

MITOGENE ACTIVATED PROTEIN KINASE (MAPK) PATHWAY

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 pathways**  **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**.

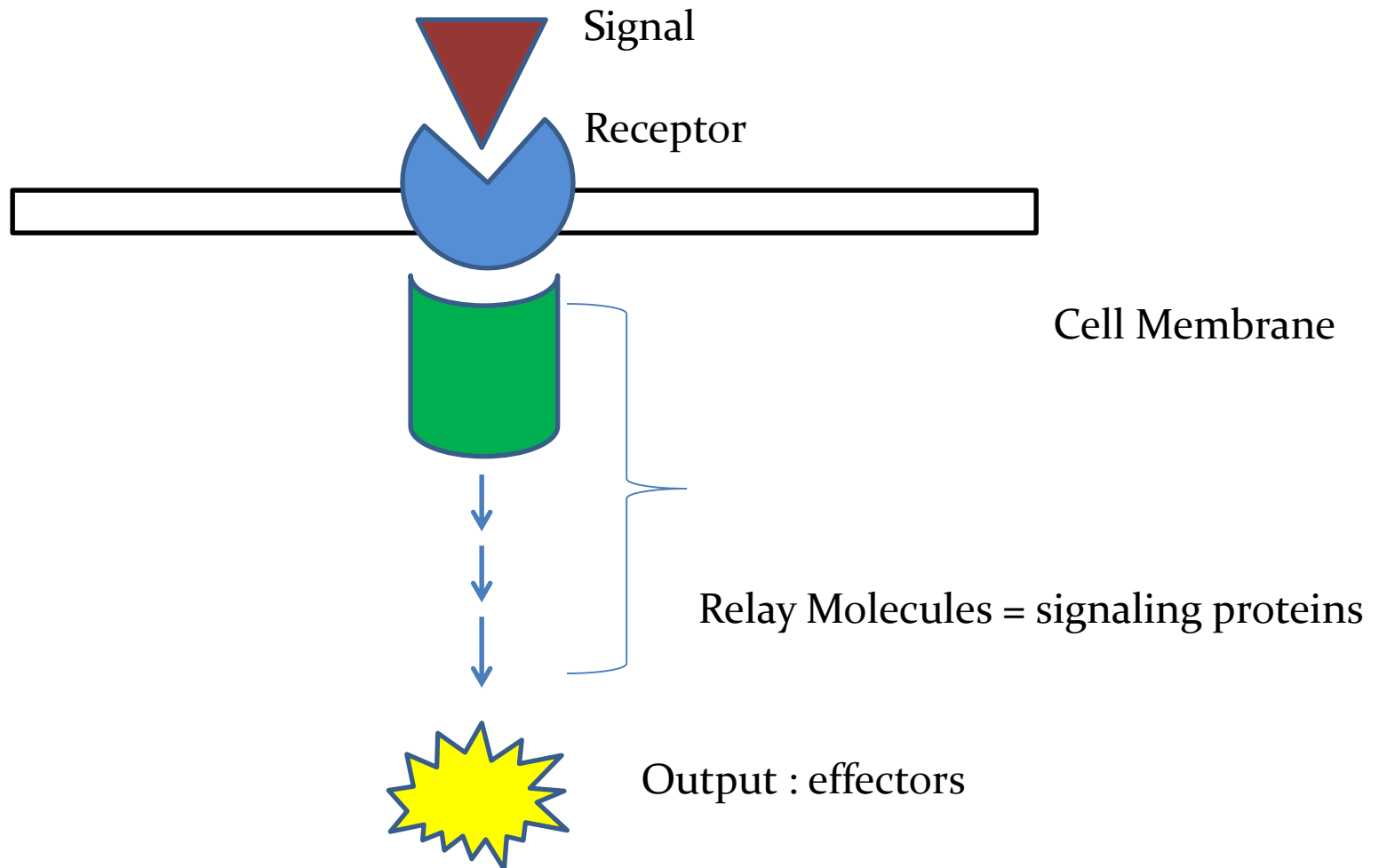
❖ The addition of ubiquitin to a substrate protein is called **ubiquitination** or less frequently **ubiquitylation**.

❖ 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



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

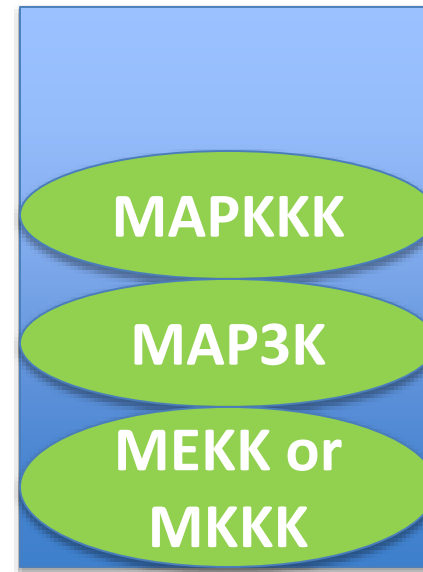
MAPK provide a physical link in the signal transduction pathway from the cytoplasm to the nucleus

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:

Extracellular signal-regulated protein kinases ERK1 ERK2

c-Jun N-terminal kinases JNK1 JNK2 JNK3

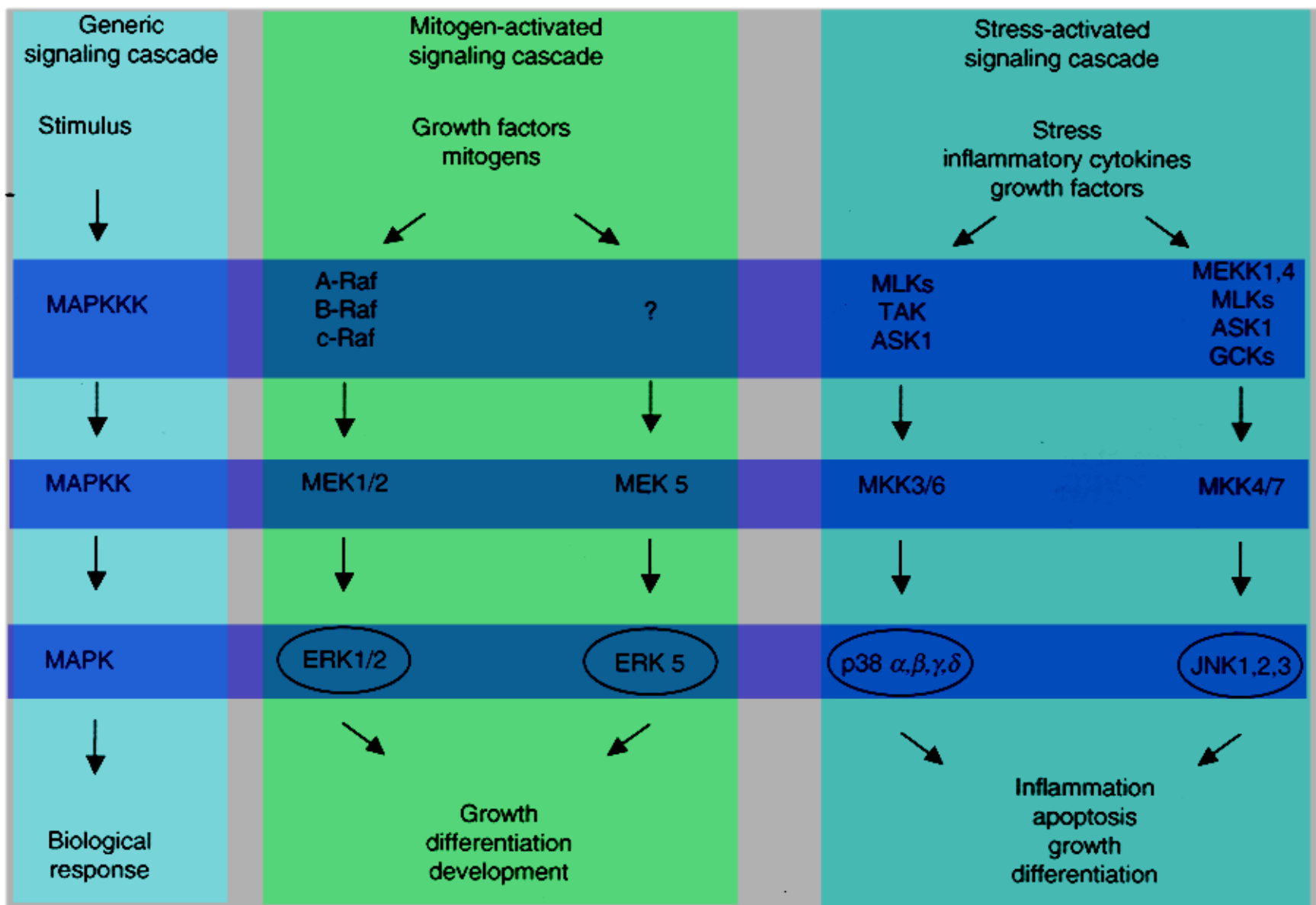
p38s p38 α p38 β p38 γ p38 δ

ERK5 ERK5

ERK3s ERK3 p97 ERK4

ERK7s ERK7 ERK8

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



ERK1 ERK2

In certain cells their activation contributes to normal and aberrant 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 to 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.

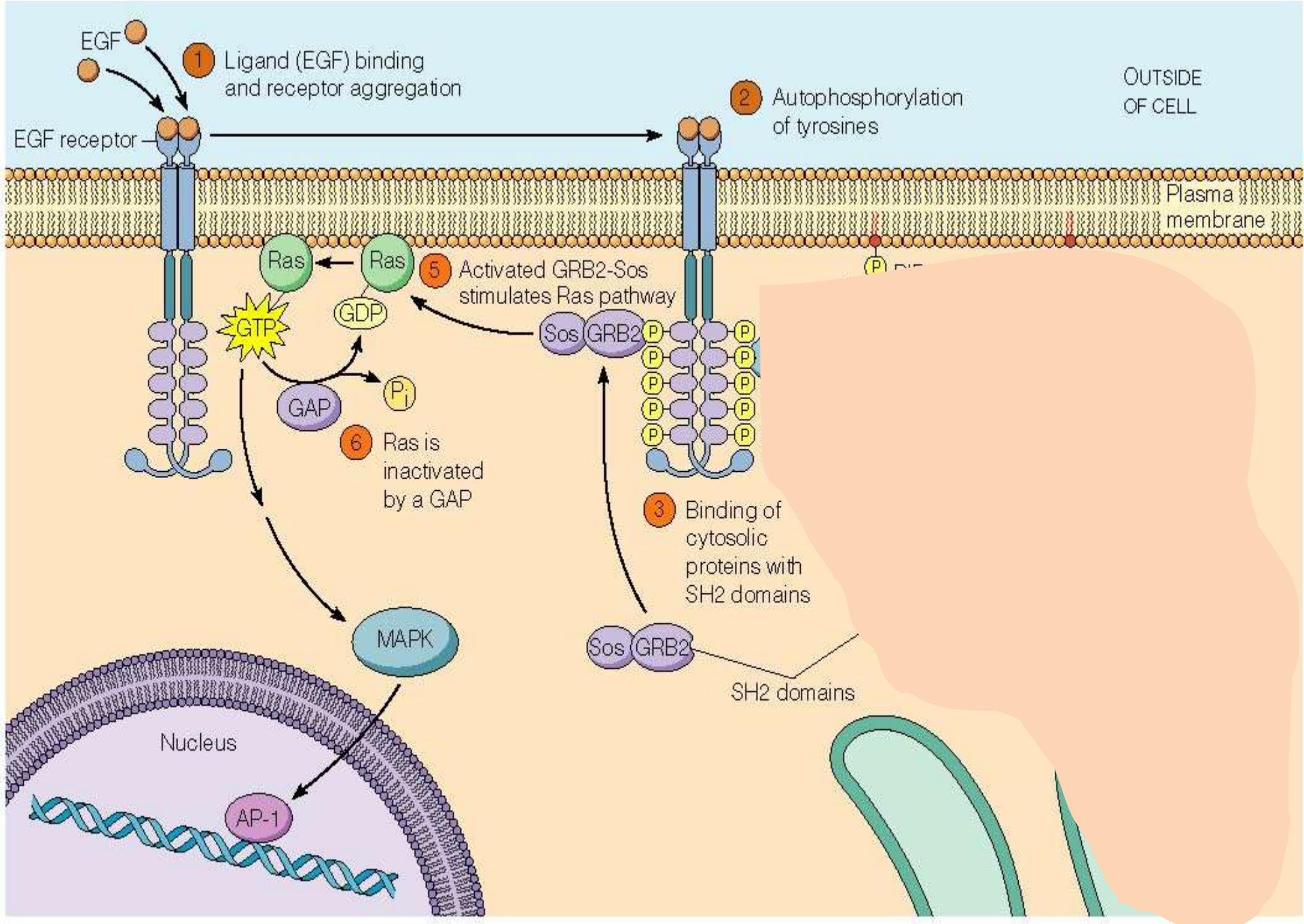
ERK3s

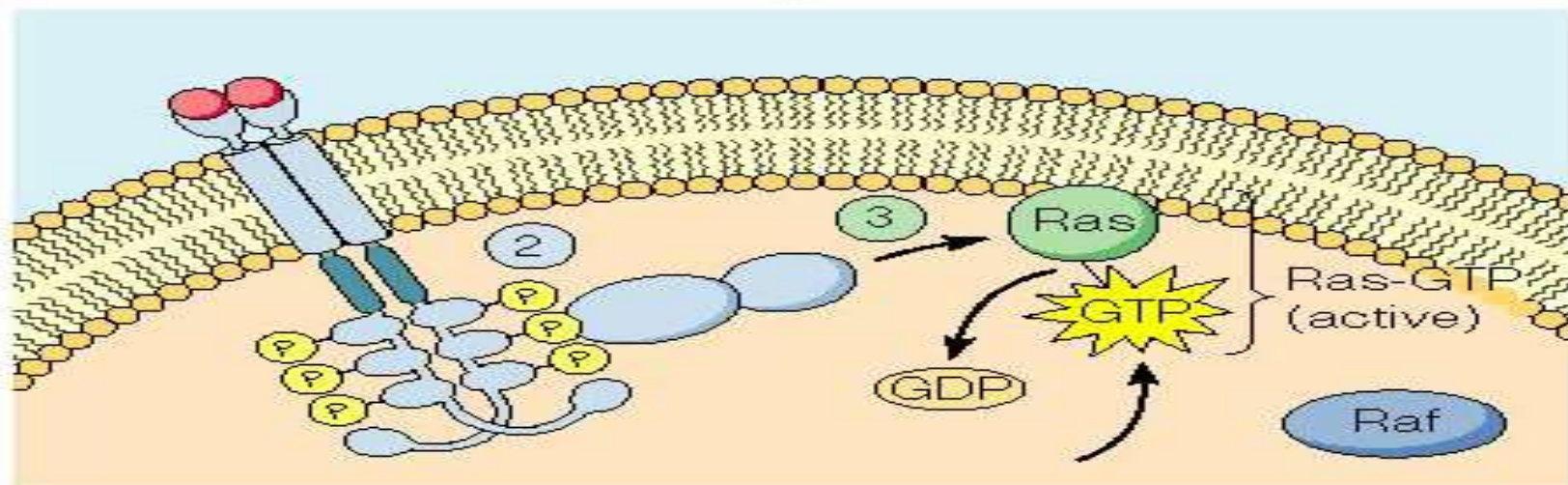
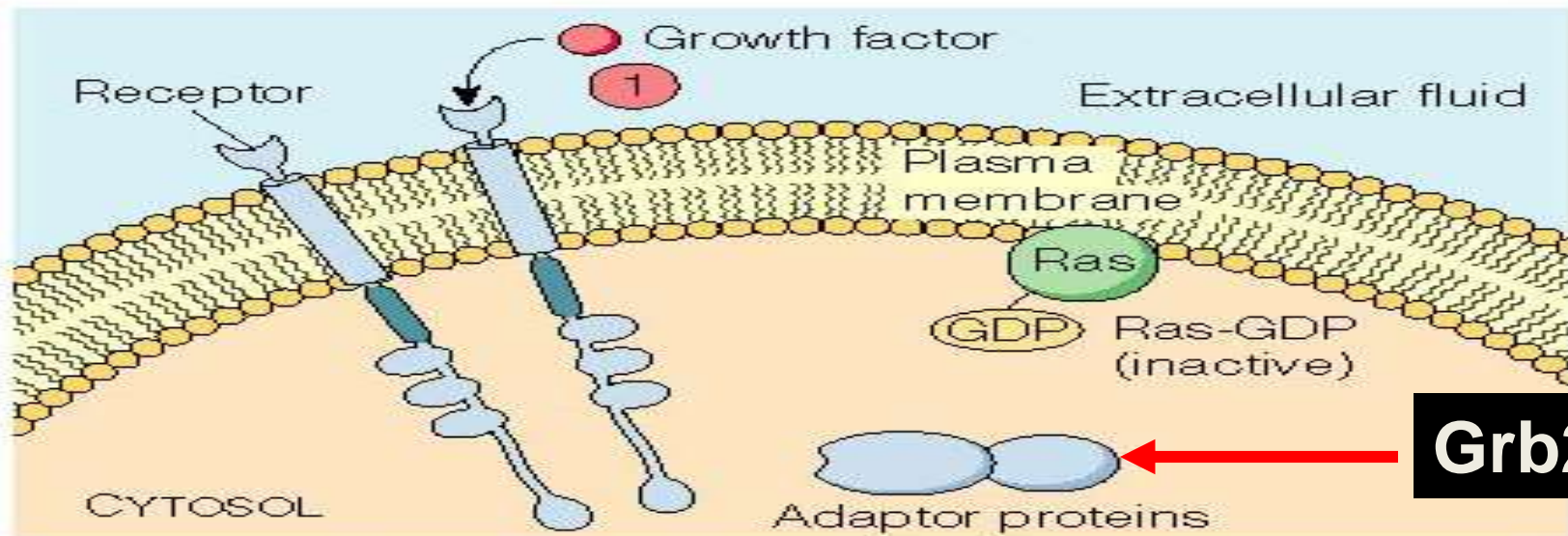
The ERK3 subfamily of MAPKs is composed of two functional genes and several pseudogenes.

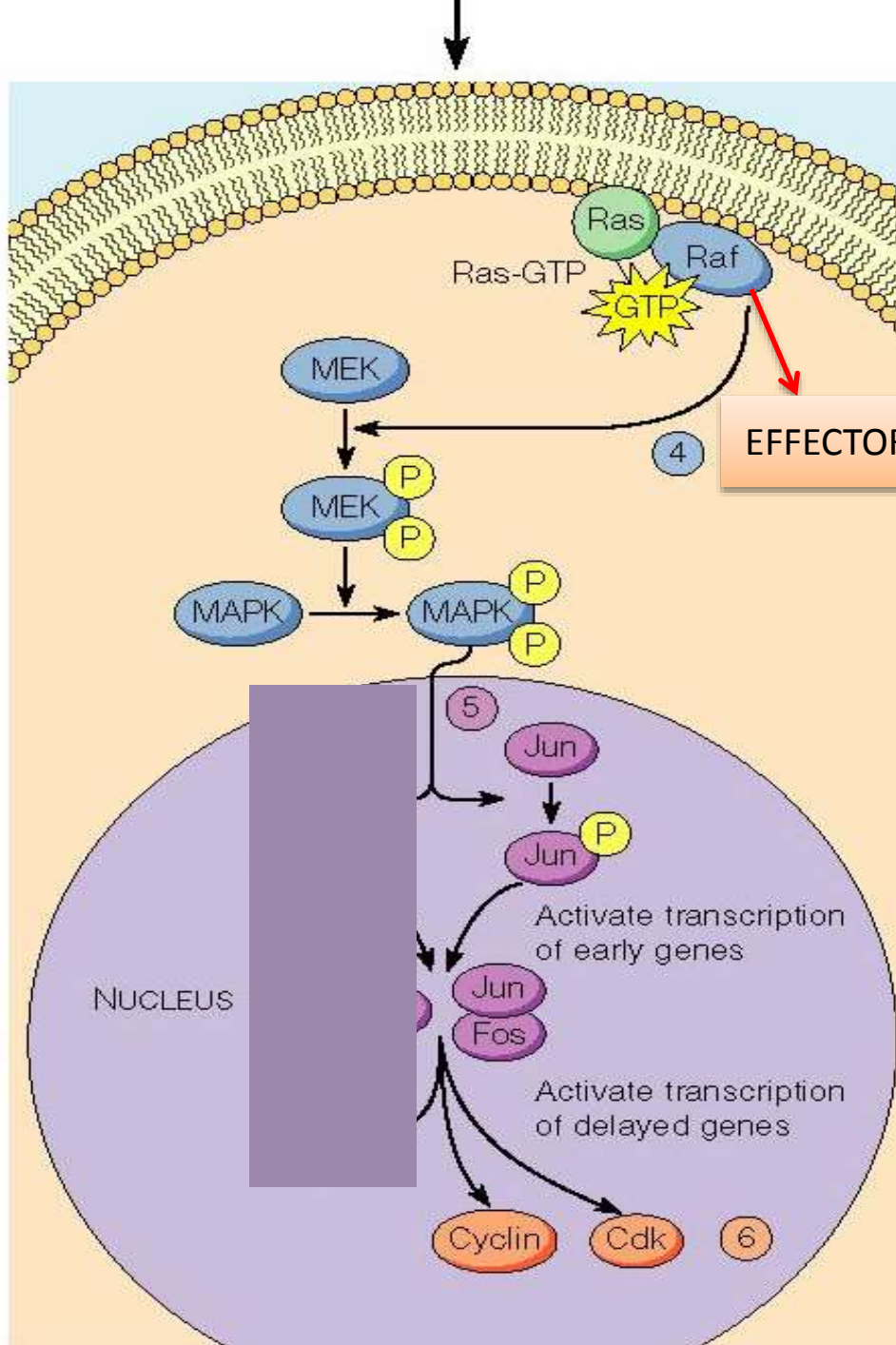
Upstream activators of ERK3 are poorly defined, and this kinase is not present in yeast or *C. elegans*.

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.

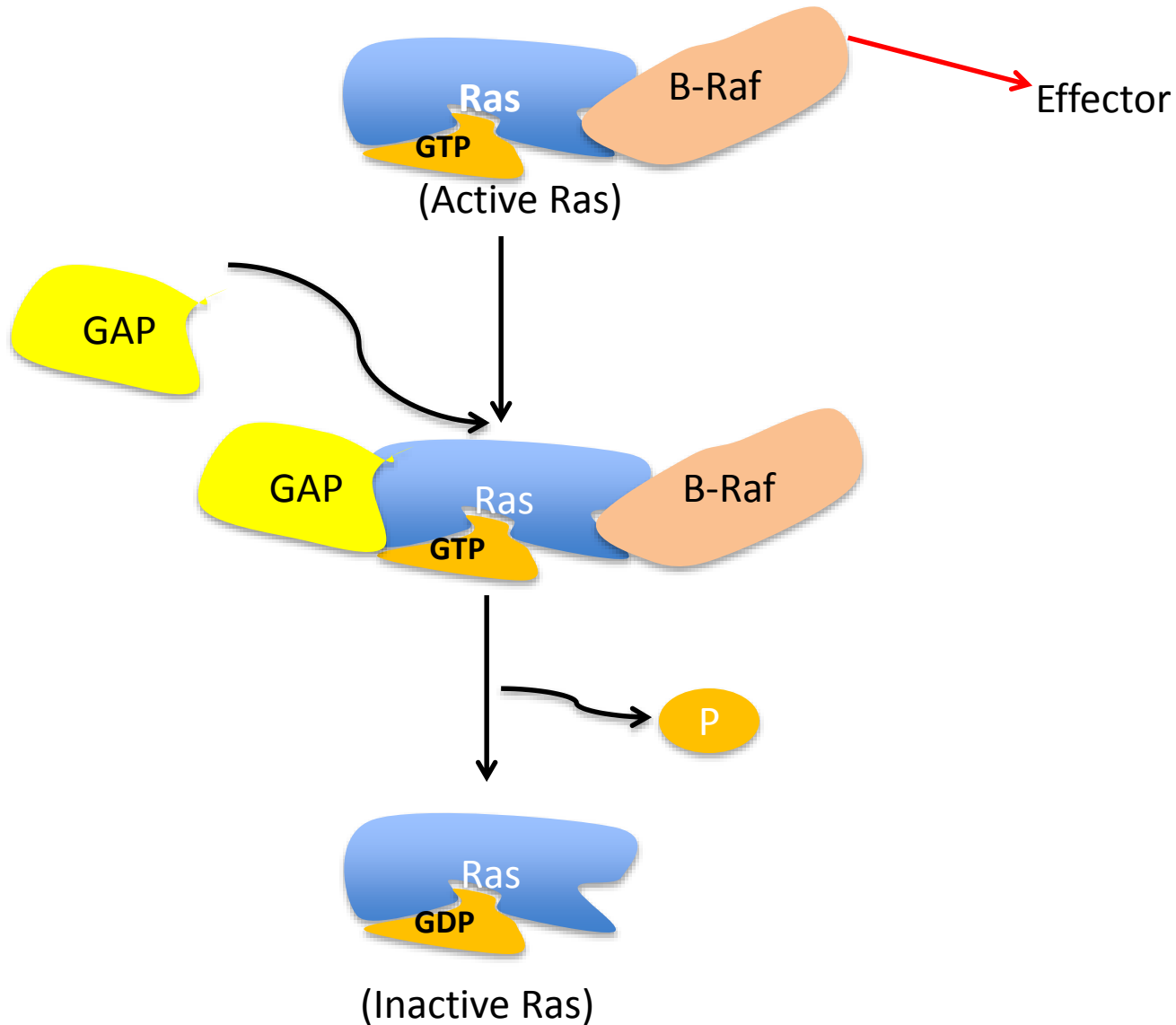






This is a kinase cascade: Raf turns on MEK by putting phosphates on it, MEK turns on map kinase by putting phosphates on it (end of kinase cascade). Once on, map kinase puts phosphates on transcription factors like Jun, which combine to form AP-1, this turns on AP-1. AP-1 turns on genes for cell division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

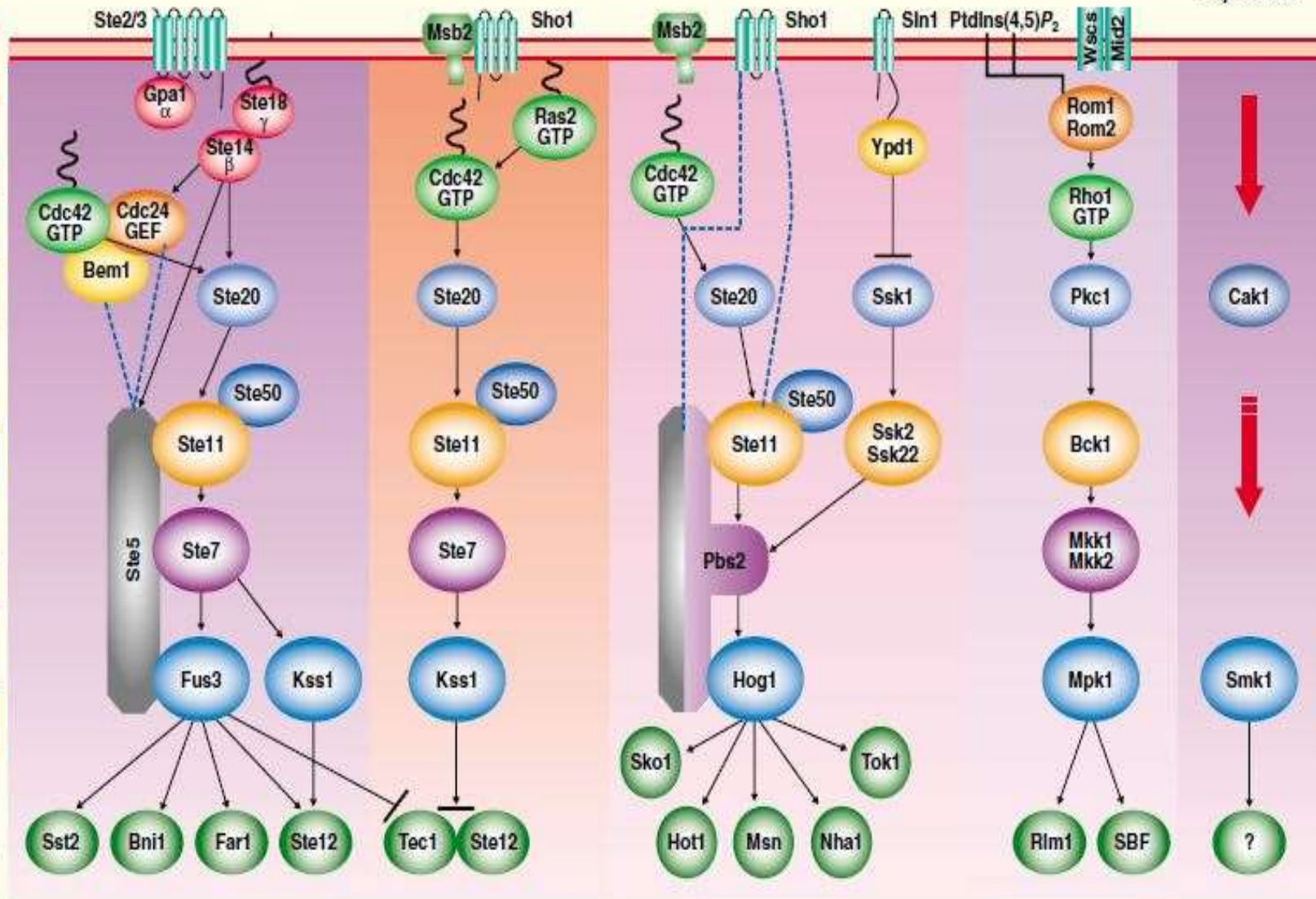
MAPKK

MAPK

Substrate

MAPK Scaffold

Output



Mating

Cell-wall integrity
Invasive growth (1n)
Pseudohyphal development (2n)

Osmolarity
response

Cell-wall
integrity

Sporulation

Mammals

