Apoptosis and autophagy

cell injury and adaptations

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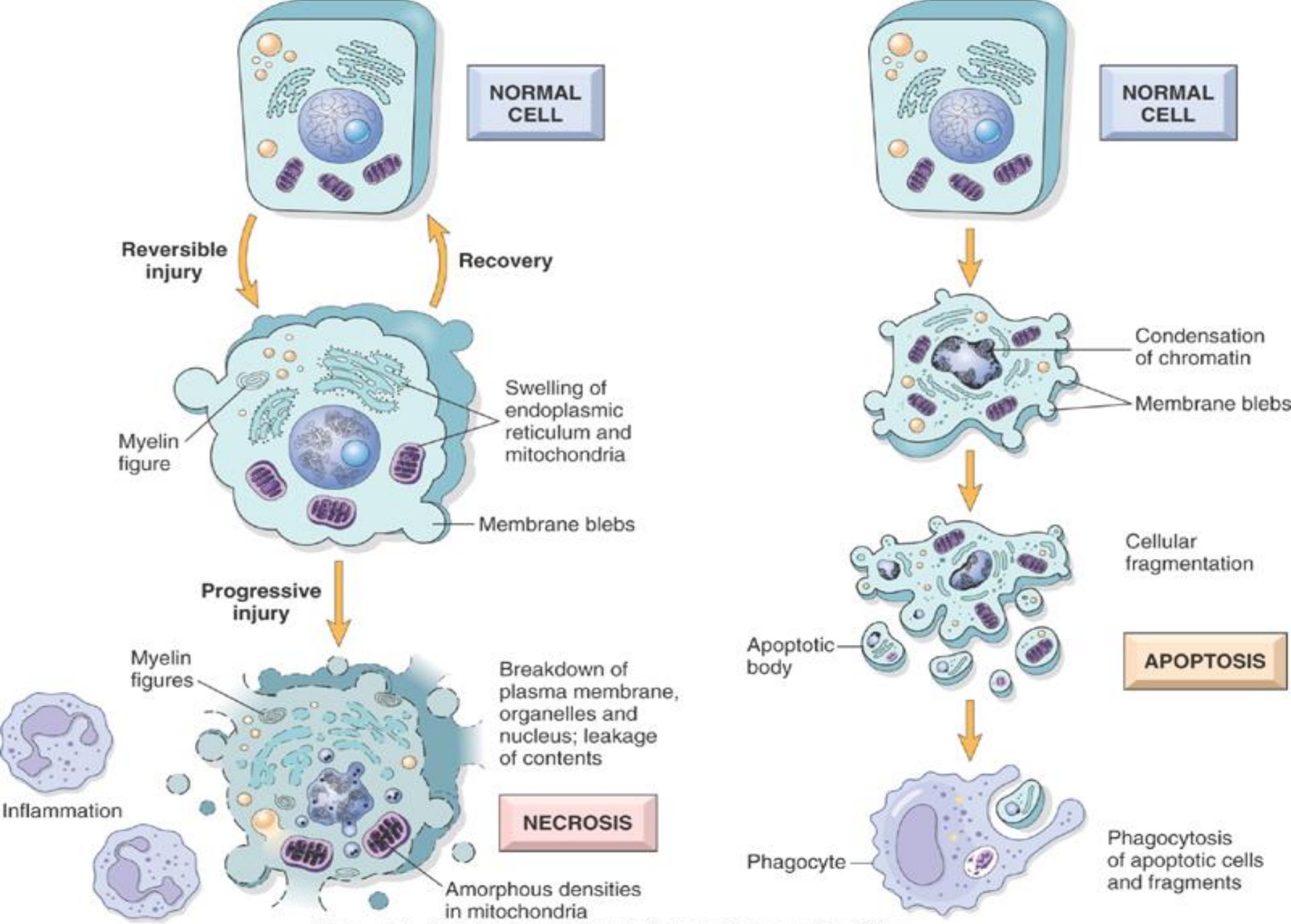
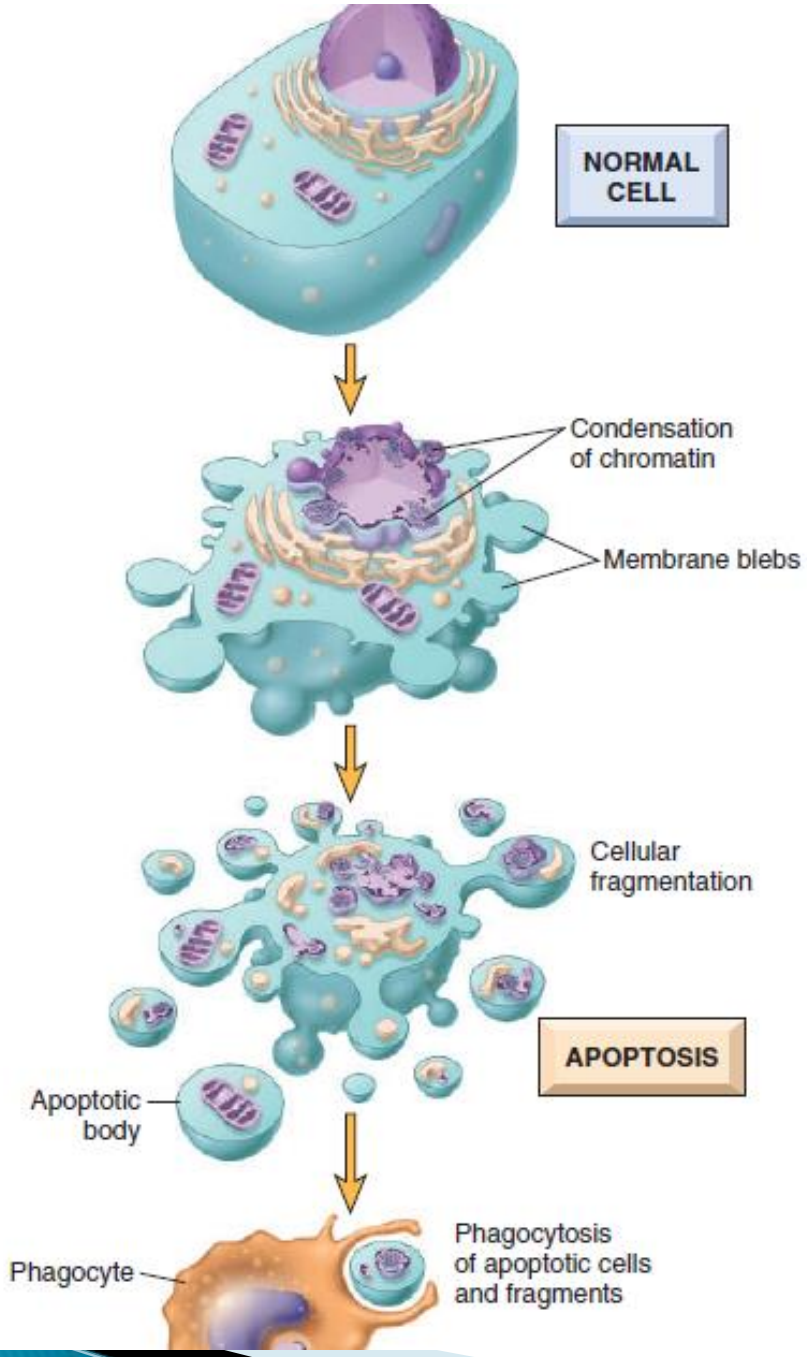
Definition

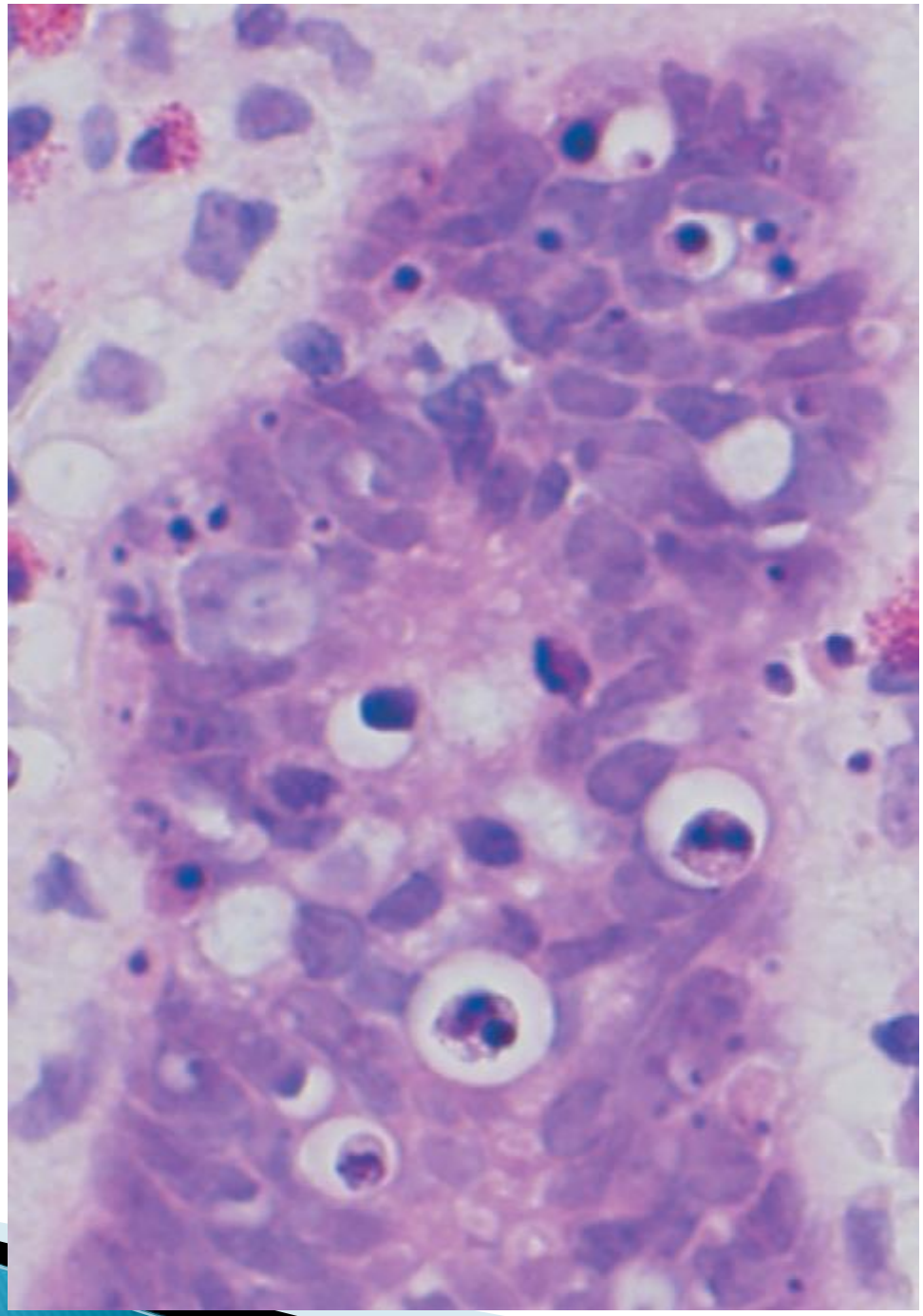
- **“Programmed cell death”**
- “a genetically determined process of cell self-destruction”
- “ pathway of cell death in which cells activate enzymes that degrade the cells’ own nuclear DNA and nuclear and cytoplasmic proteins.”
- The dead cell and its fragments are cleared with little leakage of cellular contents, NO inflammatory reaction.




NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
APOPTOSIS
Apoptotic body
Phagocyte
Phagocytosis of apoptotic cells and fragments

Feature	necrosis	Apoptosis
Cell size	Enlarged(swelling)	Reduced(shrinkage)
Nucleus	Pyknosis, Karyorrhexis, karyolysis	Fragmentation into nucleosome- size fragments
Plasma membrane	**Disrupted**	**Intact**, altered structure, especially orientation of lipids
Cellular content	Enzymatic digestion, may leak out of cell	Intact, may be released in apoptotic bodies.
Adjacent inflammation	**Frequent**	**No**
Physiologic or pathologic role	Invariably pathologic	often physiologic and may be pathologic

However, apoptosis and necrosis sometimes coexist, and apoptosis induced by some pathologic stimuli may progress to necrosis, like in ischemia.



Causes of apoptosis

- Physiologic apoptosis
- Apoptosis in pathologic conditions

Causes of Apoptosis

- **Physiologic**

- During embryogenesis
- Involution of tissues upon hormone deprivation (endometrium, lactating breast)
- Steady state population (Gut, Skin)
- End of function/life (neutrophils at end of inflammation)
- Self reacting lymphocytes

- **Pathologic:** (damaged cells beyond repair)

- DNA damage (Rx, chemoTx, tempreture, UV, hypoxia)
- Accumulation of misfolded proteins
- Some infections (adenovirus, HIV, hepatitis viruses)

Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways
Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

Mechanisms of Apoptosis

- **Activation of enzymes called caspases**
- Two distinct pathways can lead to caspase activation:
- 1) The mitochondrial pathway
- 2) The death receptor pathway

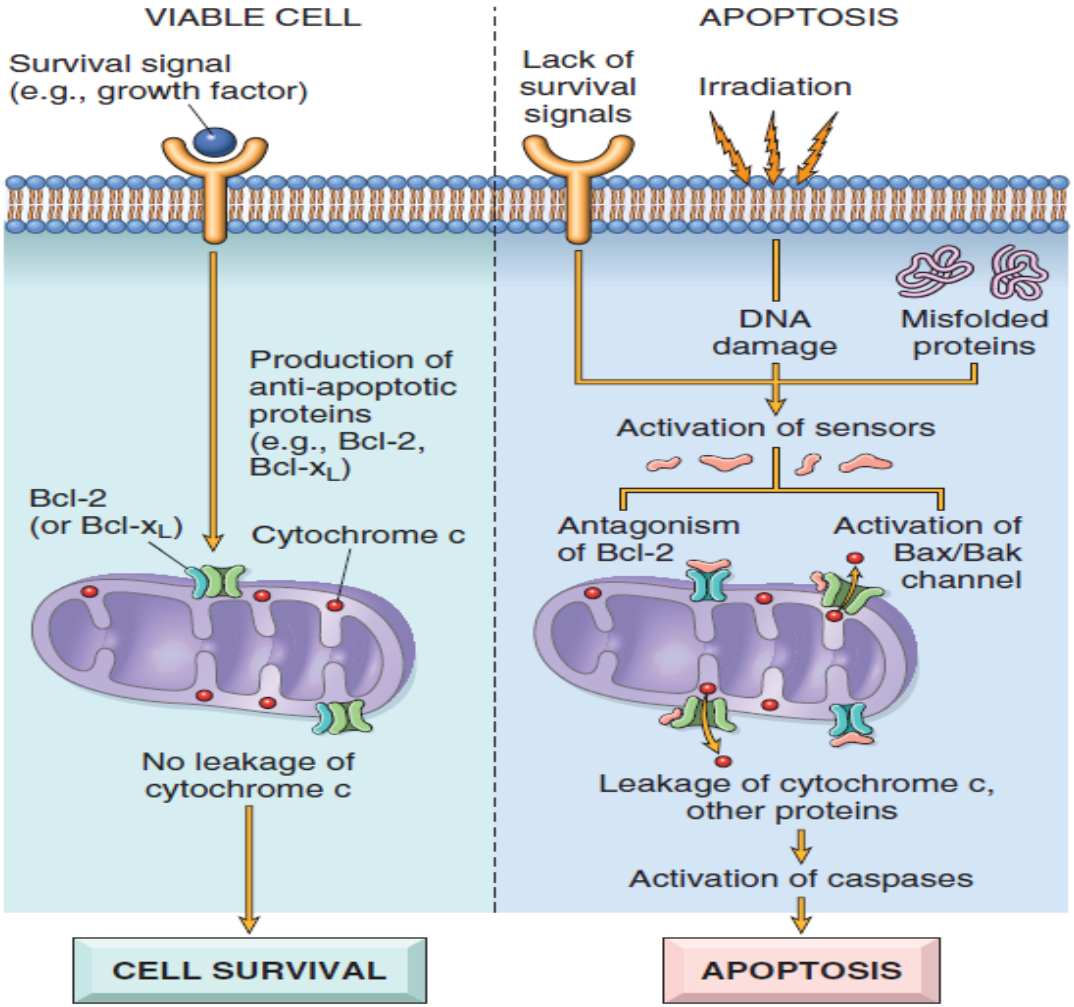
Mitochondrial (intrinsic)

Responsible for apoptosis in most physiologic and pathologic situations

Bcl2 family of proteins control mitochondrial membrane permeability

Bcl2 antiapoptotic
Bax/Bak proapoptotic
BH3 sensors

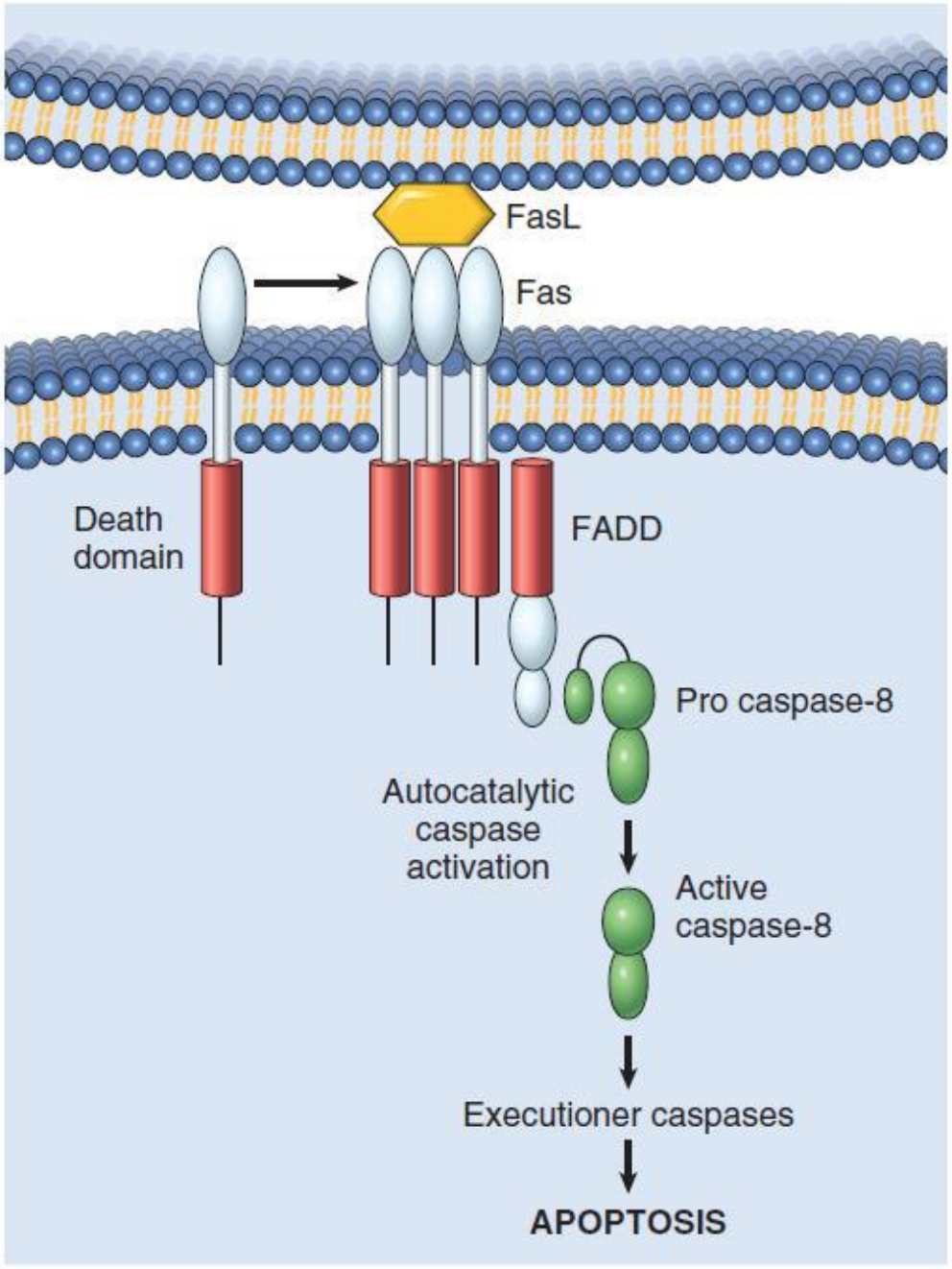
Cytochrome c activates caspase-9

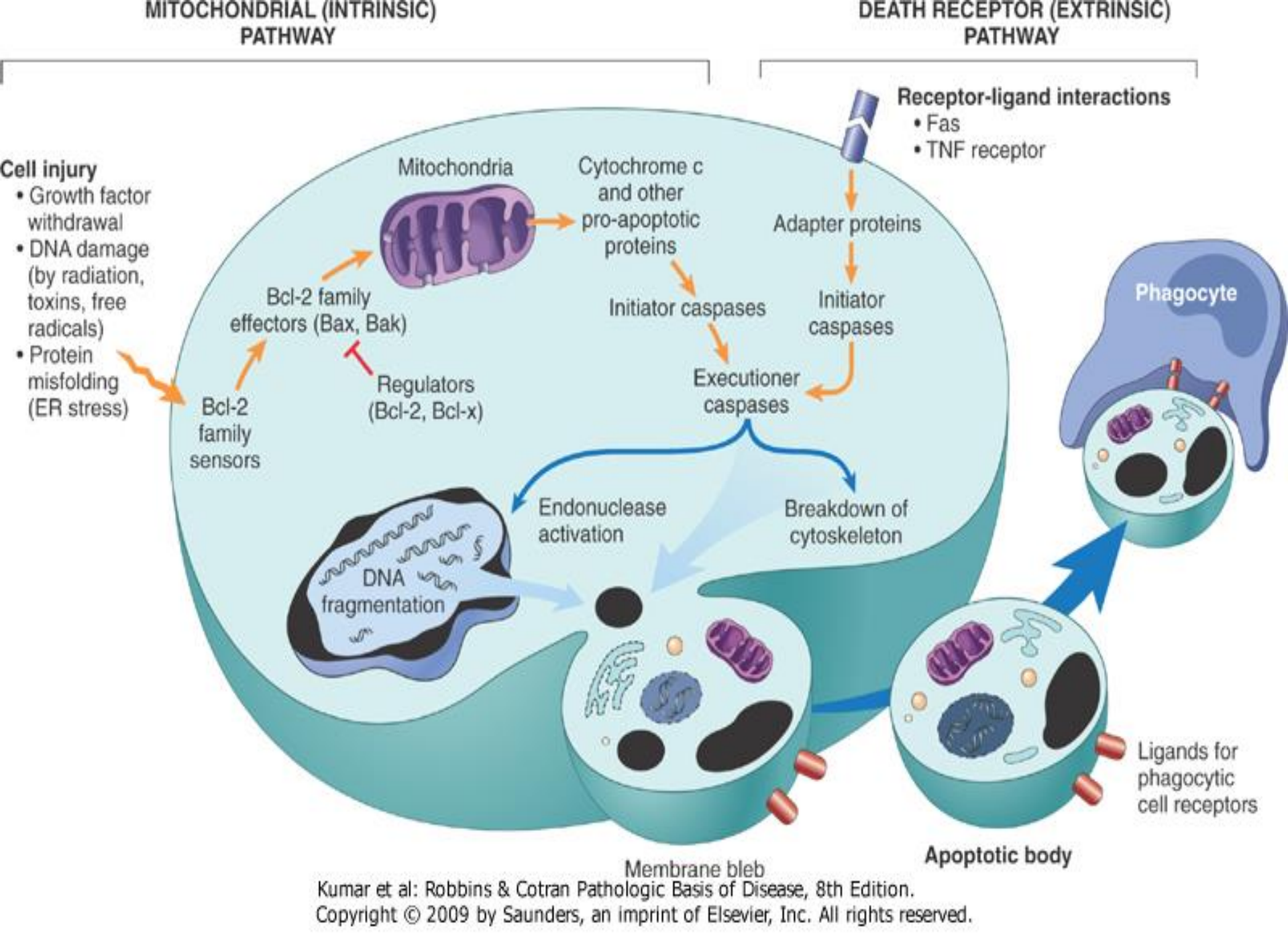


Death receptor (extrinsic)

- TNF receptor family, cytoplasmic death domain
- Prototypes: Type 1 TNF receptor and Fas
- Fas ligand on activated T lymphocytes
- Fas –FasL interaction activates death domain which in turn activates caspase 8

- **Used in:**
- Elimination of self-reactive lymphocytes
- killing of target cells by some cytotoxic T lymphocytes (CTLs)


FasL
Fas
Death
domain
FADD
Pro caspase-8
Autocatalytic
caspase
activation
Active
caspase-8
Executioner caspases
APOPTOSIS



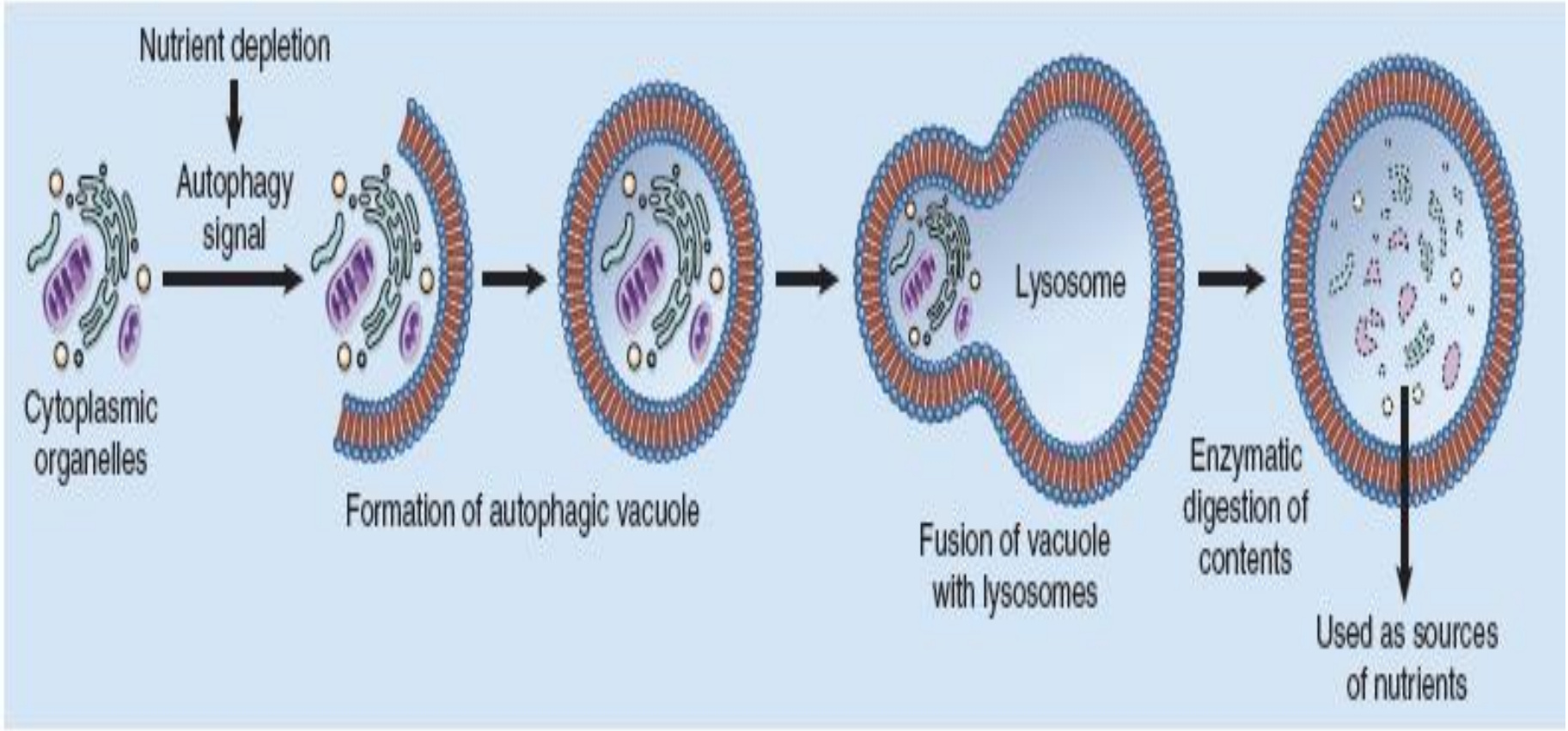
Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.

Autophagy

- Self-eating
- Lysosomal digestion of the cells own components
- Survival mechanism in times of nutrient deprivation.
- Recycling cells contents to provide nutrients and energy

- ER-derived autophagic vacuole
- Vacuole fuses with lysosome >>>autophagolysosome

- May lead to atrophy.
- Failure of adaptation >>>apoptosis


Nutrient depletion
Autophagy signal
Cytoplasmic organelles
Formation of autophagic vacuole
Lysosome
Fusion of vacuole with lysosomes
Enzymatic digestion of contents
Used as sources of nutrients