Apoptosis

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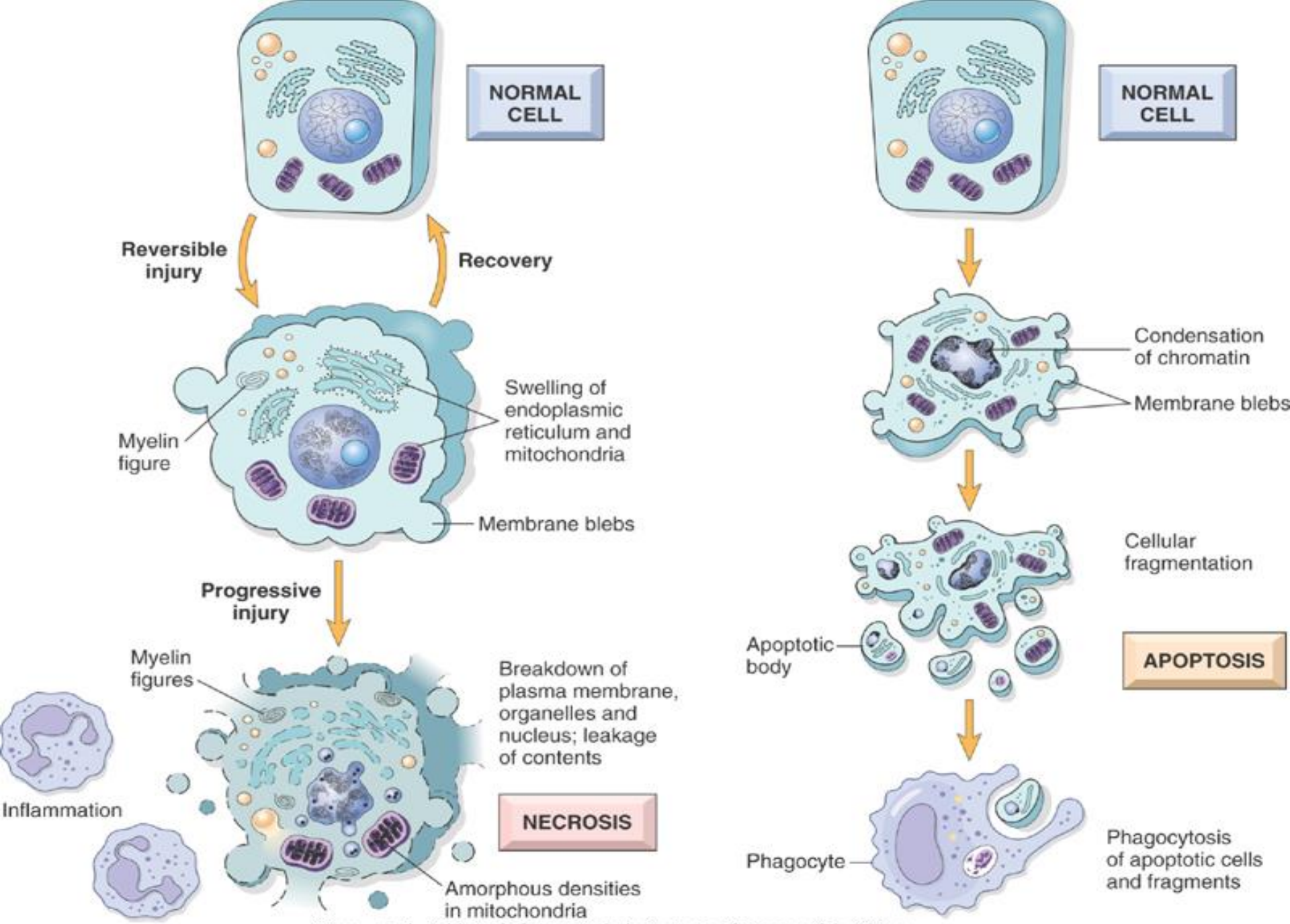
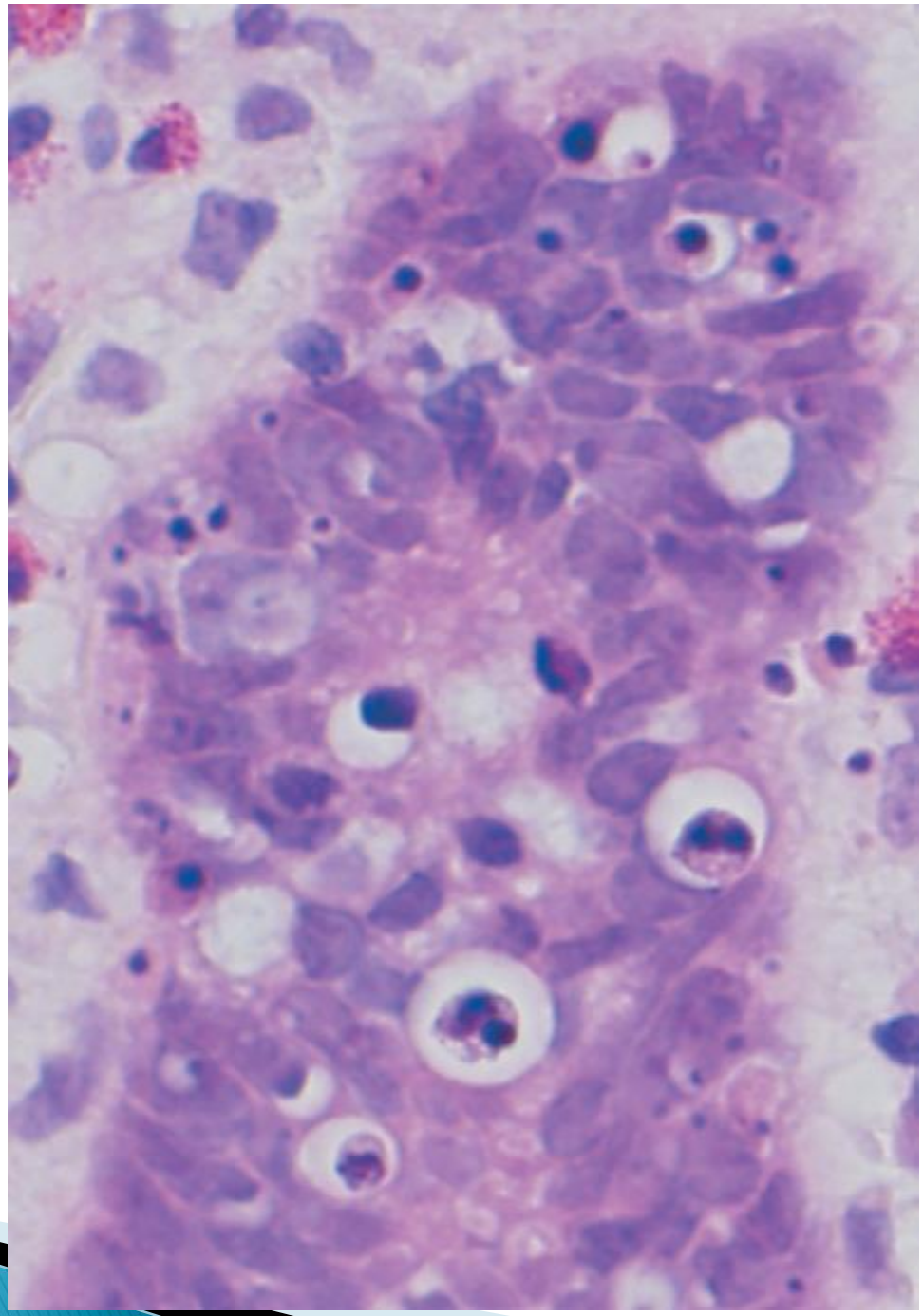
Definition

- “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	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

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



Causes of apoptosis

- **In many normal situations** to eliminate potentially harmful cells and cells that have outlived their usefulness (maintain constant number of cells).

- Also occurs **as a pathologic event** when cells are damaged beyond repair (DNA or protein damage).

Causes of Apoptosis

- **Physiologic**

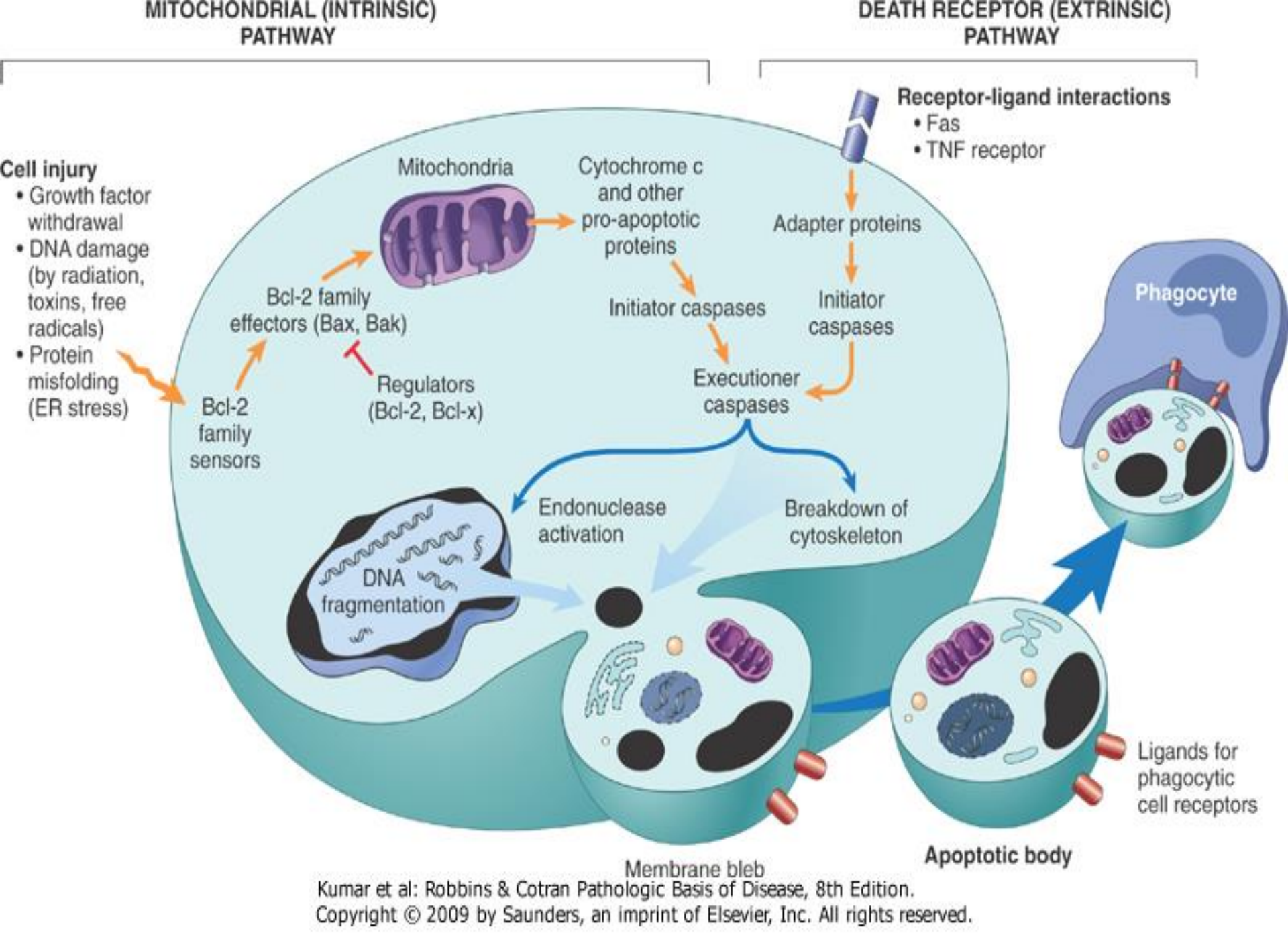
- During embryogenesis
- Involution of tissues upon hormone deprivation (endometrium, lactating breast)
- Steady state population (Gut, Skin)
- End of function/life (PMNs)
- Self reacting lymphocytes

- **Pathologic:**

- DNA damage (Rx, chemoTx, tempreture, hypoxia)
- Protein misfolding/ER stress
- Some infections (adenovirus, HIV, hepatitis viruses)
- Pathologic atrophy after duct obstruction (pancreas, parotid gland, kidney)

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

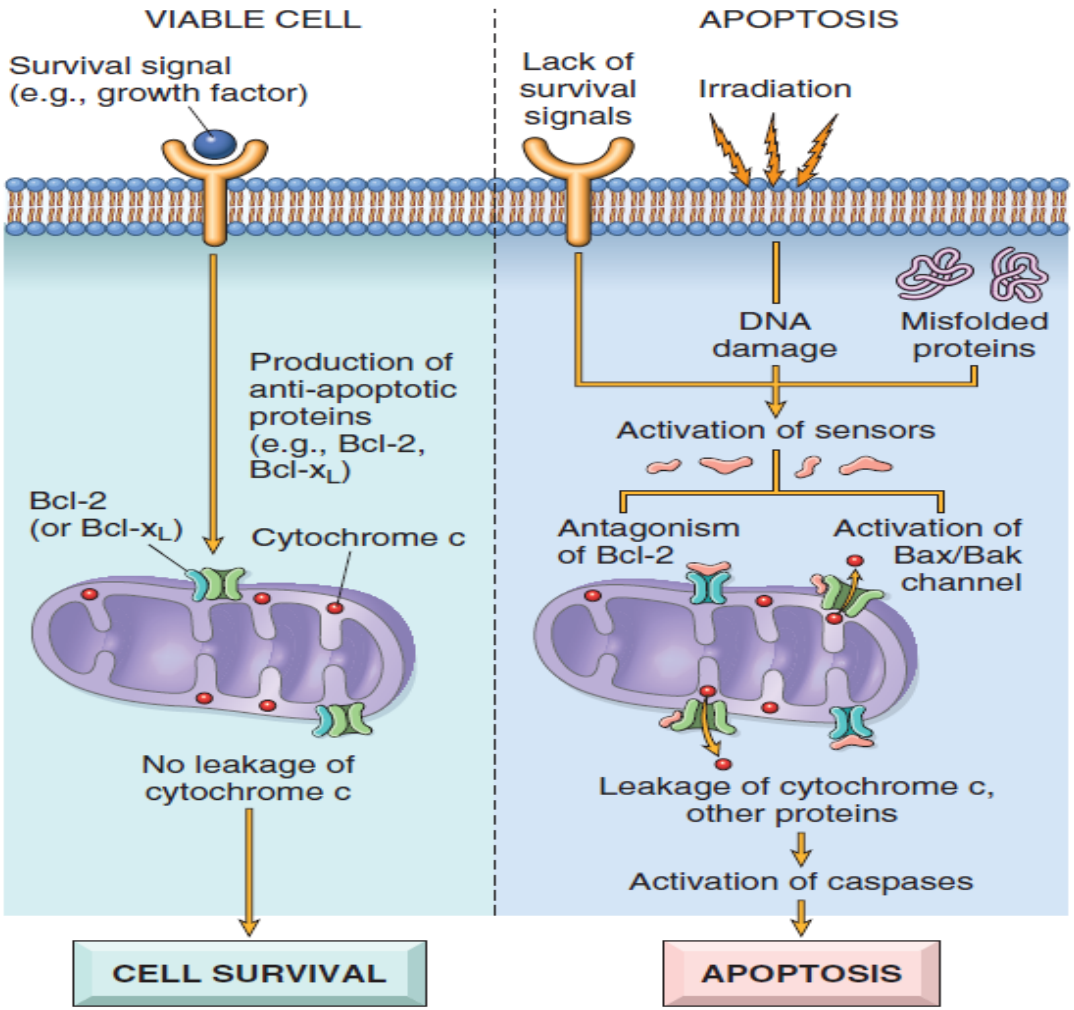


Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.

Mitochondrial (intrinsic)

The mitochondrial pathway is responsible for apoptosis in most situations

Cytochrome c activates caspase-9



Death receptor (extrinsic)

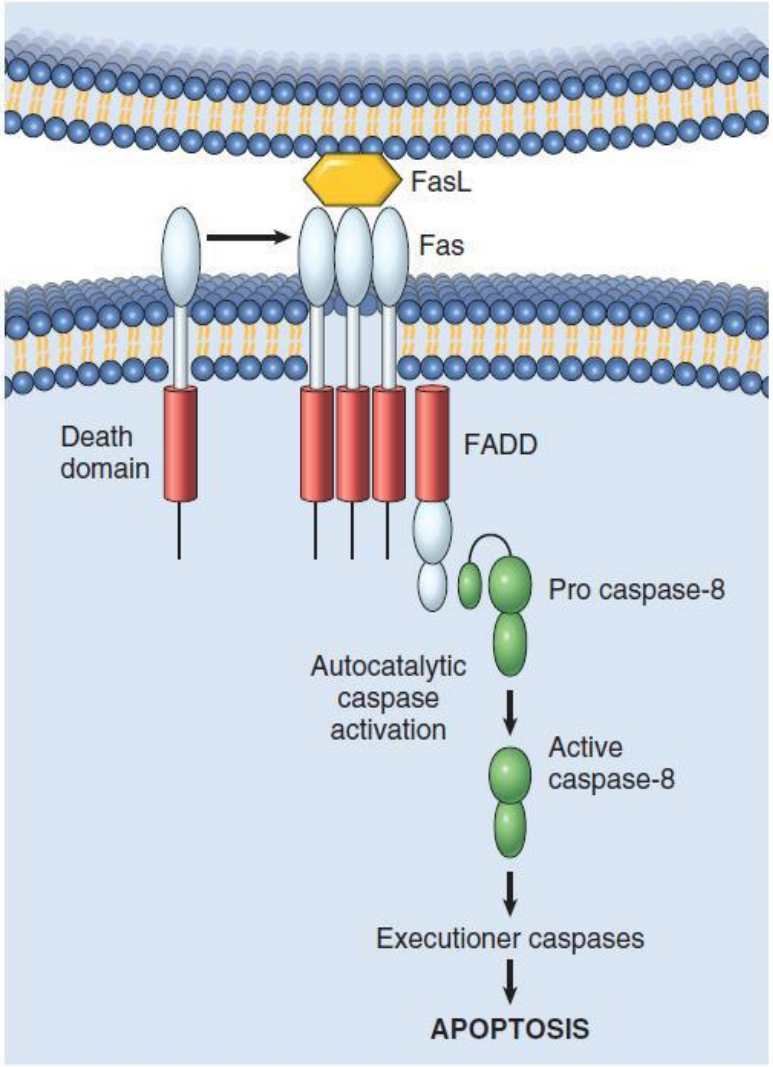
TNF receptor family
Type 1 TNF receptor and FAS

Elimination of self-reactive lymphocyte.

killing of target cells by cytotoxic T lymphocytes.

Activates caspase 8

Used by some viruses, produce FLIP, a caspase antagonist



Examples of Apoptosis

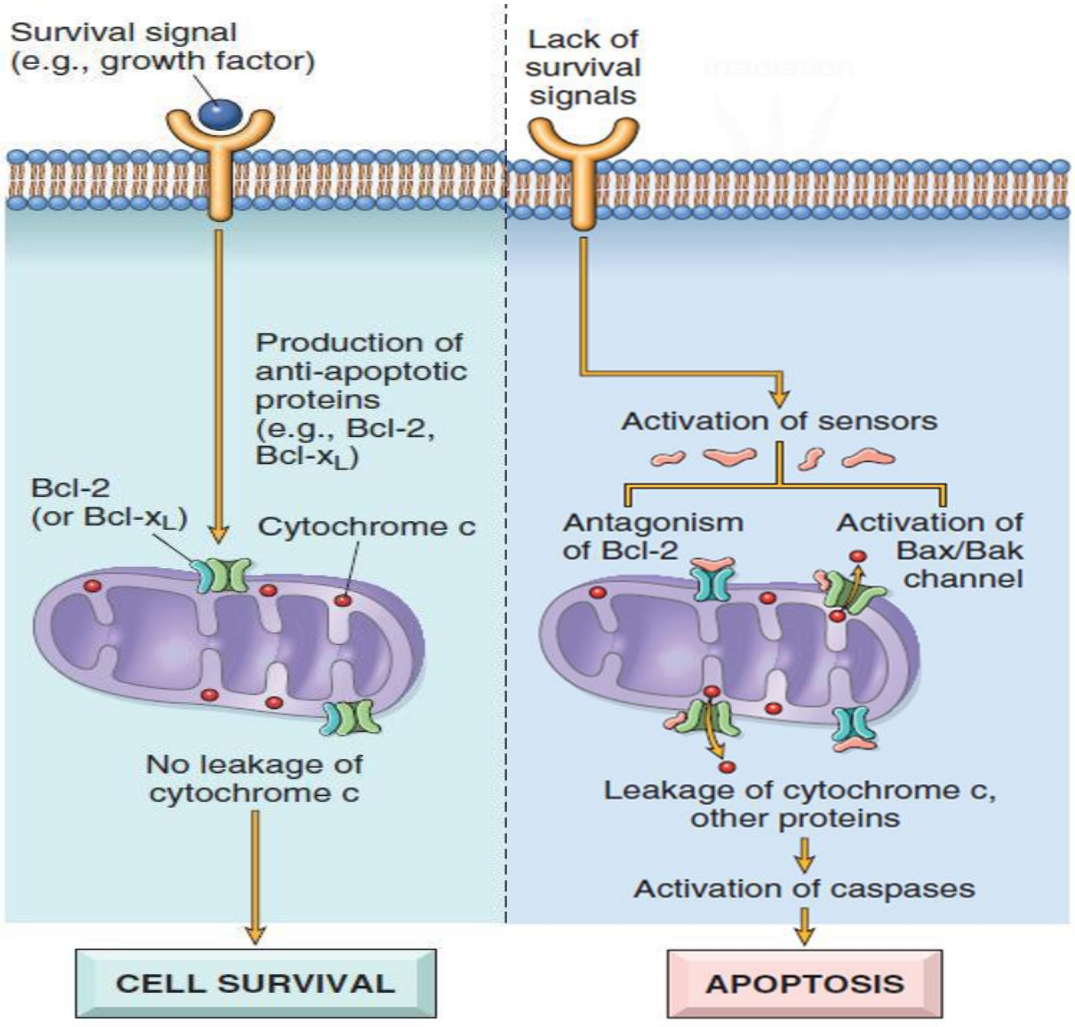
- **Growth Factor Deprivation**

Hormone-sensitive cells deprived of hormones

Unstimulated lymphocytes

Neurons deprived of nerve growth factor

By mitochondrial pathway



DNA Damage:

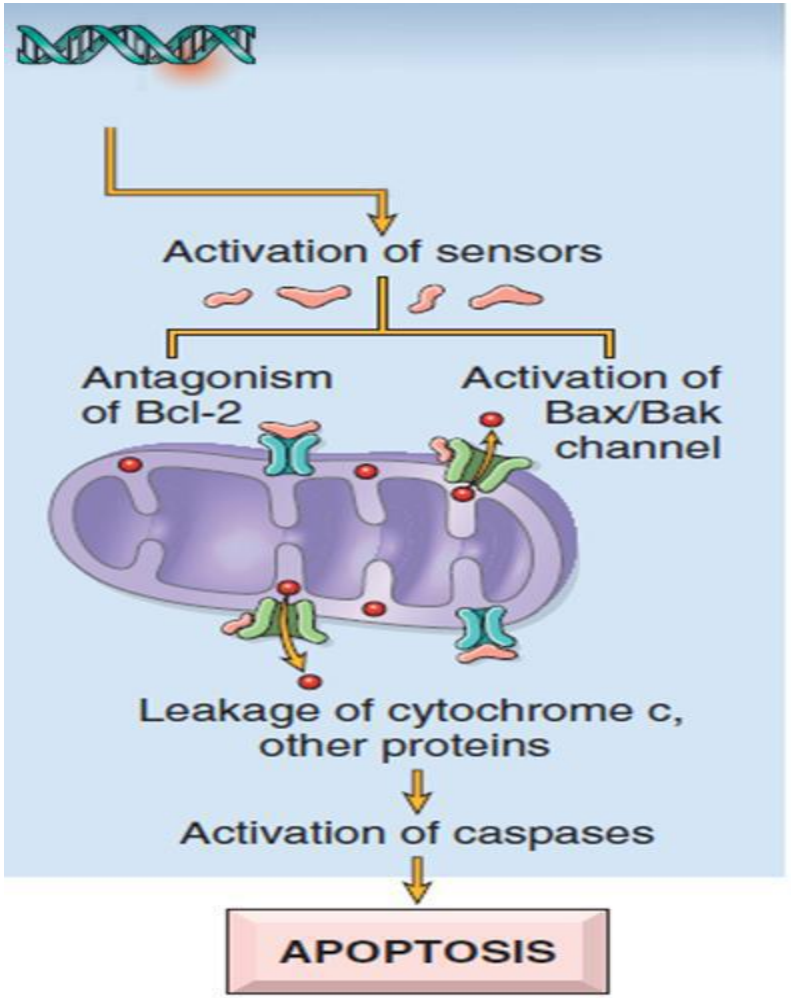
p53 protein accumulates in cells.

Arrests of cell cycle (at G1 phase) for DNA repair.

If damage is great, trigger apoptosis.

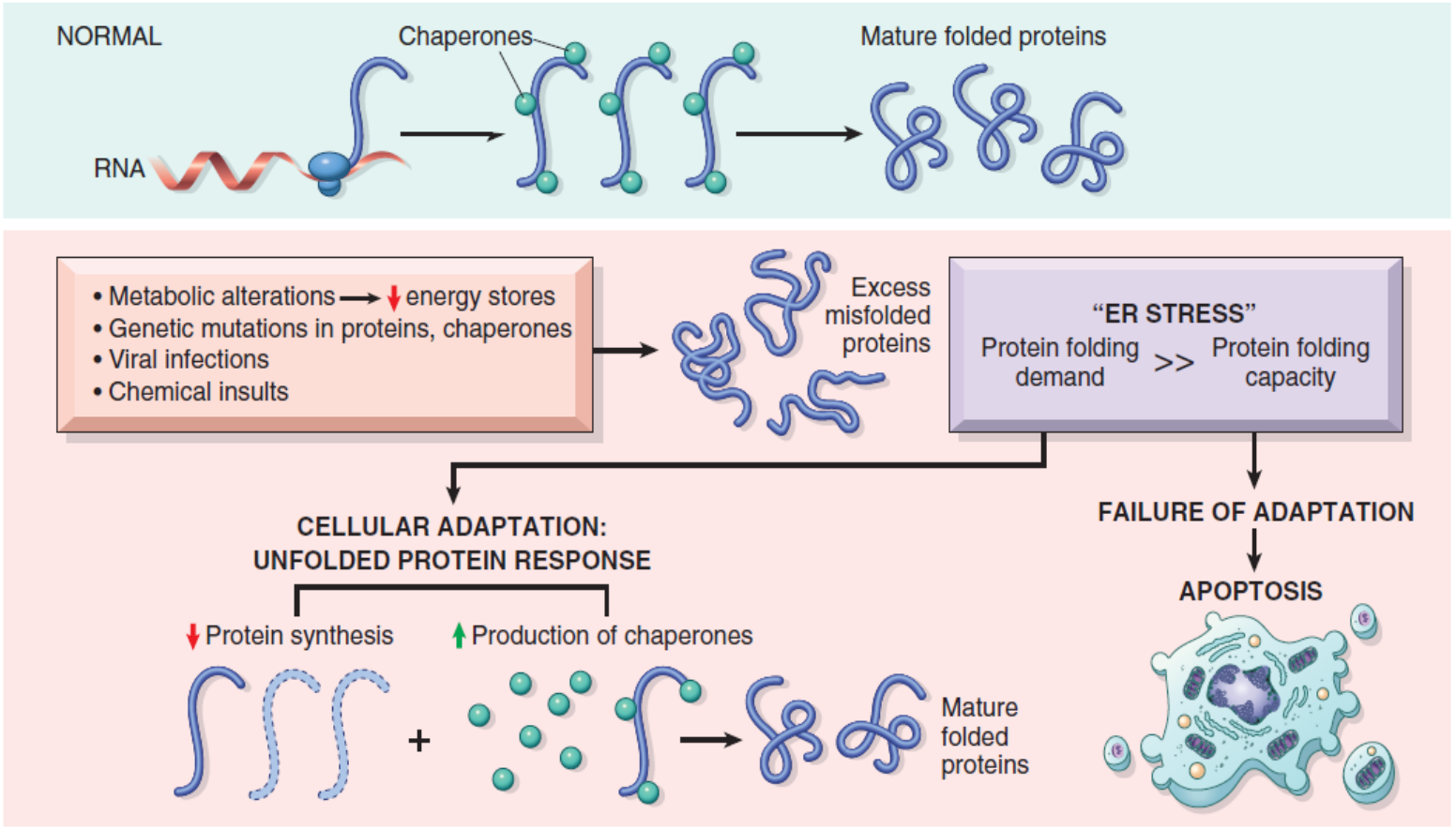
Mitochondrial pathway

With p53 mutations , as in cancer, NO APOPTOSIS , cells accumulate mutations.



Accumulation of Misfolded Proteins: ER Stress

- Cell death in neurodegenerative diseases, including Alzheimer, Huntington, and Parkinson diseases, and possibly type 2 diabetes.



Apoptosis of Self-Reactive Lymphocytes

- Lymphocytes capable of recognizing self antigens
- Mitochondrial pathway and the Fas death receptor pathway
- Failure of apoptosis of self-reactive lymphocytes is one of the causes of autoimmune diseases

Cytotoxic T Lymphocyte–Mediated Apoptosis

- Of infected host cells and tumor cells
- 1) CTLs express FasL on their surface and may kill target cells by ligation of Fas receptors. Death receptor pathway.
- 2) Also by production of granzyme that activate caspases.