Reperfusion injury

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It has been noted that many of the effects of ischemic injury seem to occur not during the ischemic episode itself but when perfusion (blood flow) is re-established to an area of tissue that has been ischemic.

The re-flowed blood encounters cells with already disrupted membranes from the initial ischemia.

Among other consequences of this membrane dysfunction that is particularly important in this context is impairment of calcium transport out of the cell and from organelles (such as mitochondria).

The rise of intracellular Ca ++ causes activation of oxygen-dependent free radicals that lead eventually to cell damage.

The necrosis of reperfusion injury appears to be of the apoptotic rather than of the conventional type.

D. mitochondrial damage

Mitochondria are important targets for virtually all types of injurious agents, including hypoxia and toxins.

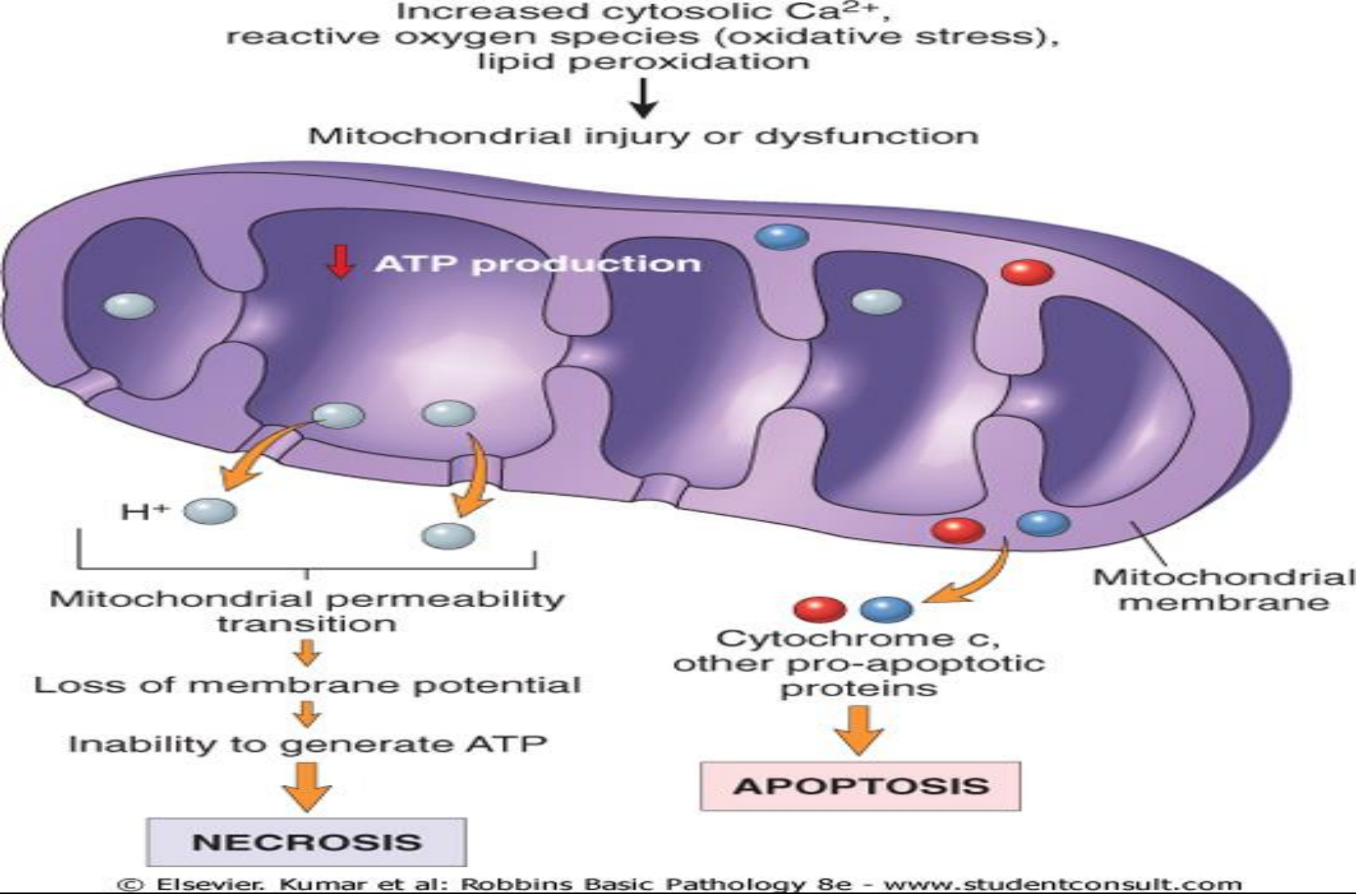
Mitochondria can be damaged by

1. Increase in cytoplasmic Ca ++.
2. Oxidative stress.
3. Breakdown of phospholipids by activated phospholipase.

Injury to mitochondria leads to increased permeability of its membrane that result in leakage from the mitochondria of H+ and cytochrome C.

The former leads to loss of mitochondrial membrane potential, which is critical for mitochondrial oxidative phosphorylation thus leading to ATP depletion.

Leakage of cytochrome c can trigger apoptotic cell death.



Consequences of mitochondrial dysfunction, culminating in cell death by necrosis or apoptosis. ATP, Adenosine triphosphate.

Factors influencing the severity of cell injury

1. **Type, duration and severity of the injurious agent.**

2. Type of the affected cells: cells differ in their susceptibility to the effects of injurious agents for e.g.

Type of cell	Susceptibility to damage by ischemia	Time required for damage
Neurons	high	3-5 min.
Myocardial cells	intermediate	30-60 min.
Skeletal muscles	low	many hr.s
Epidermis of the skin		
Fibroblasts		

Reversible cell injury

Ischemia is one of the commonest causes of cell injury.

Ischemia leads to hypoxia.

This in turn results in reduction of the available ATP.

The cell, as a result of hypoxia, switches over to anaerobic glycolysis (in an attempt to maintain energy supply).

The glycogen stores get depleted with an increase in the concentration of intracellular **lactic acid** (a byproduct of anaerobic glycolysis).

Lack of ATP results in failure of **sodium-potassium pump** with resultant influx of sodium into the cell and this is accompanied by water (to insure isotonicity). The result is swelling of the cell.

Additionally the lowering of intracellular pH (by lactic acid) interferes with the proper functions of enzymes.

Examples of reversible cell injury

I. Acute cellular swelling (hydropic change, hydropic degeneration). This is an early change in many examples of reversible cell injury; The extra-fluid may be seen by light microscopy as an increase in the size of the cell with pallor of the cytoplasm **(cloudy swelling).** With further water accumulation clear vacuoles are created within the cytoplasm **(vacuolar degeneration).**

2. Fatty change (see later)

Irreversible cell injury

Mitochondrial damage is one of the most reliable early features of this type of injury.

In irreversible injury the damage to cell membranes is more severe than in reversible injury, resulting in **leakage of the cellular constituents** outside their normal confines.

This also results in **liberation and activation of lysosomal enzymes** (proteinases, nucleases etc.), which are also normally bounded by membranes.

These liberated and activated enzymes digest both cytoplasmic and nuclear components **(autolysis).**

The end result is total cell necrosis, which is the morphological expression of cell death.

Cell death

There are two modes of cell death

1. **Necrosis.**
2. **Apoptosis.**

Necrosis

Necrosis is defined as the morphological changes that follow cell death in a living tissue or organ.

Necrosis results from the degrading action of enzymes on irreversibly damaged cells with denaturation of cellular proteins.

In necrosis there are cytoplasmic as well as nuclear changes.

Cytoplasmic changes

In the hematoxylin-eosin stain (H&E) the **hematoxylin** stains acidic materials (including the nucleus) ***blue;*** whereas **eosin** stains alkaline materials (including the cytoplasm) ***pink***.

The necrotic cell is more eosinophilic than viable cells (i.e. more intensely pinkish) this is due to

1- Loss of cytoplasmic RNA (RNA is acidic so stains with hematoxylin bluish).

2- Increased binding of eosin (which is responsible for the pinkish color of the cytoplasm) to the denatured proteins.

The cell may have more glassy homogeneous appearance than normal cells; this is due to loss of glycogen particles (which normally gives a granular appearance to the cytoplasm).

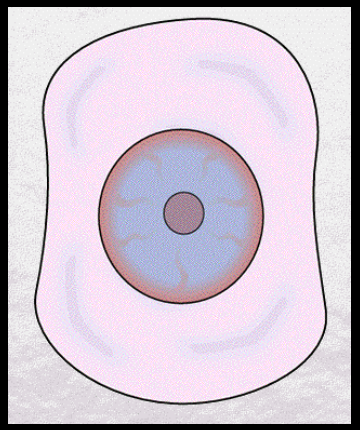
Nuclear changes The earliest change is **chromatin clumping,** which is followed by one of two changes

1- The nucleus may shrinks and transformed into small wrinkled mass **(pyknosis),** with time there is progressive disintegration of the chromatin with subsequent disappearance of the nucleus altogether **(karyolysis)** or

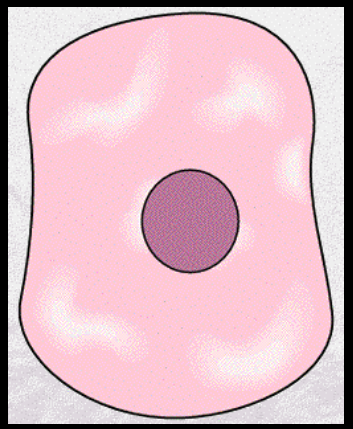
2- The nucleus may break into many clumps **(karyorrhexis).**

Cell necrosis: Nuclear changes

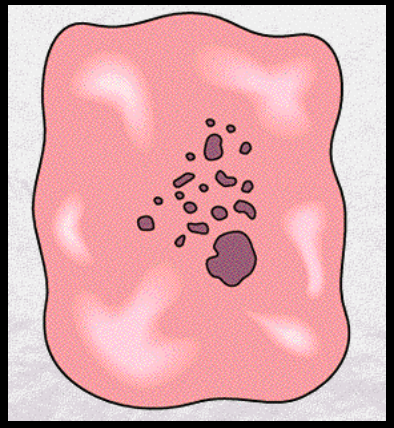
normal



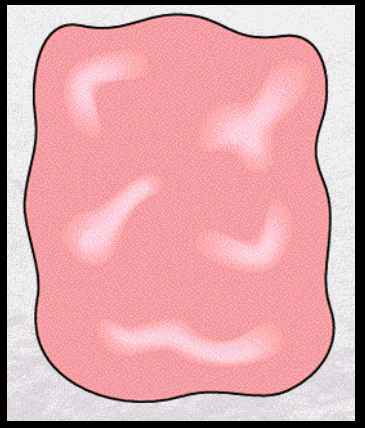
pyknosis

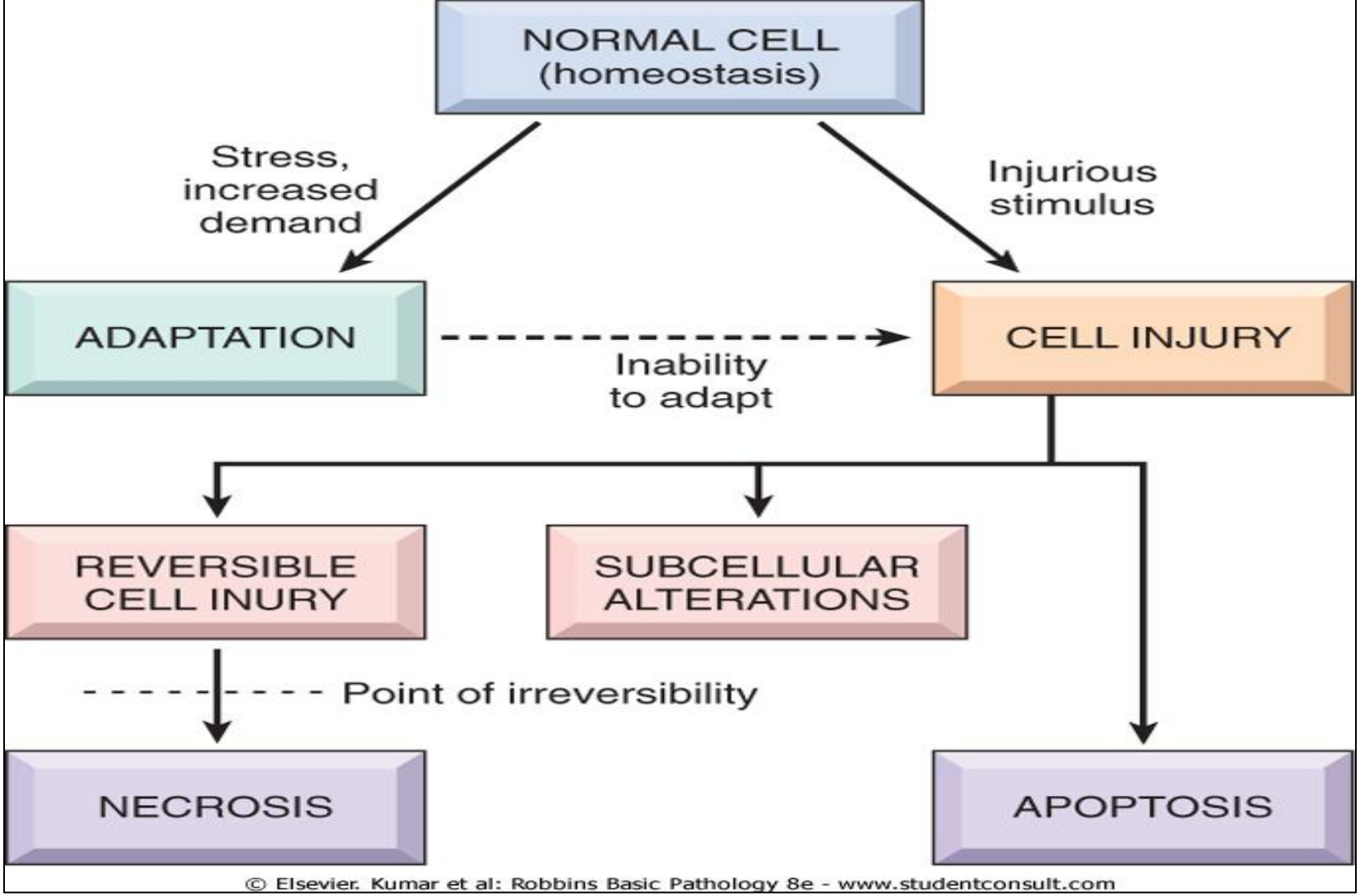


karyorrhexis

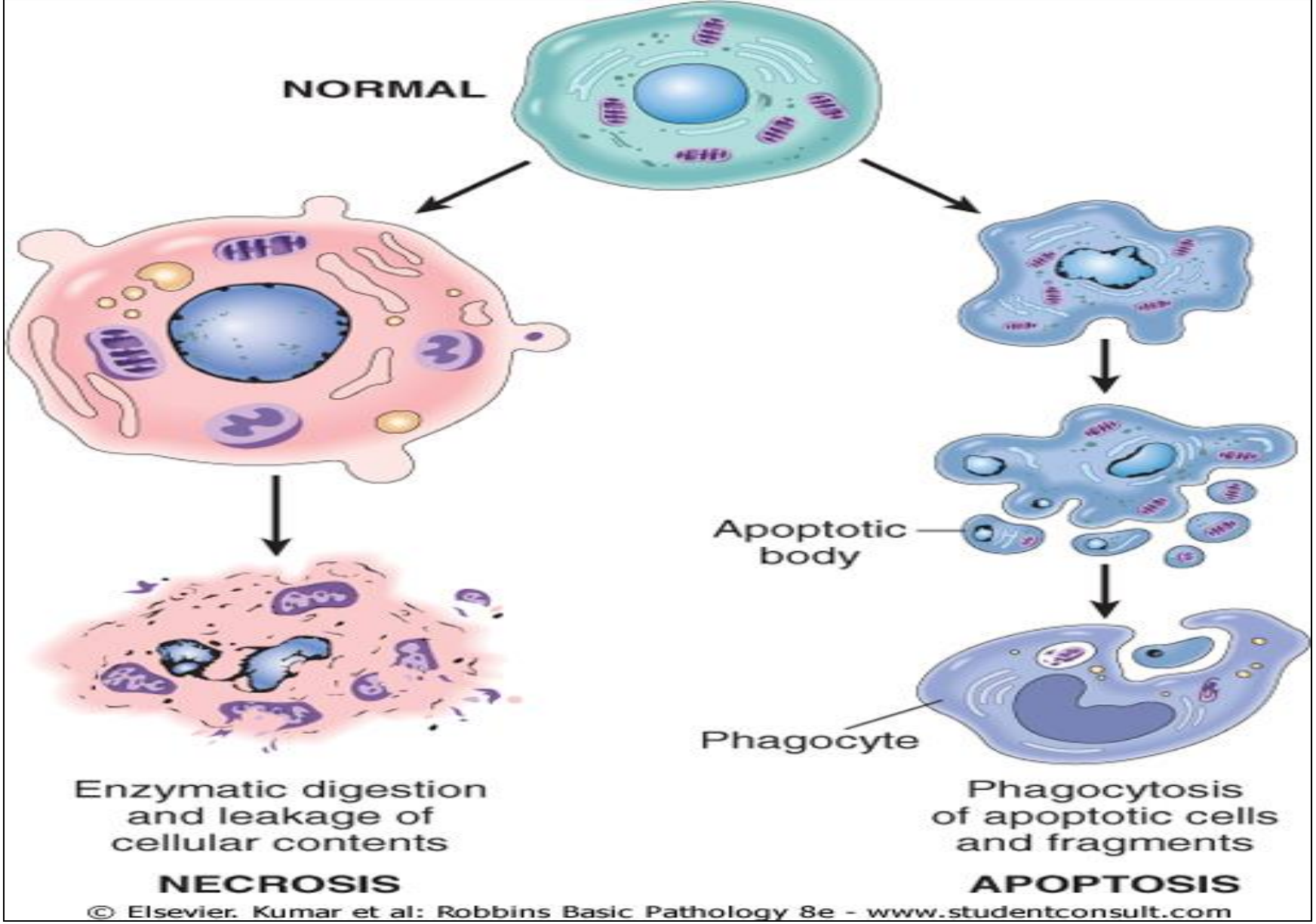


karyolysis

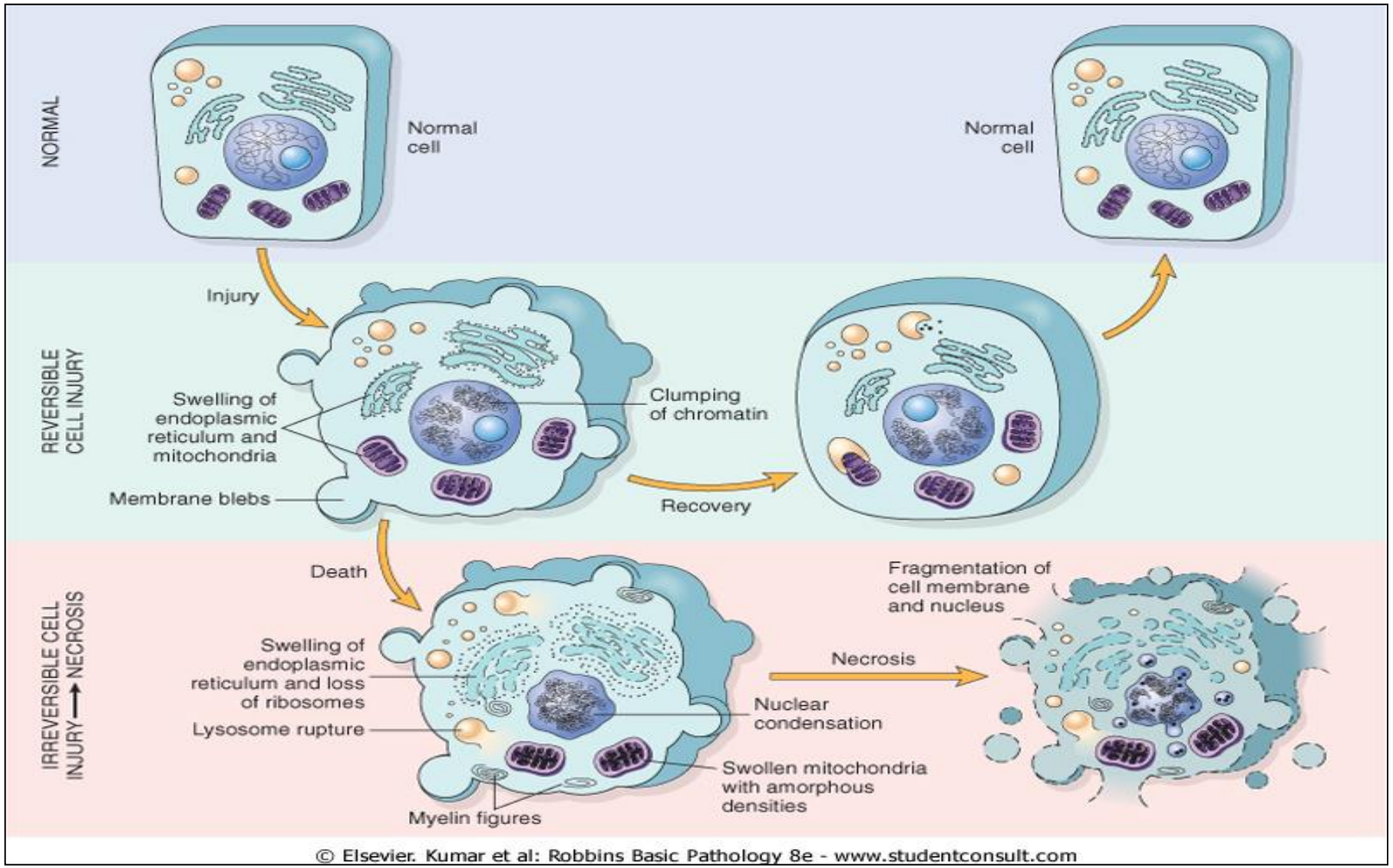




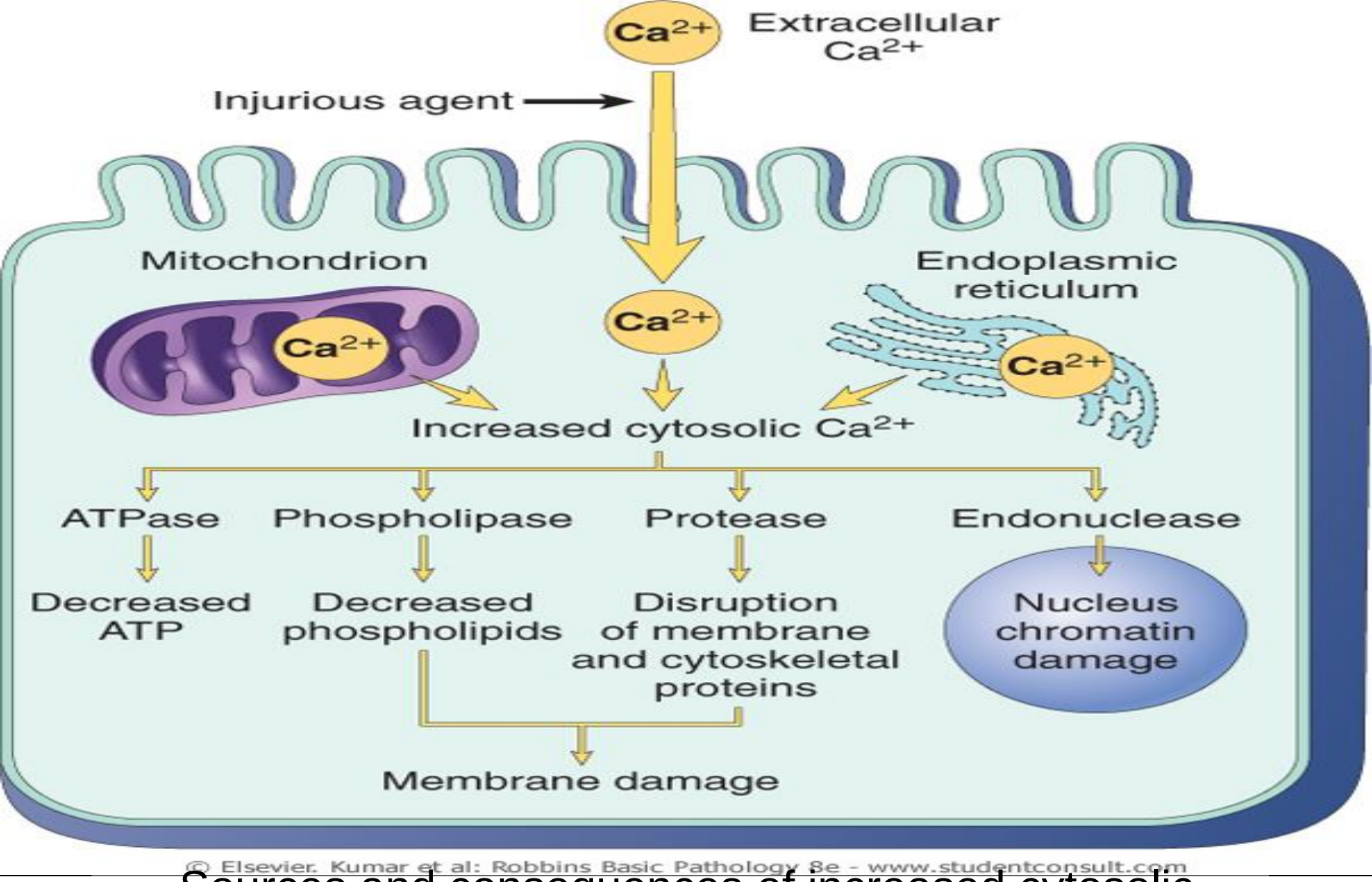
Stages in the cellular response to stress and injurious stimuli



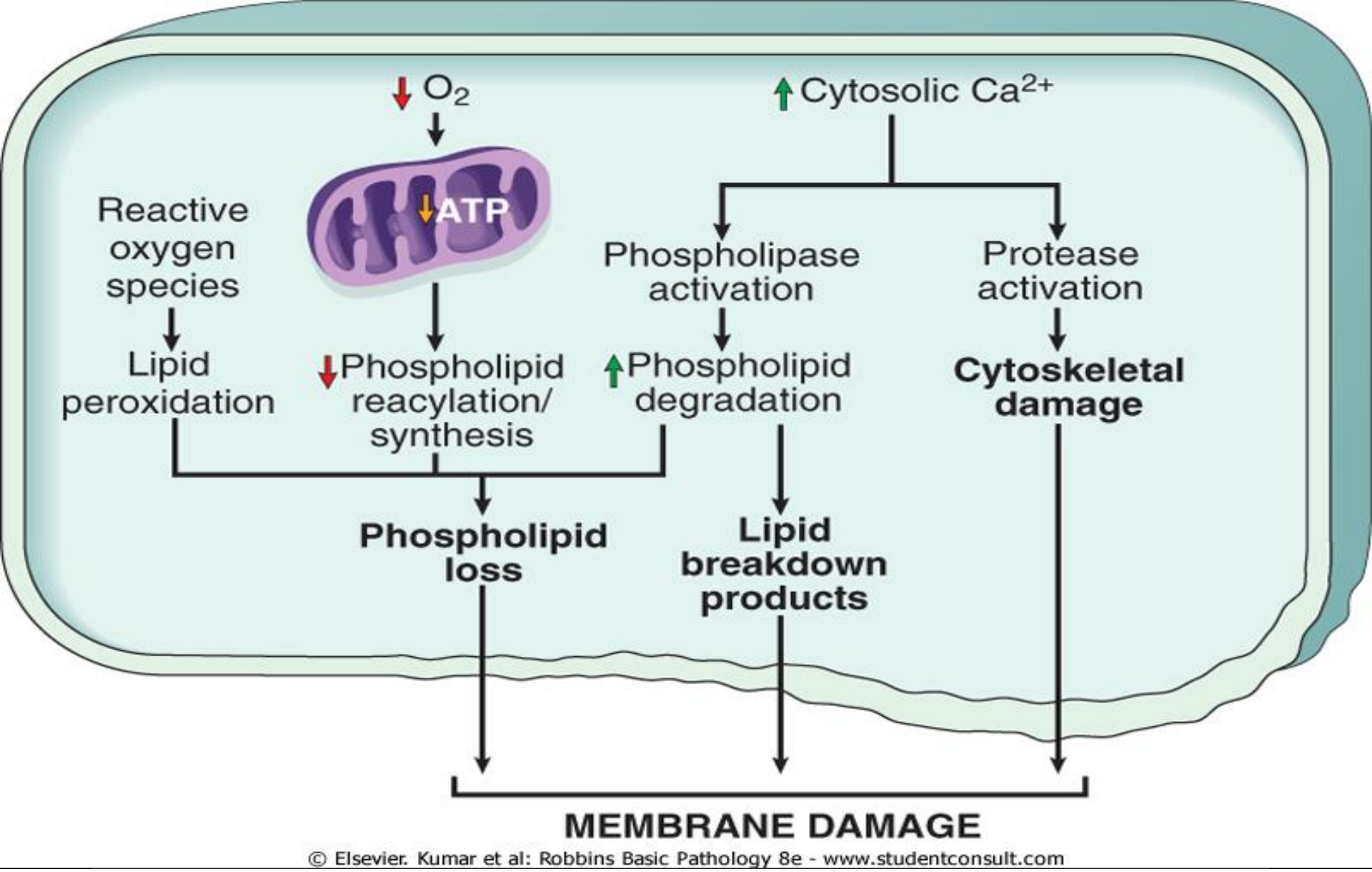
Cellular features of necrosis (left) and apoptosis (right).



A normal cell and the changes in reversible and irreversible cell injury (necrosis).



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



Mechanisms of membrane damage in cell injury. Decreased O2 and increased cytosolic Ca2+ are typically seen in ischemia but may accompany other forms of cell injury. Reactive oxygen species, which are often produced on reperfusion of ischemic tissues, also cause membrane damage (not shown).