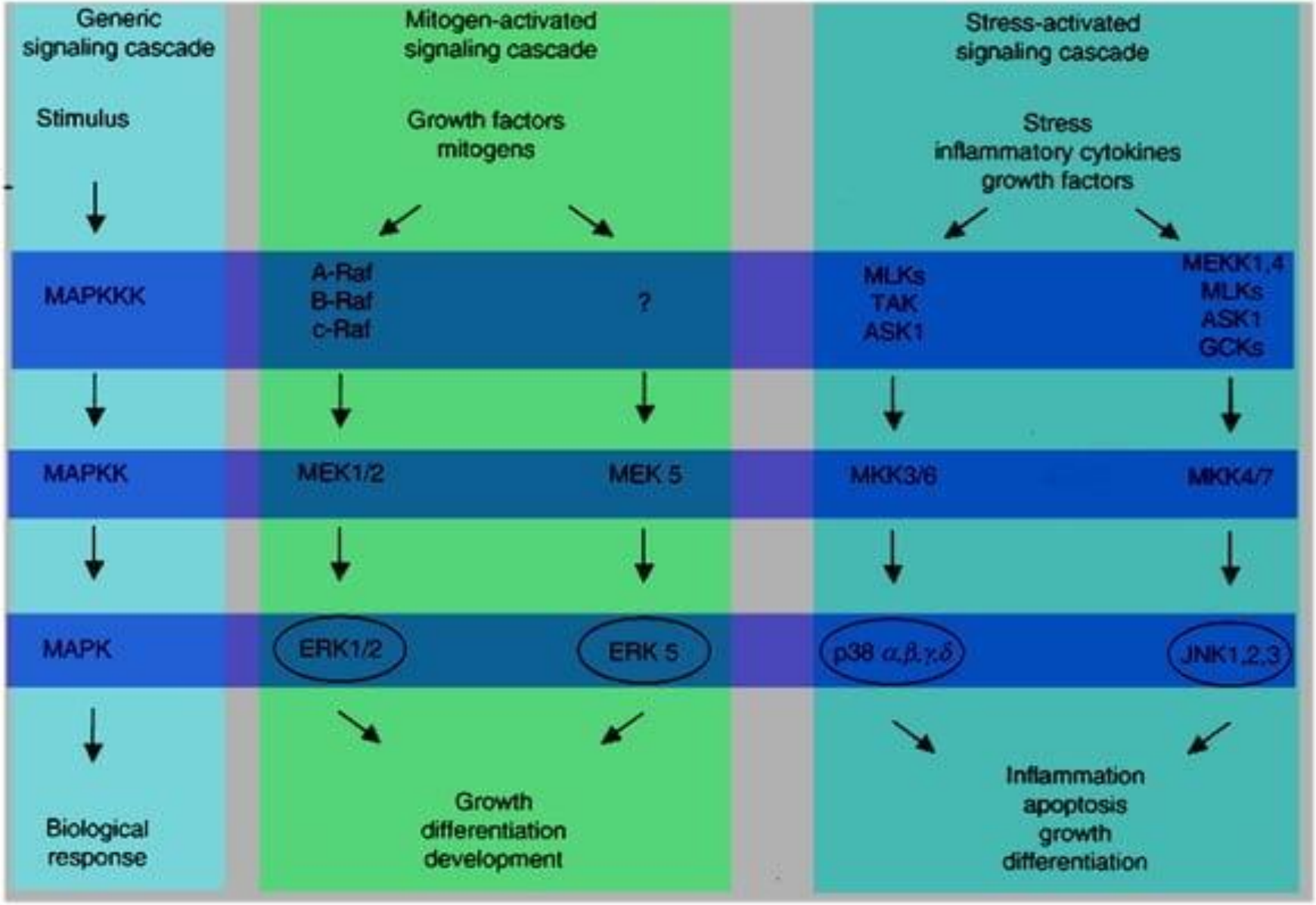
MAP kinase kinase kinase *or* MAP kinase kinase



In humans there are at least 11 members of the MAPK superfamily, which can be divided into 6 groups:



Each group of MAPK can be stimulated by a separate signal transduction pathway in response to different extracellular stimuli


Generic signaling cascade
Stimulus
Mitogen-activated signaling cascade
Growth factors mitogens
Stress-activated signaling cascade
Stress inflammatory cytokines growth factors
MAPKKK
A-Raf
B-Raf
c-Raf
?
MLKs
TAK
ASK1
MEKK1,4
MLKs
ASK1
GCKs
MAPKK
MEK1/2
MEK 5
MKK3/6
MKK4/7
MAPK
ERK1/2
ERK 5
p38 α,β,γ,δ
JNK1,2,3
Biological response
Growth differentiation development
Inflammation apoptosis growth differentiation

ERK1 ERK2

In certain cells their activation contributes to normal and abberant growth, in other cells they promote cell survival or initiate differentiation in others.

Their enzymatic activity is enhanced by dual phosphorylation on Thr and Tyr, by a group of dual-specificity protein kinases (MAPKK) represented by MEK1 and MEK2.

ERK activity is terminated by dephosphorylation on either Thr or Tyr by a Ser/Thr or Tyr phosphatase.

MEK1 and MEK2 are activated by phosphorylation mediated by MAPKKK, that include A-Raf, B-Raf, c-Raf-1.

The Raf group is activated by small G-protein Ras.

JNK1 JNK2 JNK3

JNK was discovered by its ability ti phosphorylate the N-terminal transactivating domain of the transcription factor c-Jun. Its activity was stimulated primarily by cellular stress.

The kinase cascade is initiated by the Rho family of GTPases, Rac1 and Cdc42.

MAPKKK include MEK1, MEK2, MEK3, MEK4, apoptosis-stimulated kinase 1 (ASK1), and germinal center kinase (GCK).

MAPKK comprise MKK4 and MKK7.

Substrates for JNK includes transcription factors of c-Jun family as well as several other transcription factors.

p38s

These MAPKs are stimulated by environmental stresses, they are particularly sensitive to their stimulation by exposure of the cells to endotoxins.

They are activated by dual phosphorylation on Thr and Tyr by MKK3 and MKK6.

MAPKKK are not well defined, include ASK1 and TAK1.

The specific transcription factors regulated by these MAPKs include cAMP- responsive element-binding protein (CREB) and several others. In addition, these MAPKs can also trigger the activation of other serine-threonine kinases.

ERK5

It is also known as big mitogen-activated protein kinase, being larger than any other known MAPK (80 kDa).

It is selectively activated by MEK5 but not by MEK1 or MEK2.

It can be activated by oxidative stress, and can play a role in early gene expression triggered by EGF.

This MAPK cooperates with the activated Raf or MEK, which act on ERK1 and ERK2, to promote neoplastic transformation.

The physiological role of ERK5 is unclear.

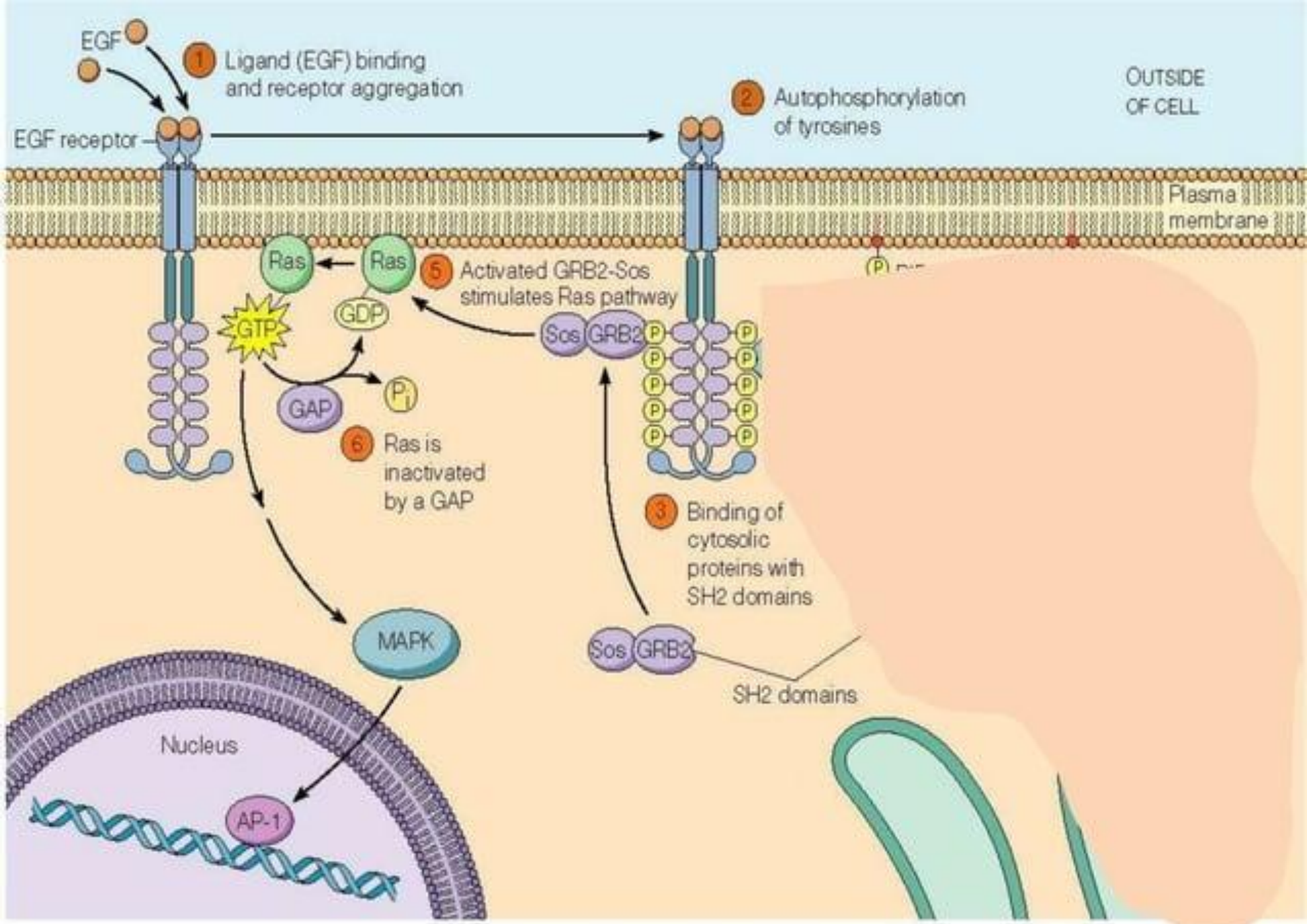
ERK3s

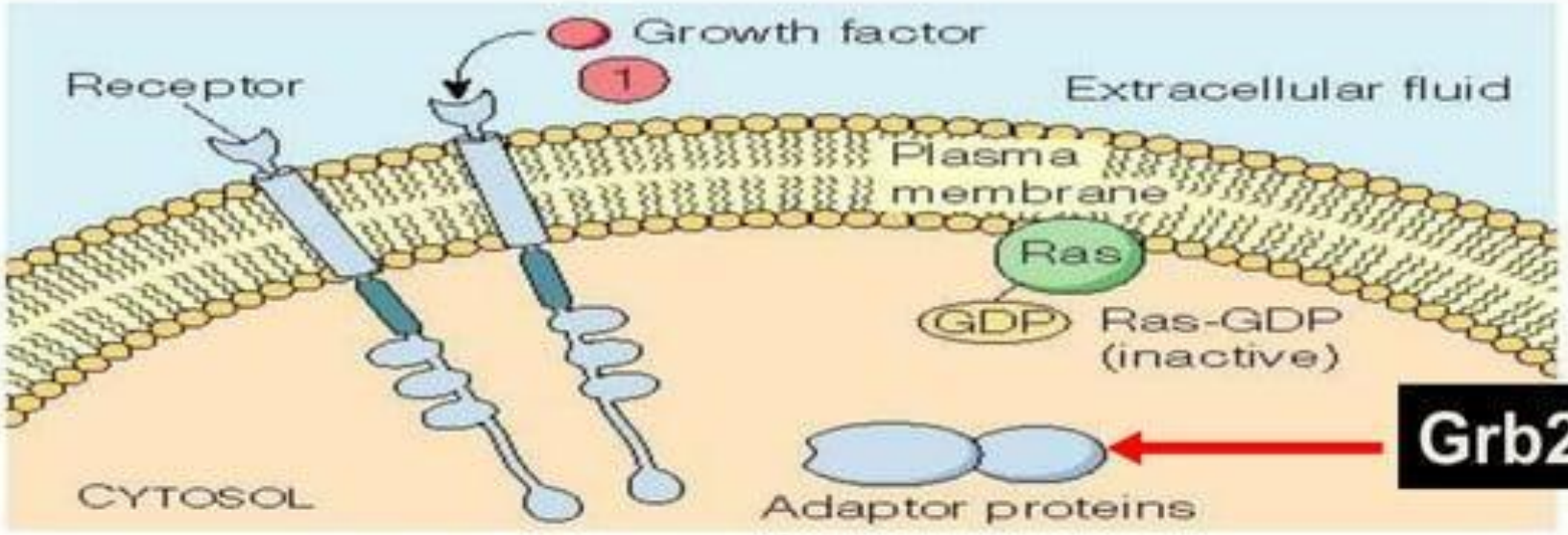
The ERK3 subfamily of MAPKs is composed of two functional genes and several pseudogenes.

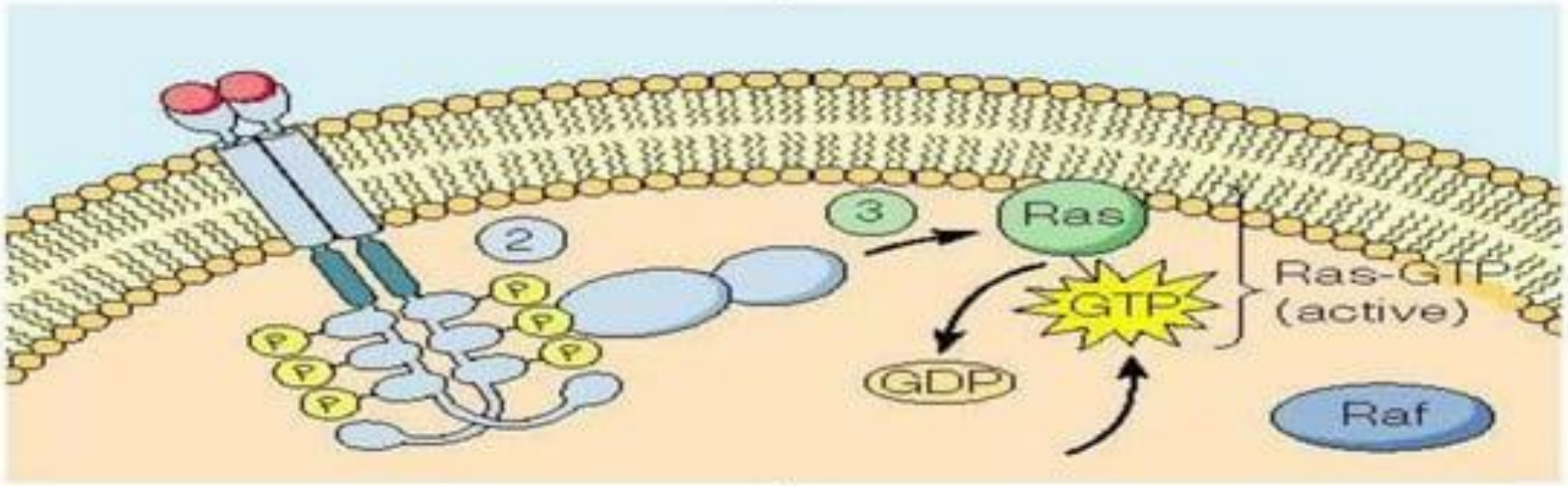
Upstream activators of ERK3 are poorly defined, and this kinase is not present in yeast or C. elegans.

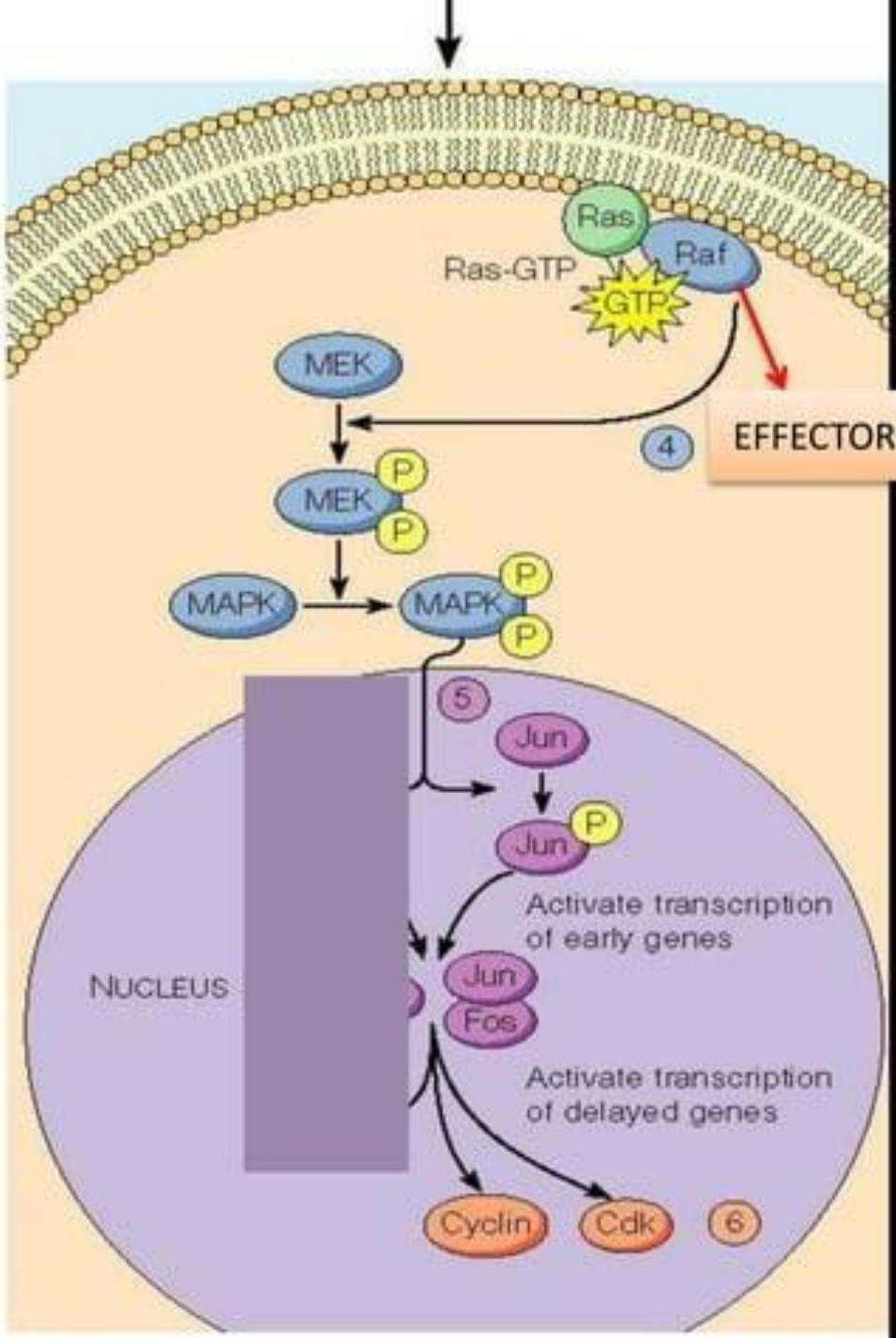
None of the currently known MEK family members is able to phosphorylate and activate ERK3 and no physiological substrate of ERK3 has been found.

ERK3 is localized constitutively to the nucleus.



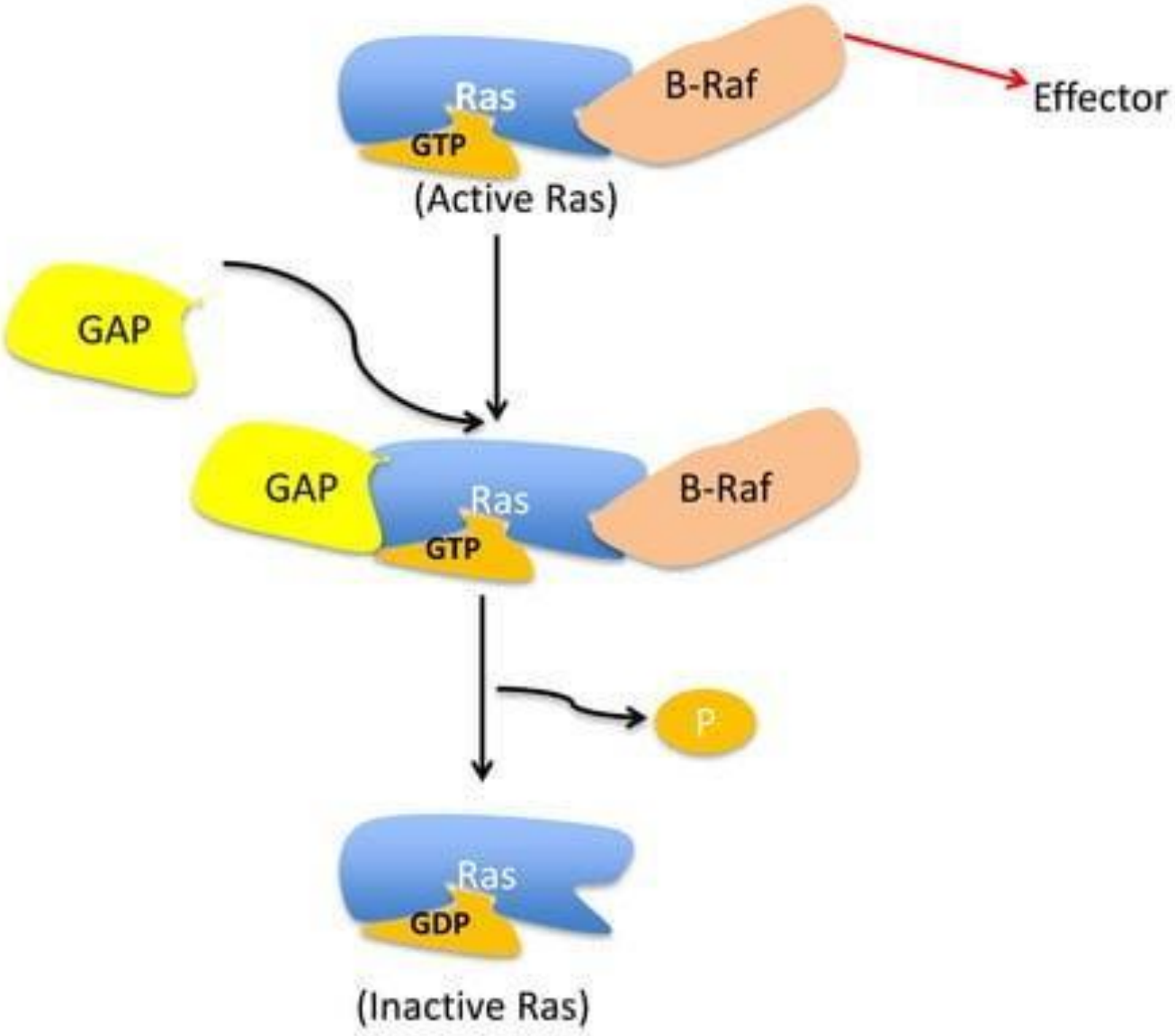

Growth factor
1
Receptor
Extracellular fluid
Plasma membrane
Ras
GDP
Ras-GDP (inactive)
Grb2, Sos
CYTOSOL
Adaptor proteins


2
3
Ras
GTP
Ras-GTP (active)
GDP
Raf



This is a kinase cascade: Raf turns on MEK by putting phosphates on it, MEK turns on map kinase by putting phosphates on it (end of kinase cascade). Once on, map kinase puts phosphates on transcription factors like Jun, which combine to form AP-1, this turns on AP-1. AP-1 turns on genes for cell division (cyclin, cdk, etc)

Inactivation of Ras :-



In cancerous cell :

STEP 1. There is a mutation in the Ras protien 

STEP 2. 

bind to 

But, does not interact with 

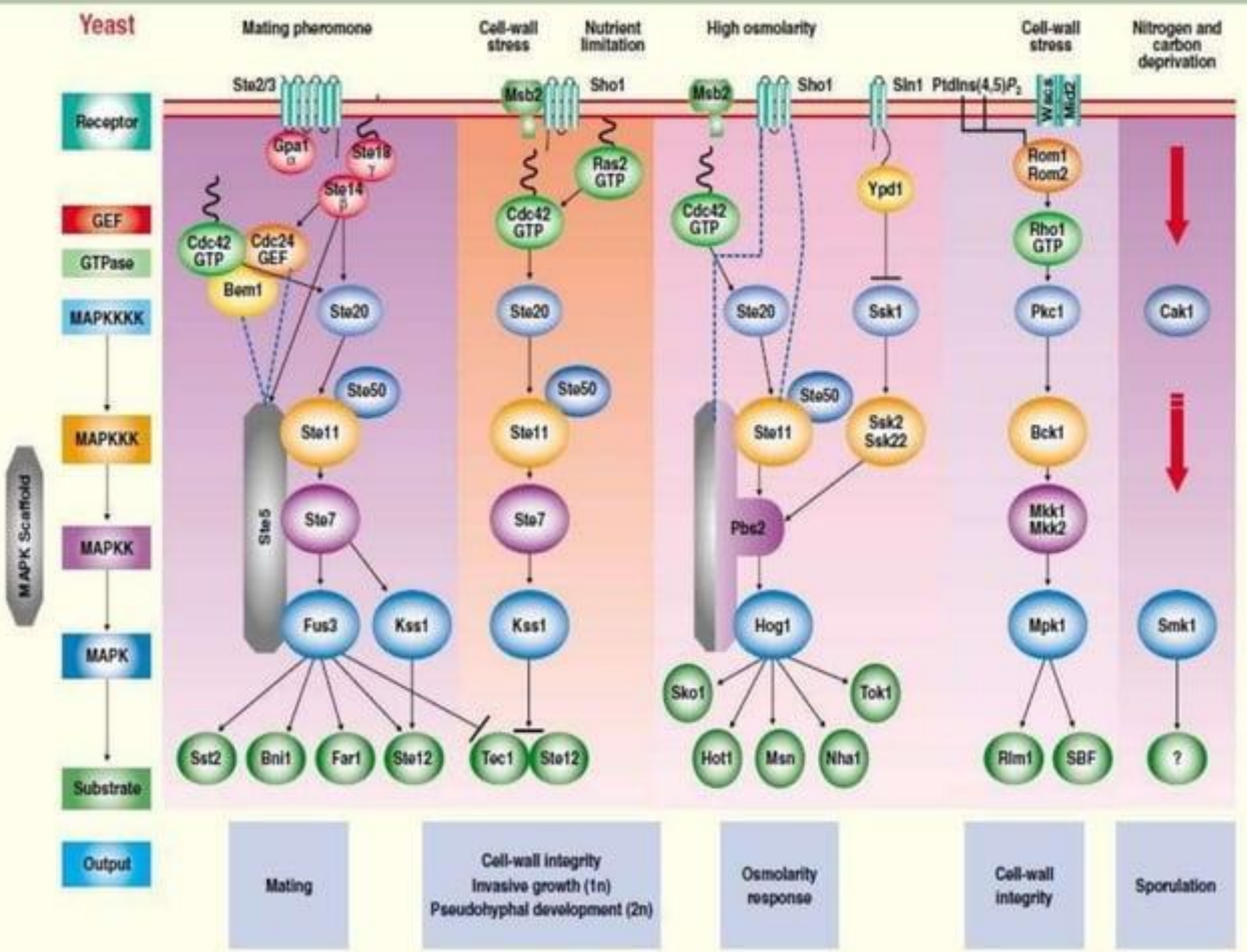
STEP 3. So, 

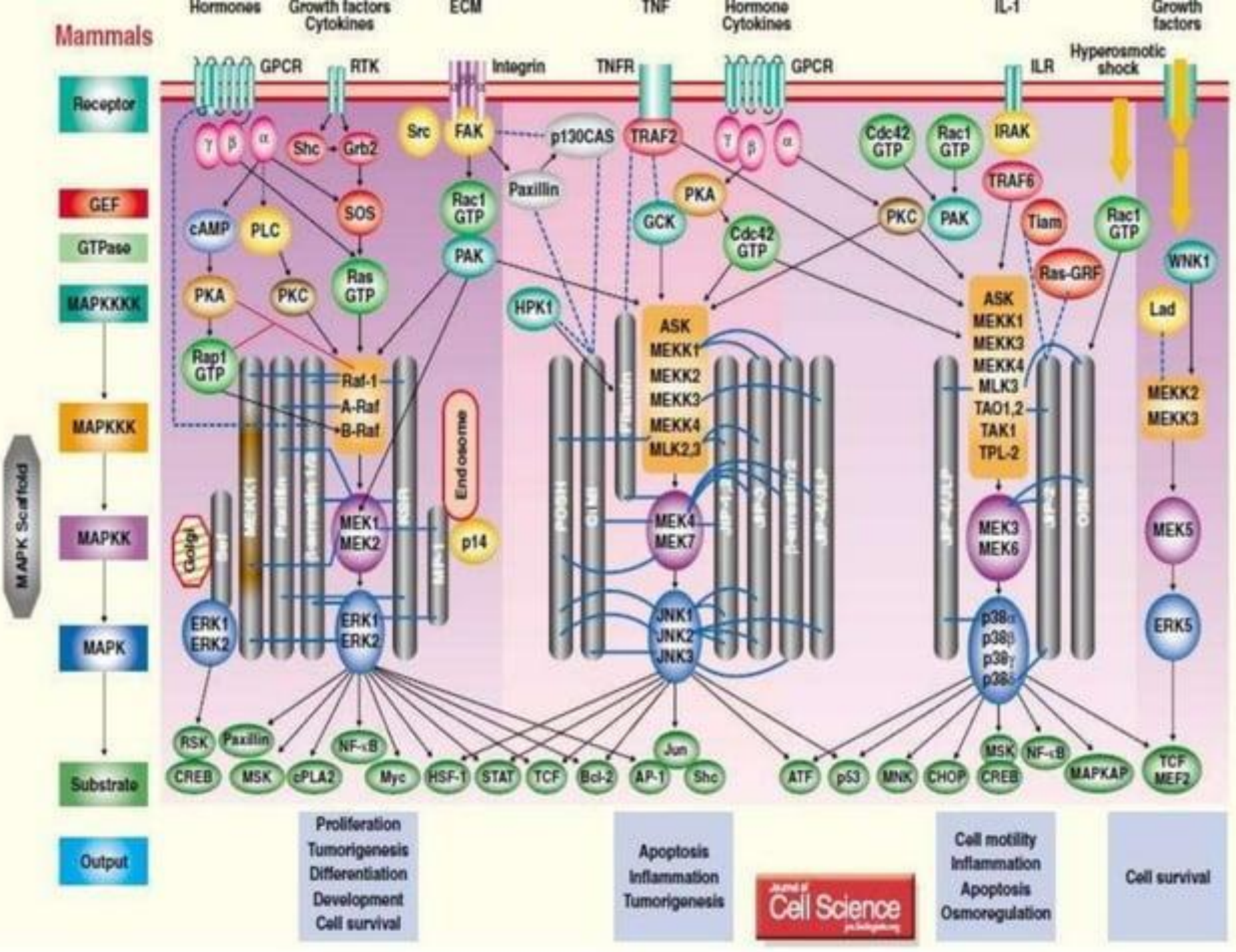
does not loose the 

and resulting 

to active

for all the time.


Yeast
Mating pheromone
Cell-wall stress
Nutrient limitation
High osmolarity
Cell-wall stress
Nitrogen and carbon deprivation
Receptor
GEF
GTPase
MAPKKKK
MAPKKK
MAPKK
MAPK
Substrate
Output
MAPK Scaffold
Ste2/3
Gpa1
Ste18
Ste14
Msb2
Sho1
Ras2 GTP
Cdc42 GTP
Cdc24 GEF
Bem1
Ste20
Ste50
Ste11
Ste5
Ste7
Fus3
Kss1
Sst2
Bni1
Far1
Ste12
Tec1
Sln1
PtdIns(4,5)P2
Wsc1
Mid2
Ypd1
Ssk1
Ssk2 Ssk22
Pbs2
Hog1
Sko1
Tok1
Hot1
Msn
Nha1
Rom1 Rom2
Rho1 GTP
Pkc1
Bck1
Mkk1 Mkk2
Mpk1
Rlm1
SBF
Cak1
Smk1
?
Mating
Cell-wall integrity
Invasive growth (1n)
Pseudohyphal development (2n)
Osmolarity response
Cell-wall integrity
Sporulation


Mammals
Hormones
Growth factors
Cytokines
ECM
TNF
Hormone
Cytokines
IL-1
Growth
factors
Receptor
GEF
GTPase
MAPKKK
MAPKKK
MAPKK
MAPK
Substrate
Output
MAPK Scaffold
GPCR
RTK
Integrin
TNFR
GPCR
ILR
Hyperosmotic
shock
Src
FAK
p130CAS
TRAF2
Cdc42
GTP
Rac1
GTP
IRAK
Shc
Grb2
Paxillin
PKA
TRAF6
SOS
Rac1
GTP
GCK
PKC
PAK
Tiam
Rac1
GTP
cAMP
PLC
Cdc42
GTP
Ras-GRF
WNK1
PKA
PKC
Ras
GTP
PAK
HPK1
ASK
MEKK1
MEKK3
MEKK4
MLK3
TAO1,2
TAK1
TPL-2
Lad
Rap1
GTP
Raf-1
A-Raf
B-Raf
ASK
MEKK1
MEKK2
MEKK3
MEKK4
MLK2,3
MEKK2
MEKK3
End osome
Golgi
MEK1
MEK2
p14
MEK4
MEK7
MEK3
MEK6
MEK5
ERK1
ERK2
ERK1
ERK2
JNK1
JNK2
JNK3
p38α
p38β
p38γ
p38δ
ERK5
RSK
Paxillin
NF-κB
Jun
MSK
NF-κB
CREB
MSK
cPLA2
Myc
HSF-1
STAT
TCF
Bcl-2
AP-1
Shc
ATF
p53
MNK
CHOP
CREB
MAPKAP
TCF
MEF2
Proliferation
Tumorigenesis
Differentiation
Development
Cell survival
Apoptosis
Inflammation
Tumorigenesis
Cell motility
Inflammation
Apoptosis
Osmoregulation
Cell survival
Journal of Cell Science

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https://en.wikipedia.org/wiki/Mitogen

https://en.wikipedia.org/wiki/Ubiquitin

https://en.wikipedia.org/wiki/Kinase

ANY DOUBT


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Thank you