Centrum pro výzkum toxických látek v prostředí

BIOMARKERS AND TOXICITY MECHANISMS

08 –Toxicity mechanisms at cell level

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Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.

EVROPSKÁ UNIE esf

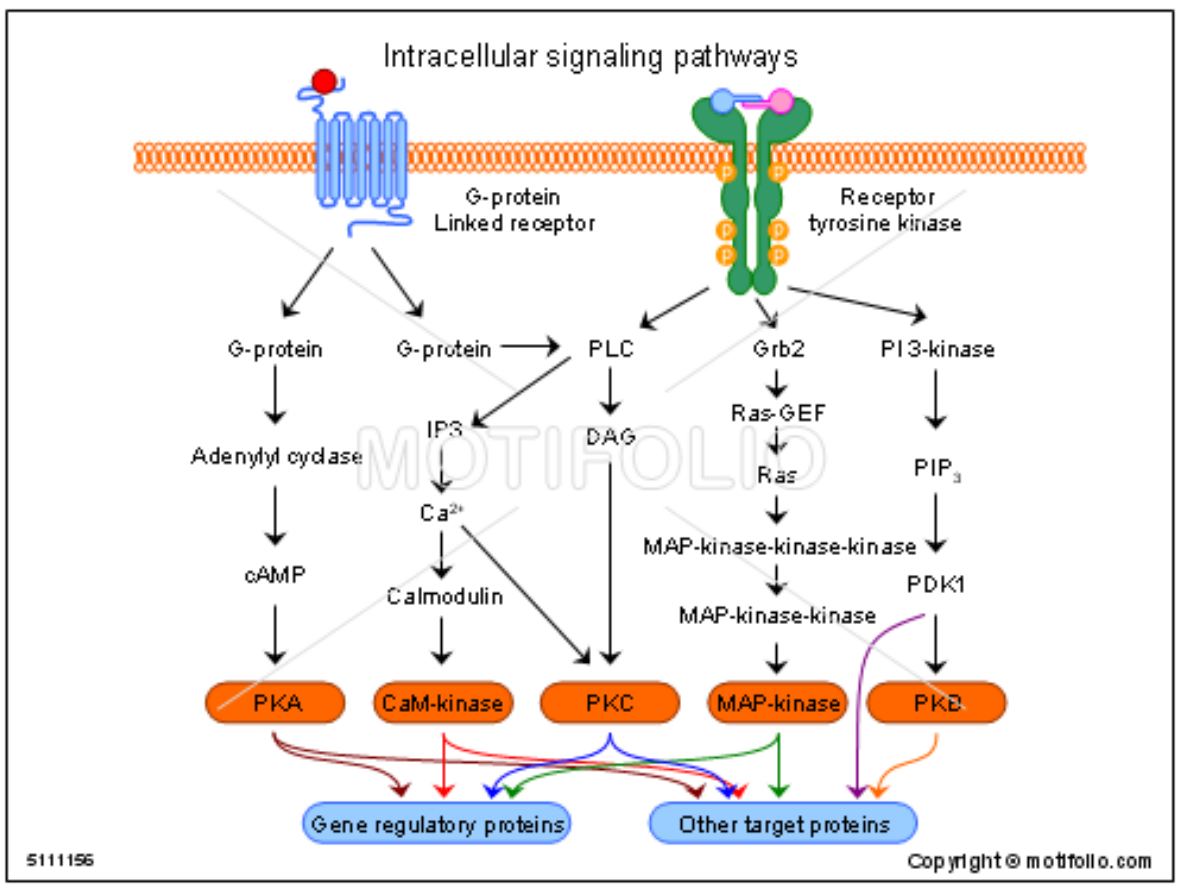
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

OP Vzdělávání pro konkurenceschopnost

UNIVERSITAS MASARYKIANA BRUNENSIS

INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

INTRACELLULAR signals as target to toxicants



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Intracellular signal transduction: target of toxicants

- **Regulation controlled by complex signalling**
  - "network" of general pathways
  - similar in all cells / different cell-specific effects

- **Consequences of signalling disruption**
  - unwanted changes in „homeostatic“ rates among proliferation / differentiation / apoptosis

  → cell transformation (carcinogenicity)
  → embryotoxicity
  → immunotoxicity
  → reproduction toxicity

  .... and other chronic types of toxicity

Signal transduction - principles

Two major intracellular signalling processes

– **protein-(de)phosphorylation**

ProteinKinases - PKs, ProteinPhosphatases - PPases

- **secondary messengers**

cAMP / IP3, PIP2, DAG, Ca2+, AA

Three major types of signalling

1: Membrane receptors - G-proteins / kinases

→ activation of protein kinase A (PKA):
major messenger: cAMP

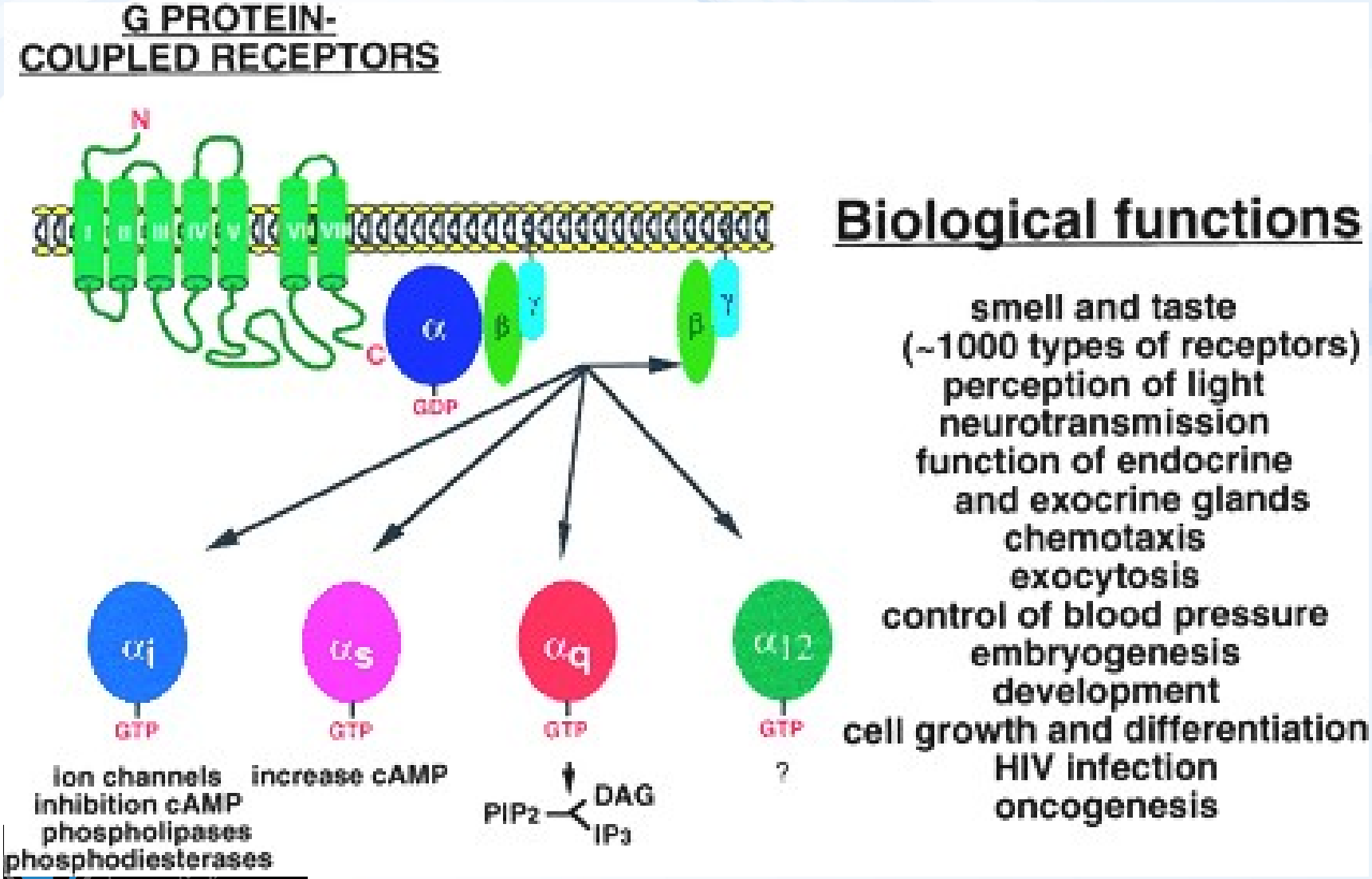
2: Membrane receptors

→ activation of membrane lipases → and later proteinkinase C
IP3, PIP2, DAG, Ca2+, AA

3: **Cytoplasmic (nuclear) receptors** (discussed in detail in other sections)

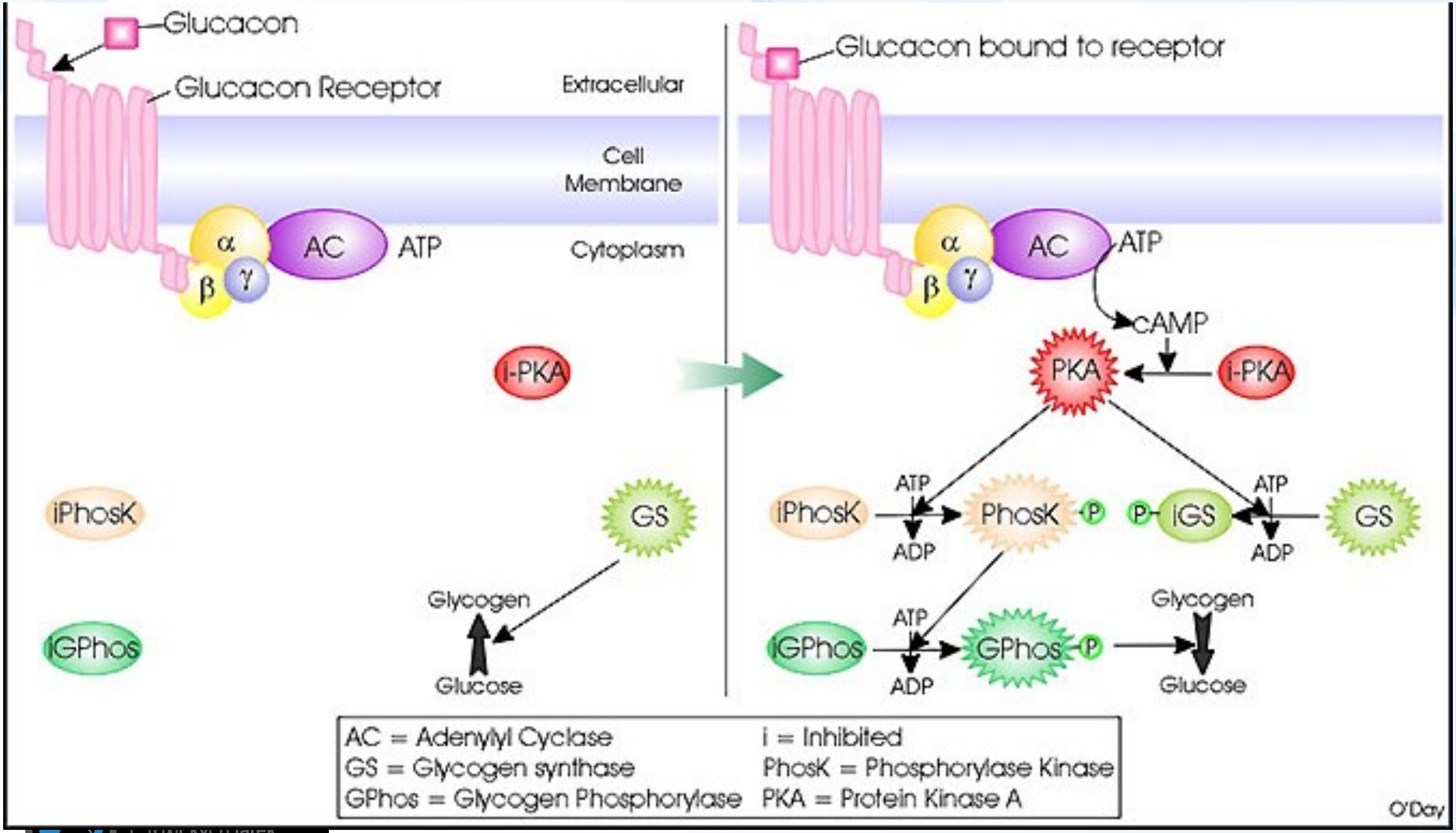
Membrane receptors acting as ProteinKinases

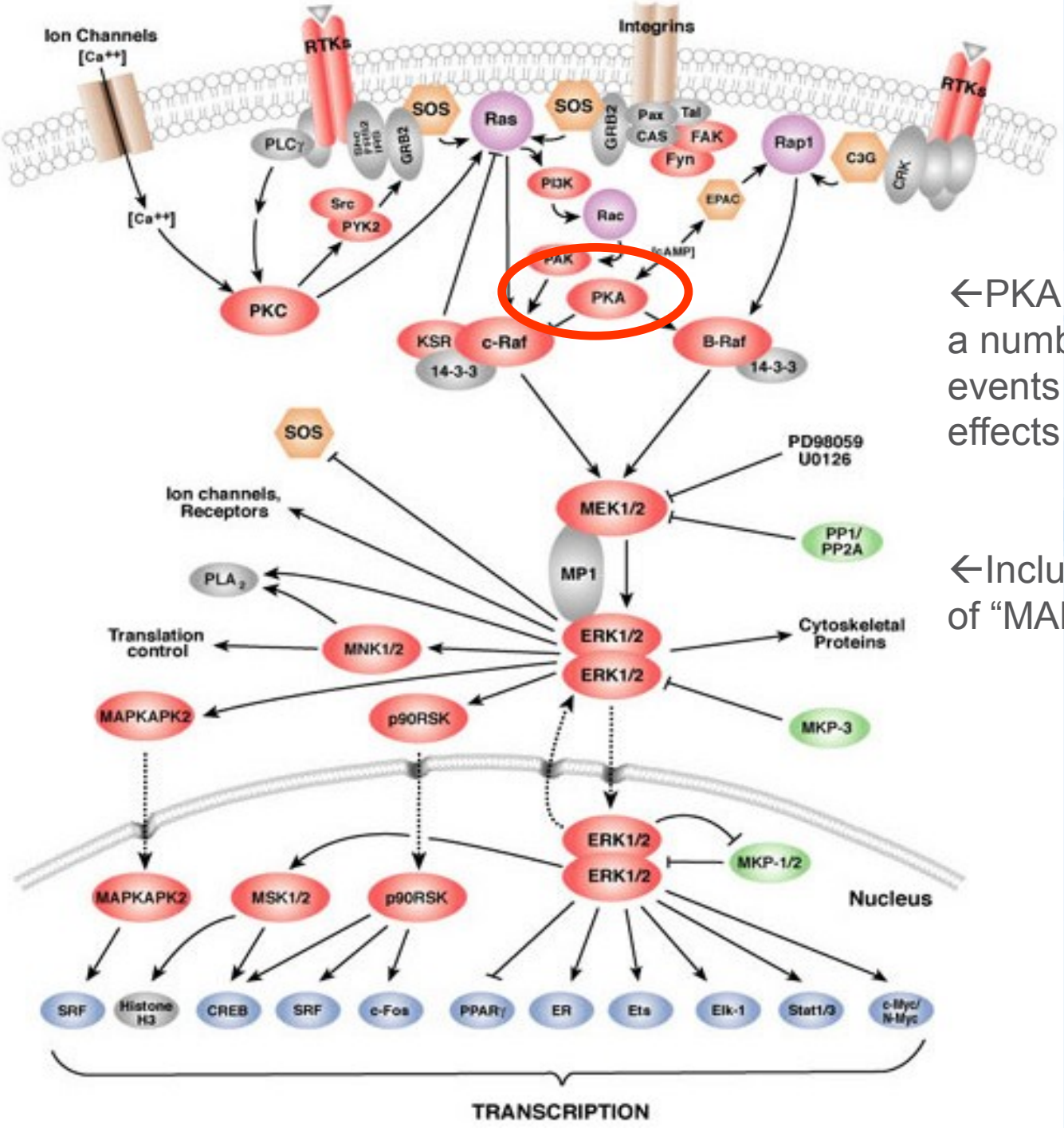
G-proteins & G-protein coupled receptors - GPCRs



Signalling mechanism 1

→ Activation of adenylate cyclase → cAMP → PKA

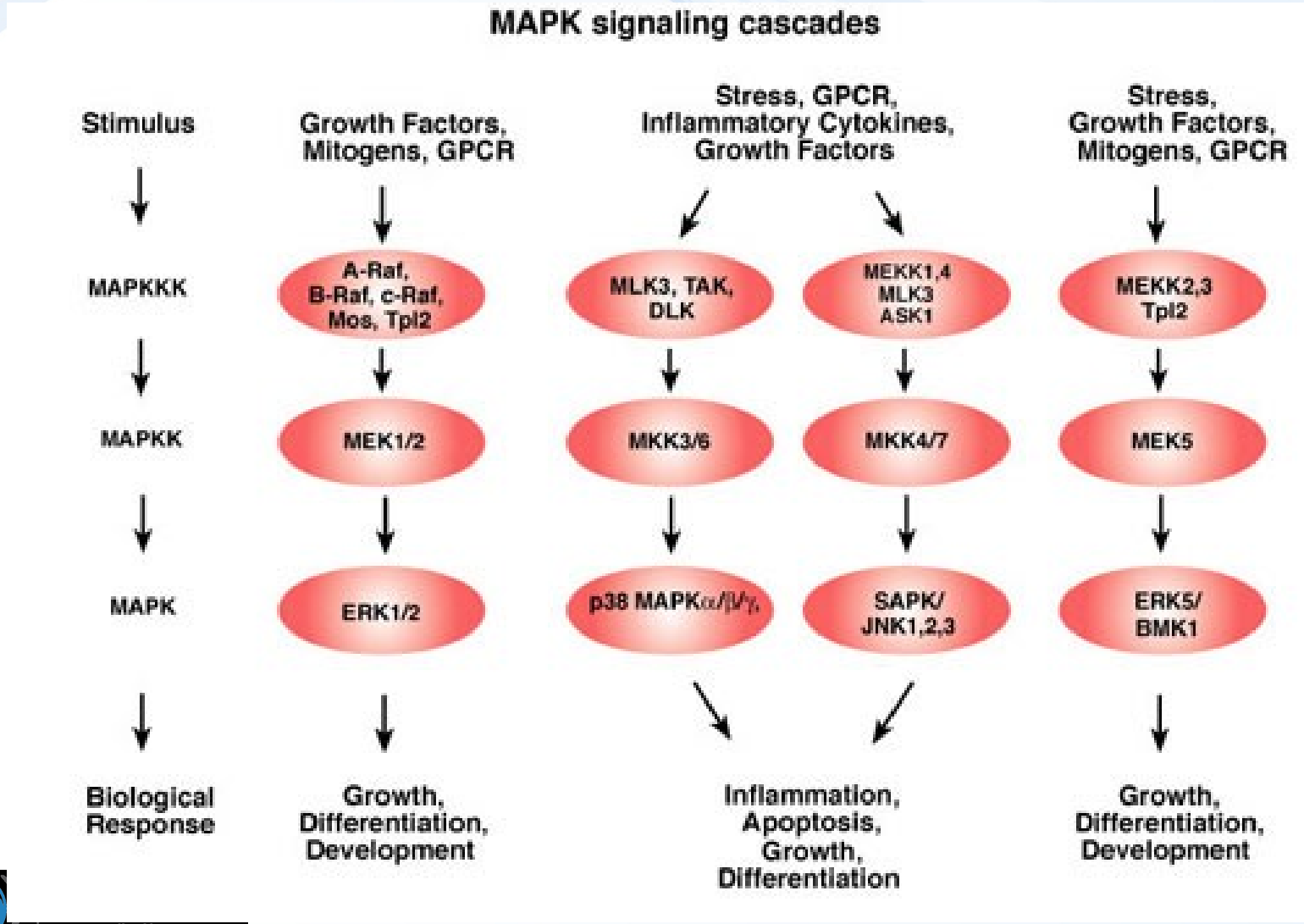




←PKA is central to a number of signalling events and following effects

←Including modulation of “MAPKs”

Mitogen Activated Protein Kinases (MAPKs) & dependent effects



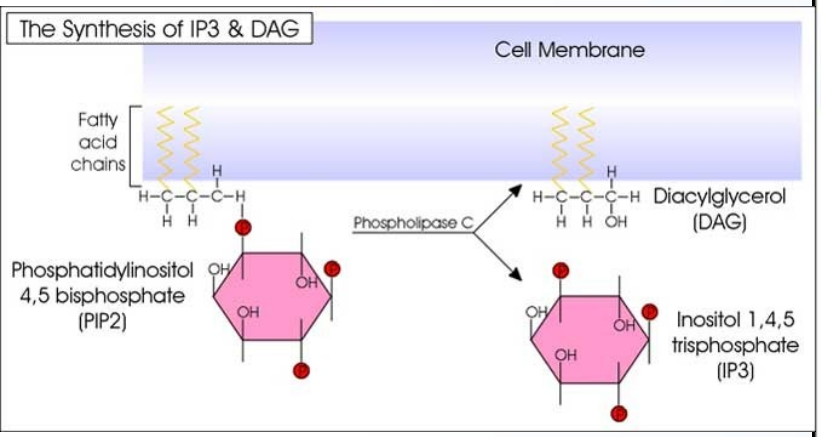
v prostředí

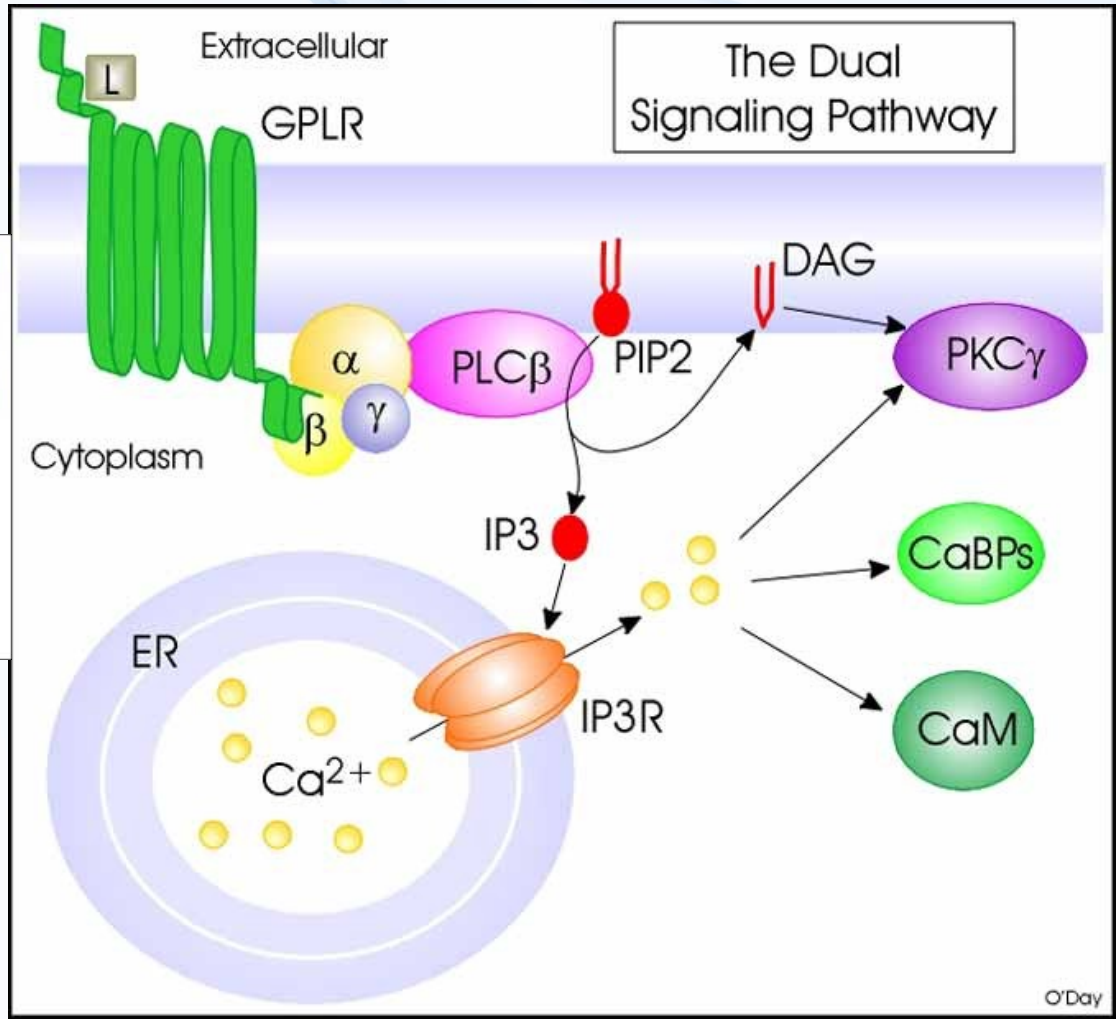
Signalling mechanism 2

Activation of Phospholipase C

→ release of PIPs → DAG → PKC / arachidonic acid

+ IP3 → activation of Ca^{2+} signalling





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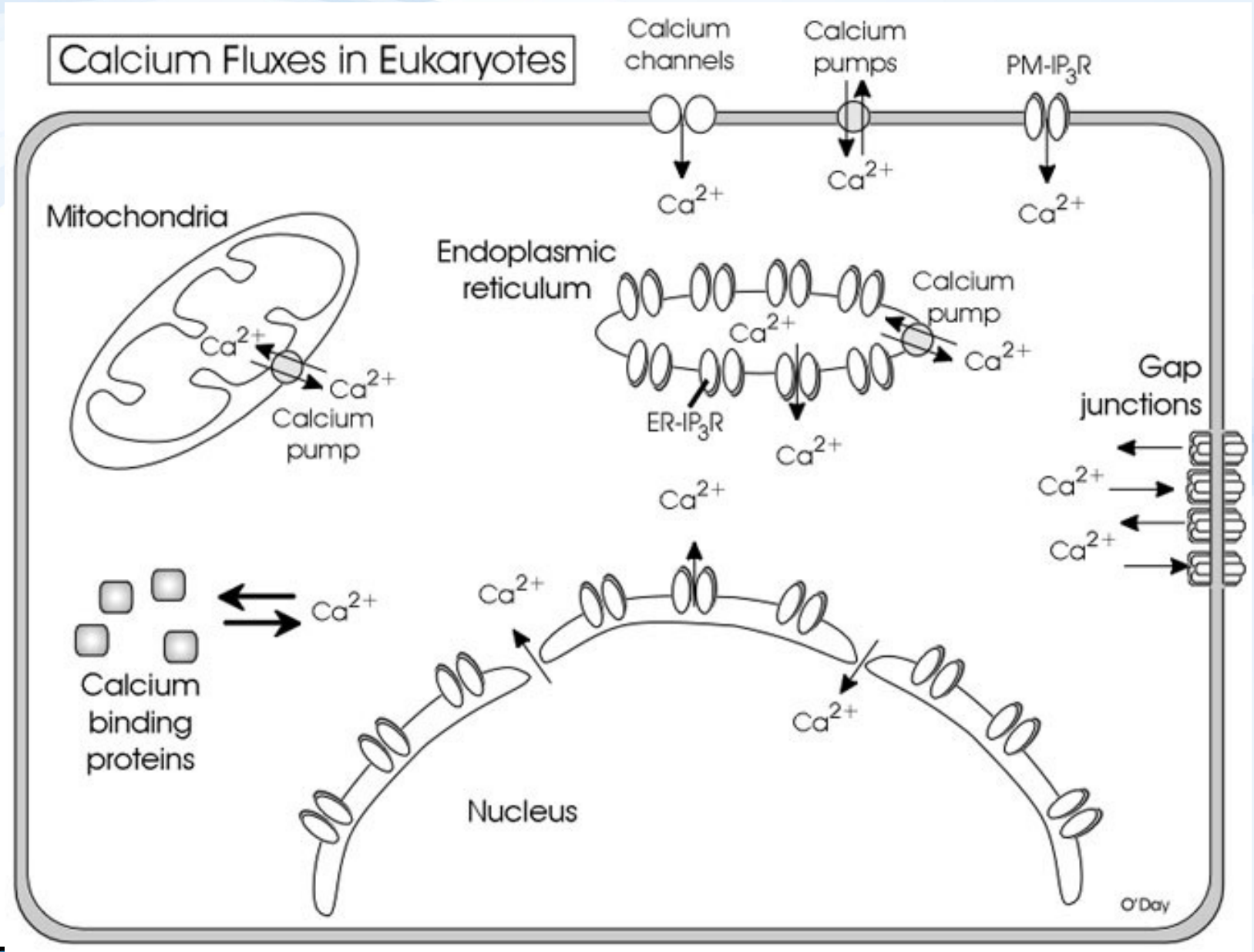
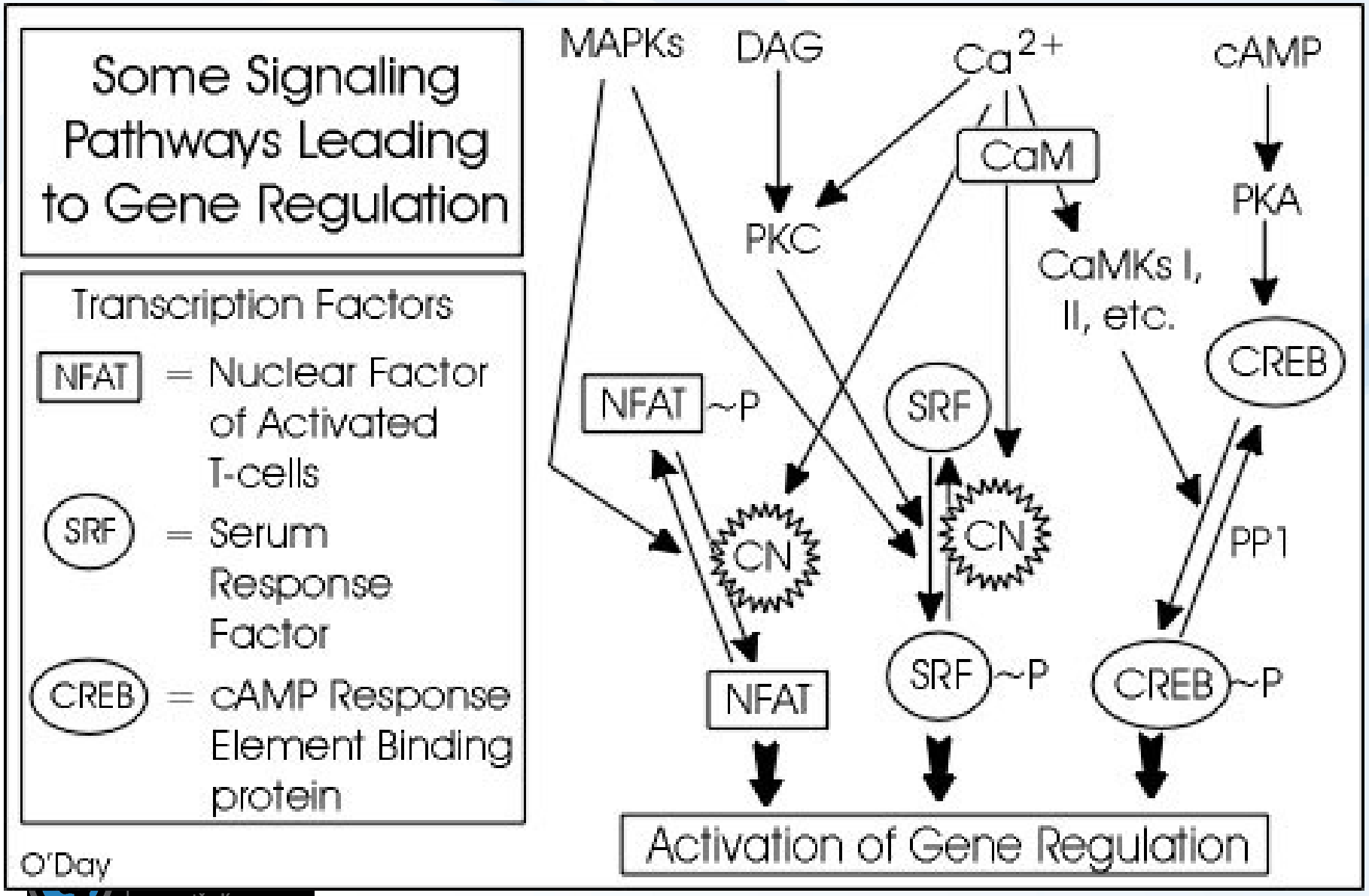


Different “types” of signalling crosstalk → networks



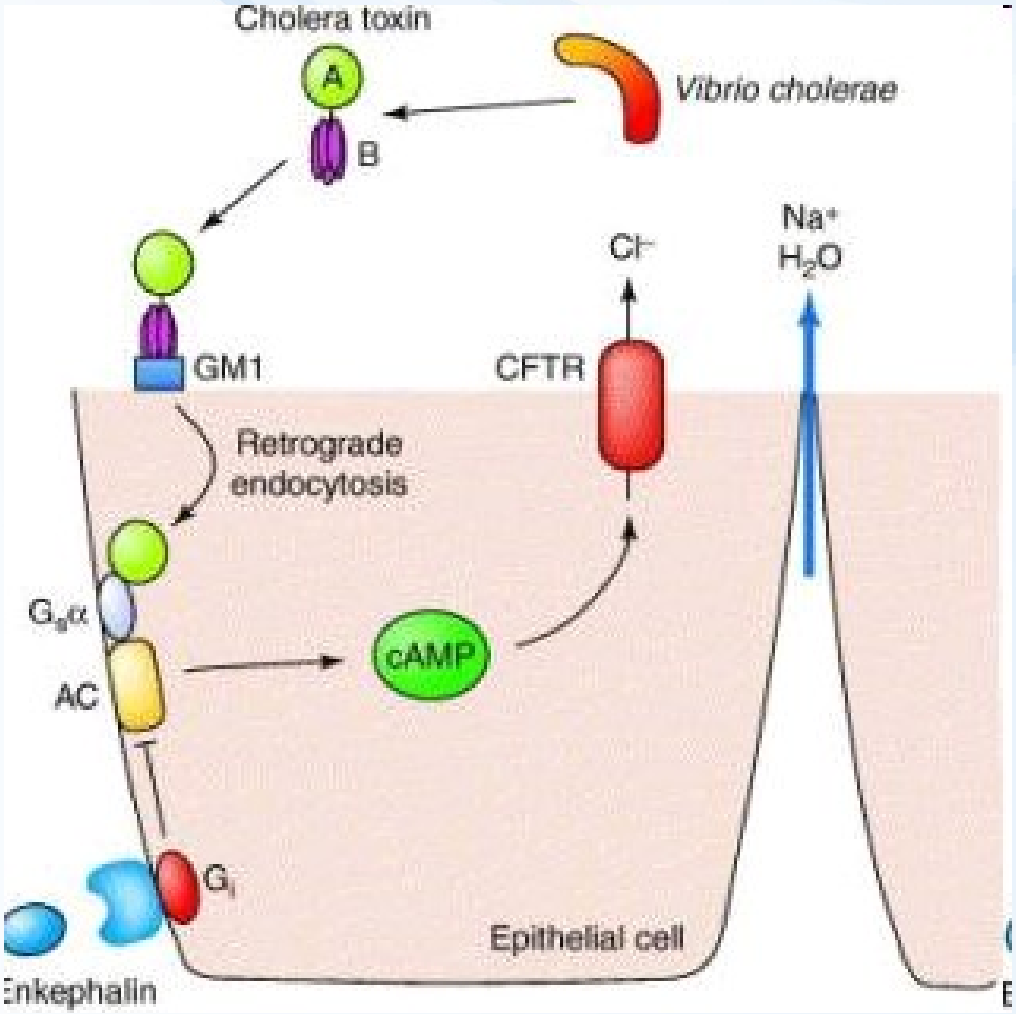
Disruption of intracellular signaling - EXAMPLES

Cholera toxin

CT acts as **adenylate cyclase** enzyme

→ increasing cAMP levels

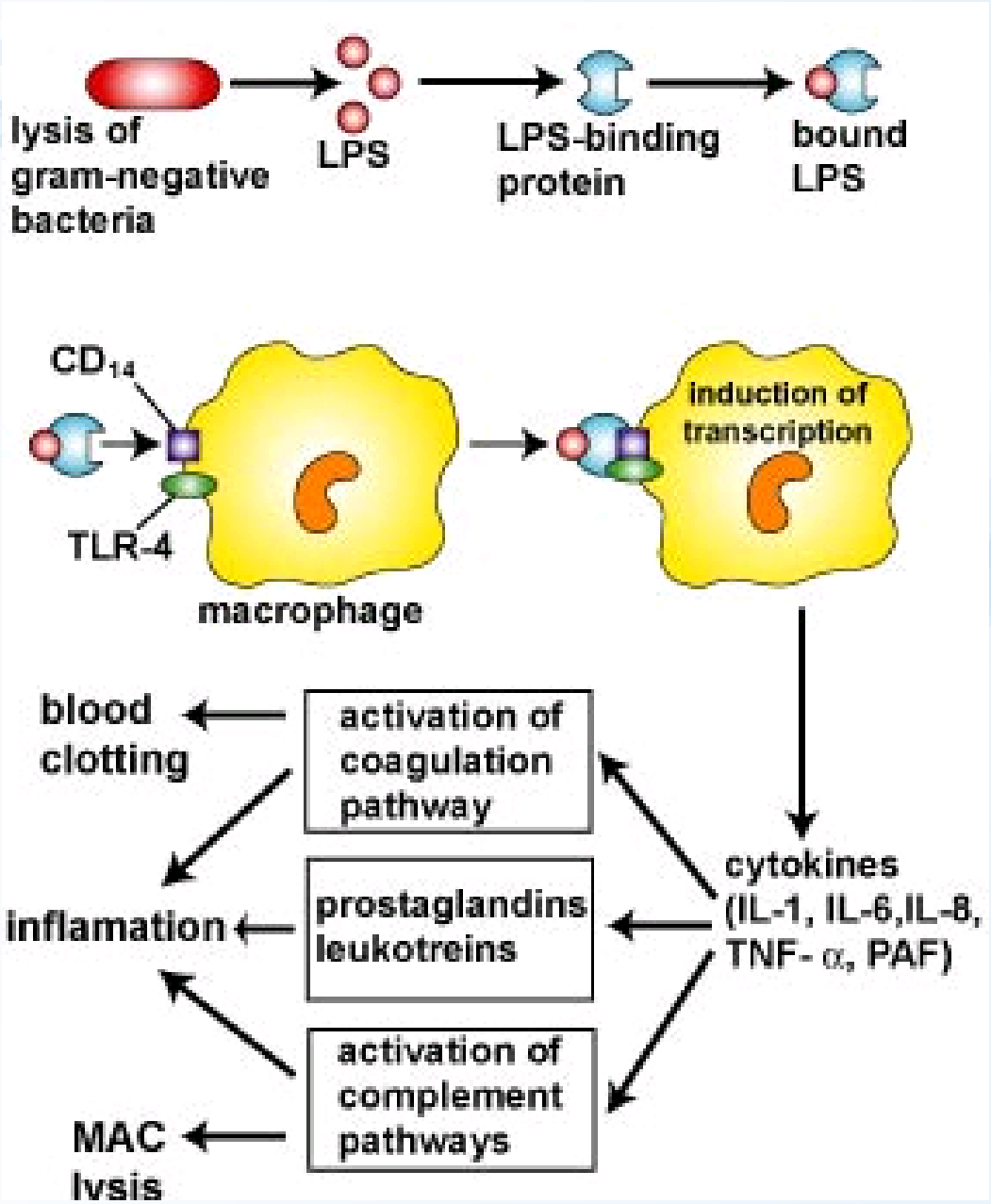
→ TOXICITY



Example:

Lipopolysaccharides (LPS) from cell walls

→ hyperactivation of intracellular signals → immunotoxicity



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Immunomodulatory Potency of Microcystin, an Important Water-Polluting Cyanobacterial Toxin

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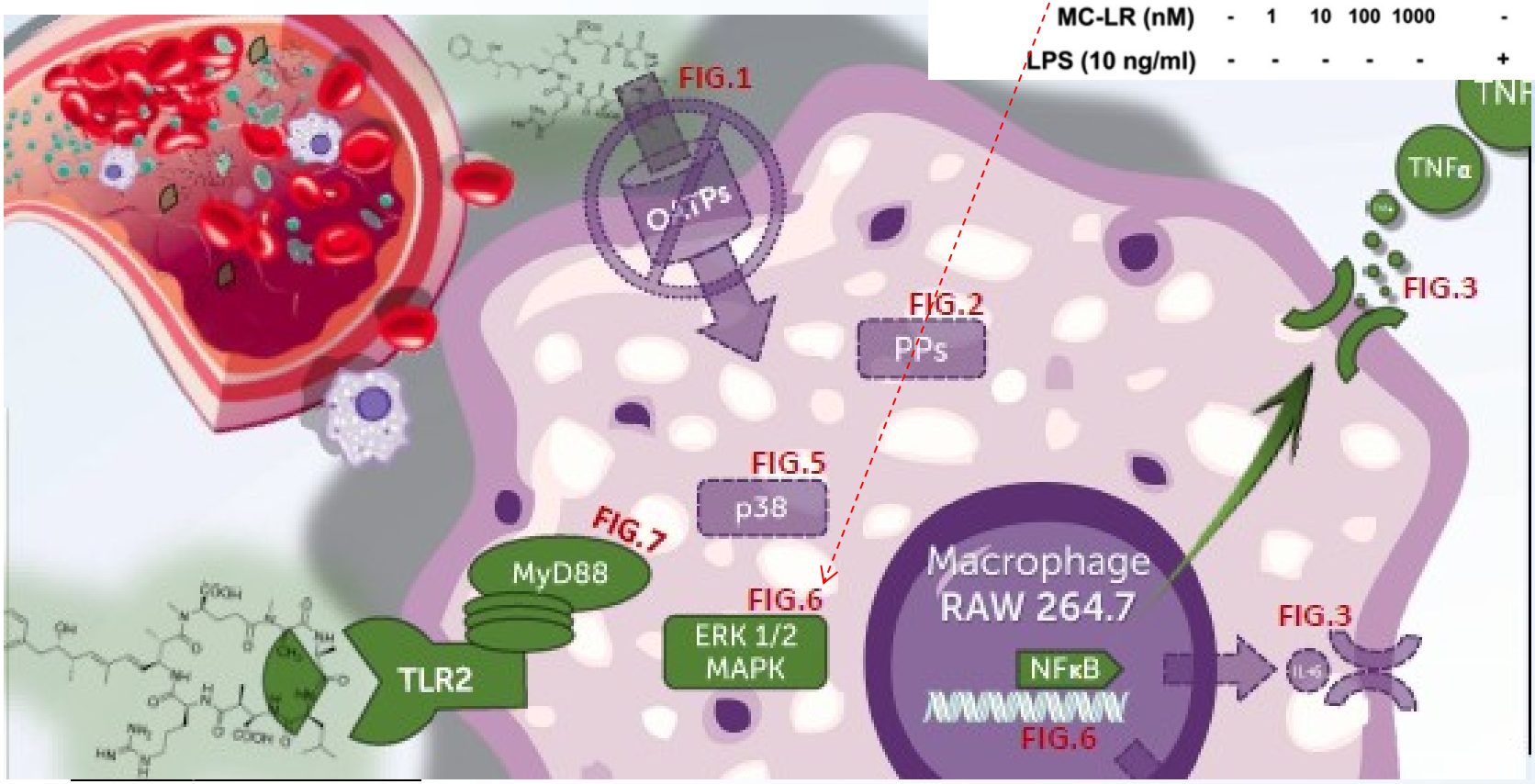
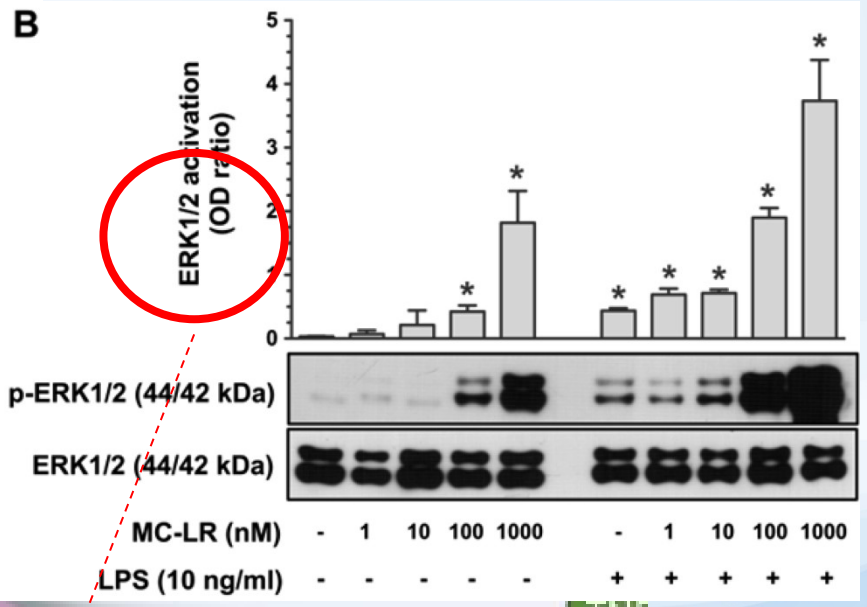
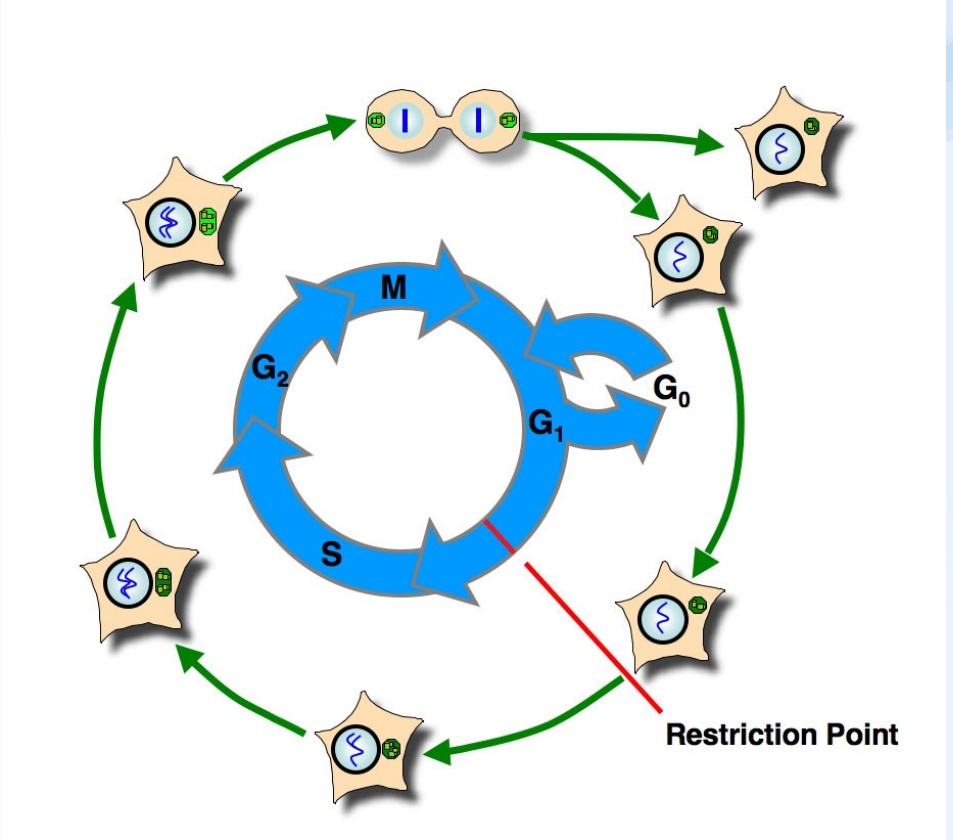




Cell and its basic functions and life trajectories

- Metabolism
- Proliferation (cell division) – cell cycle
- Diferentiation
- Senescence
- Cell death
  - Apoptosis
  - Necroptosis
  - Necrosis



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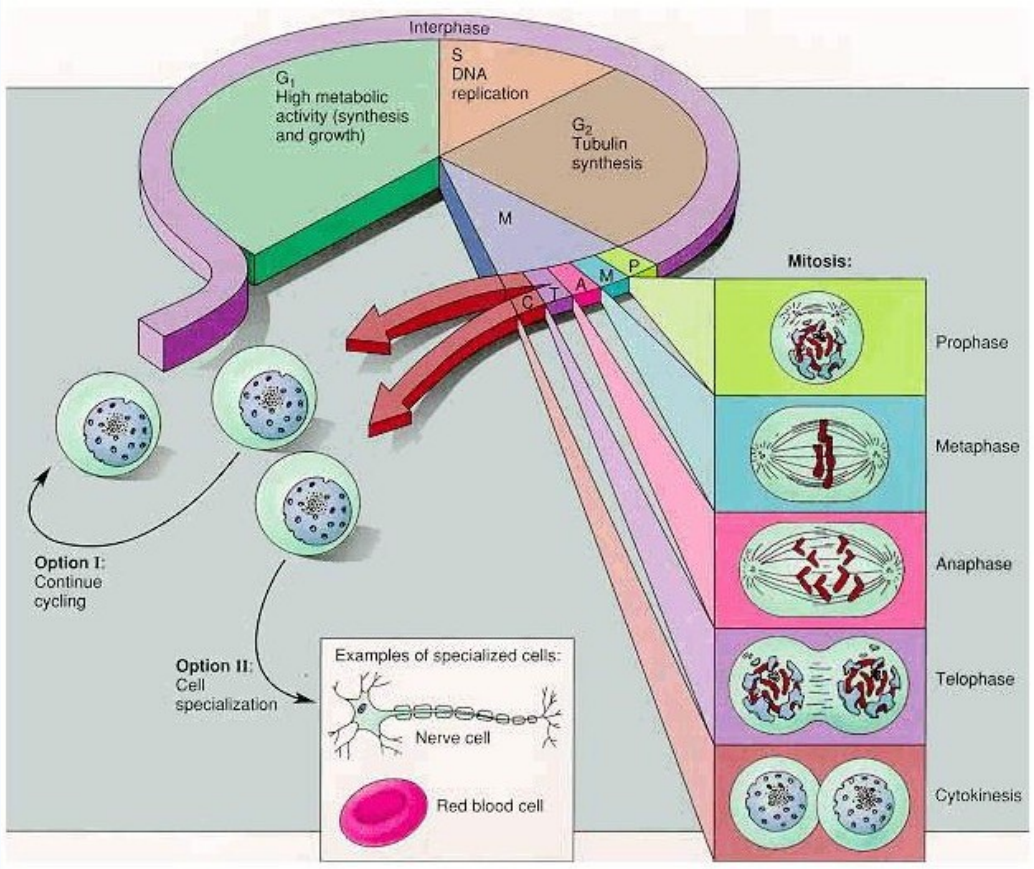
Influence of toxicity mechanisms on cellular life trajectories

- **Various toxicity mechanisms / modes of action**
  - i.e. those discussed previously
    - PROTEINS – enzyme inhibitions, protein damage/oxidation
    - DNA damage
    - MEMBRANE disruption
  - as well as others
    - **including mainly INTRACELLULAR signalling disruptions**

- **… affect the cell fate, and propagate to systemic effects**: *…examples…*
  - **Disruption of metabolism**
    - Acute → (cell) death (CO, CN-)
    - Chronic → various diseases (e.g. diabetes)
  - **Effects on proliferation (cell division) – cell cycle**
    - Tumor growth, carcinogenesis, effects on immune system / haemopoiesis
  - **Diferentiation**
    - Developmental toxicity, embryotoxicity, teratogenicity, immune system effects
  - **Senescence** (Usually not adverse or toxic)
  - **Cell death**
    - NECROSES (e.g. after irradiation)
    - APOPTOSES (bone marrow – haemopoetic effects; effects on tumors)

CELL CYCLE and its careful CONTROL - importance

- **GENERAL**
  - Control of genetic material and information (including reparation)
  - Proper distribution of genetic material into daughter cells
- **EARLY DEVELOPMENT**
  - Regulation of development, embryo- and organogenesis
- **ADULTHOOD**
  - Reconstruction and renewal of adult tissues
  - Control of proliferation / tumor growth



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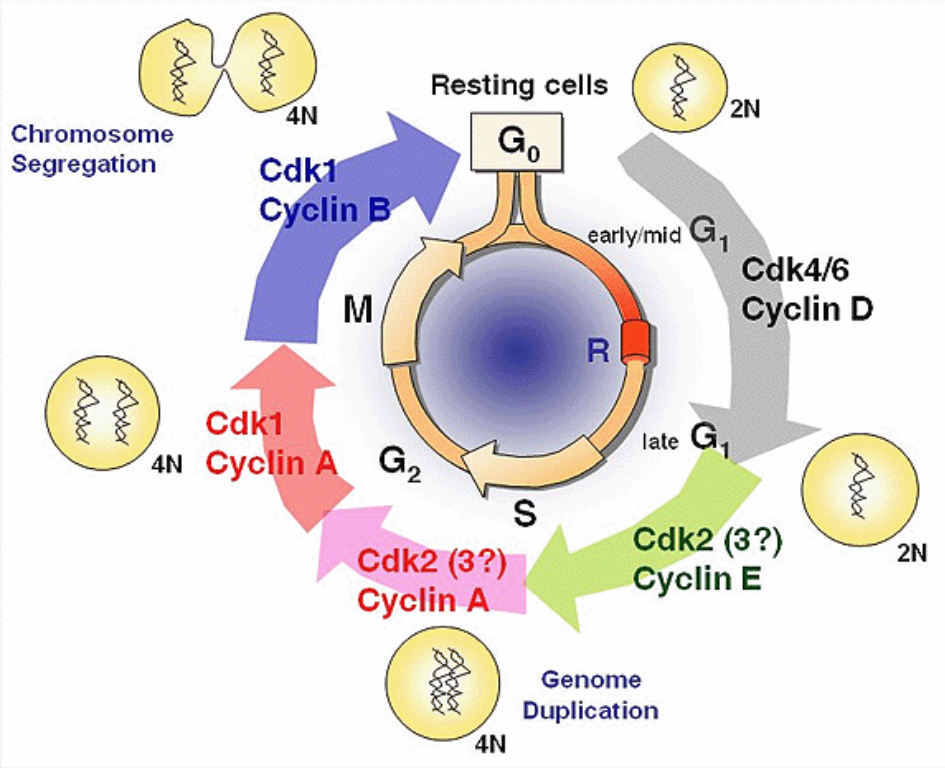
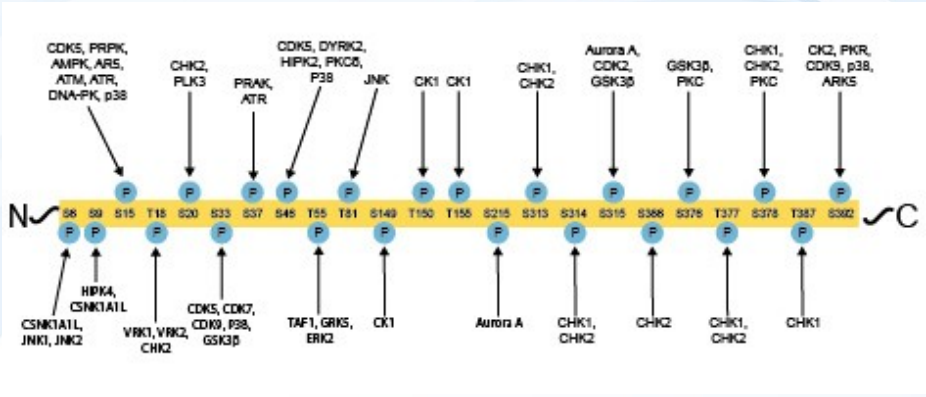
Cell cycle regulation and control

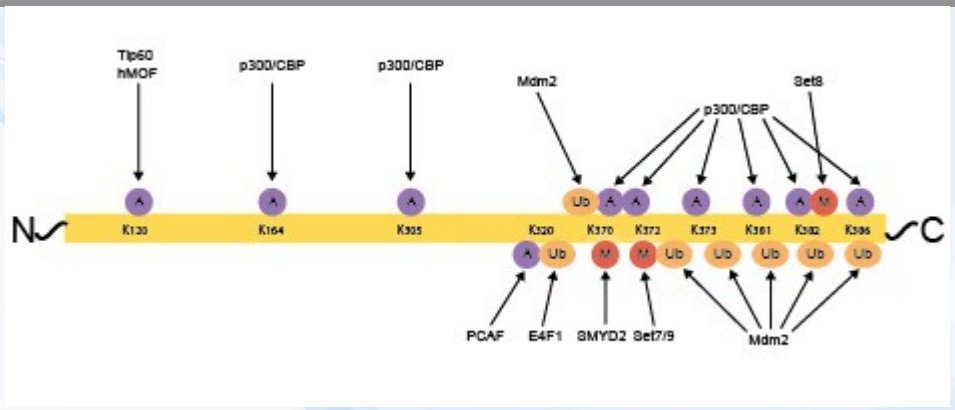
- Factors controlling proper cell cycle
  - Extracellular signals (hormones, neurotrasmitters…)
  - Intracellular „stress sensors“ and signals
    - p53 protein among others
  - Correct sequence of individual events (phases)
  - Error-free events

- Controlling principles
  - General:
    - Phosphorylation (kinases) / dephosphorylation (phosphatases) of proteins → discussed further
  - Such as … *for cell cycle:*
    - cyclines and CDK (cycline-dependent kinases)



Role and functions of **p53**



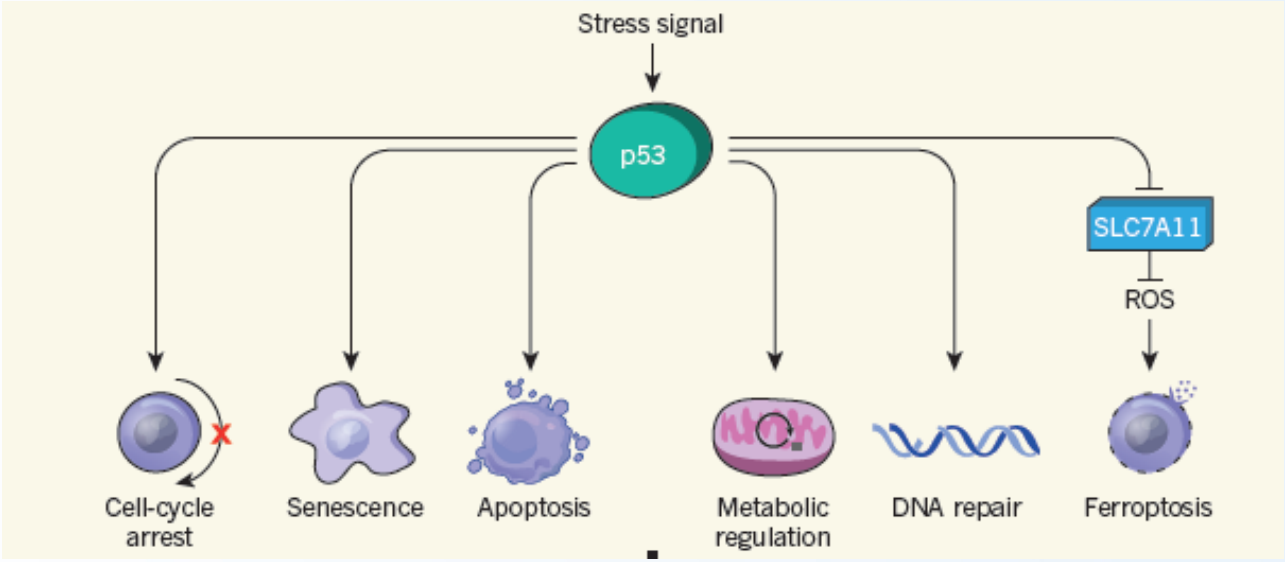


* Phosphorylation of p53

* as well as „mutations“ (SNPs) of p53

* acetylation (A), methylation (M)
* and ubiquitylation (Ub) of p53

→ Control and affect key cellular processes →



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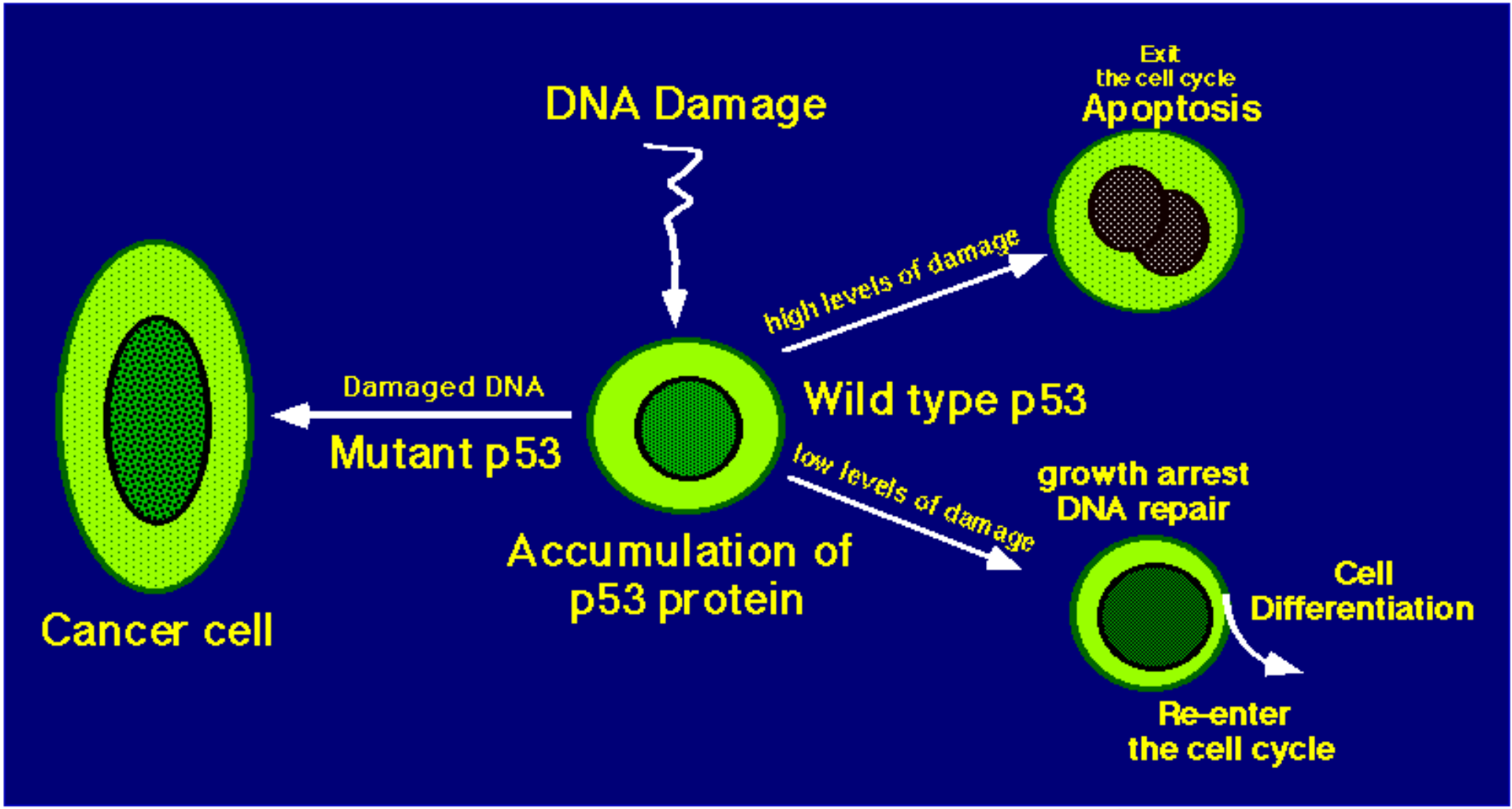
Example - p53 in control of intracellular stress / such as DNA damage



Cell deaths

Necrosis

- Pathology
- Membrane damage
- Cell „explosion“/ lysis
- Chromatin disintegration

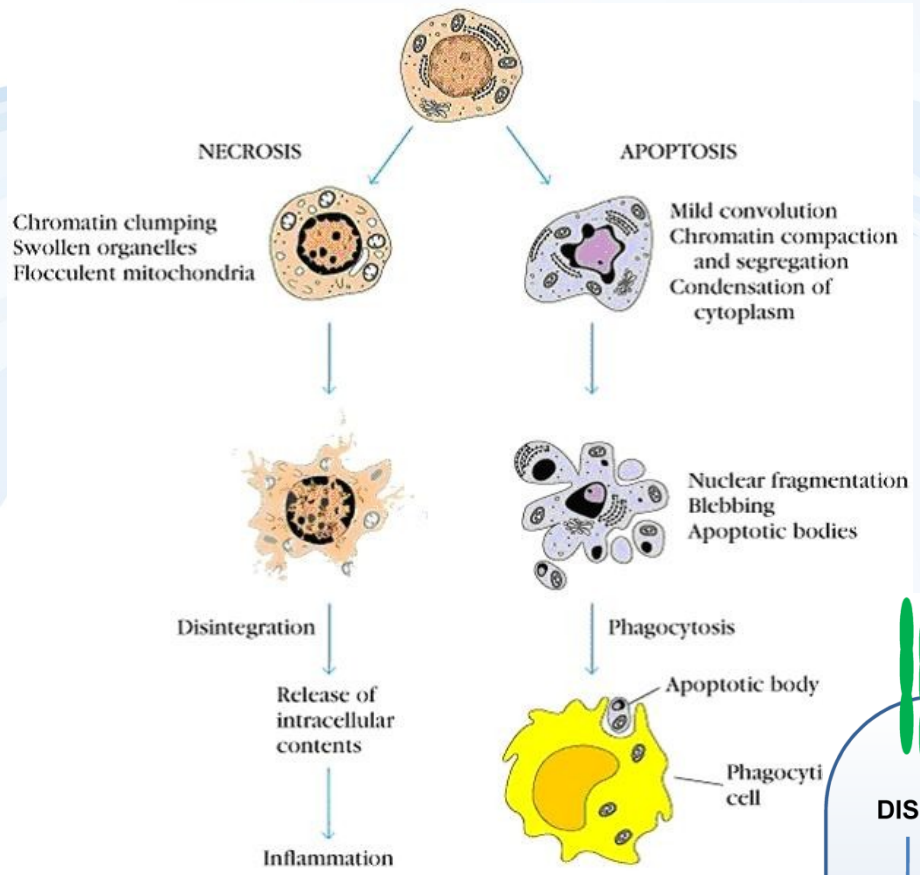
- → immune reaction (inflammation)
- „scars“ formation

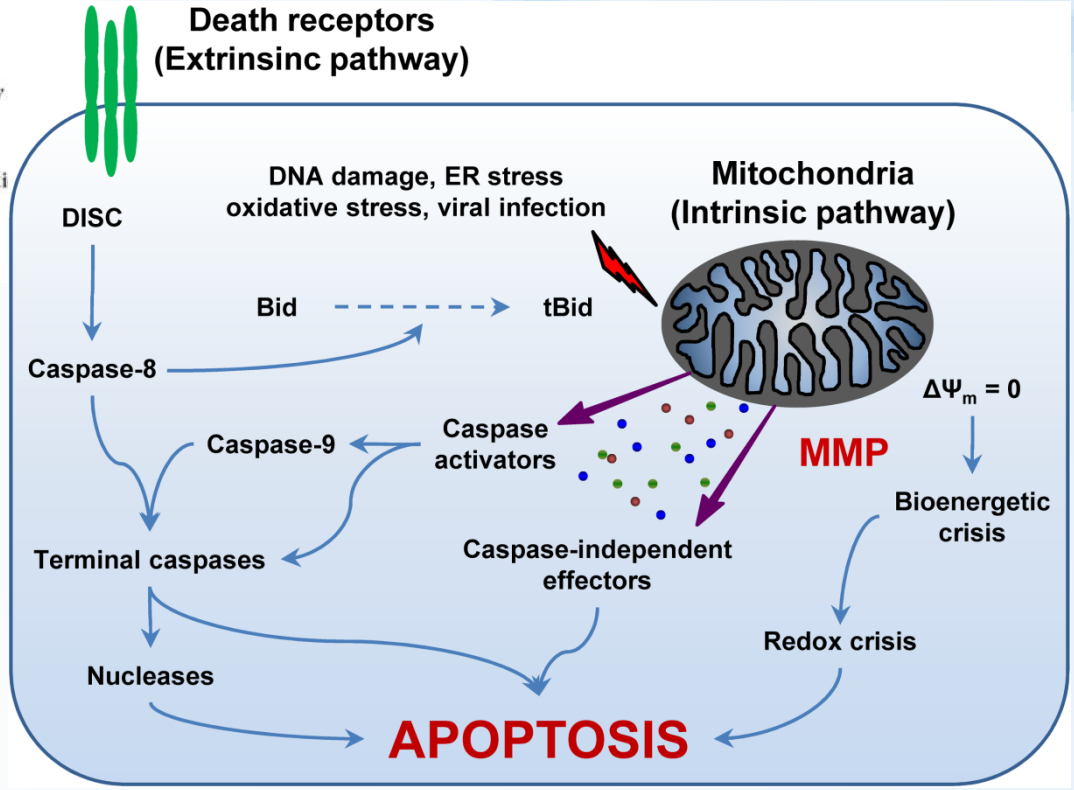
Apoptosis

- Physiological
- Suicidal process (internal
- Carefully controlled
- DNA fragmentation
- Membrane „blebbing“
- Apoptotic bodies → fagocytosis

Further cell death variants also recognized *(different cell fate and control)*

- Necroptosis
- Ferroptosis





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