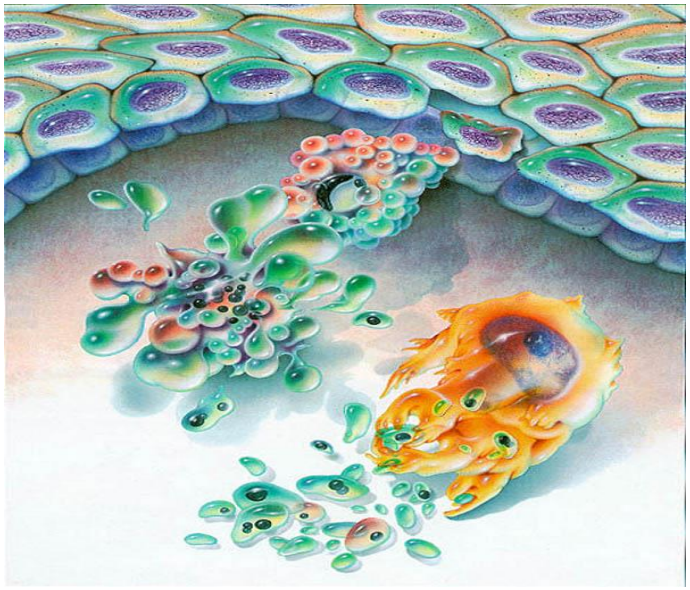
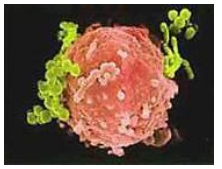
# Cellular stress responses

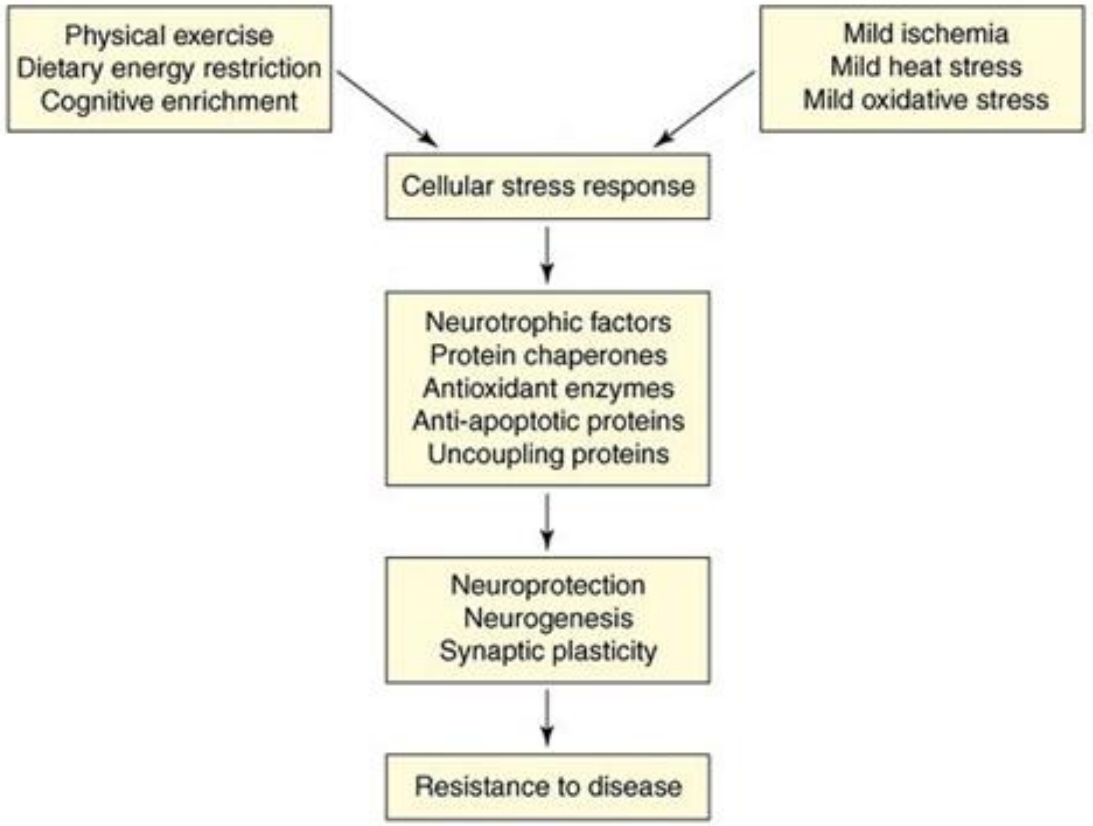


# Cellular stress responses

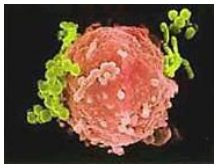


**Cellular stress responses ⟹ induction of cellular metabolic processes to maintain homeostatic state**

- **Activation of reparative processes**
- **Rearrangements of cytoplasmic components (e.g. autophagy)**
- **Changes in cellular structure (heat shock response - e.g. conformation reparation or protein destruction)**



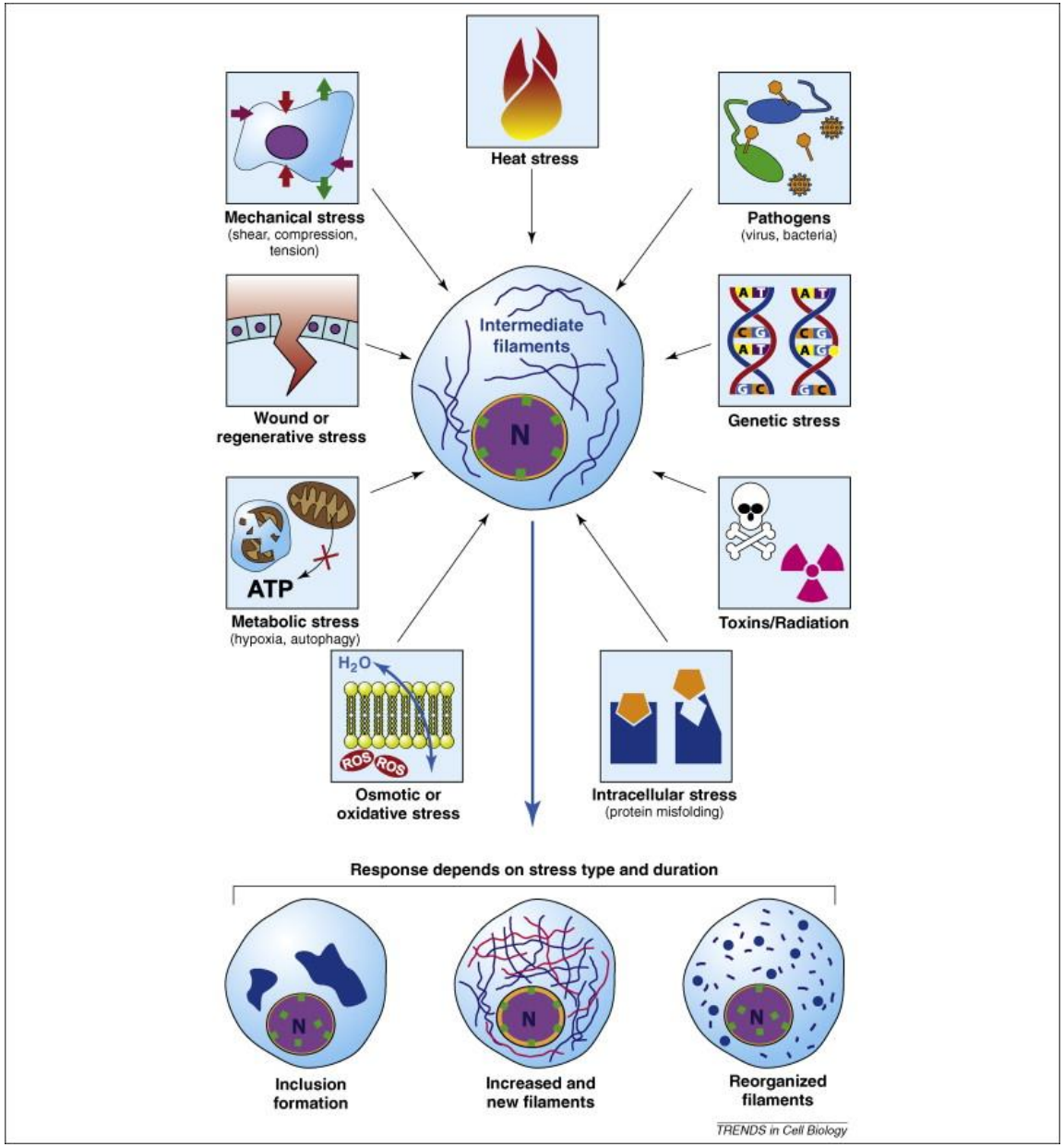
# Cellular stress responses



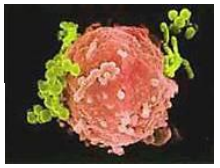
**Cellular injurious factors might be internal or external origin**

**Most important harmful factors:**

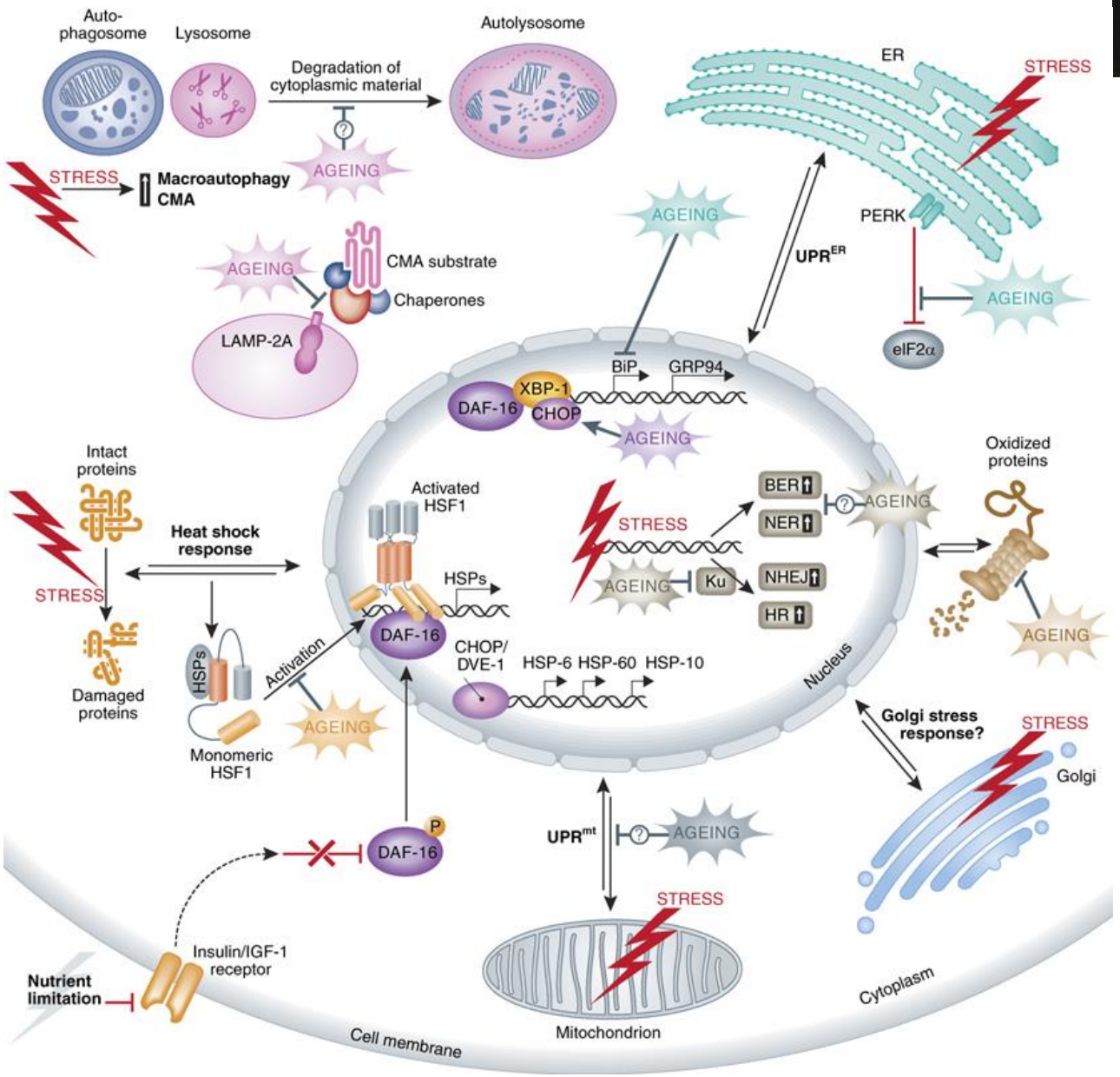
**chemicals, radiations, heat, osmotic shock, infections, oxidative stress, injuries inappropriate nutriment, aging.**



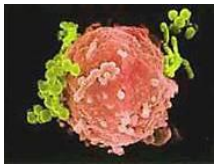
# Cellular stress responses



**Affected cellular components:**



# Cellular stress responses



## Intracellular signal transduction pathways in stress responses:

Regenerative and survival processes are activated or cell death is induced.

- Cellsurface metabotropic, G–protein coupled receptor and secondary messenger, (cAMP, $IP_3$, $Ca^{2+}$) activation

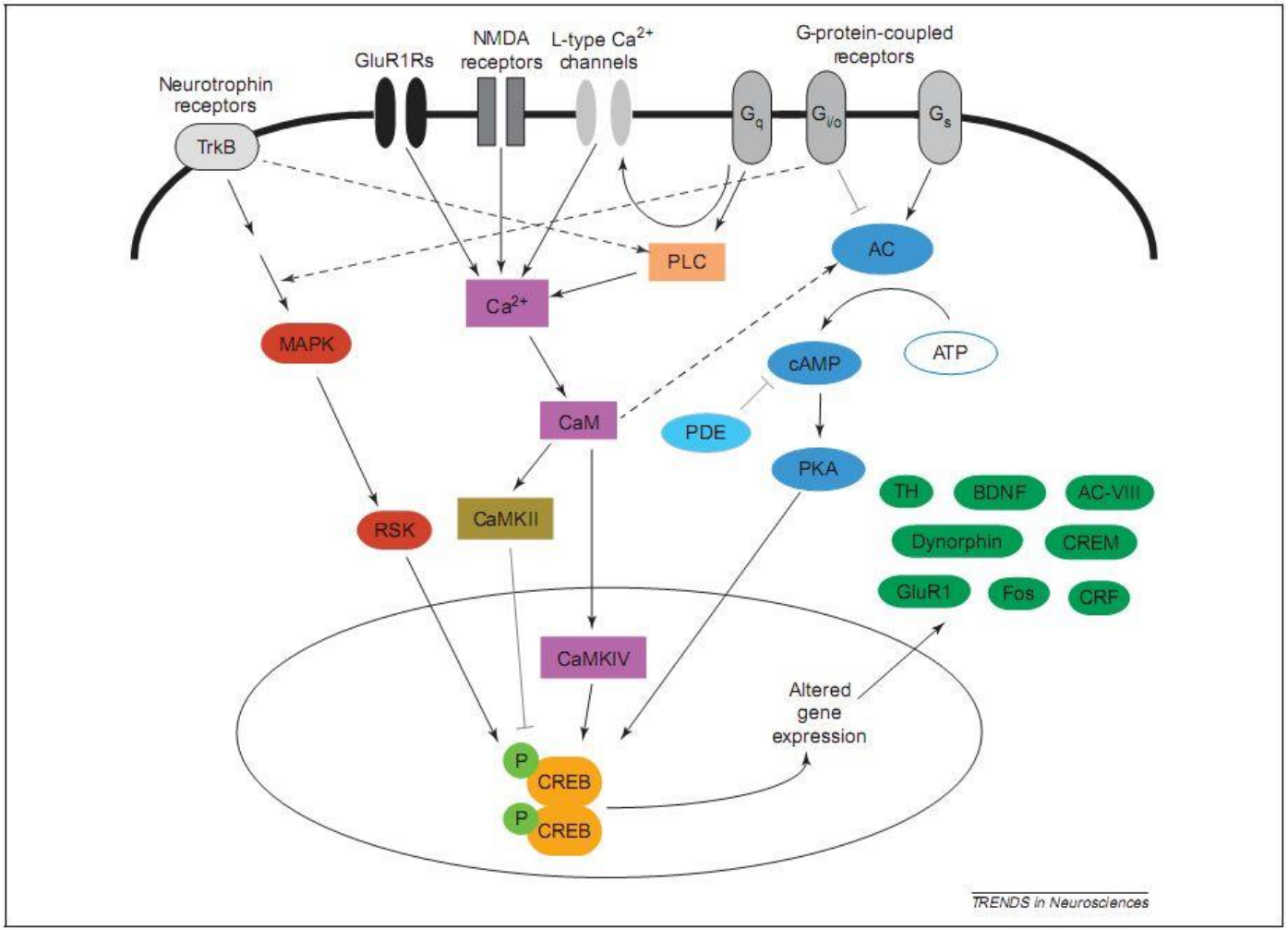
  PKA activation – the translocation of catalitic subunit (C) into the nucleus, phosphorilation of transcript factors (e.g. CREB) initiate genexpression processes
  CAMkináz – the end effect might be also CREB activation (CREB – cAMP responsive element)
  PKC – AP1 transcript factor activation (AP1- activator protein 1- fos and jun protein dimer)

- Growth factor receptor activation (PDGF-platelet-derived growth factor, EGF-epidermal g.f., FGF-fibroblast g.f., NGF-neuronal g.f., IGF-inzulin like g.f.)

  Receptor tyrosine kinase, Src-homolog (SH) protein activation ⇒
  Ras- ⇒ Raf- ⇒ MEk ⇒ ERK activation by MAP-kinases.
  ERK might be translocated into the nucleus.
  (ERK: extracellular-signal-regulated kinase)

# Cellular stress responses

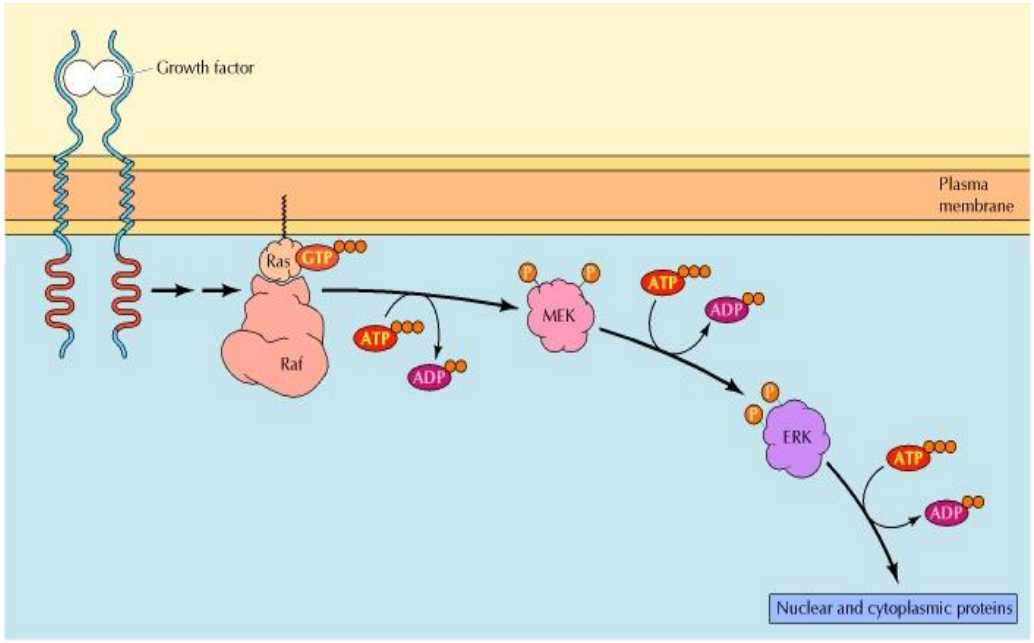
## Most important intracellular signal transduction pathways:

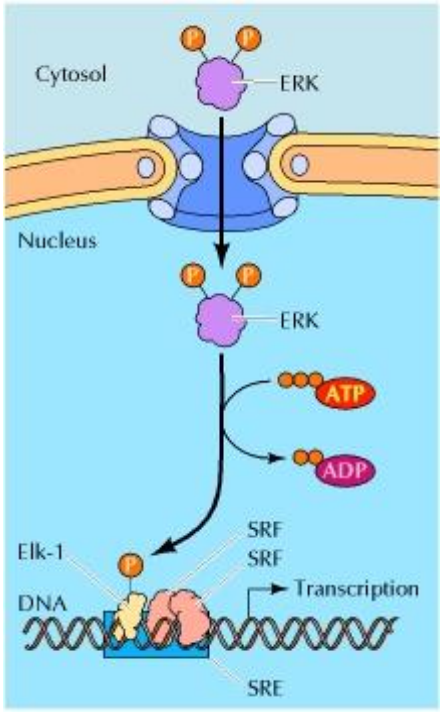



**cAMP-response-element-binding protein (CREB) is an important gene regulatory factor.**

# Cellular stress responses

## MAP kinase (Ras, Raf) pathway

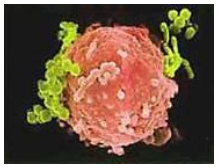



MAP: mitogen-activated protein kinases
ERK: extracellular signal-regulated kinase
SRE: serum response element
SRF: serum response factor
MEK: MAP kinase/ERK kinase.
Ras: small GTP-binding proteins
Raf: proto-oncogene serine/threonine-protein kinase

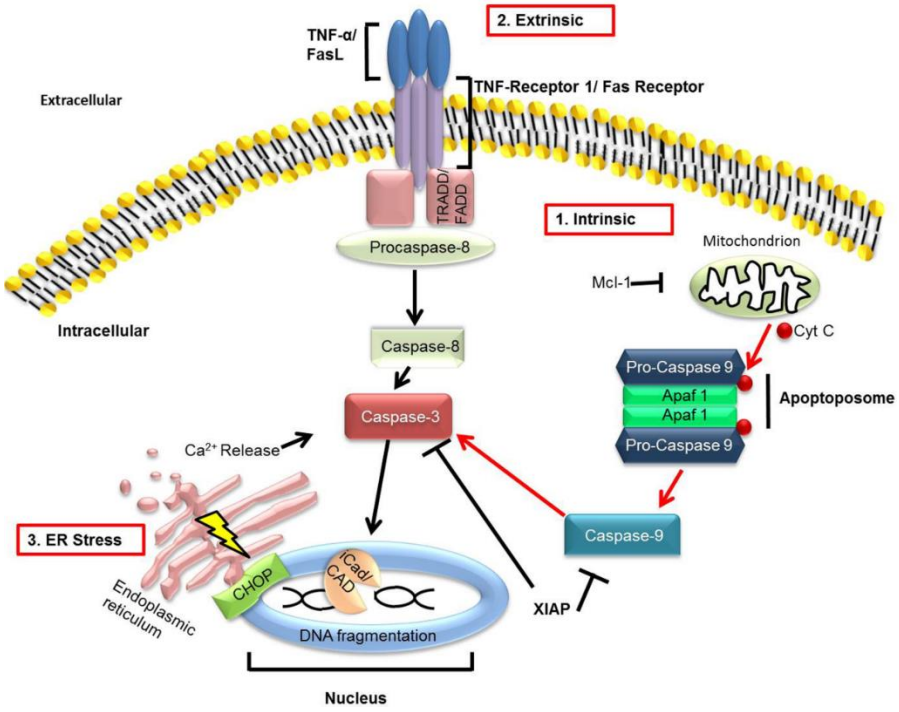
Immedite early gene activation:
c-fos, c-jun

# Cellular stress responses

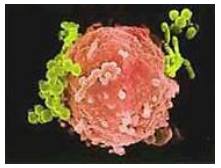


## Responses of the cells depend on the harmfull action

- Chemicals induce detoxification processes, mainly in the liver
- Immediate early gene (fos and jun genes) activation following the harmful effects – proteins appear in 20 minutes and induce secondary protective processes
- Unfolded protein responses (UPR) - ER stress reaction
- Activation of heat shock proteins (HSP-proteins). There are different subtypes: permanents (e.g. HSP 90), regulated (e.g. HSP 27, phosphorylation), inducible (e.g. HSP 70)
- Oxidative stress effects – reactive free radical formation (e.g. following ischemic reperfusion)
- DNA damaging (e.g. irradiation, chemicals, osmotic stress effect)



# Cellular stress responses



## Cell components taking place in different stress processes

**lysosome:** contain hydrolytic enzymes that can break down many kinds of biomolecules (pH 5 in the lumen, protonpump maintains it)

**peroxisome:** catabolic processes taking place in it, breaking down long fatty acids contain oxidative enzymes and catalase ⇒ toxic substances are neutralized (detoxified)

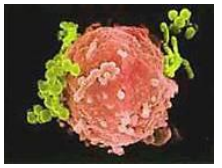
**mitochondria:** the place of citric acid cycle and oxidative phosphorylation ⇒ produce the energy currency (ATP ) of the cell, however free radicals are also arosed. This may destruct the mitochondrial DNA

**endoplasmic reticulum (rough):** the site of protein synthesis, toxic effects may influence the protein structure

**Golgi apparatus:** place of protein modification and destination for secretion

**nucleus:** it contains the cell's hereditary information and controls the cell's growth and metabolic processes.

# Cellular stress responses



## Cellular impairing effects and protective processes

Different natural and synthetic chemicals activate the defensive activity of the cells. Cytochrom P450 (CYP) enzymes support the transformation, primarily in the liver. About 500 gene were identified determining these types of functions (genetic polymorphism).

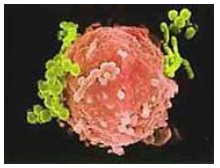
water soluble compounds are less dangerous – depleted by the kidney
lipid soluble ones has to be transformed to water-soluble

$$\text{apolar substrate} + O_2 + NADPH + H^+ \Rightarrow \text{polar substrate-}OH + NADP^+ + H_2O$$

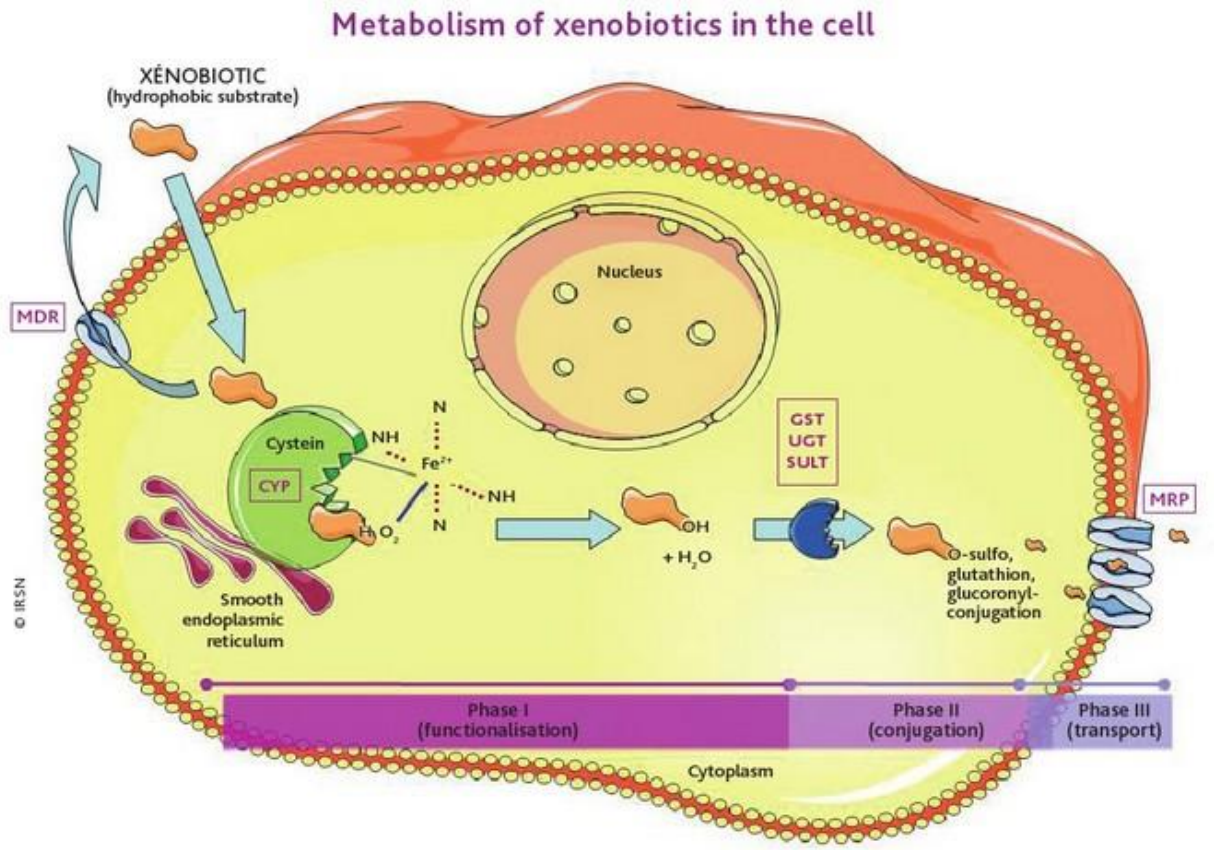
Cytochromes P450 (CYPs) are a family of enzymes containing heme as a cofactor that function as monooxygenases. In mammals, these proteins oxidize long fatty acids, steroids and xenobiotics. They are important for the clearance of different compounds.

Xenobiotic (chemical substance found within an organism that is not naturally produced within the organism – foreign chemicals), e.g. drugs, insecticides, food improvers

# Cellular stress responses



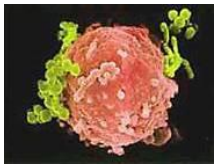
## Detoxification processes in the liver




Microsomal P450 systems: human CYPs are primarily membrane-associated proteins located either in the inner membrane of mitochondria or in the endoplasmic reticulum

But: toxic detoxification maight be also possible, epoxids (carcinogenic effect)

# Cellular stress responses



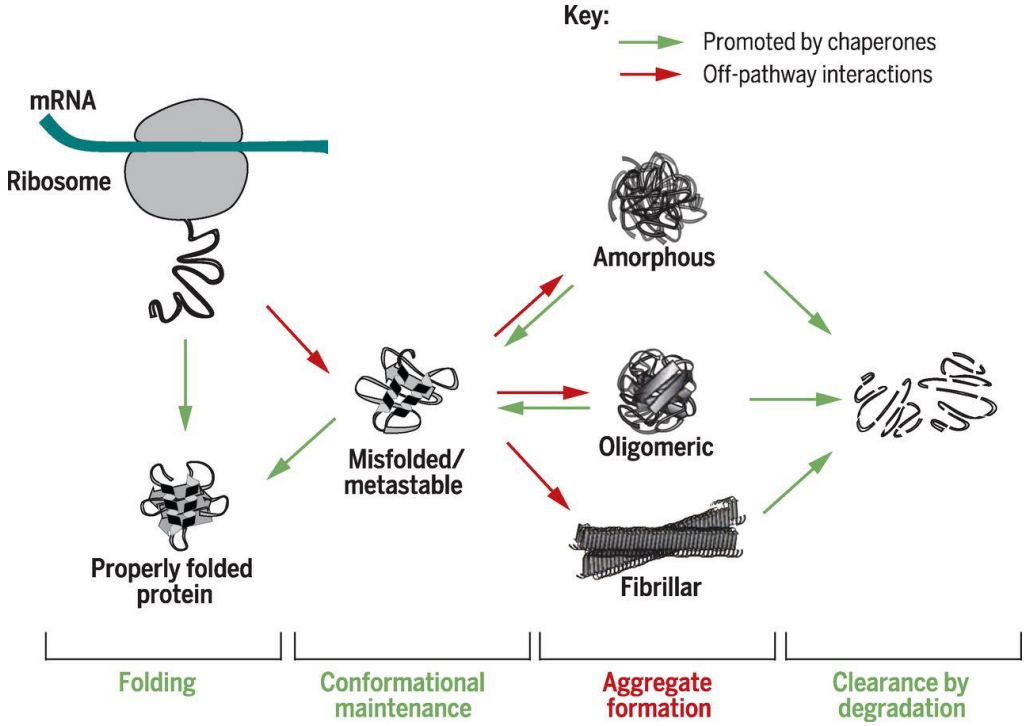
## Endoplasmic reticulum stress

Endoplasmic reticulum (ER) has several different functions:

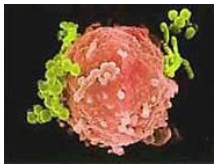
- $Ca^{2+}$ store
- protein synthesis and store

Injured ER activity – damaged protein structures (unfolded, misfolded proteins) (e.g. viral infection)

ER stress adaptation: improving mechanisms are induced in the cytoplasm to restore protein homeostasis (kinases activation)



# Cellular stress responses

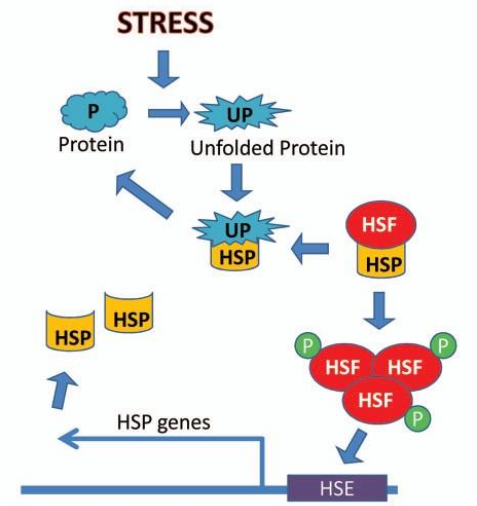


The heat shock response was described in 1962.
Several (50-200) genes are identified which may be activated after heat shock or other stressfull input, and different protein appear in 1-2 hours.

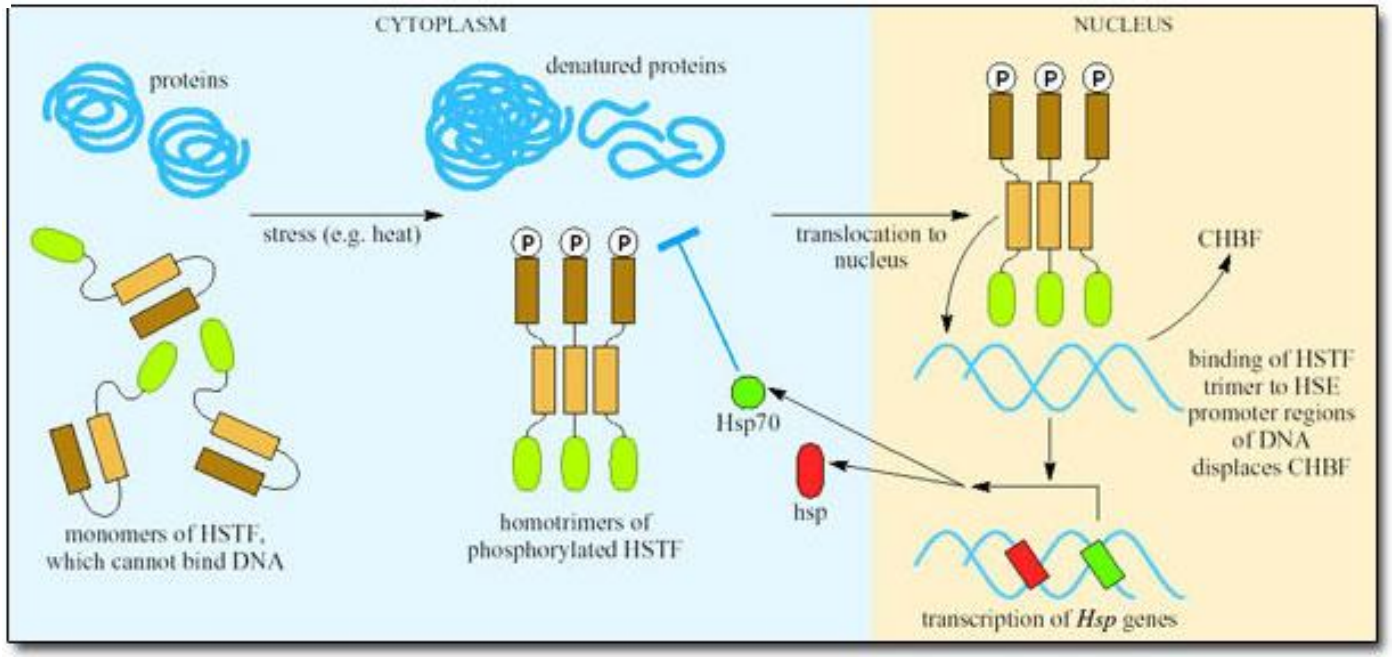
1 – classical heat shock proteins (molecular chaperones)
2 - proteolytic enzyme family
3 – stress-induced DNA damage repair enzymes
4 – metabolic processes enzymes (energy household stabilization)
5 – transcript factors and kinases (further stress-response activation)
6 – cell structure protein synthesis
7 – membrane bound and transport proteins

# Cellular stress responses

## The role of heat shock proteins

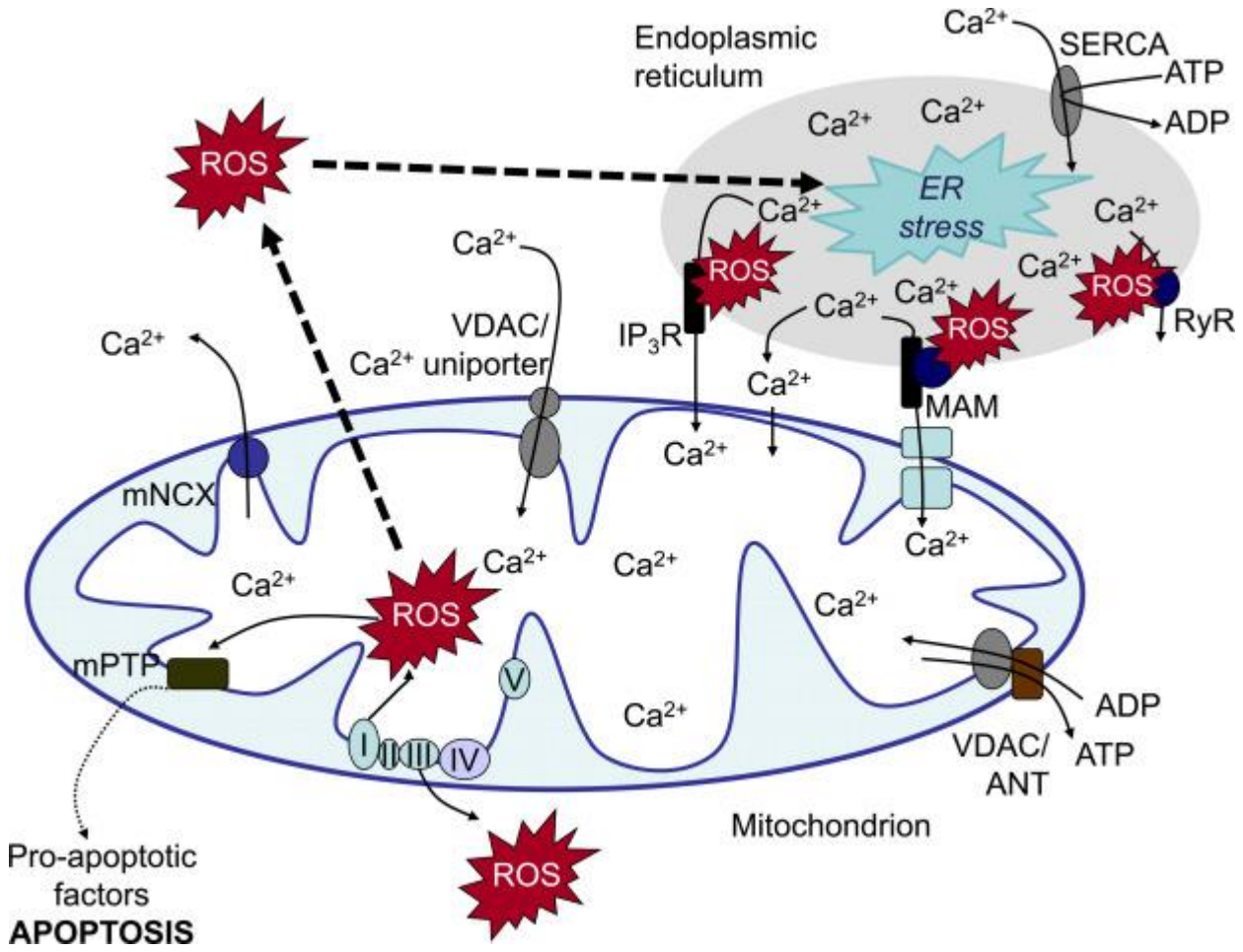



**HSTF- heat shock transcription factor /**
**HSF1- heat shock factor 1: the activator of HSP production**

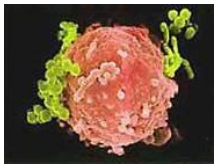


# Cellular stress responses

## The role of ER in citoplasmic $Ca^{2+}$ level regulation



# Cellular stress responses



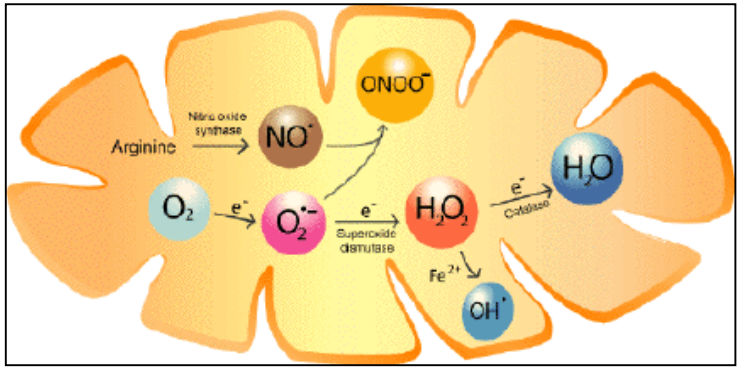
## Cellular damaging effects - oxidative stress

**Free radicals:** they posses unpaired electrons, and are very reactive, free radicals form also during the normal cell processes

**Harmful effects:** $O_2 \Rightarrow$ superoxide ($O_2^{\bullet}$) $\Rightarrow H_2O_2 \Rightarrow OH^{\bullet} \Rightarrow H_2O$
- lipid peroxidation (membrane damaging)
- cytotoxic effect
- nitrogen monoxide formation

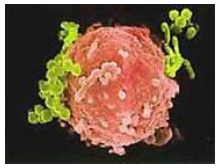
**Cause of their formation:** ultraviolet and radioactive radiation, smoking, smog, high amount of alcohol consumption chemicals, environmental pollution, toxins

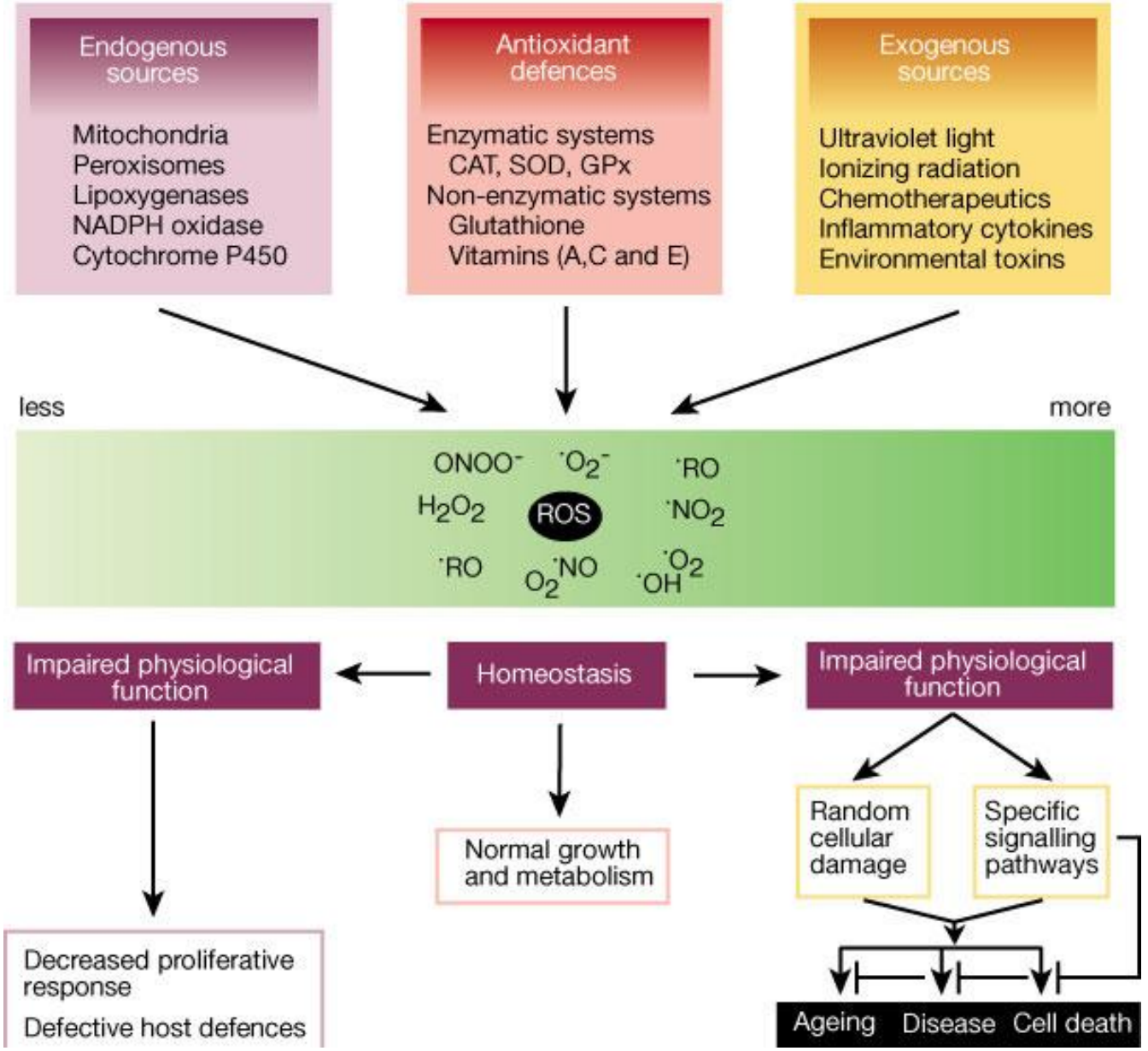
Free radicals form mainly in the mitochondria



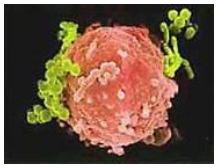

**consequences:** DNA destructions
protein damaging
cell degeneration

# Cellular stress responses

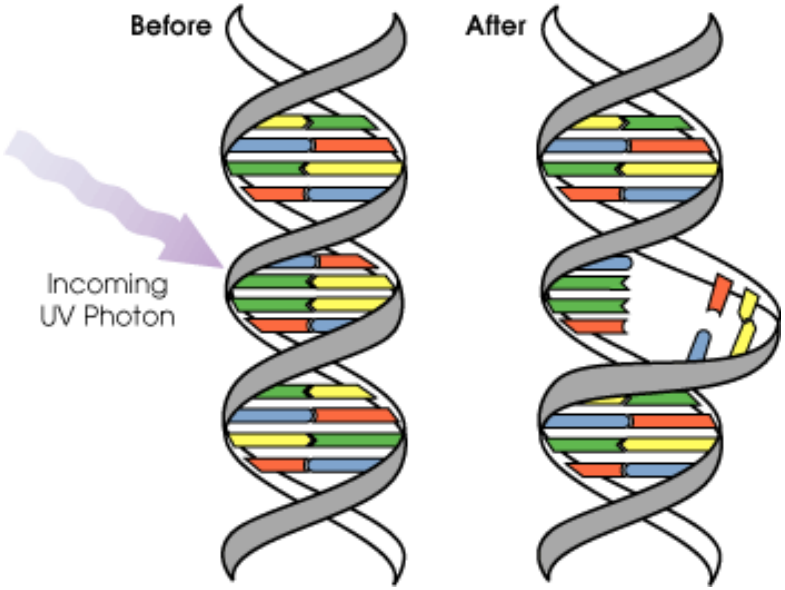


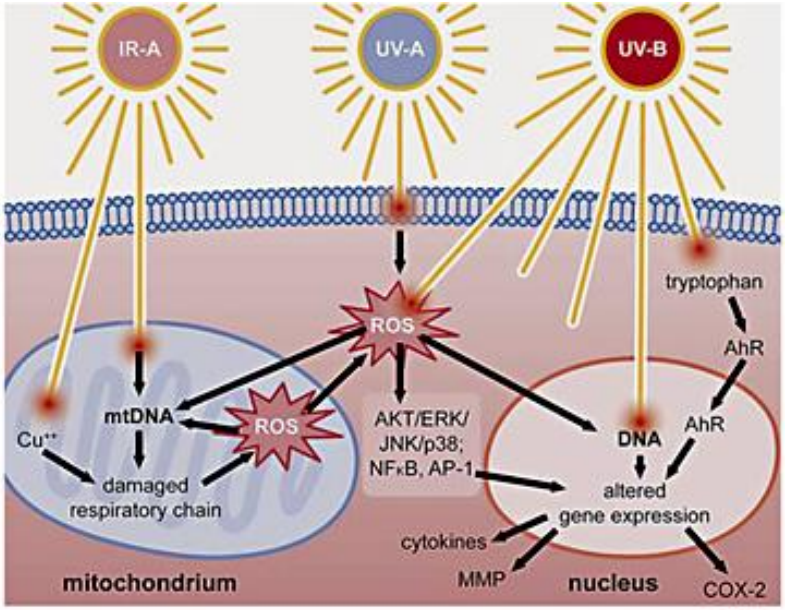


# Cellular stress responses



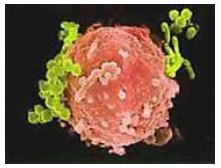
## Effects of ultraviolet radiation



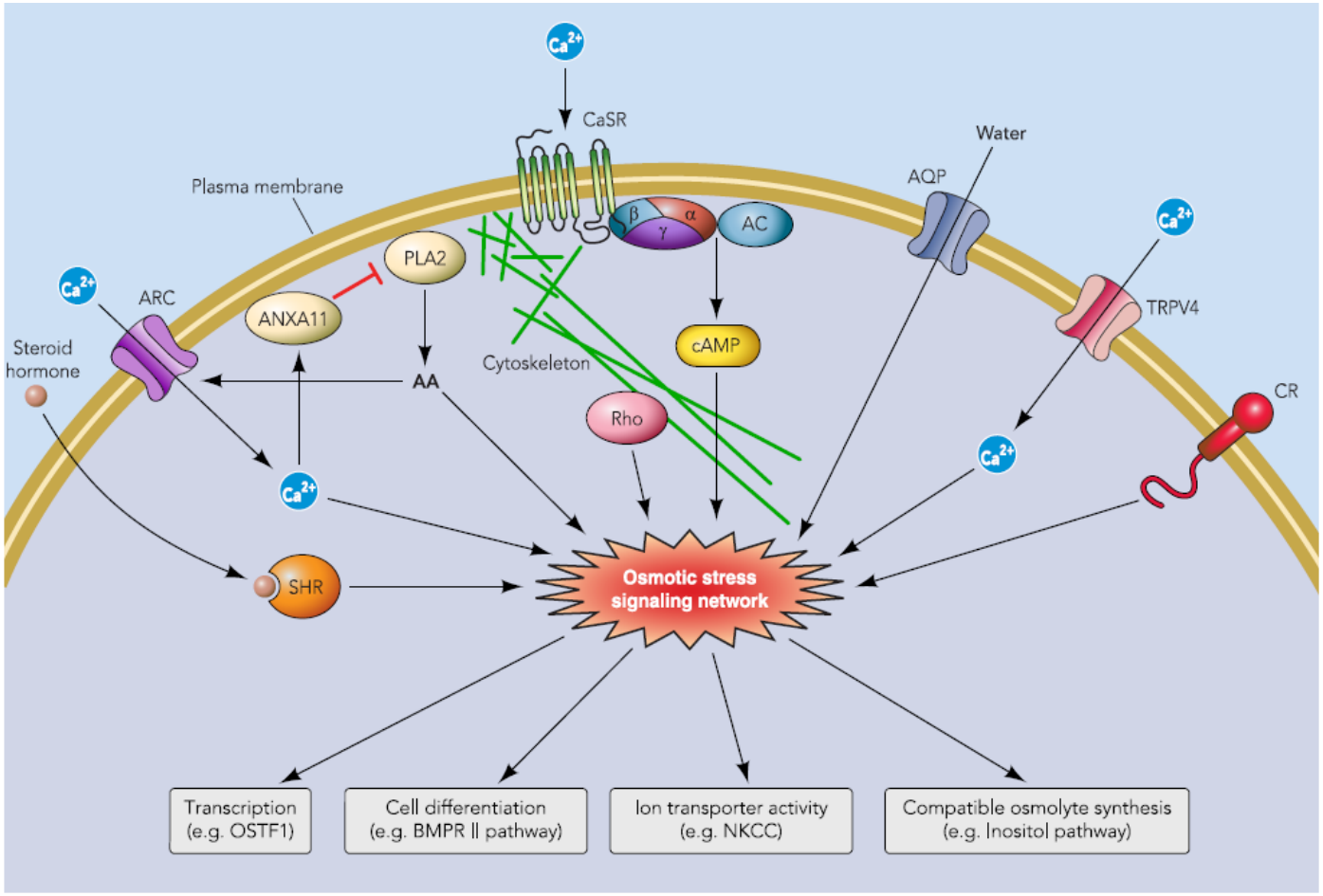



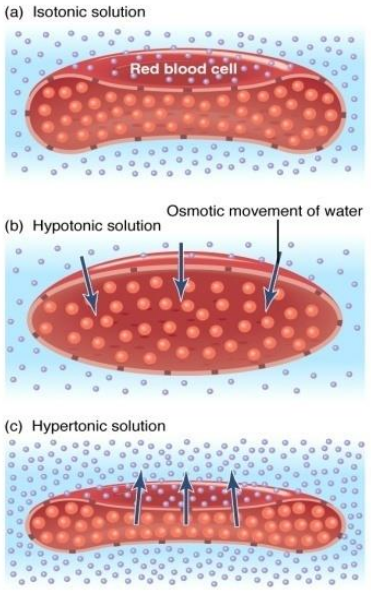

DNS damaging stress reactions cause cellular destruction.

# Cellular stress responses



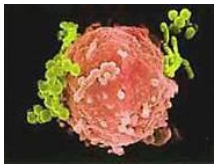
## Osmotic stress



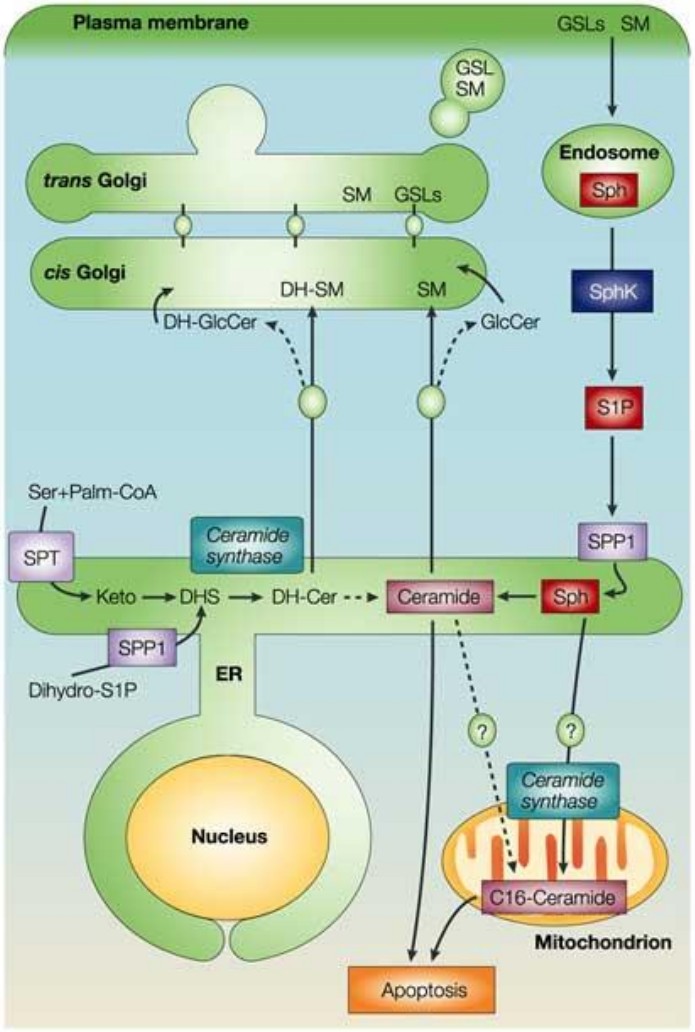




**Missregulation of water movement**

# Cellular stress responses



## Membrane synthesis problems

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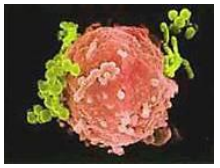
# Cellular stress responses



If the repairing processes are not effective – cell death develops

- Processes leading to degeneration - apoptosis, necrosis, autophagy

apoptosis: caspase- or calpain dependent, programed cell death, pathological process

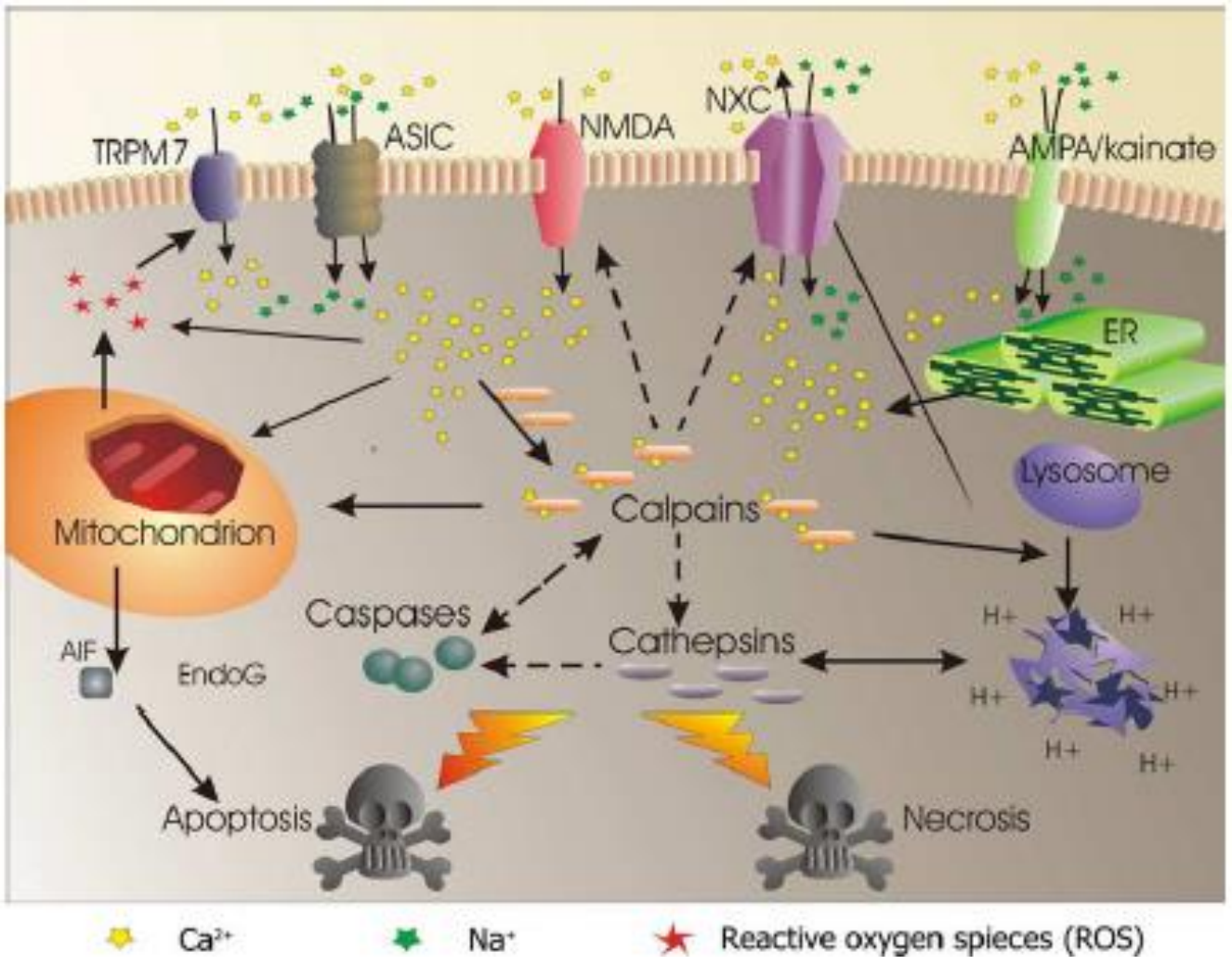
autophagy: vesicular processes taking place, abnormal metabolic pathway activations are in the background

necrosis : „accidental" cell death – swelling is characteristic (ischemia, glutamate toxicity)

Activated diseases: cancer, neurodegenerative diseases, infarcts

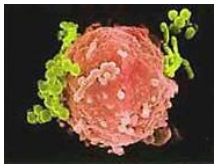
# Cellular stress responses

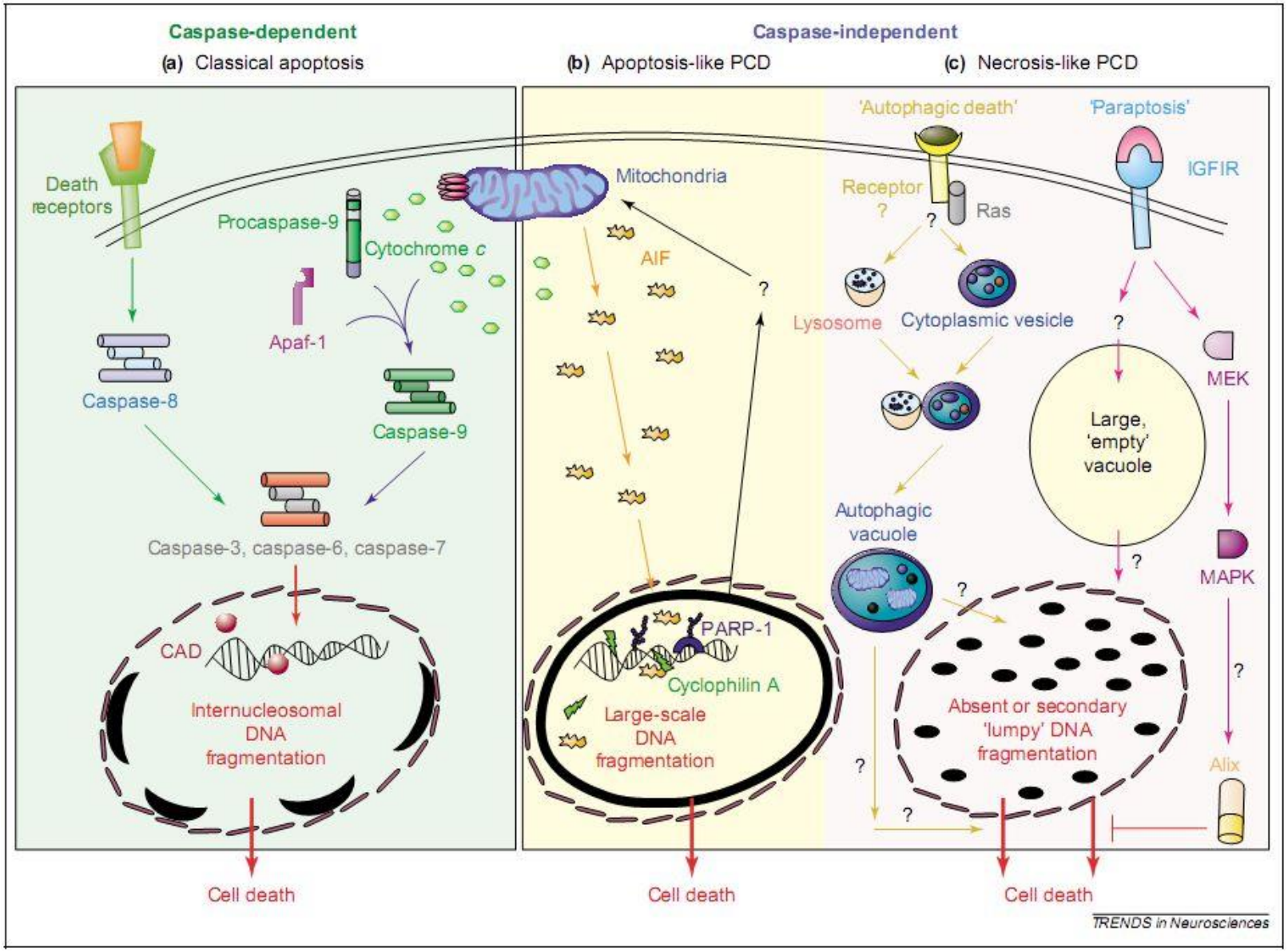
## Effects of proteases




TRPM7: transient receptor potential channel, ASIC: acid sensing ion channel, NXC: non selective ion channel

# Cellular stress responses





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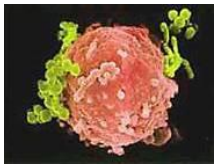
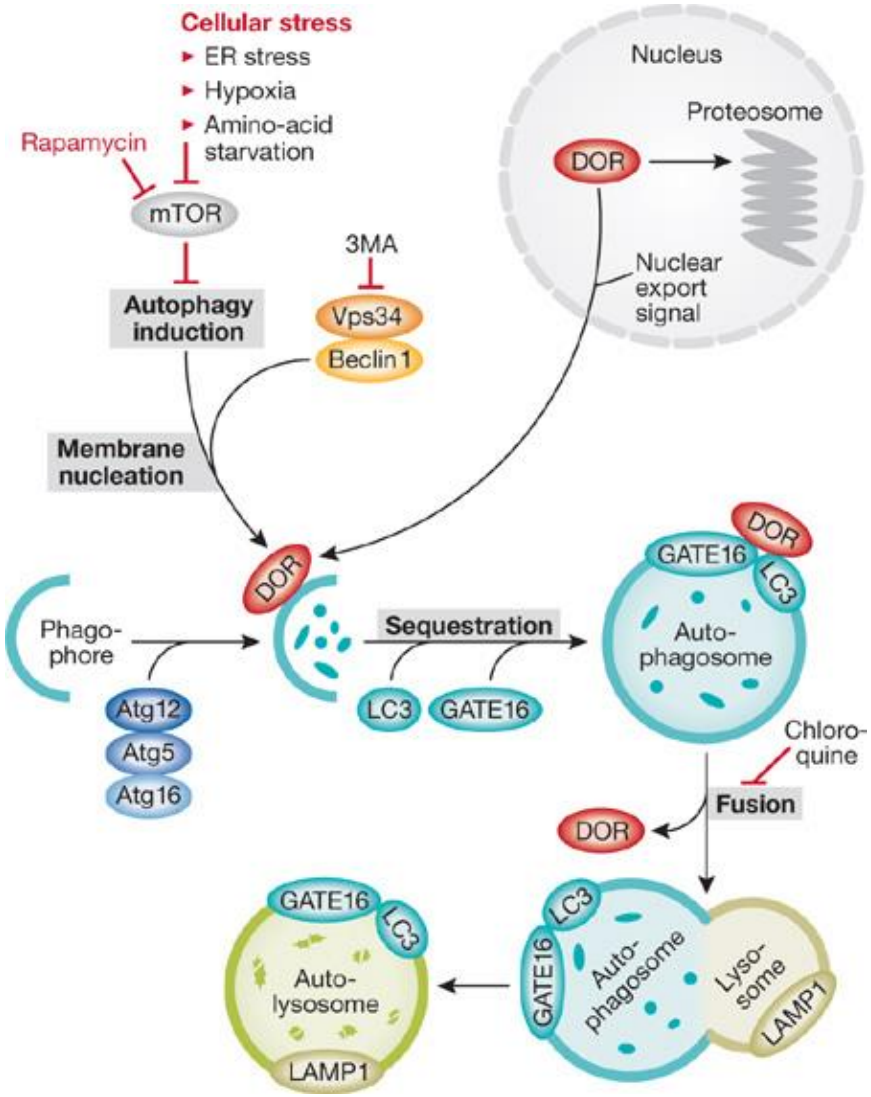
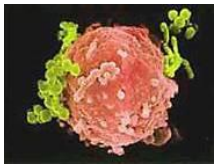


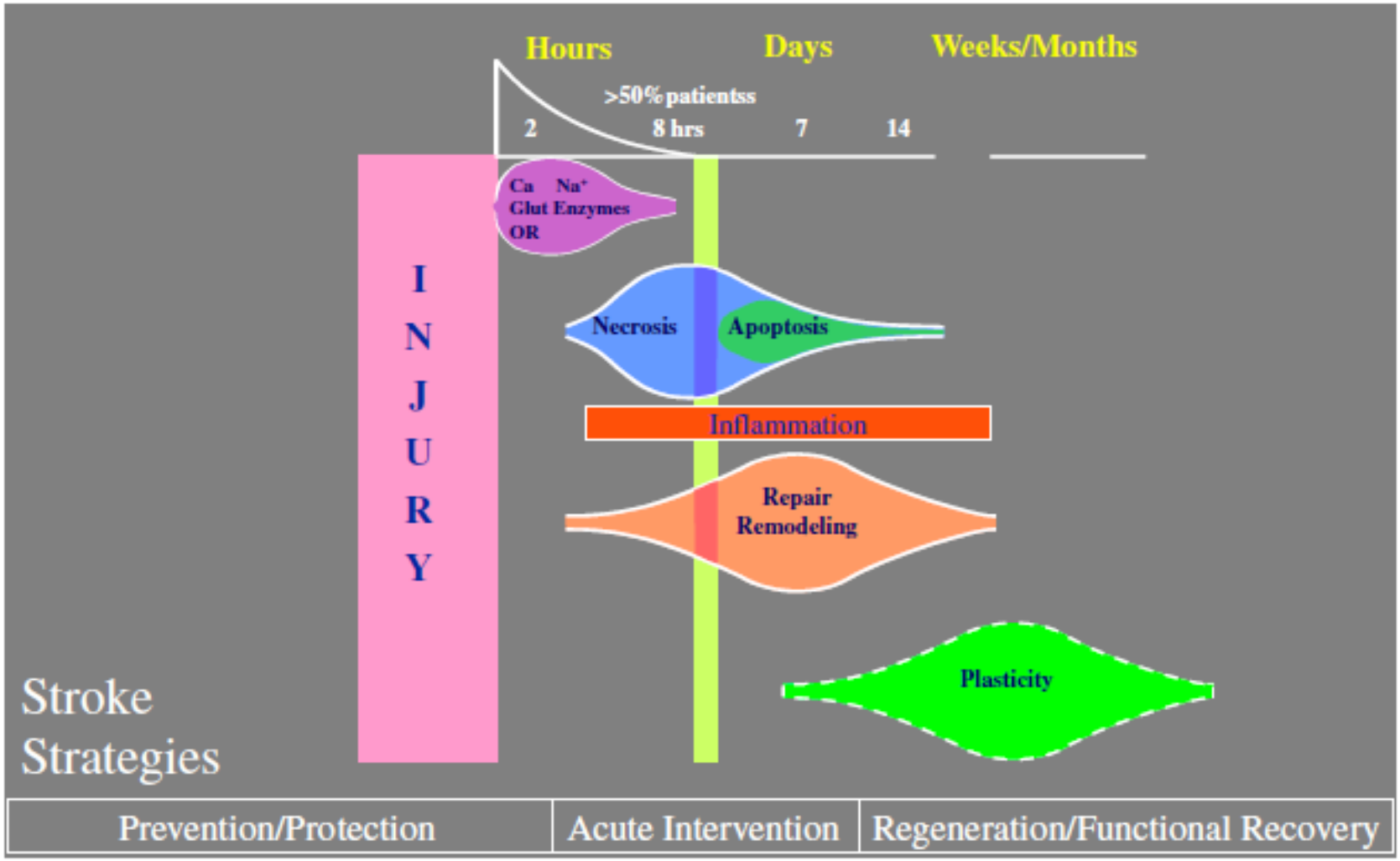



**Autophagy activation**

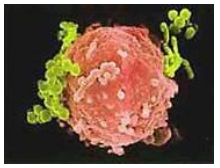
# Cellular stress responses



## Timescale of stress-activated cellular processes

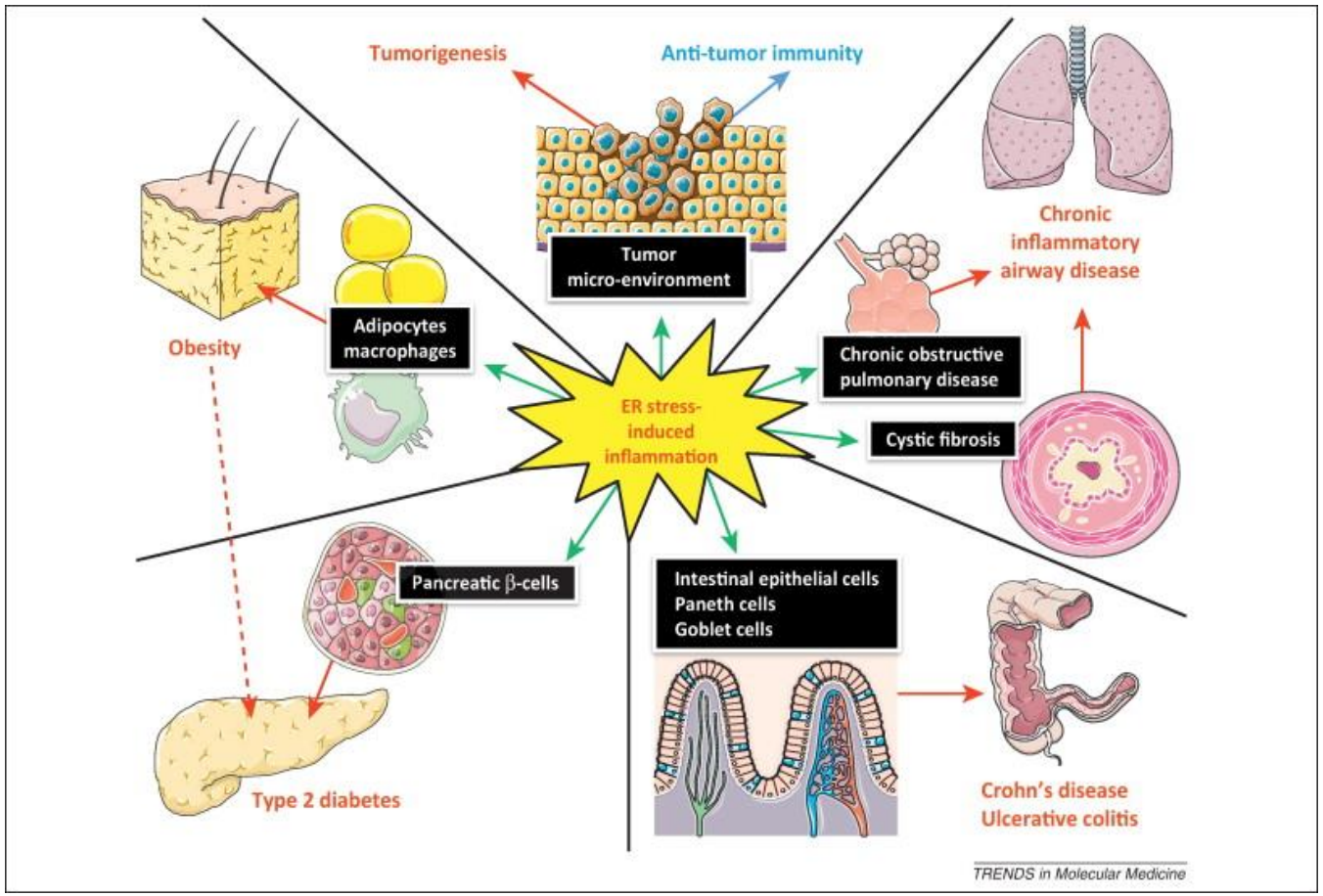


# Cellular stress responses

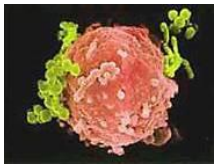


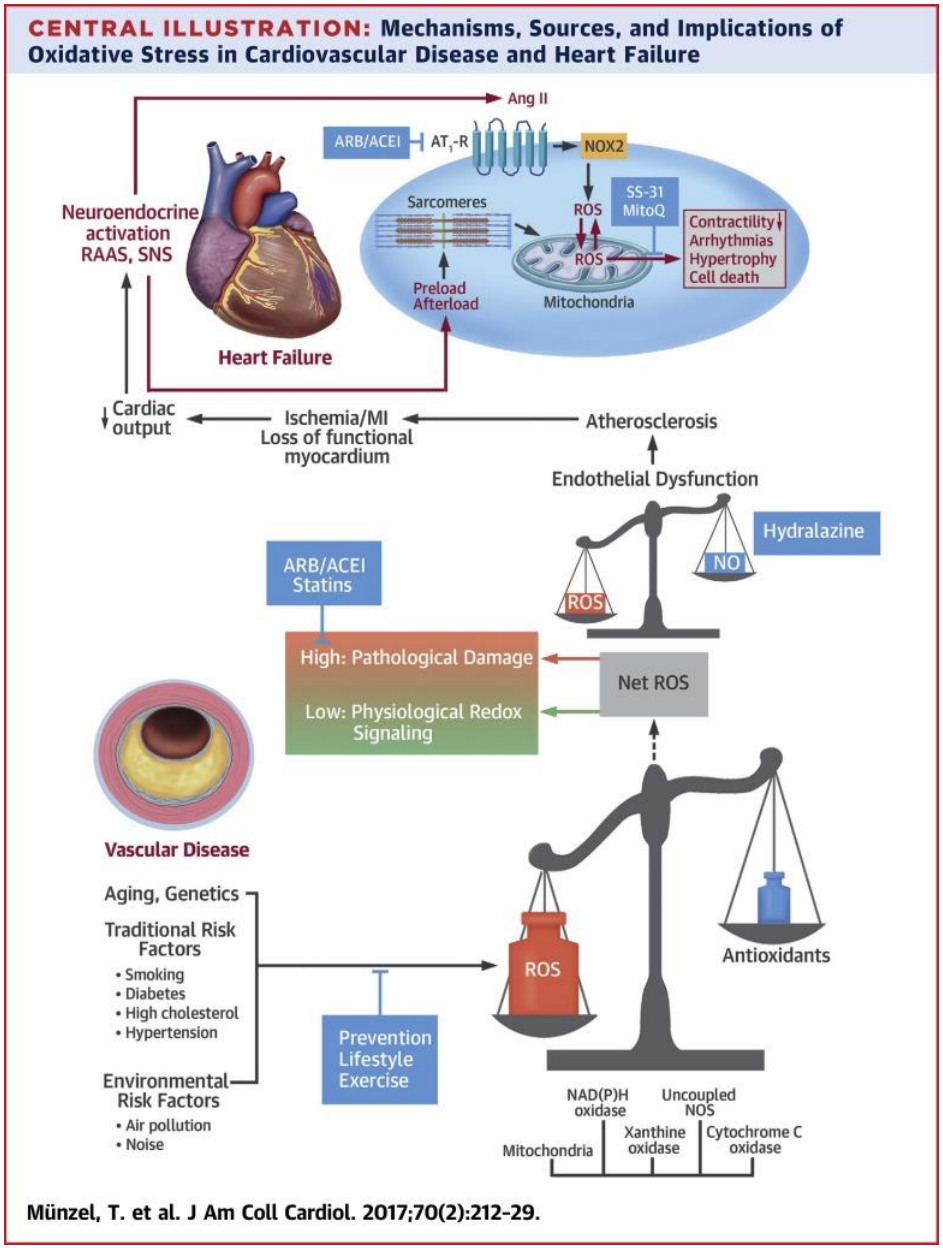
## Diseases develop as a consequence of cellular damage

autoimmune diseases
heart attack
Parkinsonian disease
Alzheimer disease
mitochondrial dysfunction

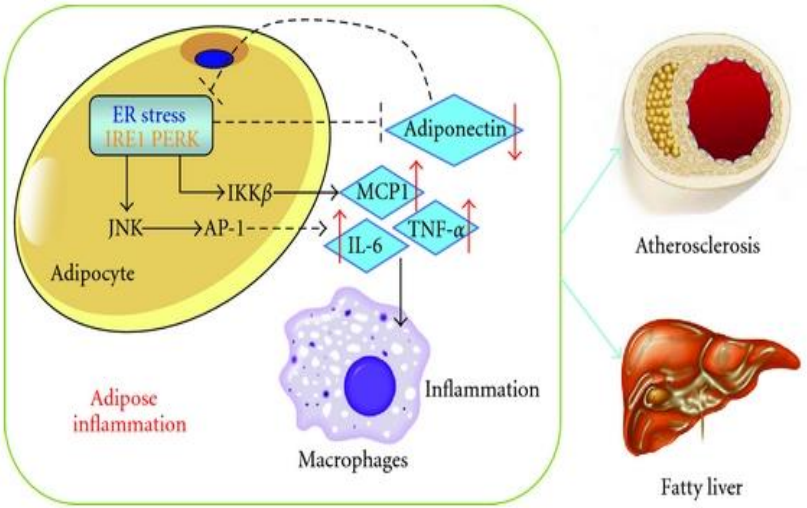


# Cellular stress responses

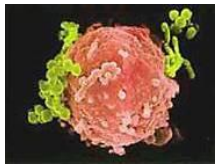




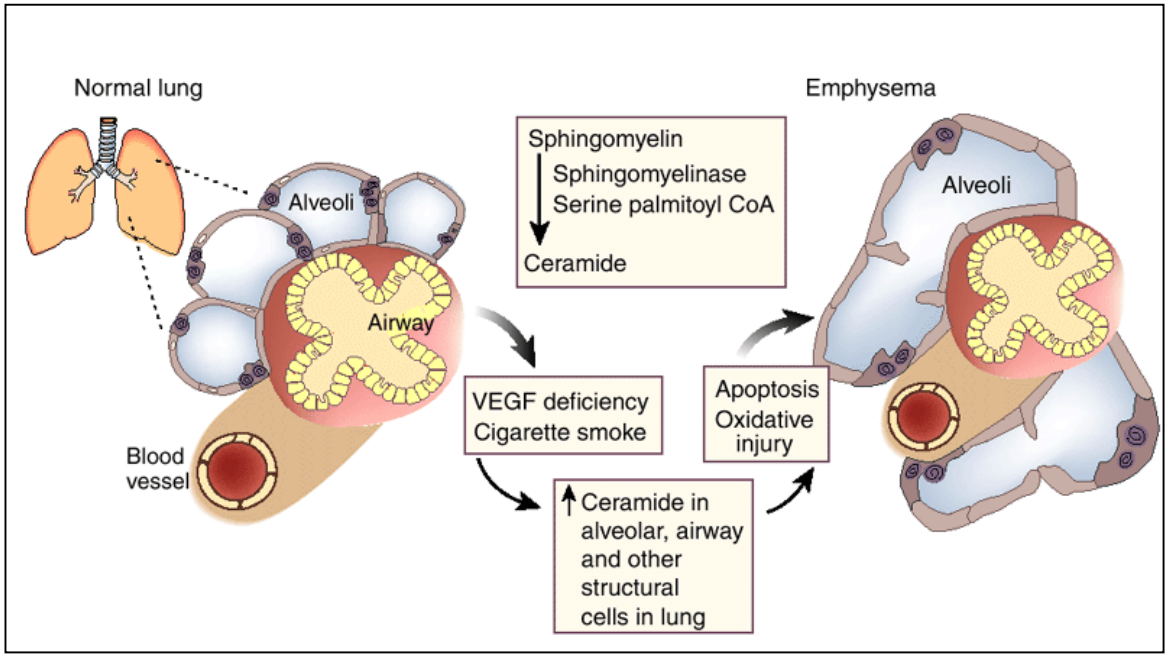

Münzel, T. et al. J Am Coll Cardiol. 2017;70(2):212-29.



# Cellular stress responses

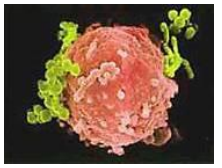


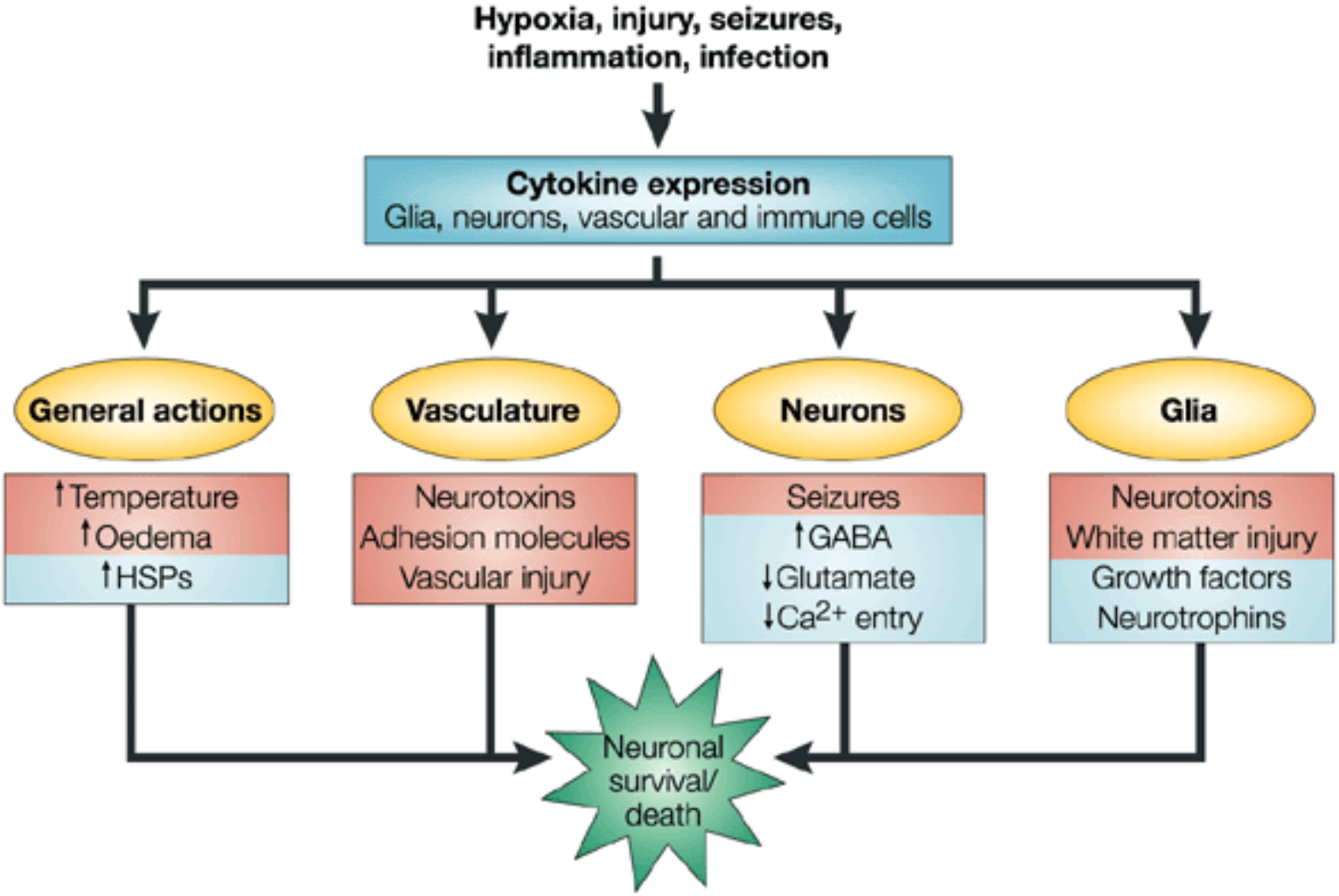
## Lung destruction




**Pathological ceramide synthesis in the alveoli**
**Smoking induce altered ceramide synthesis, the (membrane)structure of the endothelian and epithelian cell will change**

# Cellular stress responses



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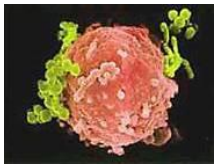
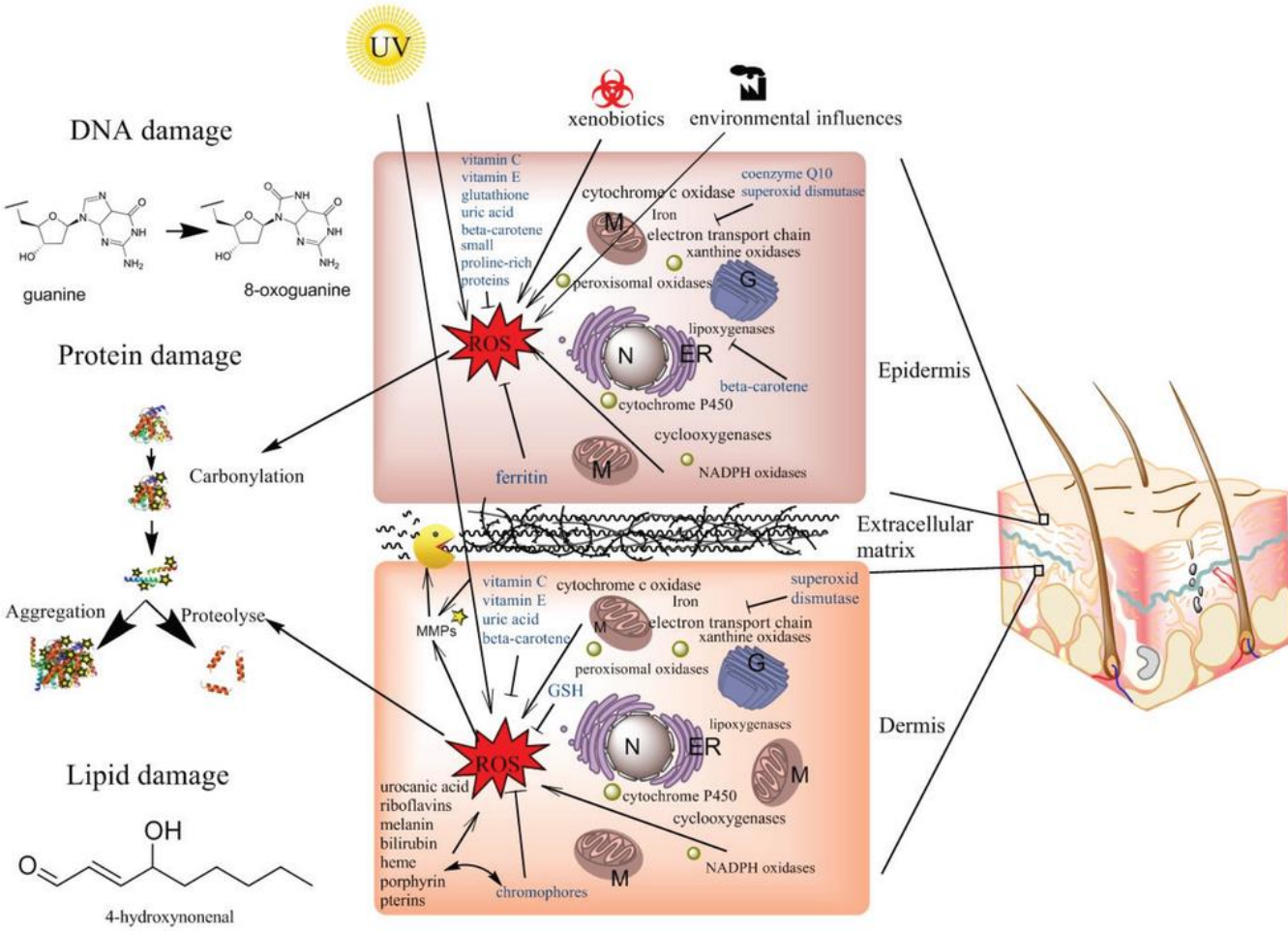
# Cellular stress responses

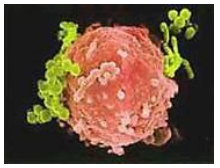


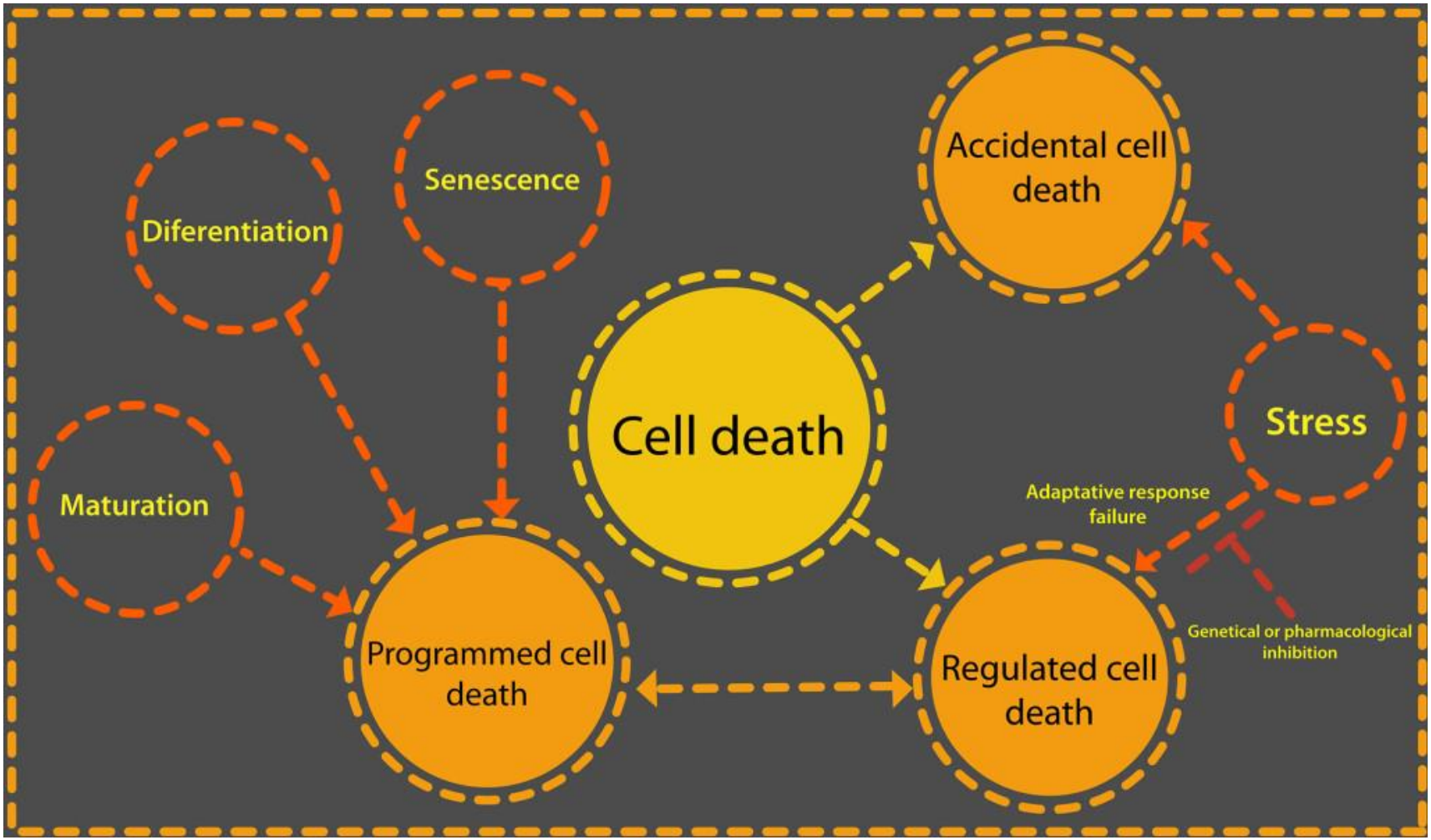
## Environmental effects

**Different effects on the skin in twins**



# Cellular stress responses






Thanks for the attention