Al muthanna University **Pharmacy college**
Lecturer Zainab sattar Ali **Theo. Pathophysiology lec.1**

Pathophysiology

The study of the disturbance of normal mechanical, physical and biochemical functions either caused by a disease or abnormal syndrome or condition that may not qualify to be called a disease (they correlate with the underlying abnormalities and physiological disturbances(

Through this circumstances patient's body is maintaining of homeostasis by:

- **Blood pressure change**
- **Pulse**
- **Temperature change**
- **Fluid imbalance**

Can be adjusted based on:

- **Age**
- **Gender**
- **Genetics**
- **Environment**
- **Activity Level**

Signs= objective (What the Dr. See's)-felt, heard or seen Ex. Lesions, redness swelling.

Symptoms= subjective (what the patient experiences) not visible outwards to others

Ex. Nausea, headache

Syndrome: collection of signs and symptoms that occur together.

Cell Injuries, Adaptation & Cell Death

Cells are active participants in their environment, constantly adjusting their structure function to accommodate changing demands and extracellular stresses, for maintain their normal homeostasis.

Cellular adaptations include:

Atrophy--shrinkage of cells

Hypertrophy--increase in the size of cells which results in enlargement of the organs

Hyperplasia--increased number of cells in an organ or tissue

Metaplasia--transformation or replacement of one adult cell type with another

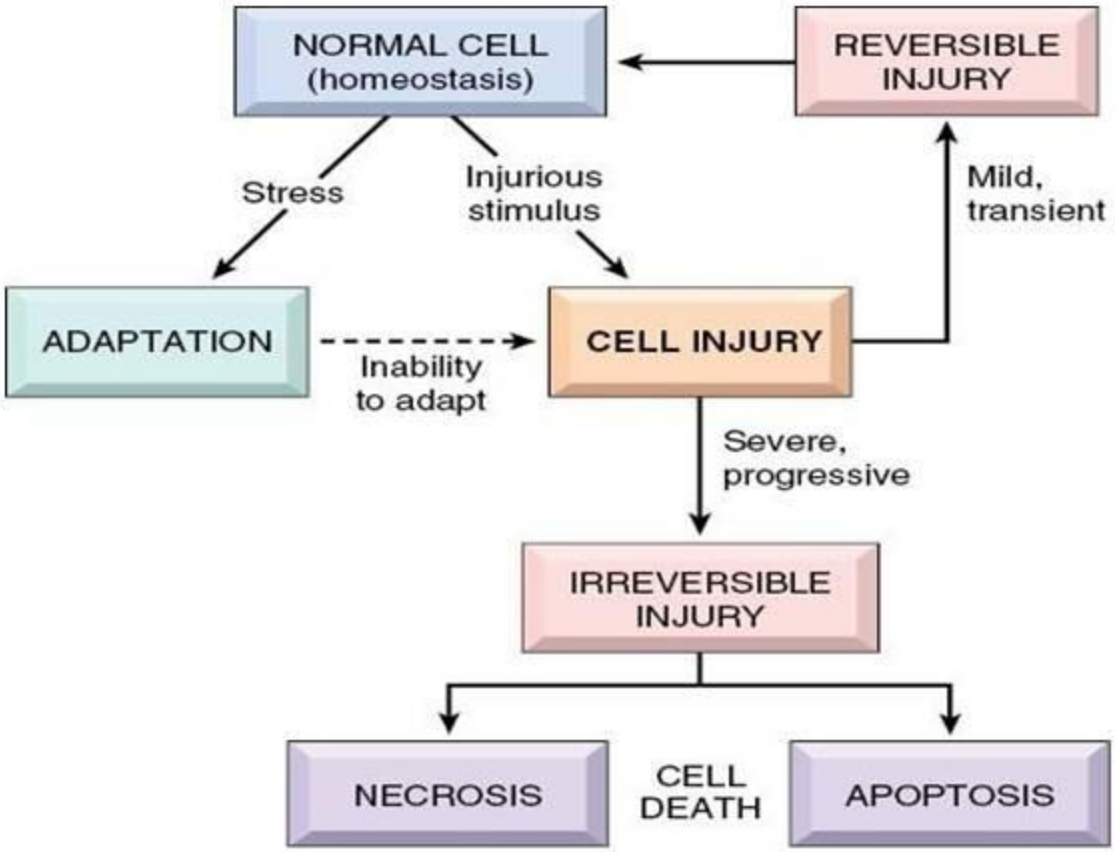


FIGURE 1–1 Stages of the cellular response to stress and injurious stimuli.

Adaptations: are reversible changes in the cells in response to changes in their environment, work demands or threats to survival by changing their size (atrophy and hypertrophy), number (hyperplasia), and form (metaplasia.(

CELL INJURY PRINCIPLES

- **The cellular response to injurious stimuli depends on the type of injury, its duration and its severity.**
- **The consequences of cell injury depend on the type, state, and adaptability of the injured cell**

- **Cell injury results from different biochemical mechanisms acting on several essential cellular components**

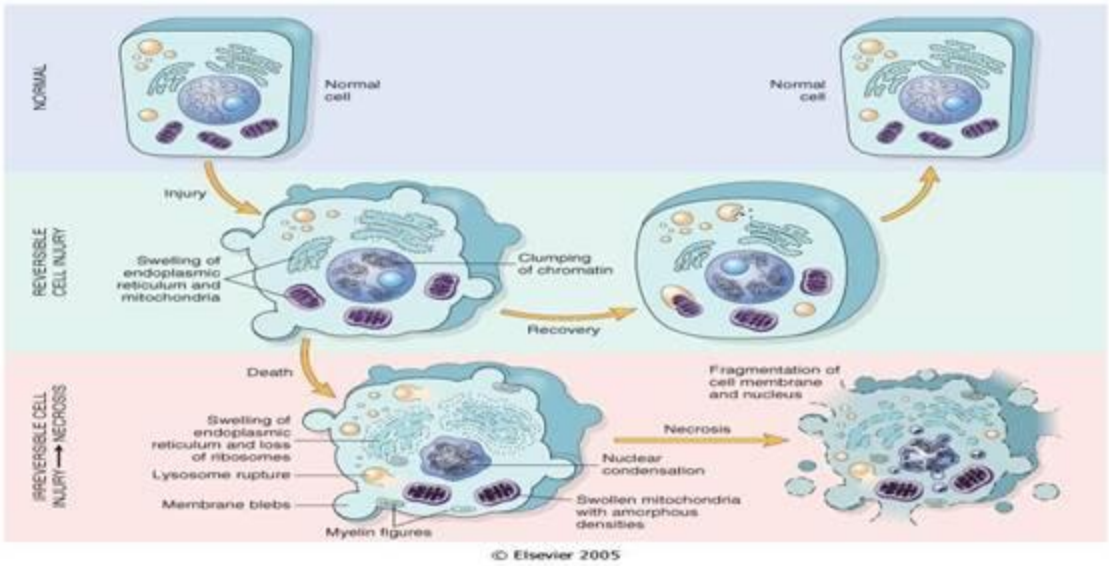
Cellular Changes Secondary to Injury:

REVERSIBLE

- **Cellular swelling**
- **Cell membrane blebs**
- **Detached ribosomes**
- **Chromatin clumping**

IRREVERSIBLE

- Lysosomes rupture
- Dense bodies in mitochondria
- Cell membrane rupture



❖ Degeneration:

A lesion group involving cytoplasmic changes when non-pigmented substances accumulate in the cytoplasm ,10 types of degeneration Based on the type of substance which accumulate in the cytoplasm .These substances are normal substances including H_2O, CHO, Protein and Fat.

❖ NECROSIS:

A Lesion group involving cytoplasmic, nuclear and membrane changes 8 types of necrosis based on 2 criteria:

- **Based on the gross appearance of the necrotic tissue**
- **Based on the type of tissue affected**

❖ Hypertrophy

is an increase in the size of cells resulting in increase in the size of the organ e.g hypertrophy of individual skeletal muscle cells in Weightlifter, cardiac enlargement that occurs in patients with hypertension.

- These changes usually revert to normal if the cause is removed.
- Hypertrophy is mediated by different mechanisms.

❖ Hyperplasia:

Is an increase in cells number resulting in increase in the size of the organ eg enlargement of female breast at puberty and during pregnancy.

Hyperplasia can be classified as:

- physiologic--hormonal (e.g., breast and uterus during pregnancy(
- compensatory--regeneration of liver following partial hepatectomy. Various growth factors and interleukins are important in such hyperplasia.
- pathologic--excessive hormonal stimulation, viral infection (papilloma viruses); neoplasms

❖ Metaplasia

is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type . e.g The normal ciliated columnar epithelial the trachea and bronchi are focally or widely replaced by squamous epithelial cell in the respiratory epithelium in habitual cigarette smokers. Metaplasia also occurs in mesenchymal tissue (e.g., formation of bone in skeletal muscle.(

- Metaplastic changes usually result from chronic irritation.
- Metaplastic changes seem to precede the development of cancer, in some instances.
- Metaplasia is thought to arise from reprogramming of stem or undifferentiated cells that are present in adult tissue.

❖ Atraphy

is reduced size of an organ or tissue resulting from a decrease in cell size and number eg When a fractured bone is immobilized in a plaster cast or when a patient is restricted to complete bed rest, skeletal muscle atrophy rapidly ensues

- Physiologic--due to decreased work load (e.g., decreased size of uterus following child birth, or disease(

- **Pathologic--primarily due to denervation of muscle, diminished blood supply, nutritional deficiency**

If the adaptive capability is exceeded or the external stress is inherently harmful, cell injury develops.

Cell injury: either is

)I) reversible cell injury (the cells return back to their stable baseline state after removal the cause of cell injury.

(2irreversible Cell injury (Cell death & Necrosis) (cells can not return to their baseline state after removal the cause of cell injury.

Causes ell Injury

.1Hypoxia(ATP DEPLETION – ISCHAEMIA: (

O2. Deprivation this is the common cause of cell injury & cell death. It means low level of oxygen reaches the hypoxia should be differentiate from ischemia which means loss of blood supply due to ischemia impeded arterial flow or reduce venous drainage. It means that any case of ischemia with hypoxia, while not any case of hypoxia associated with ischemia

.2 Chemical agents.

a(Glucose or Salts can cause cell injury, especially when their level was increased.

b(High partial pressure of O_2

c(Other chemicals insecticide, CO asbestos, ethanol & drugs(

.3 Infectious agents. B Include virus, Rickettsia bacteria, fungi & parasites(

.4 Immunologic reactions

a) Anaphylaxis (sensitivity to fore protein or drugs.(

b) Autoimmune reactions (immunologic reactions can insult the body tissue.(LSE

(5)Genetic abnormalities Many chromosomal abnormalities can result in many congenital syndromes (Down syndrome, Sickle cell anemia

(6)Nutritional Imbalance either

- **Nutritional deficiency like (protein insufficiency, vitamins deficiency...)this common in underdeveloped countries.**
- **Excesses of nutrients, like obesity which increase e risk of Type Il Diabetes mellitus Also high animal fat diet increases the risk of Atherosclerosis& Cancer.**

(7)Physical agents

Like Trauma, extremities of temperature, electric shock & sudden change in atmospheric pressure.

(8)Aging: cause low tolerance of body cells to the injury

Mechanisms of cell injury

❖ **ATP deprivation:**

- ATP is important in every processes in the cell like (protein synthesis, cellular osmolarity & transport processes (Na+ pump fails→ Na+ and water enter and K+ is lost , Ca++ pump fails- Ca++ into cells (toxic(
- Loss of ATP results in rapid shutdown of most critical homeostatic pathways. Glycolysis depletes glycogen and lowers pH (loss of enzyme activity(
- Decreased protein synthesis (ribosomes detach(
- Unfolded protein response

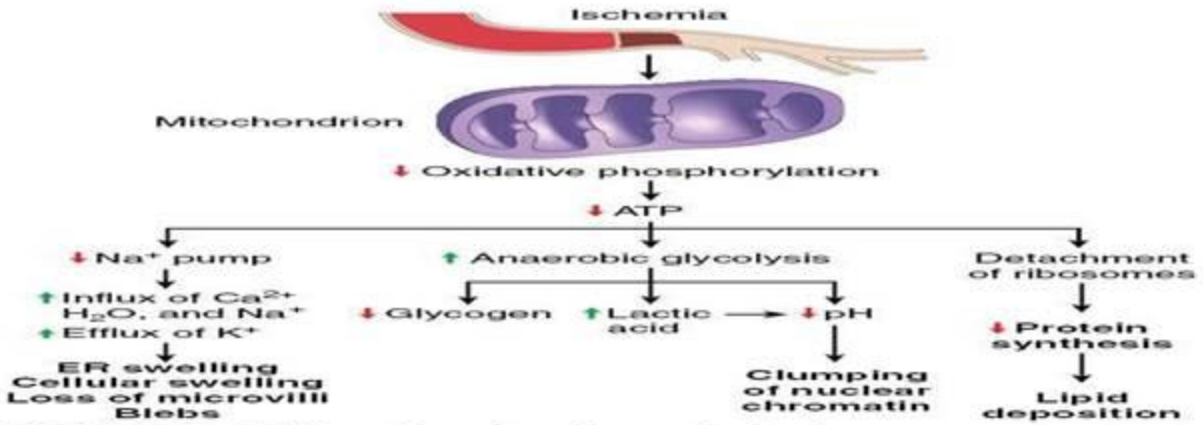


FIGURE 1–17 Functional and morphologic consequences of decreased intracellular ATP during cell injury. The morphologic changes shown here are indicative of reversible cell injury. Further depletion of ATP results in cell death, typically by necrosis. ER, endoplasmic reticulum.

(2)Generation of free Radicals (Discussed later(

(3Loss of Ca^{+2} homeostasis

Normally, the extra cellular concentration of Ca^{+2} is higher than the cytosolic free Ca^{+2}. (this is maintain by ATP dependent transport(

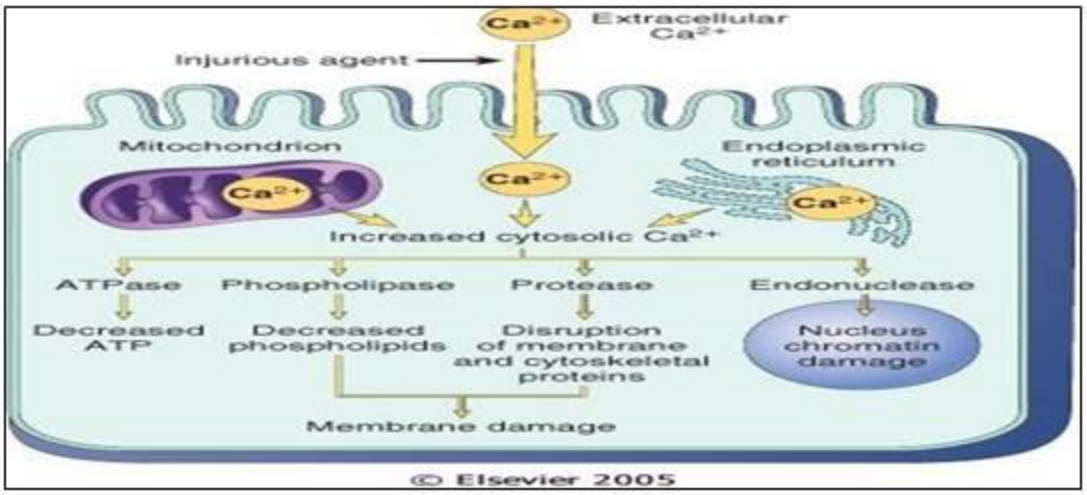
Also the Ca^{+2} normally is stored intracellular at Mitochondria & Endoplasmic Reticulum.

In the cell injury(ischemia, toxins) allow a net of influx extracellular Ca^{+2} across the cell membrane, follow by release of Ca^{+2} from intracellular stores & this result in increased cytosolic Ca^{+2}

Ca++ activates phospholipases (damages cell membranes),proteases (damages cell membranes and cytoskeleton) and endonucleases (damages DNA).

This is one of the main mechanisms of cell death, either through severe damage to membranes of lysosomes and leakage of lysosomal enzymes or triggering apoptosis.

Occurs particularly in hypoxia and ischaemia and with certain toxins. Preventing the rise in Ca++ or restoring to normal levels prevents cell death.



(4Defect in plasma membrane permeability

Defect in membrane permeability will result in the change of concentration of metabolites across the cell membrane. Mechanisms include those occurring with hypoxia/ischaemia and free radicals immune mechanisms as with complement activation perforin from lymphocyte attack on cells infected with a virus. All membranes may be damaged and ruptured by mechanical force as in trauma, or by ice crystals as in extreme cold.

5) Mitochondrial damage:

this non-selective pore may be reversible or become permanent leading to cell death.

Leakage of cytochrome c can trigger apoptosis.

MORPHOLOGY OF EREVERSIBLE INJURY

Two patterns of morphologic changes are reversible cell injury include:

cellular swelling

Fatty change

Free Radicals

induced cell injury are chemical species with a single unpaired in orbital. In such chemical state are extremely unstable & readily react with inorganic & organic chemical

Sources OF Free Radicals

-1Redox reactions (reduction -oxidation reaction(

This reaction normally occurs in the mitochondria. During this reaction small amount of toxic intermediate species are formed include (superoxide O_2^-, hydrogen peroxide H_20_2 & OH)

Nitric Oxide (NO)

Nitric oxide is normally synthesized by a variety of cell types which then act as free radicals by itself or by conversion to highly reactive Nitrite species.

-2Absorption of radiant energy (uv light X-ray), these radiation can hydrolyze the water into OH & hydrogen free radicals (H(

-3During Enzymatic Metabolism of exogenous chemicals like CCL4

-4Free radicals can generate as a part of routine cellular activities like respiration process, defense mechanisms.

Mechanisms of cell Injury by FREE RADICALS

Free radicals can injured the cells by the following mechanisms:

Lipid peroxidation: