Causes of Cell Injury

1- **oxygen deprivation (anoxia)**

2- **physical agents**

3- **chemical agents**

4- **infections agents**

5- **immunologic reactions**

6- **genetic defects**

7- **nutritional imbalances**

Mechanisms of Cell Injury

The cellular response to injurious stimuli depends on :-1-The type of injury 2-Duration 3- Severity . Thus, low doses of toxins or a brief duration of ischemia may lead to reversible cell injury, whereas larger toxin doses or longer ischemic intervals may result in irreversible injury and cell death.

The principal targets and biochemical mechanisms of cell injury are:

(1) mitochondria and their ability to generate ATP and ROS under pathologic conditions.

(2) disturbance in calcium homeostasis.

(3) damage to cellular (plasma and lysosomal) membranes.

(4) damage to DNA and misfolding of proteins.

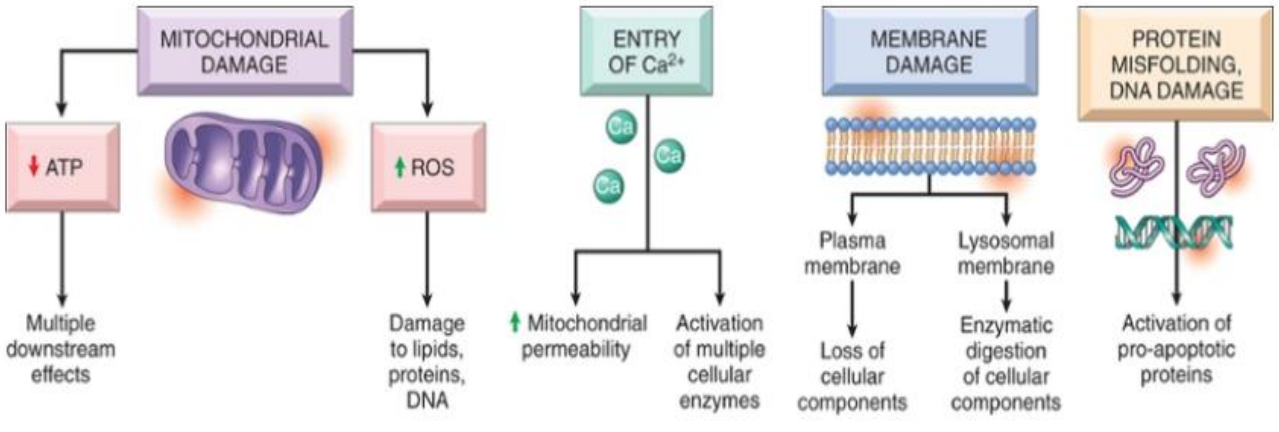


Figure 1–14 The principal biochemical mechanisms and sites of damage in cell...

Depletion of ATP:- The major causes of ATP depletion are reduced supply of oxygen and nutrients, mitochondrial damage, and the actions of some toxins (e.g., cyanide). Tissues with a greater glycolytic capacity (e.g., the liver) are able to survive loss of oxygen and decreased oxidative phosphorylation better than are tissues with limited capacity for glycolysis (e.g., the brain). Depletion of ATP lead to :-

1- **The activity of plasma membrane ATP-dependent sodium pumps is reduced, resulting in intracellular accumulation of sodium and efflux of potassium. The net gain of solute is accompanied by iso-osmotic gain of water, causing cell swelling and dilation of the ER.**
2- **There is a compensatory increase in anaerobic glycolysis in an attempt to maintain the cell's energy sources. As a consequence, intracellular glycogen stores are rapidly depleted, and lactic acid accumulates, leading to decreased intracellular pH and decreased activity of many cellular enzymes.**
3- **Failure of ATP-dependent Ca^{2+} pumps leads to influx of Ca^{2+}, with damaging effects on numerous cellular components.**
4- **Prolonged or worsening depletion of ATP causes structural disruption of the protein synthetic apparatus, manifested as detachment of ribosomes from the rough ER (RER) Ultimately, there is irreversible damage to mitochondrial and lysosomal membranes, and the cell undergoes necrosis.**

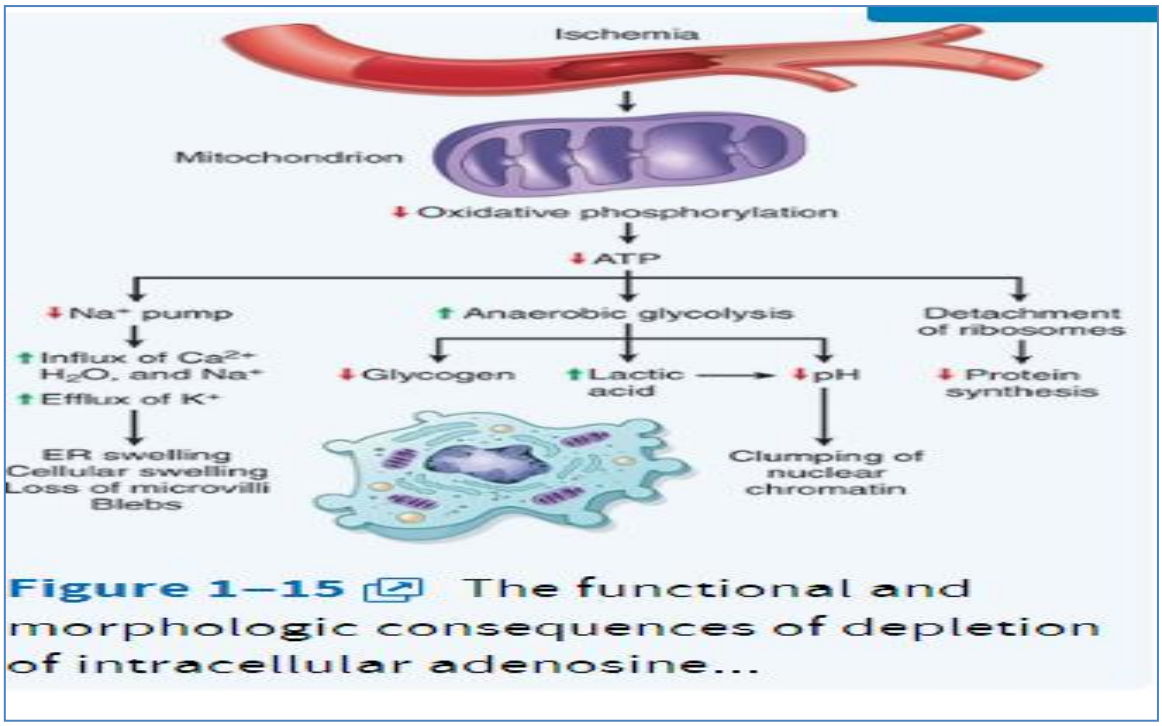
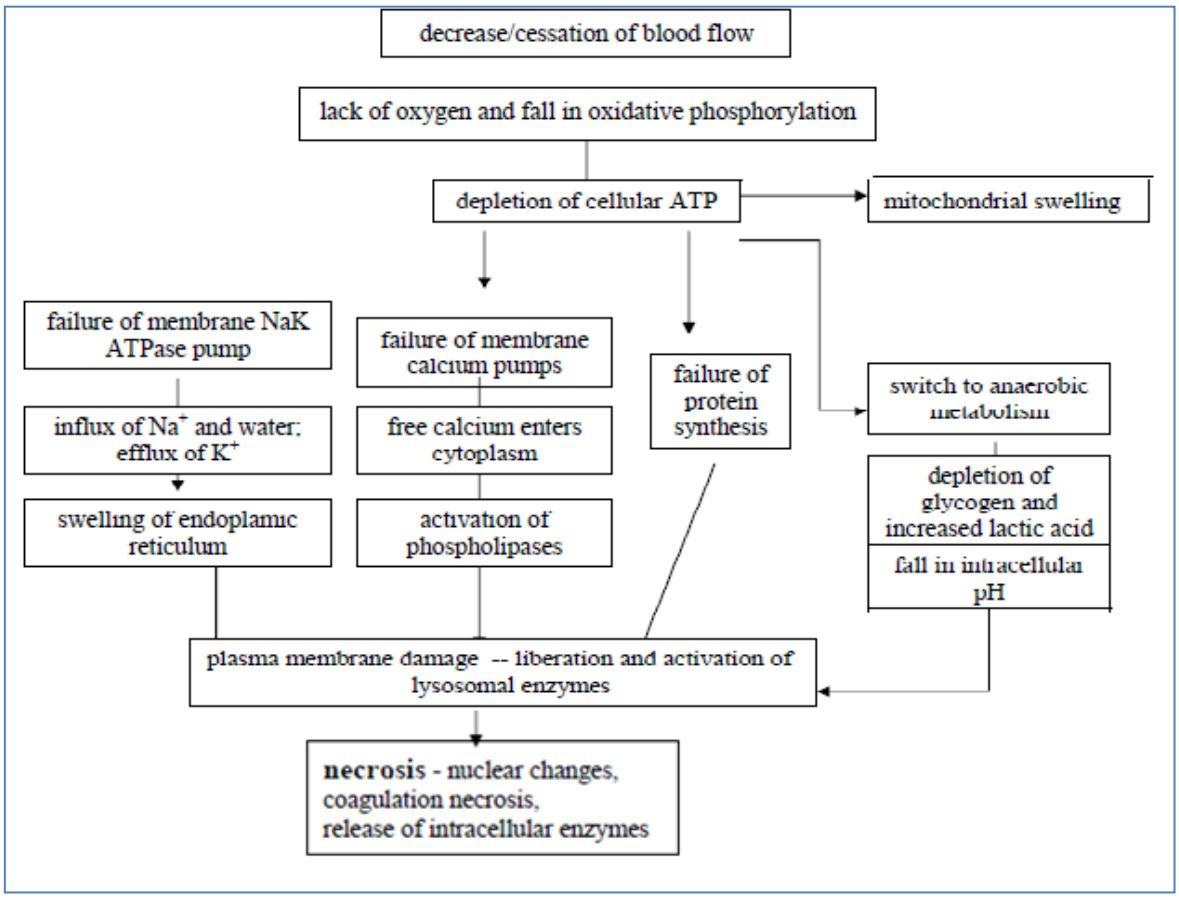


Figure 1–15 The functional and morphologic consequences of depletion of intracellular adenosine...



Mitochondrial Damage and Dysfunction

Mitochondria are sensitive to many types of injurious stimuli, including :-

1-Hypoxia

2- Chemical toxins

3- Radiation

Mitochondrial damage may result in several biochemical abnormalities:

1- **Failure of oxidative phosphorylation leads to progressive depletion of ATP, culminating in necrosis of the cell.**
2- **Abnormal oxidative phosphorylation also leads to the formation of reactive oxygen species, which have many deleterious effects.**
3- **Damage to mitochondria is often associated with the formation of a high-conductance channel in the mitochondrial membrane, called the mitochondrial permeability transition pore. The opening of this channel leads to the loss of mitochondrial membrane potential and pH changes, further compromising oxidative phosphorylation.**
4- **The mitochondria also contain several proteins that, when released into the cytoplasm, tell the cell there is internal injury and activate a pathway of apoptosis.**

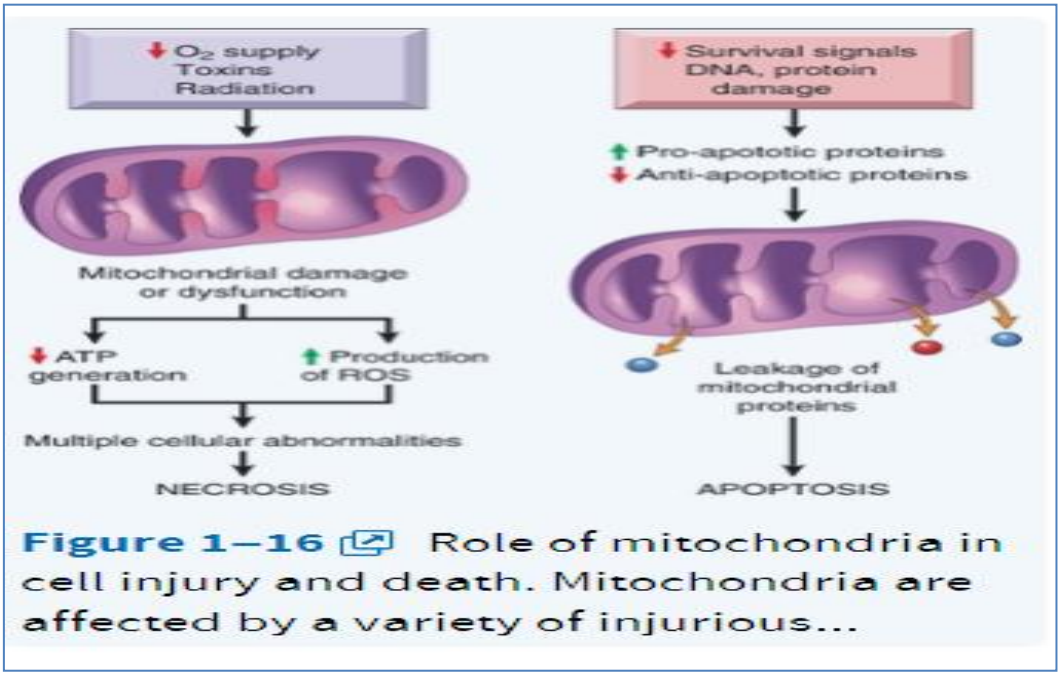


Figure 1–16 Role of mitochondria in cell injury and death. Mitochondria are affected by a variety of injurious...

Influx of Calcium:- Figure 1–17 Sources and consequences of increased cytosolic calcium in cell injury. Cytosolic free calcium is normally maintained by ATP-dependent calcium transporters at concentrations as much as 10,000 times lower than the concentration of extracellular calcium or of sequestered intracellular mitochondrial and ER calcium.

Ischemia and certain toxins cause an increase in cytosolic calcium concentration, initially because of release of Ca^{2+} from the intracellular stores, and later resulting from increased influx across the plasma membrane. Increased

cytosolic Ca^{2+} activates a number of enzymes, with potentially deleterious cellular effects. These enzymes include phospholipases (which cause membrane damage), proteases (which break down both membrane and cytoskeletal proteins), endonucleases (which are responsible for DNA and chromatin fragmentation), and adenosine triphosphatases (ATPases) (thereby hastening ATP depletion). Increased intracellular Ca^{2+} levels may also induce apoptosis, by direct activation of caspases and by increasing mitochondrial permeability.

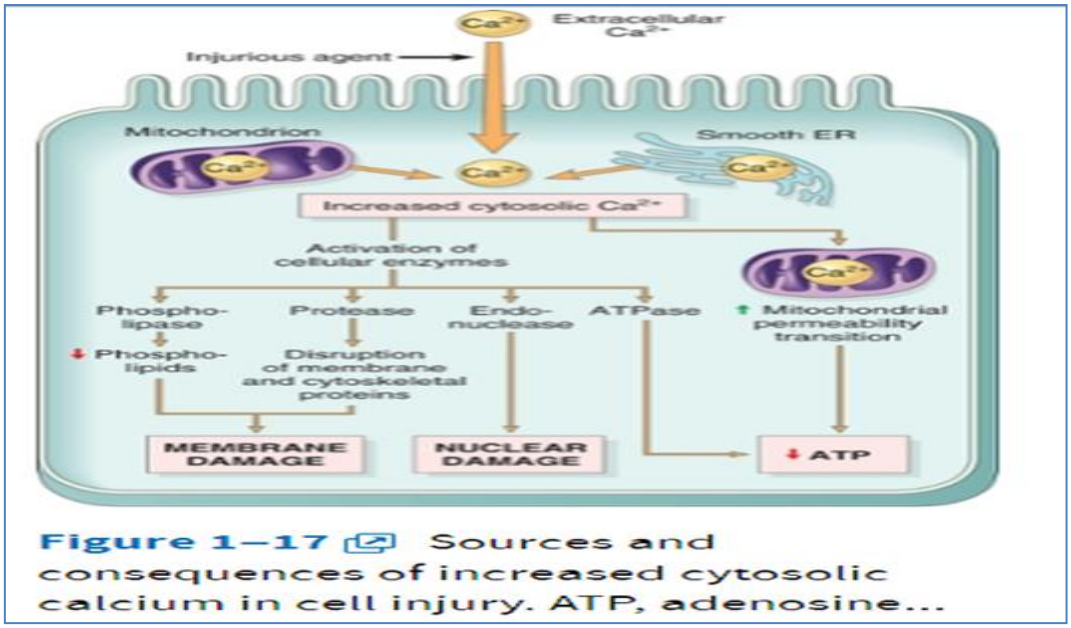


Figure 1–17 Sources and consequences of increased cytosolic calcium in cell injury. ATP, adenosine...

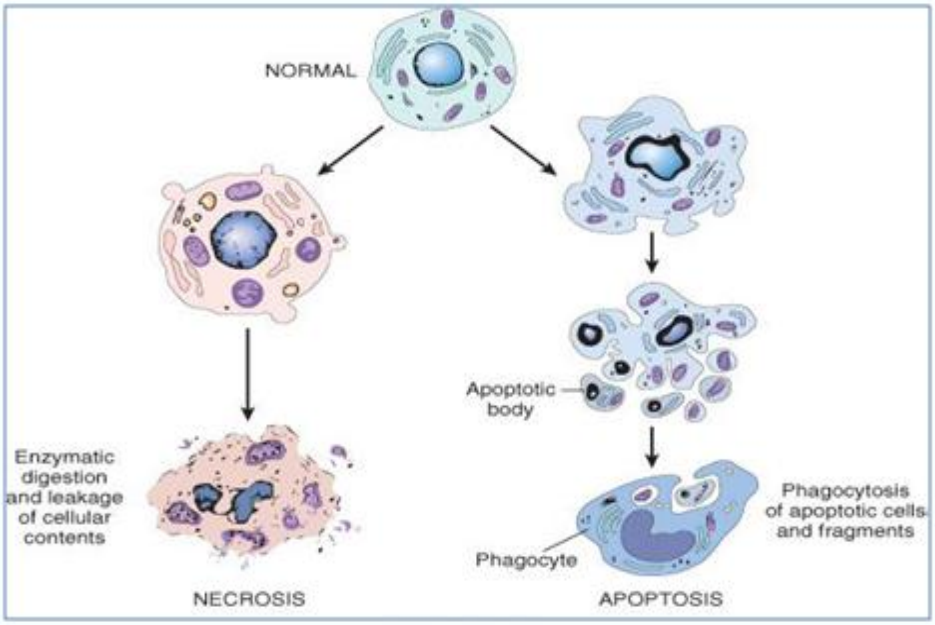
<u>Necrosis</u>--(irreversible injury) changes produced by enzymatic digestion of dead cellular elements

<u>Apoptosis</u>--vital process that helps eliminate unwanted cells--an internally programmed series of events effected by dedicated gene products

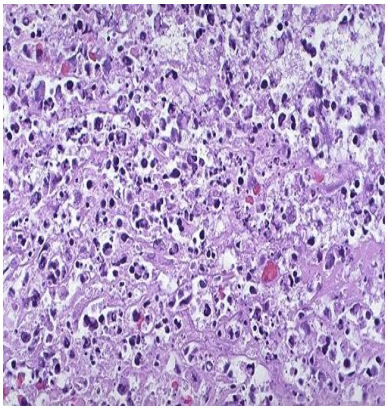
-comparisons between apoptosis and necrosis
The most common types of reversible cell injury are manifested by accumulation of fluid (cellular swelling) and of fat (fatty change). Irreversibly injured cells die and have altered morphology.

Although necrosis is only recognized by morphologic changes occurring during and after cell death (i.e., enzymatic digestion, "coagulation", etc.), apoptosis is an active (programmed) form of cell death that can be detected both by morphology and gene expression changes. Necrosis is always pathologic (the end point of irreversible injury). Apoptosis may be physiologic or pathologic.

	Apoptosis	Necrosis
Histology	Single cells	Groups of cells; disruption of tissue structure
Cytology	Shrunken cells Cell fragmentation (apoptotic bodies) Chromatin condensed in the periphery of nuclei Generally morphologically intact mitochondria	Generally swollen, enlarged cells Pyknotic or fragmented nuclei Dilated ER; high amplitude swelling of mitochondria Outline of the cell initially maintained
Effects on Tissue	No inflammation Phagocytosis by adjacent cells	Disrupted membrane permeability; leakage of cellular products into the blood Acute inflammatory response Possible scar formation



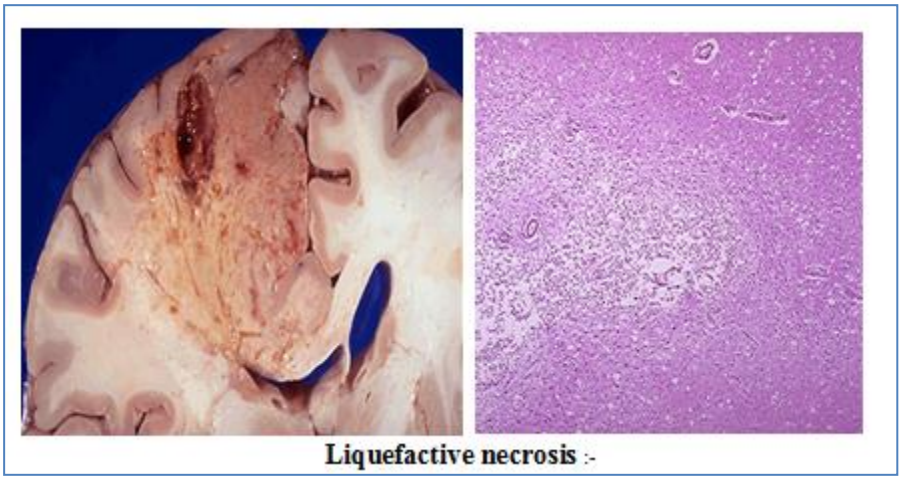
Nuclear Changes: - 1- Pyknosis 2- Karyohexis 3- Karyolysis



1- **Coagulative necrosis :- When there is marked cellular injury, there is cell death. This microscopic appearance of myocardium is a mess because so many cells have died that the tissue is not recognizable. Many nuclei have become pyknotic (shrunken and dark) and have then undergone karorrhexis (fragmentation) and karyolysis (dissolution). The cytoplasm and cell borders are not recognizable. Nuclei disappears, but cell appears normal . E.g. myocardial infarct**

2- **Liquefactive necrosis :- Normal cell structure disappears , E.g. old cerebral infarct This is liquefactive necrosis in the brain in a patient who suffered a "stroke" with focal loss of blood supply to a portion of**

cerebrum. This type of infarction is marked by loss of neurons and neuroglial cells and the formation of a clear space at the centre left.



Liquefactive necrosis :-

3-**Caseous necrosis** :- **"cheesy" necrosis- normal cell structure gone but granular material remains , E.g. pulmonary TB specific form of coagulation necrosis typically caused by mycobacteria (e.g. tuberculosis)**

4-**Fat Necrosis** :- **Lipids autodigested by lipases, E.g. acute pancreatitis**

5- **Gangrenous necrosis**: **Necrosis (secondary to ischemia) , usually with superimposed infection. Example: necrosis of distal limbs, usually foot and toes in diabetes. In this case, the toes were involved in a frostbite injury. This is an example of "dry" gangrene in which there is mainly coagulative necrosis from the anoxic injury.**

6-**Haemorrhagic necrosis** **is due to blockage of the venous drainage of an organ or tissue (e.g. in testicular torsion**).

7-Fibrinoid necrosis **is caused by immune-mediated vascular damage. It is marked by deposition of fibrin-like proteinaceous material in arterial walls, which appears smudgy and eosinophilic on light microscopy.**