MECHANISMS OF CELL INJURY

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Injurious agents induce cell injury through their effects on one or more of the following five cellular targets:

1. Aerobic respiration.
2. Cell membranes.
3. Protein synthesis.
4. Cytoskeleton.
5. Genetic apparatus (chromosomes and their contents of genes).

The attack on one or more of the above targets is mediated by one or more of the following mechanisms:-

1. ATP depletion.
2. Loss of cell membranes permeability and cell membranes damage.
3. Accumulation of oxygen-derived free radicals (oxidative stress).
4. Mitochondrial damage.

A- ATP depletion:

Decreased ATP synthesis and depletion are frequently caused by hypoxia or toxic chemicals.

ATP is required for many cellular anabolic as well as catabolic processes; these include:

1. Transport through cell membrane.
2. Protein synthesis.
3. Lipid synthesis.
4. Phospholipids turnover.

There are two ways of ATP synthesis:

1. **Oxidative phosphorylation** of ADP to ATP within mitochondria; this is the physiological way and occurs in the presence of adequate O2 supply.

2. Anaerobic glycolysis; this occurs under conditions of oxygen lack (hypoxia).

Glucose from the body fluids or through hydrolysis of glycogen is utilized for the production of ATP.

Depletion of ATP produces the following:

1. **Reduction of the activity of plasma membrane energy-dependent sodium pump.**

This causes Na+ to accumulate within the cell and K+ to diffuse out (opposite normal).

Na+ retention holds with it water (isosmotic gain of H_2O).

The eventual outcome is cellular edema.

2- A switch to anaerobic glycolysis.

One of the important causes of ATP depletion is lack of O2 which blocks oxidative phosphorylation for ATP production.

The cell tries to maintain energy supply through anaerobic glycolysis.

This depletes glycogen and also results in the liberation of lactic acid and inorganic phosphates.

As a result, there is a drop intracellular pH (increased cellular acidity) that interferes with the optimal activity of many cellular enzyme.

3- increased in intracellular Ca++.

Failure of the calcium pump leads to influx of Ca++ that has damaging effects on several cellular components (see blow).

4- Structural disruption of the protein synthesis apparatus.

With prolonged or worsening ATP depletion there is a reduction in protein synthesis due to:-

A- Detachment of ribosomes from the rough endoplasmic reticulum.

B- Dissociation of polysomes into monosomes.

5- Unfolded protein response

A protein is initially a linear polymer of amino acids linked together by peptide bonds.

Various interaction between constituent amino acids in this linear sequence stabilize a specific folded three-dimensional configuration specific for each protein.

After their synthesis within ribosomes, the protein are drawn into the endoplasmic reticulum lumen where they assume their folded conformation .

They are eventually transported by vesicles to Golgi apparatus.

Cellular proteins may become abnormally configured (misfolded or unfolded) in a number of situations that include:

A-O2 or glucose deprivation (both lead to ATP depletion).

B-Exposure to heat.

C-Damage by enzymes & free radicals.

These abnormally configured proteins can not be mobilized and this leads to their accumulation within the endoplasmic reticulum , which is harmful to the cell and may lead to cell injury and even apoptosis.

Such an abnormal situation triggers a cellular reaction called unfolded protein response through certain proteins within EPR that sense the accumulation of the misfolded proteins.

As a response they trigger signaling pathways that lead eventually to slowing down the synthesis of misfolded proteins in the cell.

This, in essence, is an adaptive response (to avoid cell injury).

However, cell injury and apoptosis occur when the misfolded proteins continue to accumulate despite the adaptive response.

Failure of this response is now thought to be the pathogenetic mechanism in a number of several neurodegenerative diseases such as Alzheimer and Parkinson diseases, and possibly also type II diabetes mellitus.

B- Loss of cell membrane permeability and cell membrane damage.

Loss of selective membrane permeability (that leads eventually to overt membrane damage) is a regular feature of most forms of cellular injury.

The effect is not limited to the cell membrane only but may also involve that of the mitochondria, ribosomes and lysosomes.

Membrane defects are the result of ATP depletion (see above).

The outcome of this depletion are not only dysfunction of Na+-K+ pump only but also failure of the Ca++ pump that leads to influx of Ca++ with subsequent rise of intracellular Ca++ levels.

Elevation of intracellular Ca++ leads in turn to activation of a number of intracellular enzymes that include:

1- ATPase, which hastens ATP depletion.

2- Different degrading enzymes as phospholipases, proteinases and endonucleases that cause destruction of the cell membranes proteins and other cellular components including RNA and DNA.

These enzymes are normally contained within lysosomes in the inactive forms.

They are set free within the cytoplasm as a result of damage to lysosomal membranes.

They become activated by the elevated levels of Ca++ .

These activated enzymes cause degradation of phospholipids (cell membrane damage), protein (including structural cytoskeleton proteins), glycogen, RNA & DNA. With such extensive damage there is no further possibility of survival and the cell starts to die.

There are certain injurious agents that can directly damage the cell membrane e.g. bacteria of gas gangrene that elaborate phospholipases, which attack phospholipids in cell membrane.

C- Accumulation of oxygen-derived free radicals (oxidative stress).

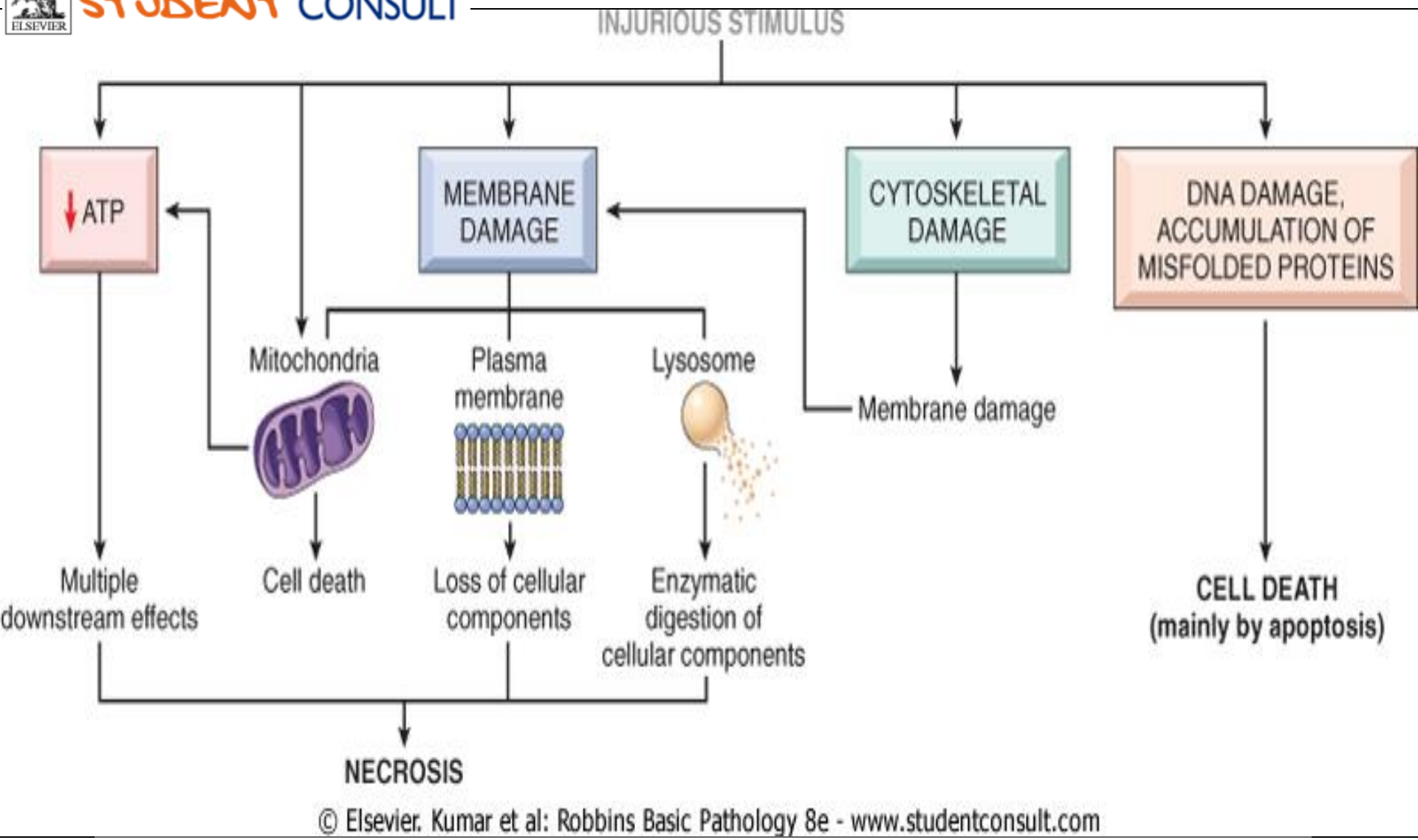
Oxygen-derived free radicals are produced as a byproduct of mitochondrial respiration.

These are chemically reactive; having a signal unpaired electron in the outer orbit, examples include O2_. (superoxide),H2O2 (hydrogen peroxide), OH_. (Hydroxyl radical) and 1O2 (single oxygen).

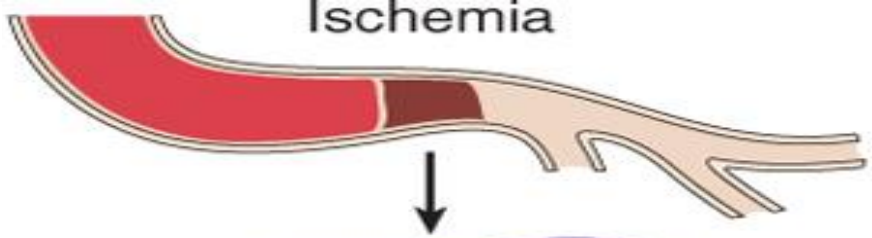
They can damage lipids, proteins and nucleic acids leading to various forms of cell injury.

Cells normally have defense mechanisms to terminate these products and prevent injury caused by them. An imbalance between generation and removal results in excess of these products. This situation is known as **oxidative stress.**

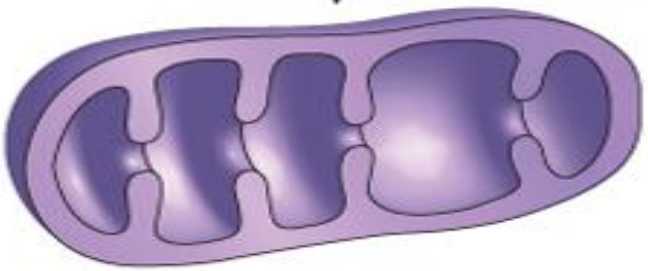
Oxidative stress is associated with cell injury seen in many pathological conditions e.g. inflammation, radiation, oxygen toxicity, various chemicals and reperfusion injury.



The principal cellular and biochemical sites of damage in cell injury. Note that loss of adenosine triphosphate (ATP) results first in reversible injury (not shown) and culminates in necrosis. Mitochondrial damage may lead to reversible injury and death by necrosis or apoptosis.



Mitochondrion



↓ Oxidative phosphorylation

↓ ATP

↓ Na^+ pump

↑ Influx of Ca^{2+}, H_2O, and Na^+

↑ Efflux of K^+

ER swelling
Cellular swelling
Loss of microvilli
Blebs

↑ Anaerobic glycolysis

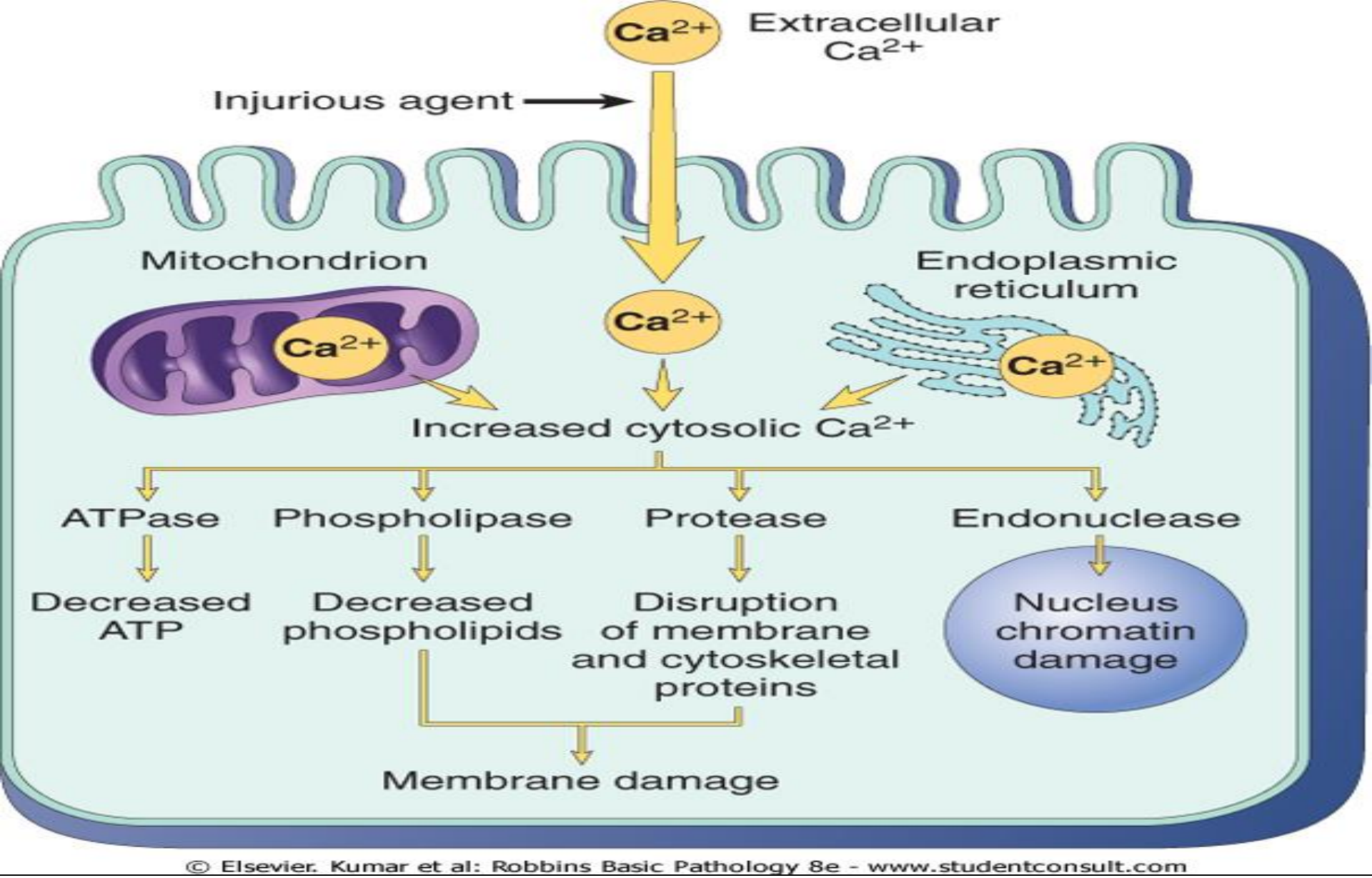
↓ Glycogen

↑ Lactic acid → ↓ pH

Clumping of nuclear chromatin

Detachment of ribosomes

↓ Protein synthesis



Sources and consequences of increased cytosolic calcium in cell injury. ATP, Adenosine triphosphate; ATPase, adenosine triphosphatase.