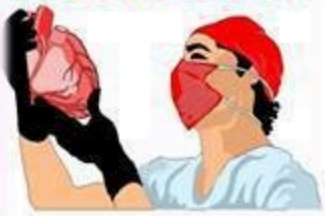
PATHOLOGY



Medical Committee
The University of Jordan

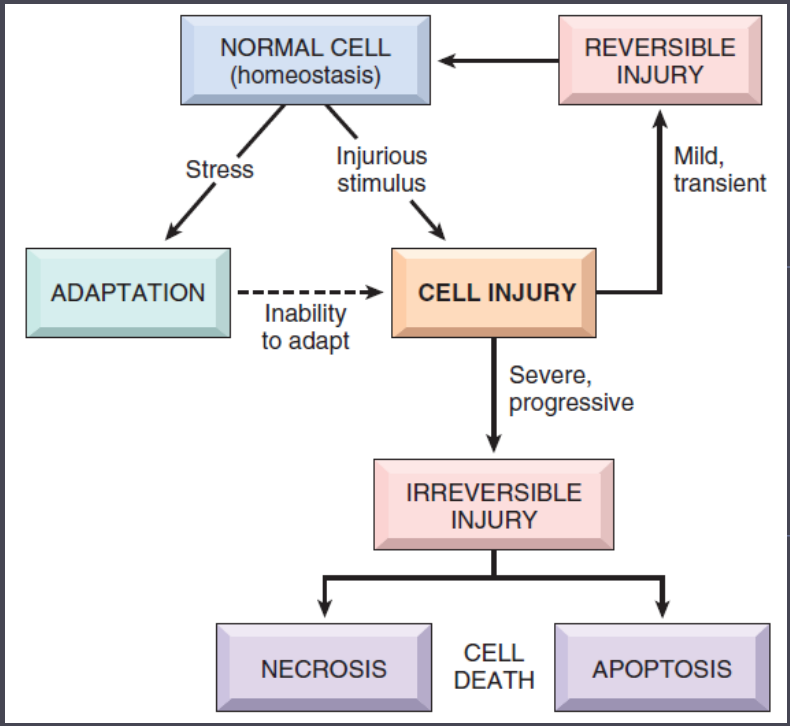
☐ SHEET

■ SIIDE

Slide : 2- Cell Injury

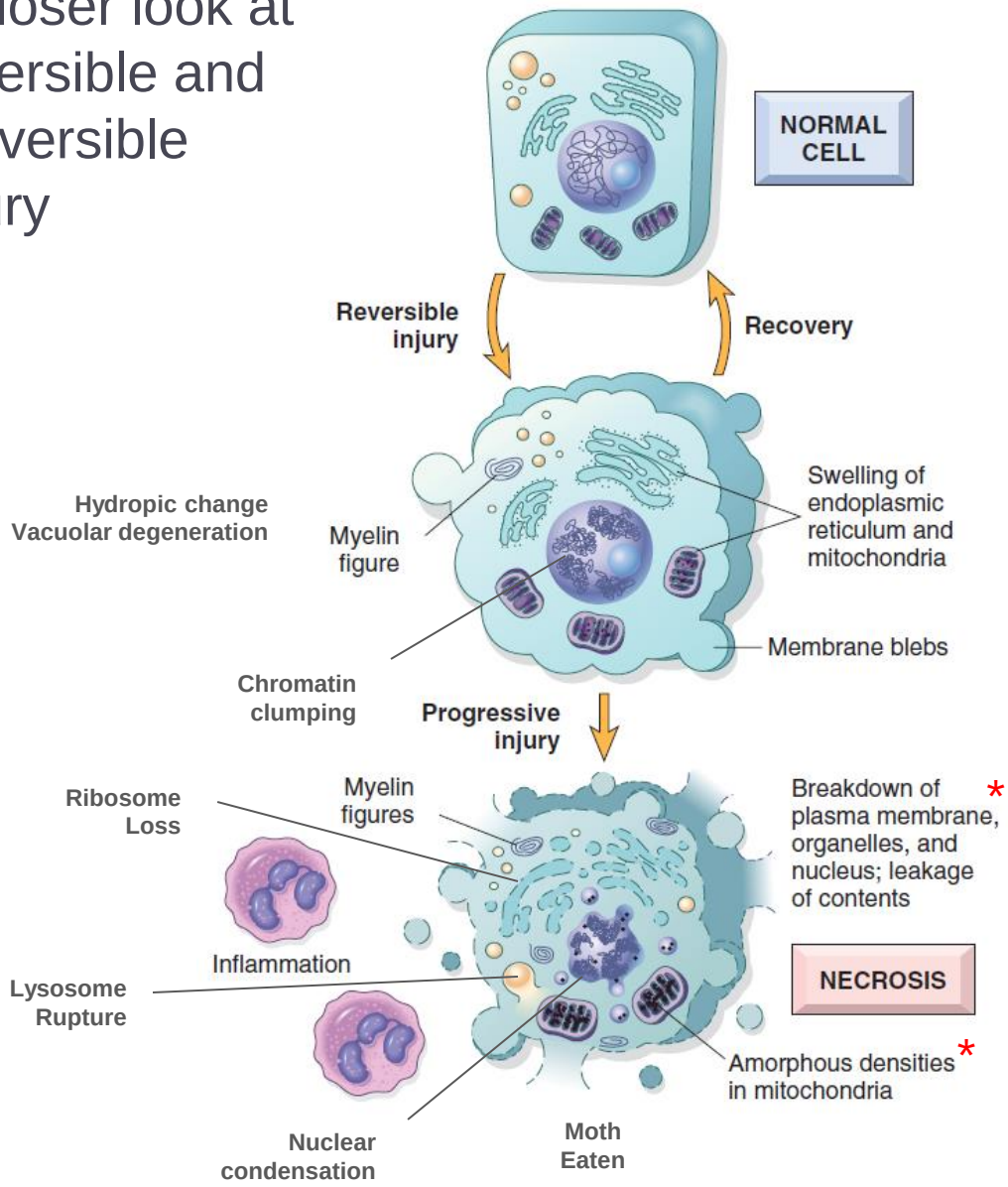
Doctor: Mazen Al-Salhi

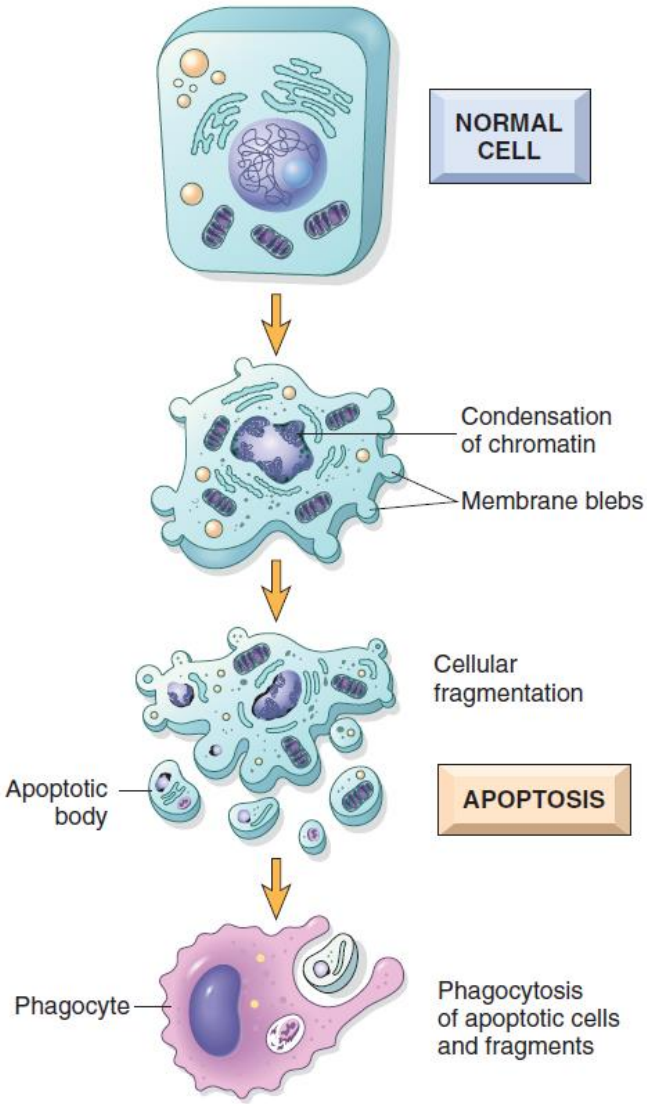
Designed by: Majida Al-Foqara'



Cell Injury & Death

A closer look at reversible and irreversible injury





- * Irreversible membrane dysfunction & mitochondrial dysfunction ≈ Irreversible injury

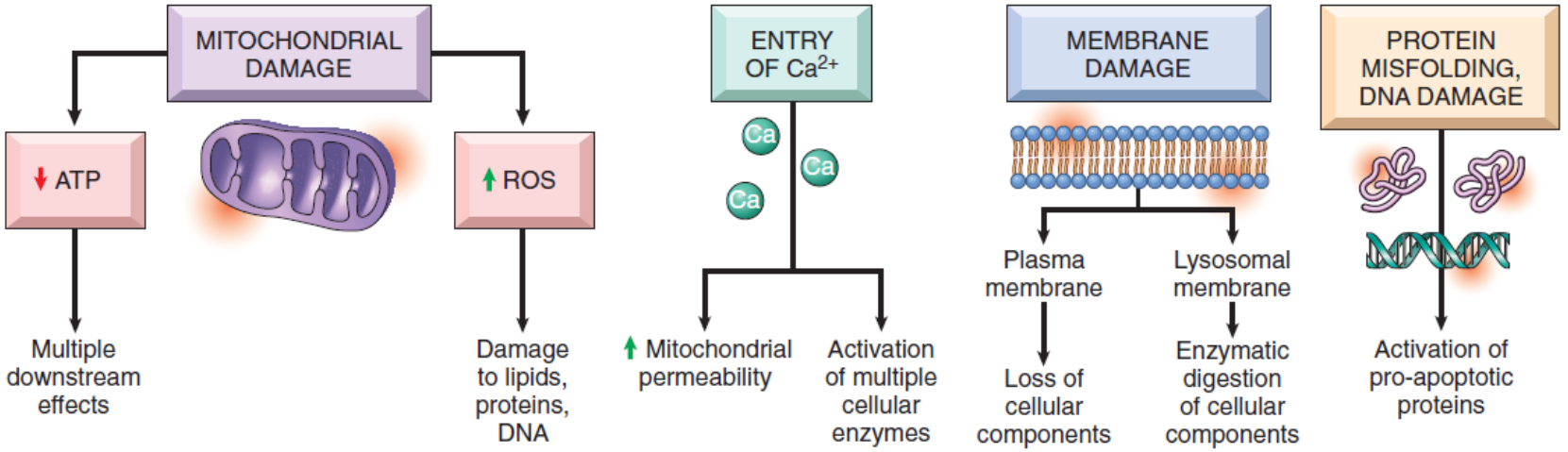
Causes and Mechanisms of Cell injury

Causes of Cell Injury Quiz!

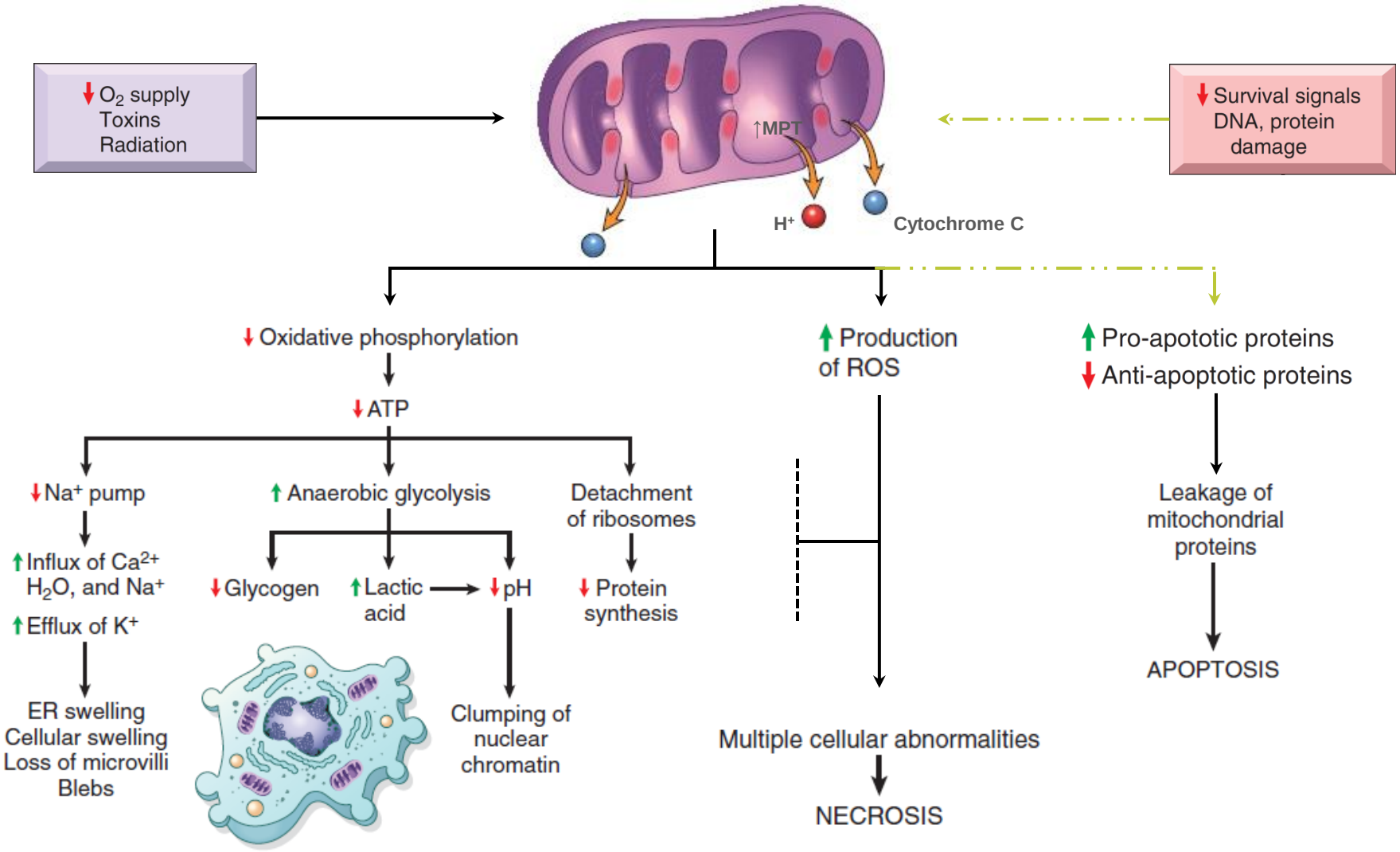
- Hypoxia and ischemia
- “Chemical” agents
- “Physical” agents
- Infections
- Immunological reactions
- Genetic defects
- Nutritional defects
- Aging

Principles & mechanisms of cell injury

- Injury outcome depends on:
  - Injury
    - Type
    - Duration
    - Dose
  - Cell
    - Type (including genetic makeup and polymorphisms)
    - Adaptability (including basal state)

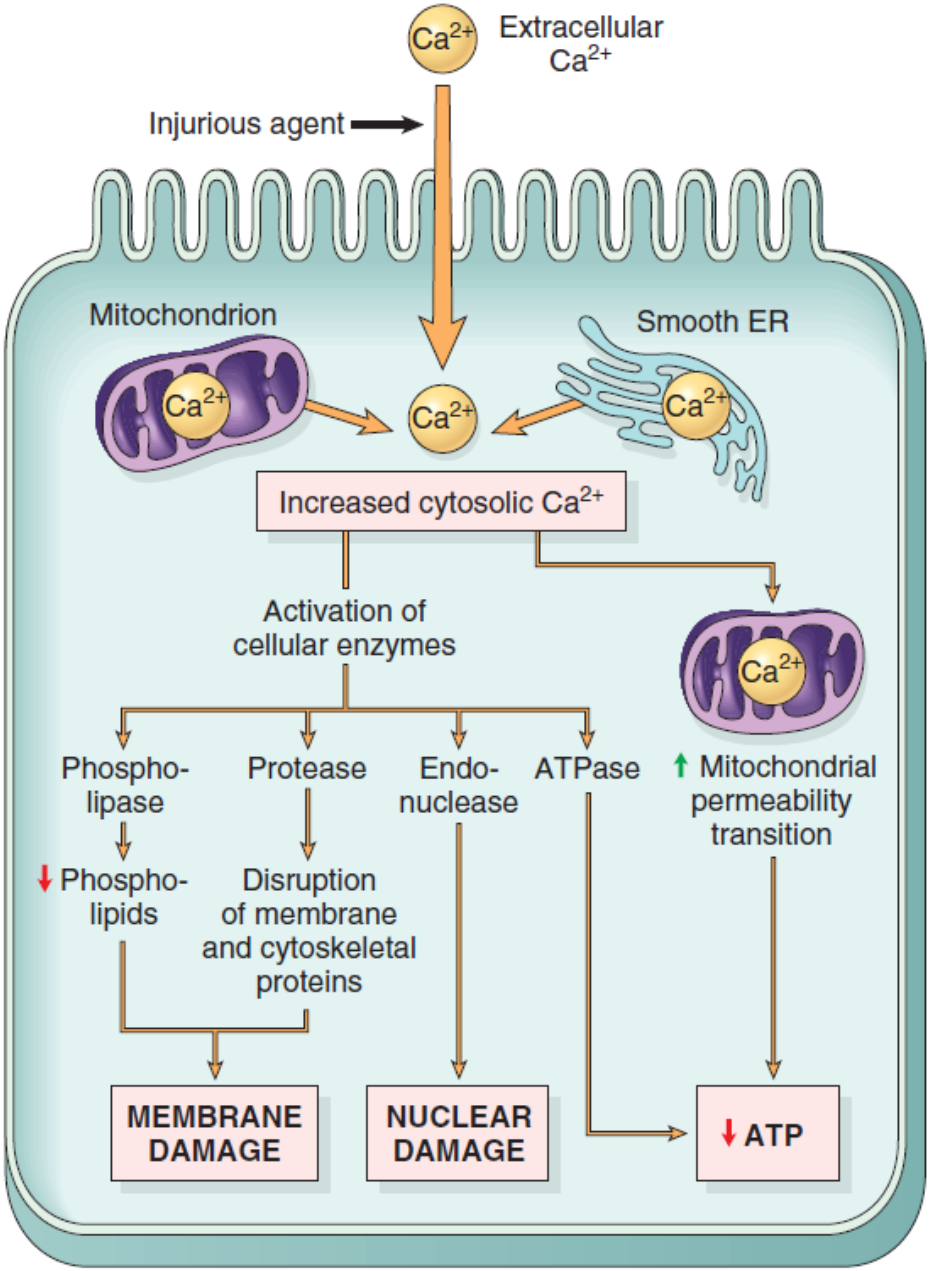


Mitochondria

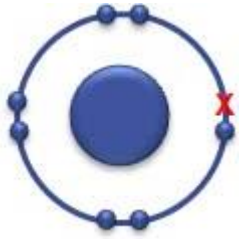


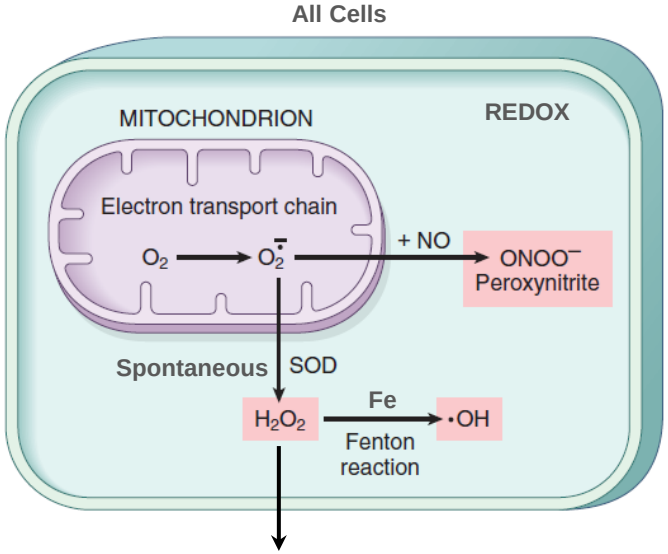
Ca^{2+} influx

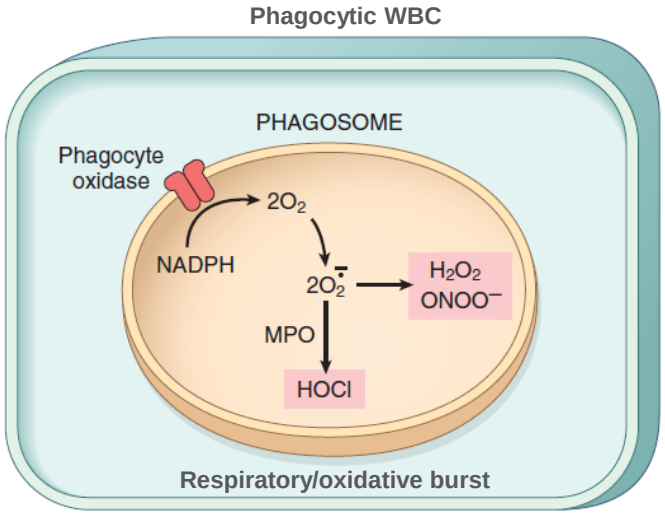
- 10,000x difference in conc.
- ATP dependent conc. Gradient
- Low EC Ca^{2+} delays cell death

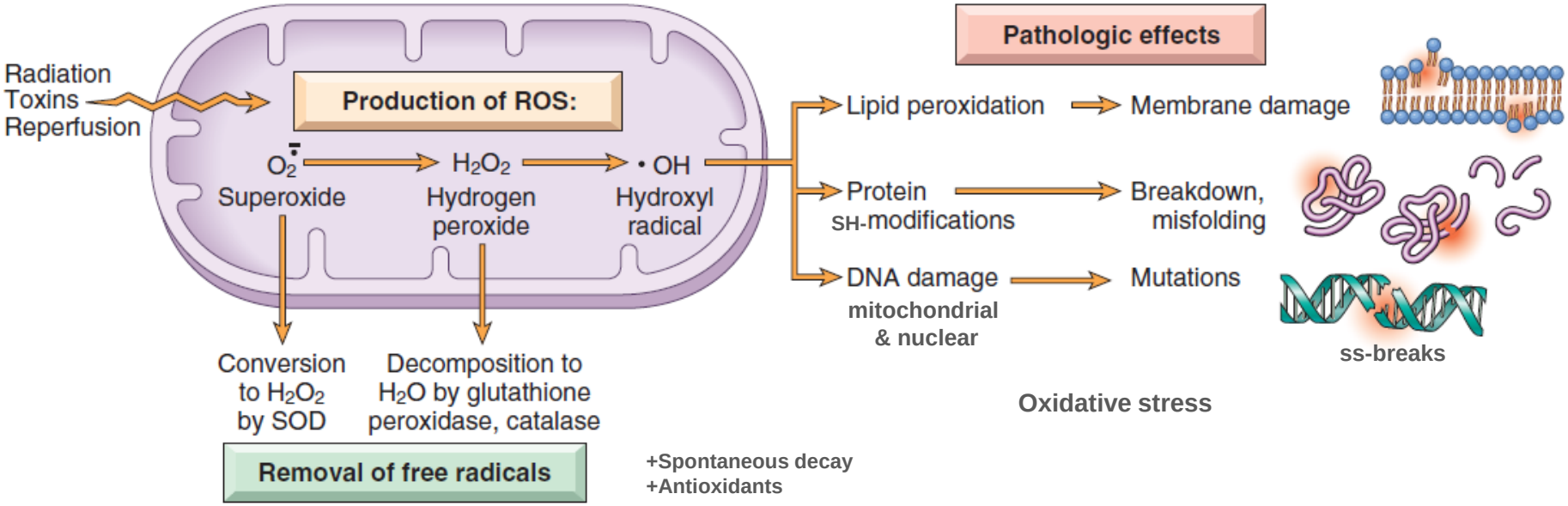


Free radicals & ROS

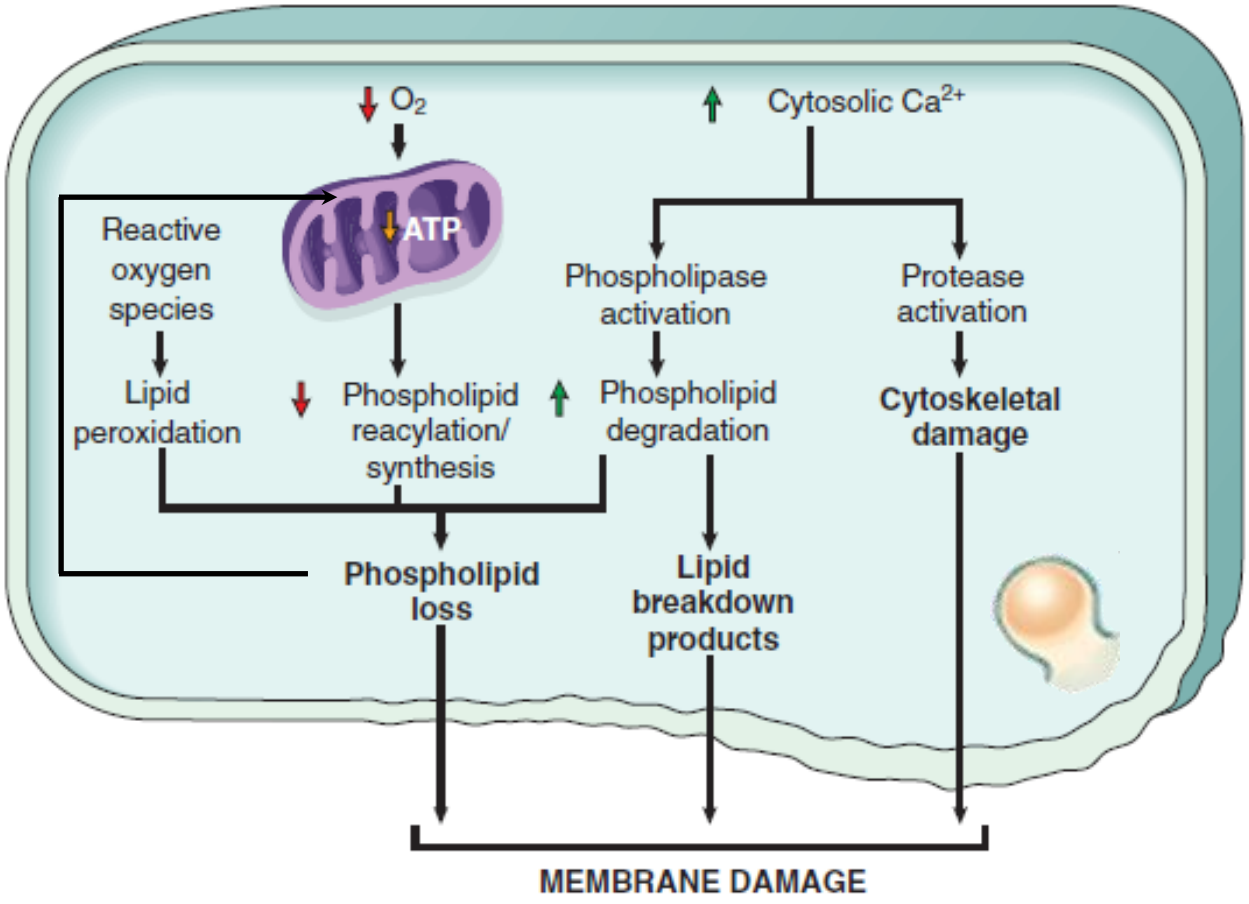








Membrane damage



Causes and Mechanisms of Cell injury in practice

Hypoxia
Ischemia

2

*

1

↓ Oxidative phosphorylation

↓ ATP

↓ Protein synthesis

↓ Glycogen

↑ Lactic acid

Pump failure cell swelling

↓ pH

↑ Influx of Ca^{2+}

↑ Mitochondrial permeability transition

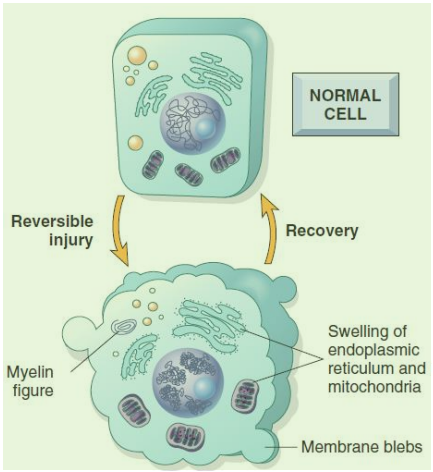
+

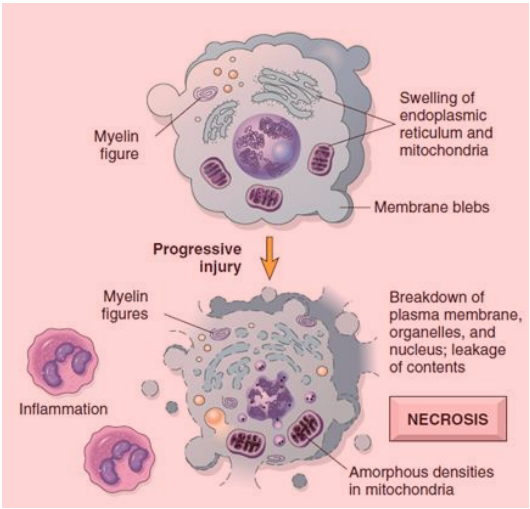
Activation of cellular enzymes

Accumulation of ROS

Phospholipid loss

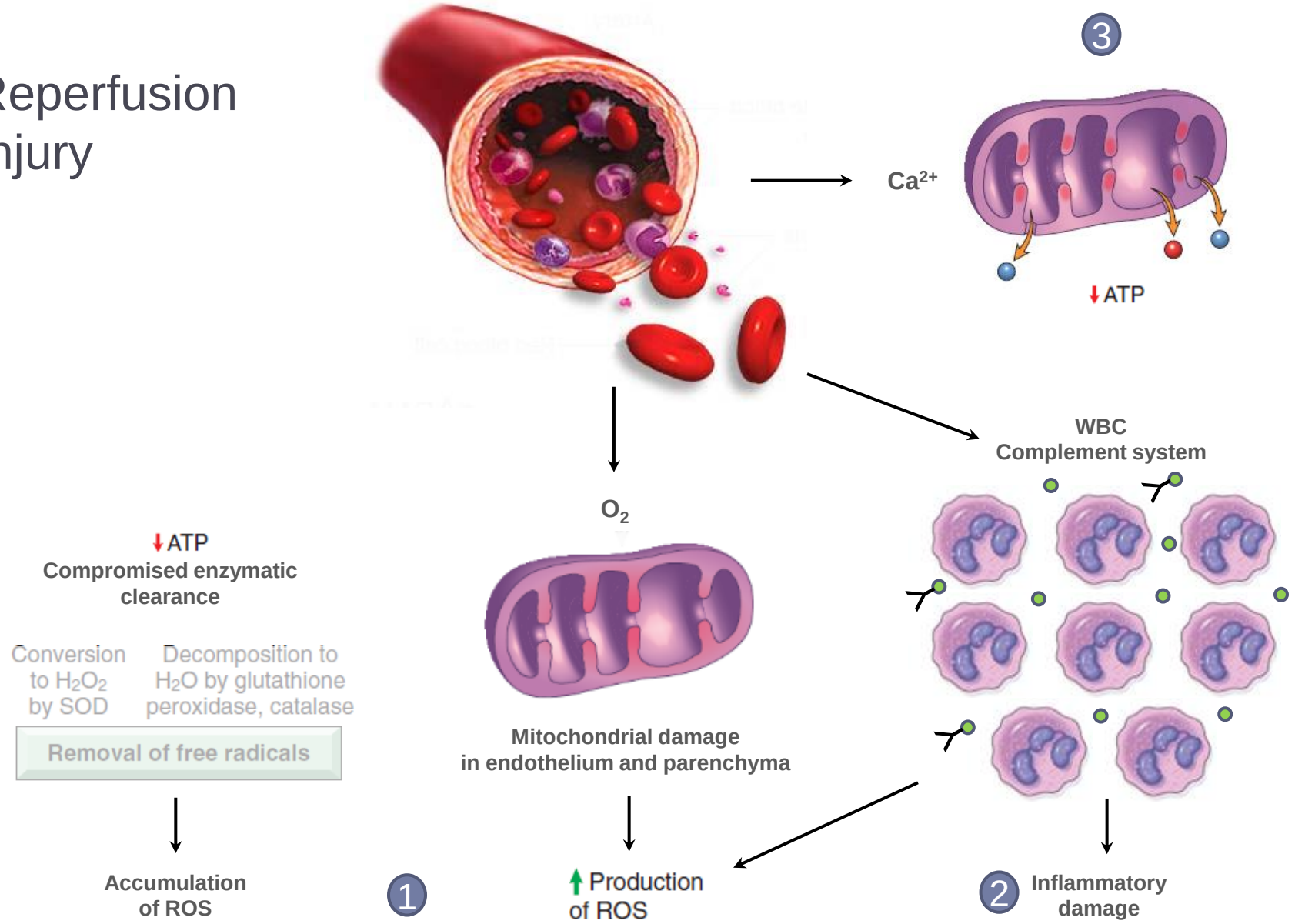
3





* Some apoptosis may also occur due to leakage of pro-apoptotic molecules

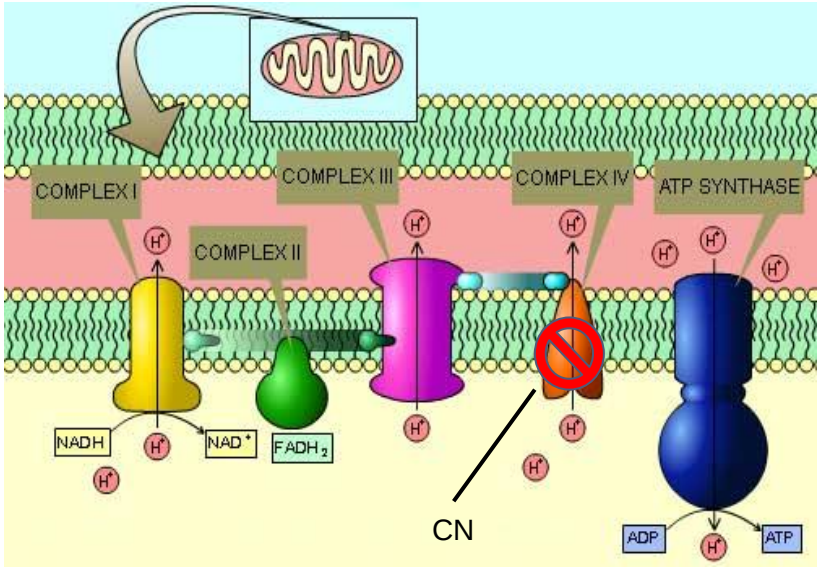
Reperfusion Injury



Chemical (Toxic) Injury

Direct toxicity

- Cyanide



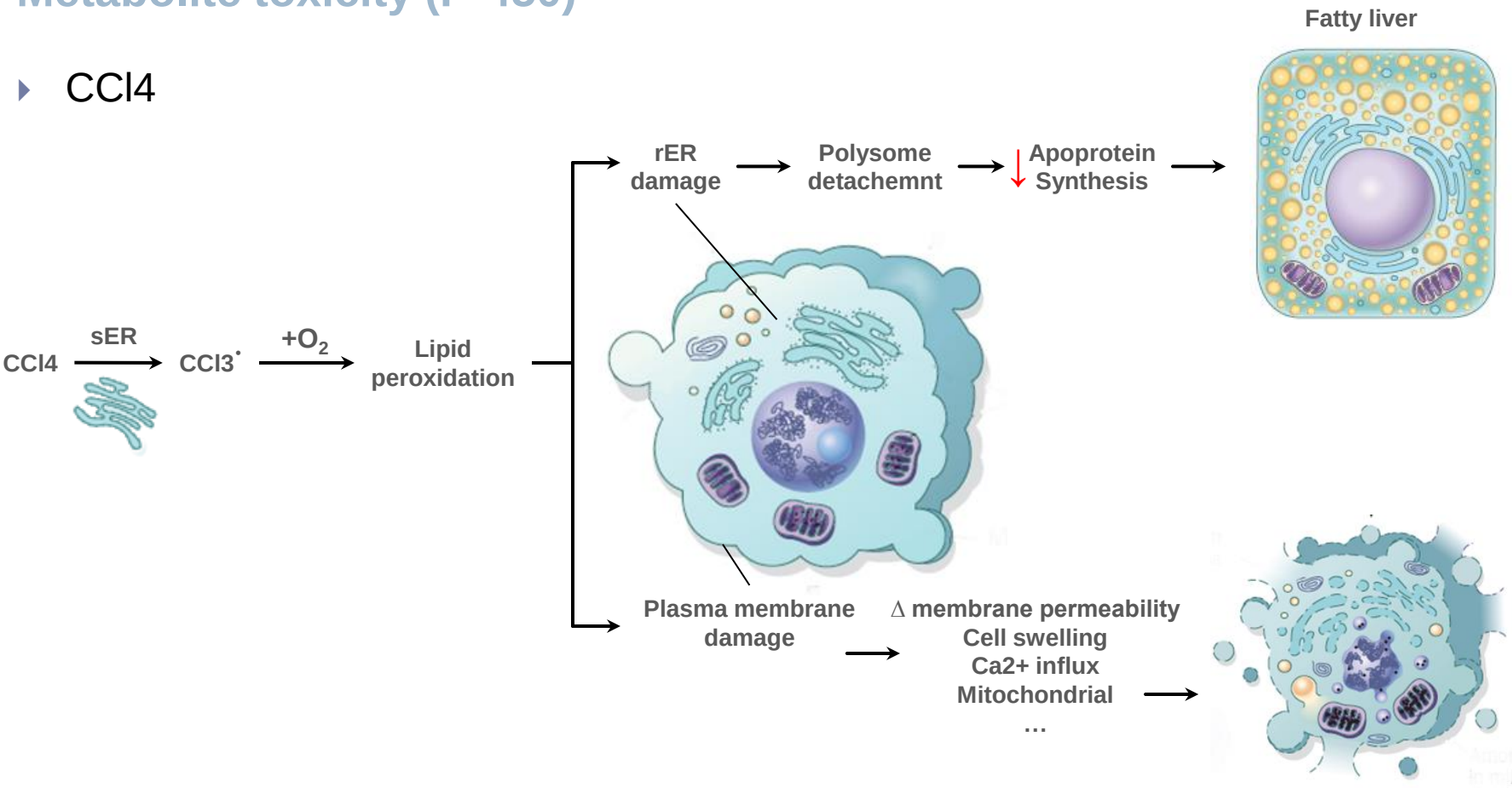
- Mercuric chloride (seafood)
  - SH-membrane proteins
  - Δ membrane permeability

The greatest damage is usually to the cells that use, absorb, excrete, or concentrate the chemicals.

Chemical (Toxic) Injury

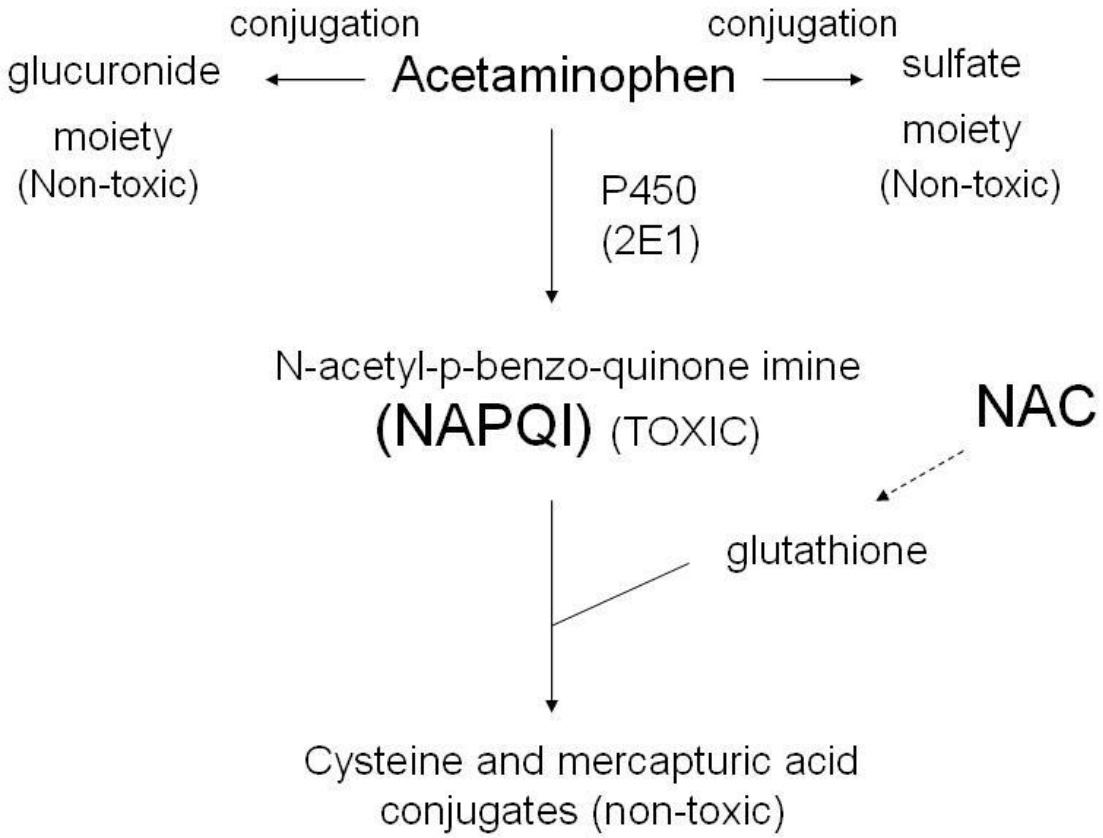
Metabolite toxicity (P-450)

- CCl4



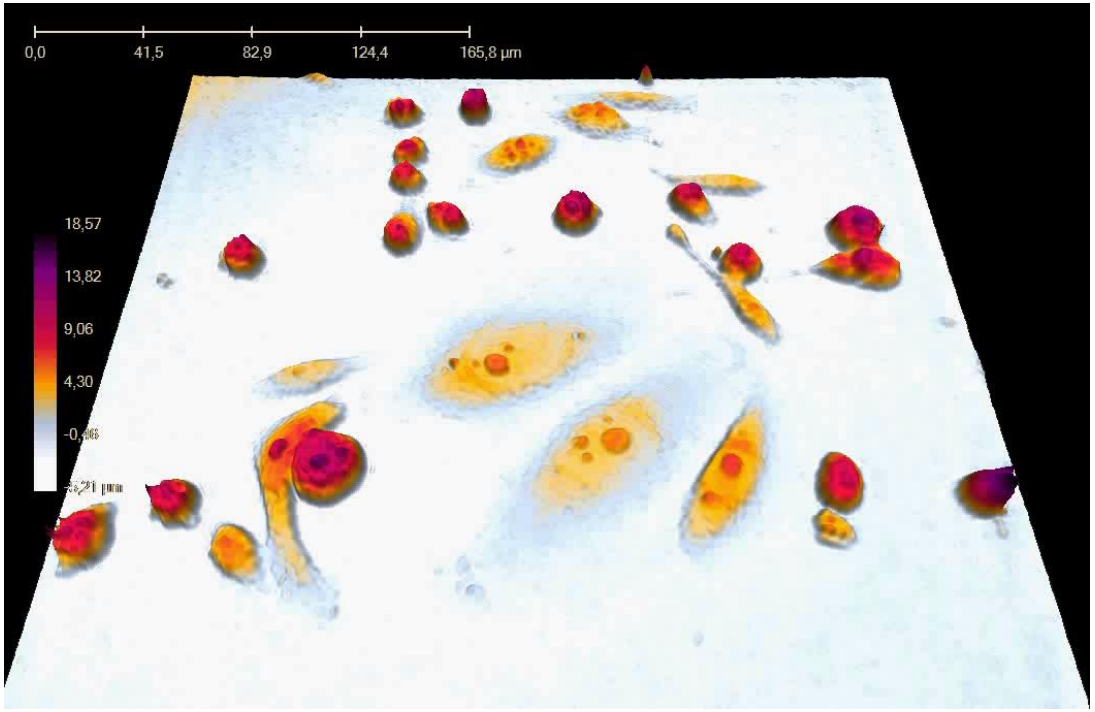
Chemical (Toxic) Injury

Metabolite toxicity (P-450)



Apoptosis

To fall away from (Ancient Greek)



Definition

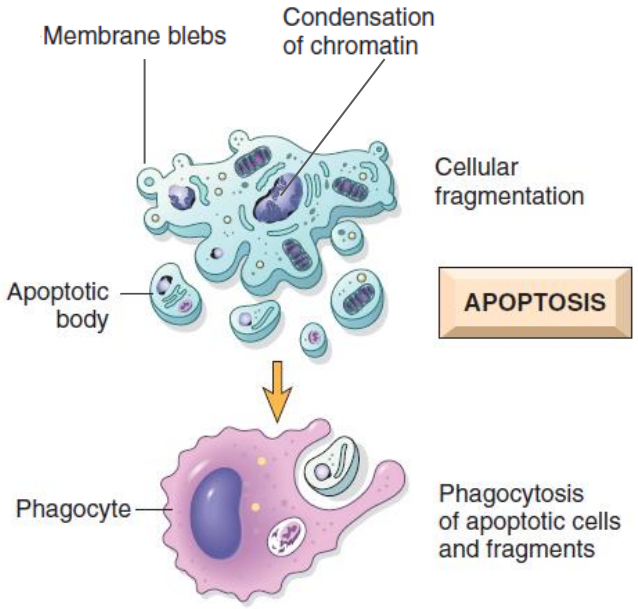
“Apoptosis is a pathway of cell death in which cells activate enzymes that degrade the cells’ own nuclear DNA and nuclear and cytoplasmic proteins.”

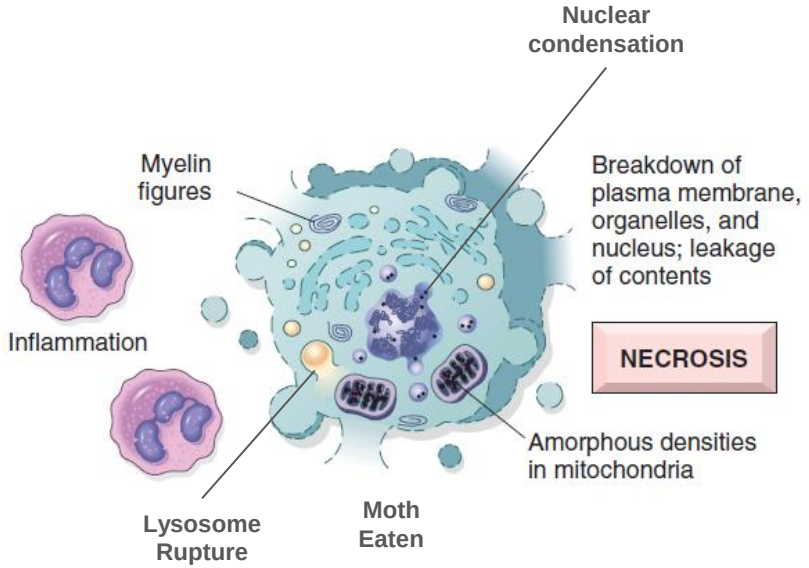
“a genetically determined process of cell self-destruction”

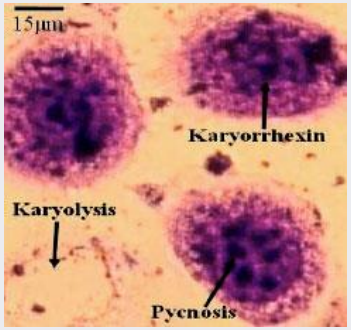
“a form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area”

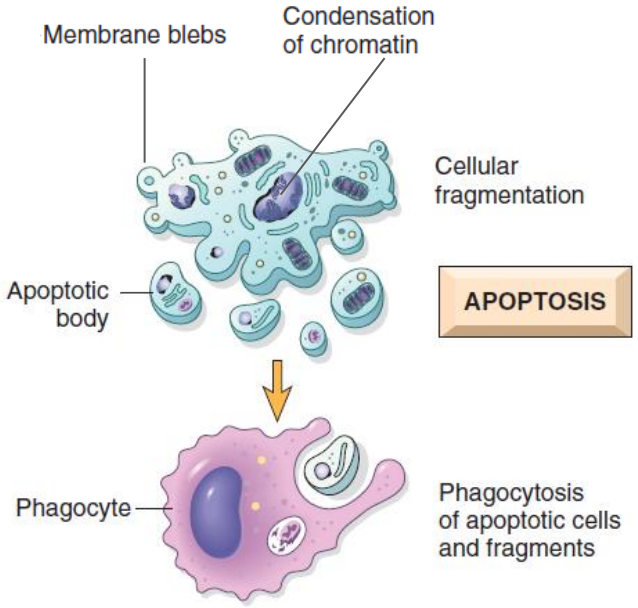
“Programmed cell death”

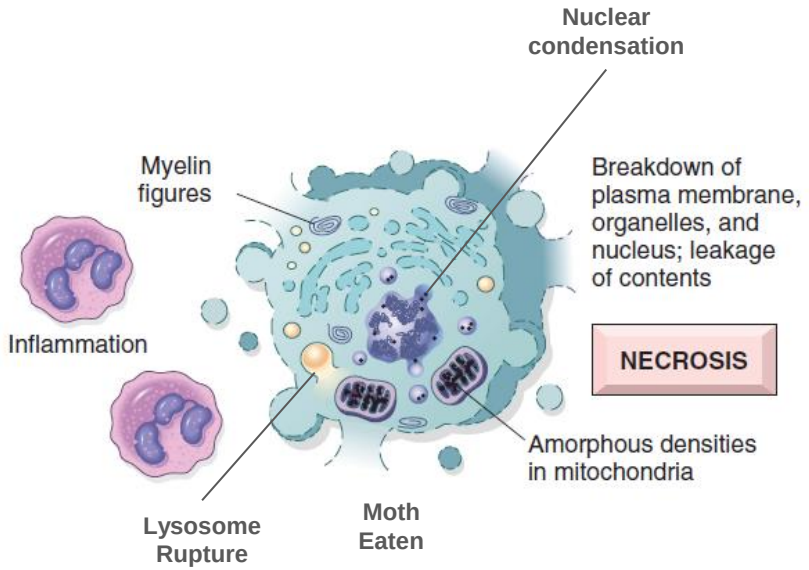
Feature	Apoptosis	Necrosis
Plasma membrane	Intact, altered structure	disrupted
Cellular contents	Intact, release in apoptotic bodies	Enzymatic digestion, leakage
Adjacent inflammation	No	Frequent
Physiologic vs pathologic	Often, but not always, physiologic	Always pathologic





Feature	Apoptosis	Necrosis
Cell size	Reduced	Enlarged
Nucleus	Fragmentation into nucleosome size fragments (Karyorrhexis)	Karyolysis, Karyorrhexis, Pyknosis 





Causes & Mechanisms of Apoptosis

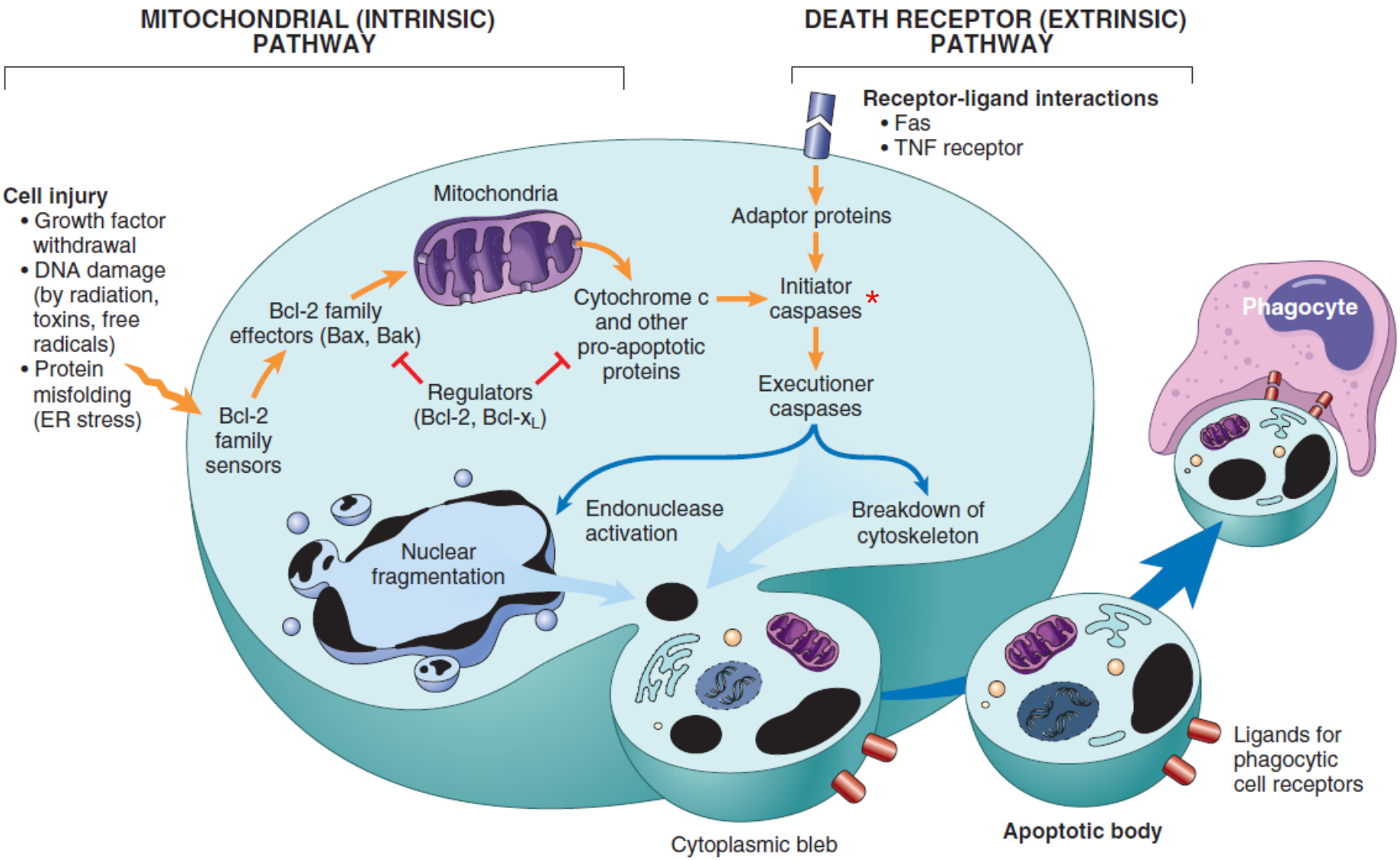
Causes of Apoptosis Quiz!

Physiologic

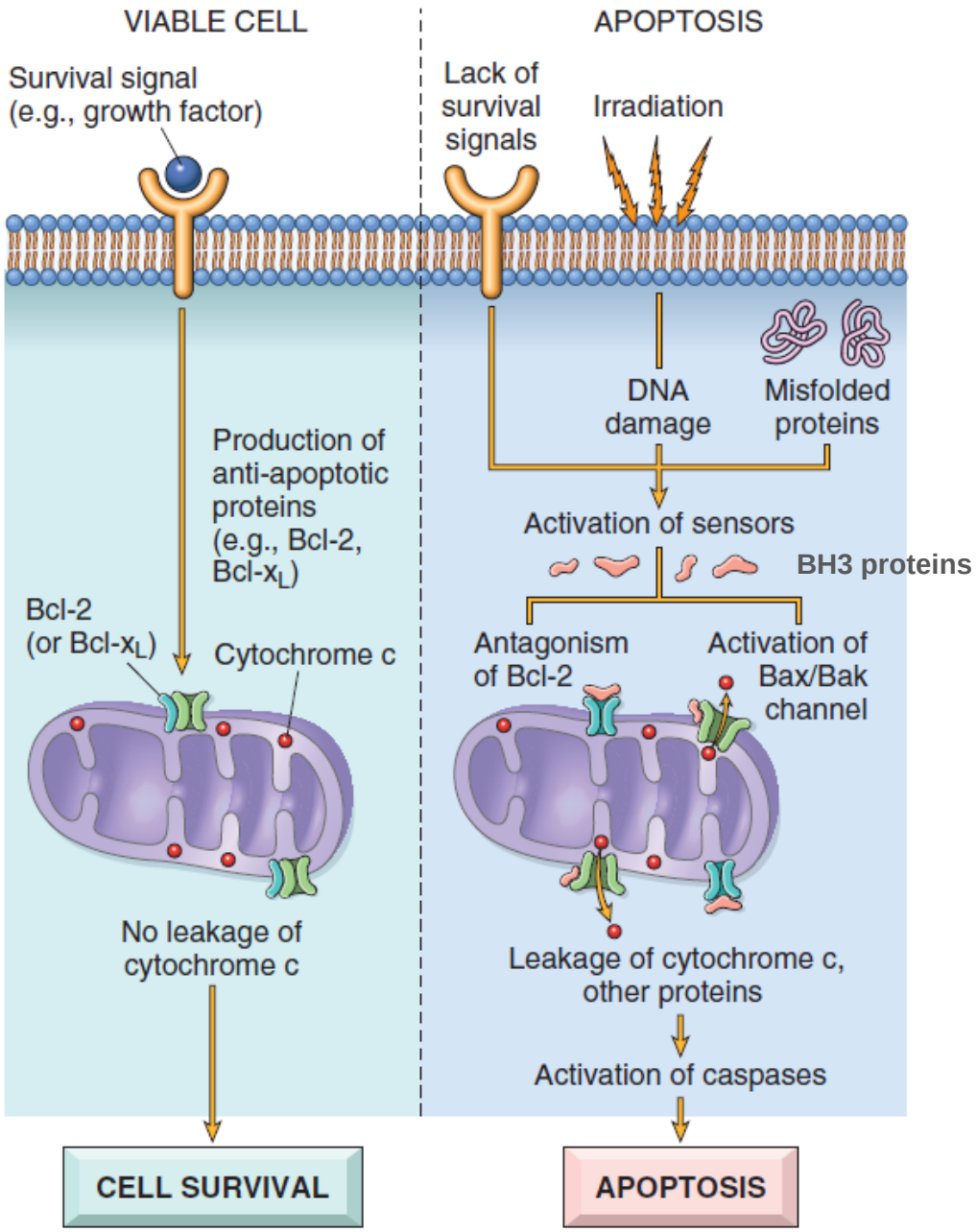
- PCD during embryogenesis
- Hormone withdrawal
- Steady state population
- End of function/life
- Self reacting lymphocytes

Pathologic

- DNA damage
- Protein misfolding/ER stress
- Some infections/Cytotoxic T cell induced
- Pathologic atrophy after duct obstruction



*cysteine proteases that cleave proteins after *asp*artic residues



Mitochondrial (intrinsic)

Mitochondrial permeability is key

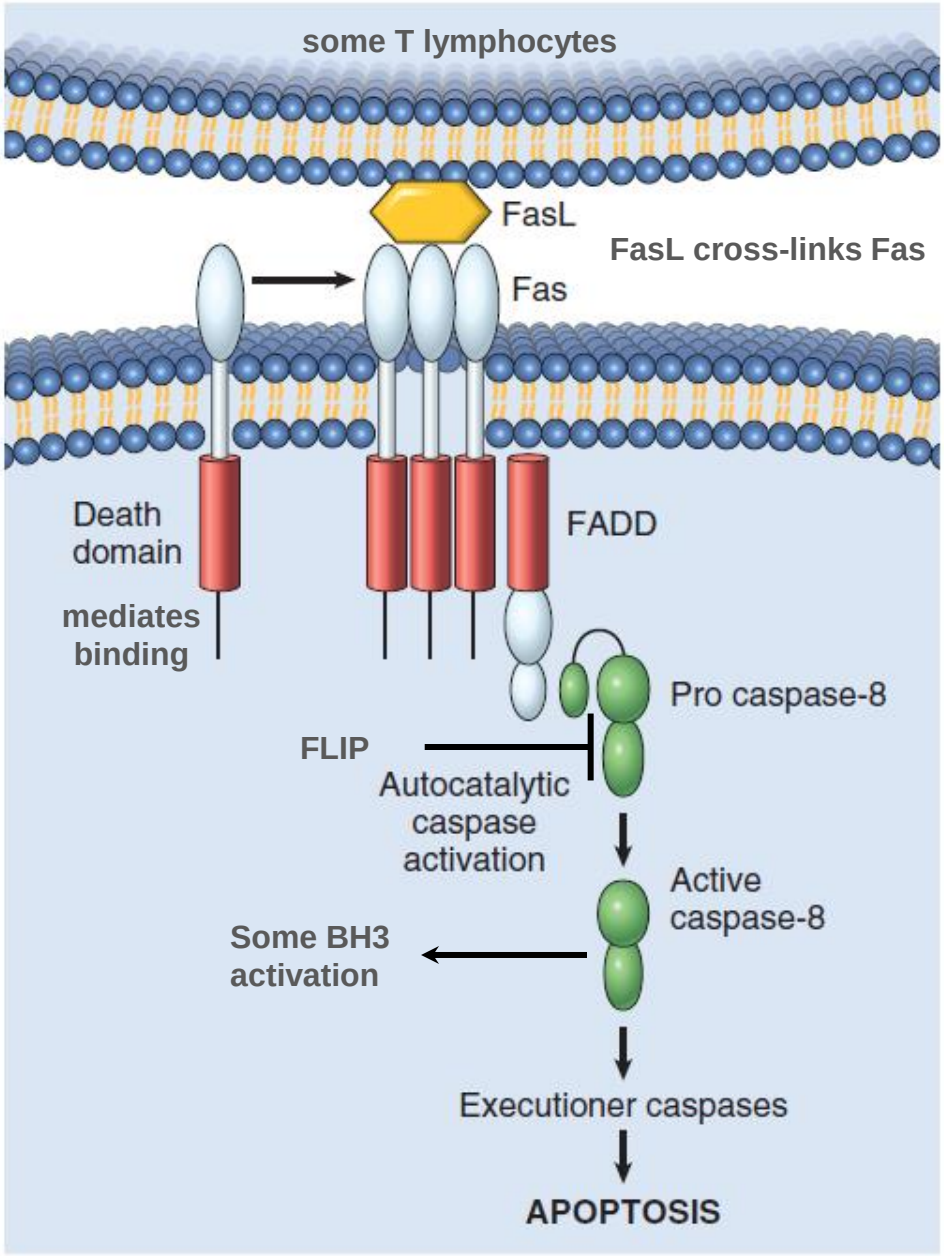
controlled > 20 proteins

Cytochrome c + cofactors, activates caspase-9

Anti-apototic proteins are inhibited

Bcl-2 & Bcl-x_L levels are reduced

Responsible for apoptosis in most situations



Death receptor (extrinsic)

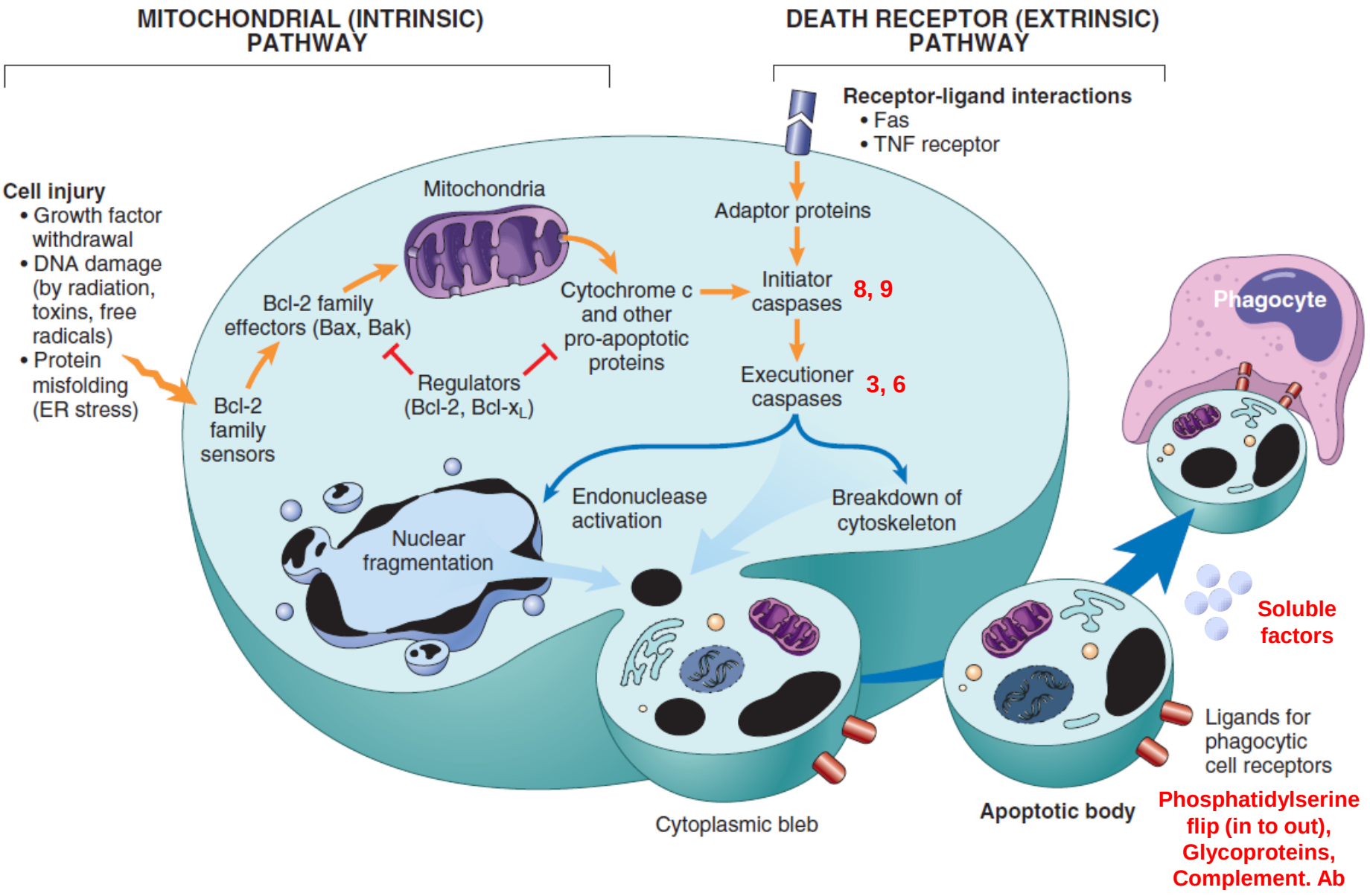
TNF receptor family

Responsible for apoptosis of self-reactive lymphocytes and target cells of some cytotoxic T lymphocytes

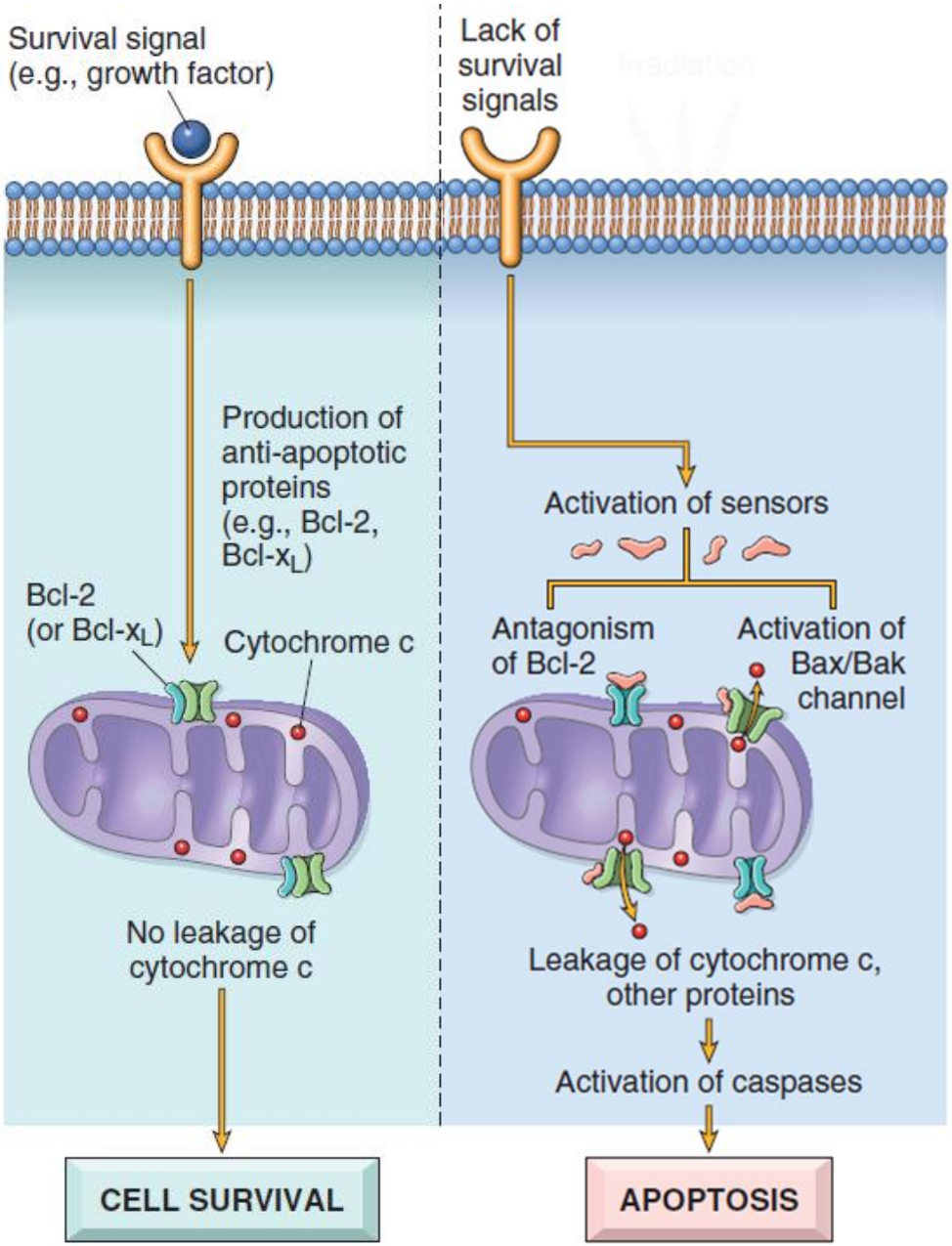
Fas or FasL mutations result in autoimmune diseases

Caspase-8 may cleave and activate Bid a “BH3 sensor” activating the mitochondrial pathway

Some viruses produce homologues of FLIP


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
Bcl-2 family effectors (Bax, Bak)
Cytochrome c and other pro-apoptotic proteins
Initiator caspases
8, 9
Regulators (Bcl-2, Bcl-xL)
Executioner caspases
3, 6
Bcl-2 family sensors
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Soluble factors
Ligands for phagocytic cell receptors
Cytoplasmic bleb
Apoptotic body
Phosphatidylserine flip (in to out), Glycoproteins, Complement. Ab

Causes & Mechanisms of Apoptosis in practice



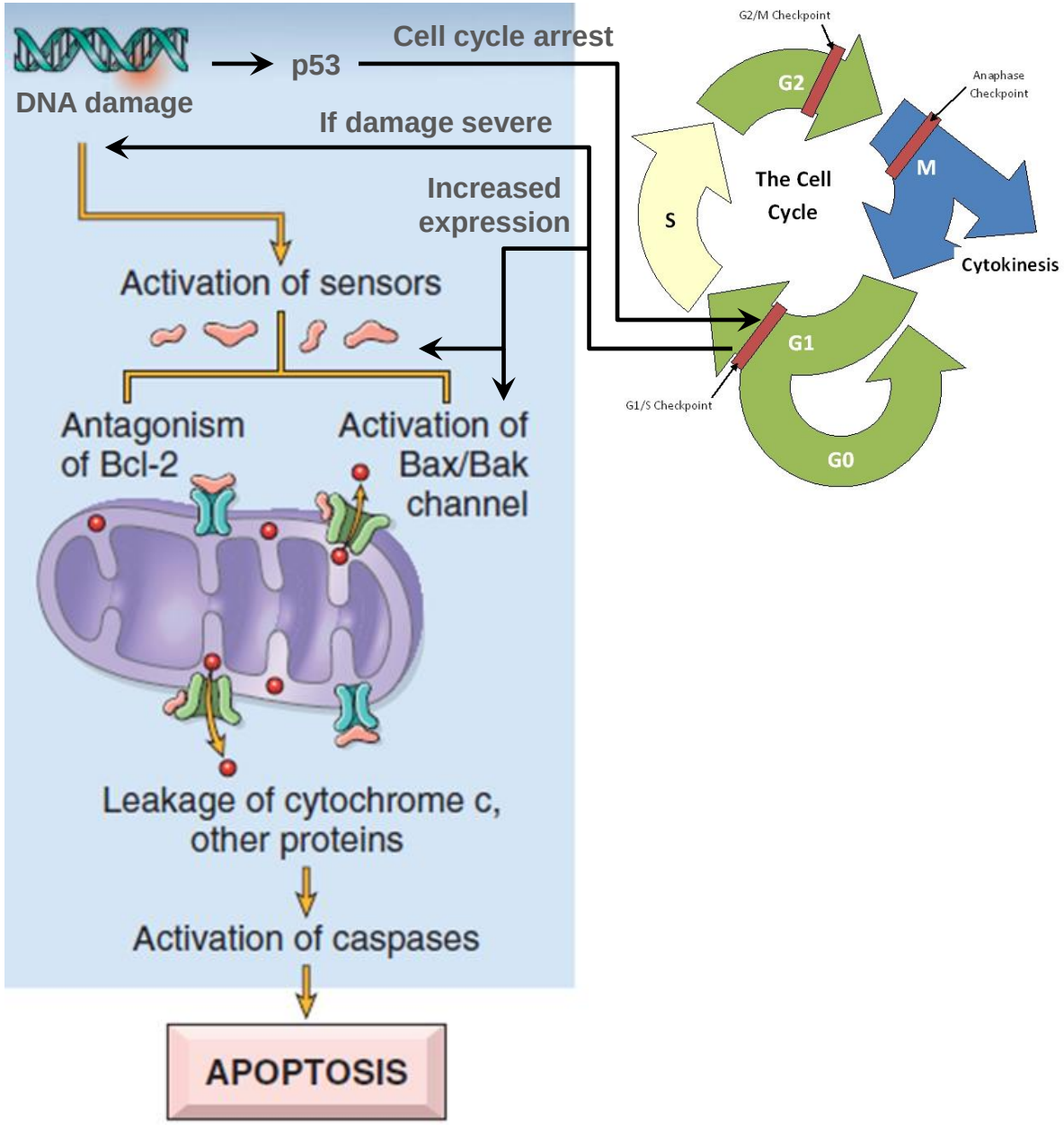
Growth Factor Deprivation

Hormone-sensitive cells sans hormone

Unstimulated lymphocytes

Neurons deprived of nerve growth factor

Triggered by the mitochondrial (intrinsic) pathway



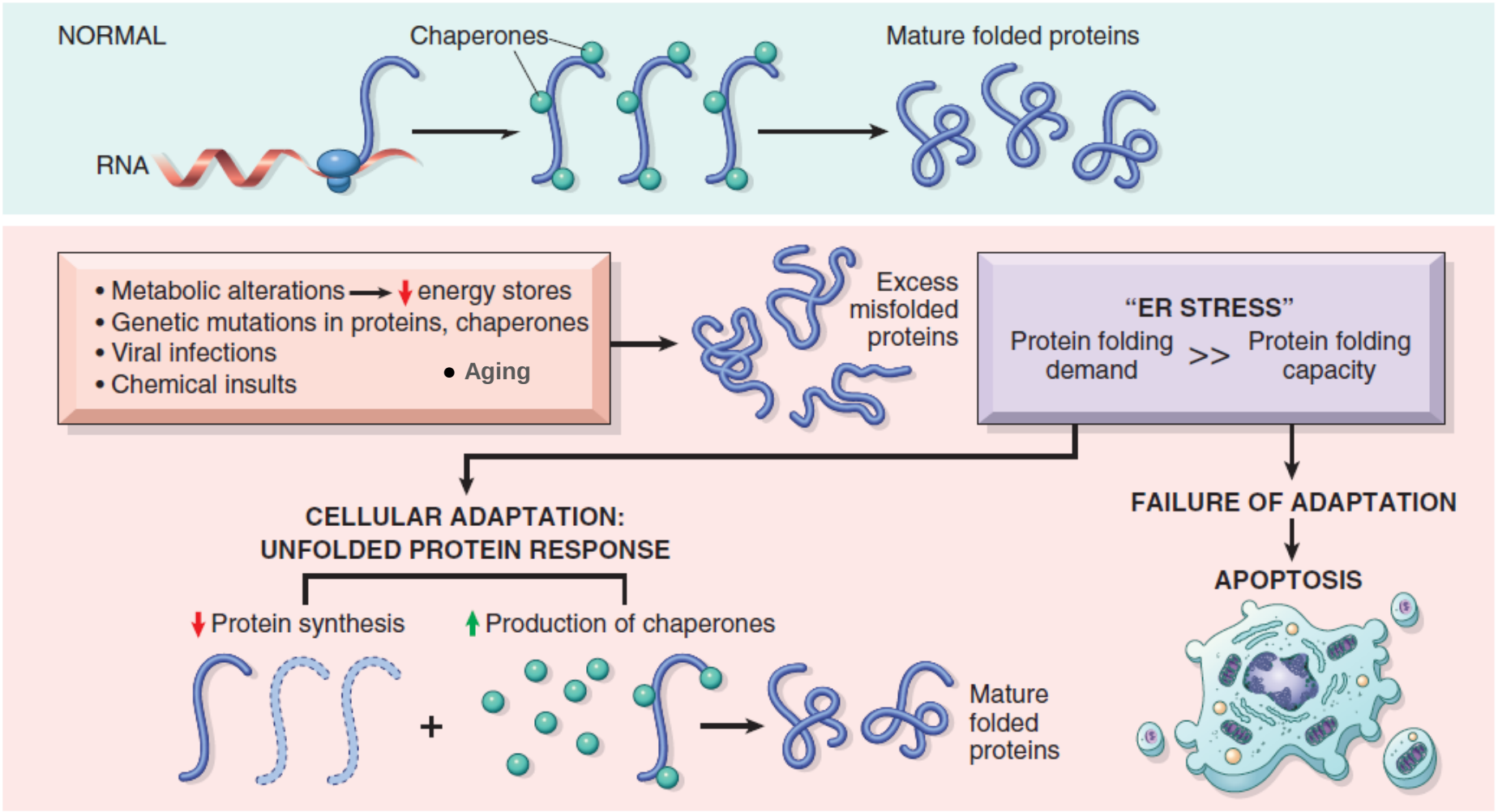
DNA damage

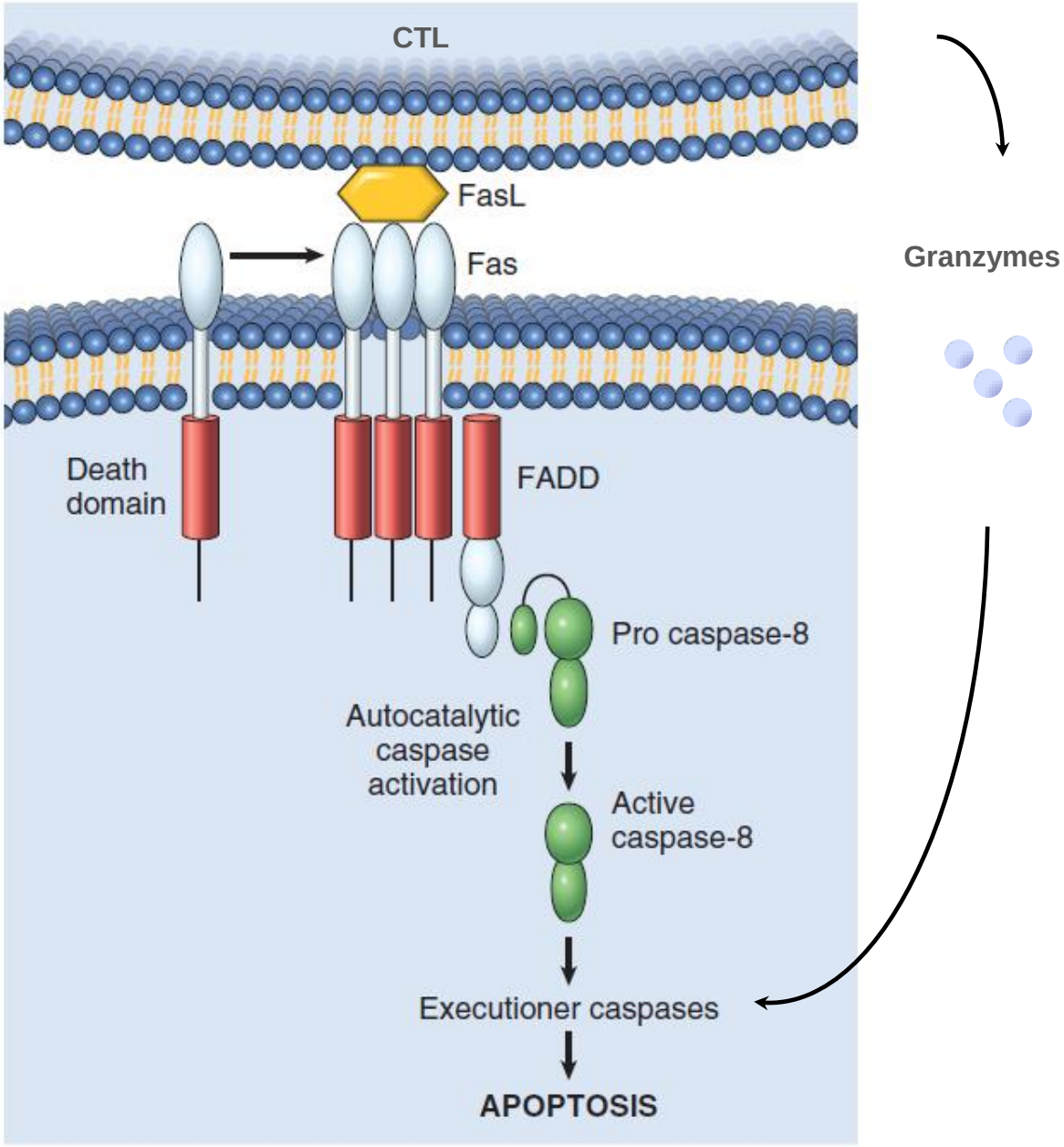
p53 accumulation

G1 arrest

p53 absence/mutation in certain cancers

Misfolded proteins
ER Stress





CTL

Recognize tumors and viral infected cells

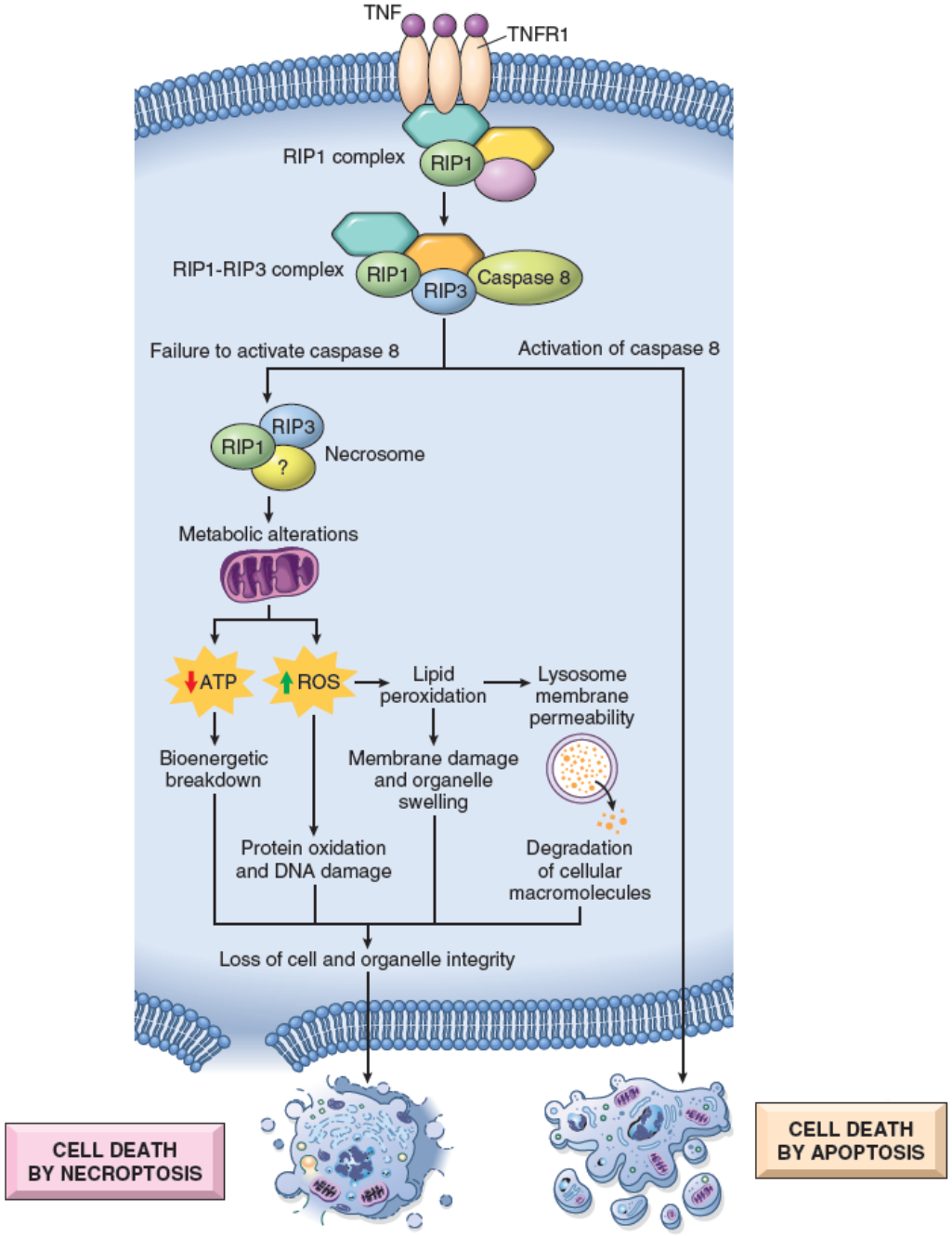
Granzymes cleave proteins at aspartate residues

CTL kill target cells by directly inducing the effector phase of apoptosis

Also induce through Fas

Necroptosis

“programmed necrosis”



Necroptosis

Physiologic & Pathologic

During formation of the mammalian bone growth plate

Acute pancreatitis

Reperfusion injury

Parkinson disease

Backup against viruses that encode caspase inhibitors (e.g., CMV).