CELL INJURY

INTRODUCTION

- Cells are the basic units of tissues, which form

organs and systems in the human body.

- Traditionally, body cells are divided into two main types: epithelial and mesenchymal cells. In health,the cells remain in accord with each other.
- In 1859, Virchow first published cellular theory of disease, bringing in the concept that diseases occur due to abnormalities at the level of cells.
- In general, cells of the body have in built mechanism to deal with changes in environment to an extent.

CELL INJURY

Cell injury is defined as a variety of stresses a cell encounters as a result of changes in its internal and external environment.

The cellular response to stress may vary and depends upon the following variables:

i) The type of cell and tissue involved.

ii) Extent and type of cell injury.

Various forms of cellular responses to cell injury are,

1. When there is increased functional demand, the cell may adapt to the changes which are expressed morphologically and then revert back to normal after the stress is removed(cellular adaptations).
2. When the stress is mild to moderate, the injured cell may recover (reversible cell injury), while when the injury is persistent cell death may occur (irreversible cell injury).
3. The residual effects of reversible cell injury may persist in the cell as evidence of cell injury at subcellular level (subcellular changes), or metabolites may accumulate within the cell (intracellular accumulations).

CAUSES OF CELL INJURY

The cells may be broadly injured by two major ways:

A. By genetic causes

B. By acquired causes

A. Genetic causes

- Developmental defects – error in morphogenesis
- Chromosomal abnormalities
- Mutations

B. Acquired causes

Hypoxia and ischemia:

(hypoxia- deficiency in oxygen supply to cells, ischemia –decreased supply of blood to cells due to interruption)

Cells and tissues require oxygen to generate energy and perform metabolic functions. Hypoxia results in failure to carry out these activities by the cells. Hypoxia is the most common cause of cell injury. Hypoxia may result from ischemia. Hypoxia may result from other causes as well e.g. disorders of oxygen-carrying RBCs (e.g. anemia, carbon monoxide poisoning), heart diseases, lung diseases and increased demand of tissues. Due to ↓ Blood Supply, Heart & Lung diseases or Anemia.

Physical agents:

Physical agents in causation of disease are asunder:

mechanical trauma (e.g. road accidents);

thermal trauma (e.g. by heat and cold);

electricity;

radiation (e.g. ultraviolet and ionising); and

rapid changes in atmospheric pressure.

Chemicals and drugs:

An ever increasing list of chemical agents and drugs may cause cell injury.

Important examples include the following:

chemical poisons such as cyanide, arsenic,

mercury;

social agents such as alcohol and narcotic drugs;

therapeutic administration of drugs.

Microbial agents:

Injuries by microbes include infections caused by bacteria, rickettsiae, viruses, fungi, protozoa, metazoa, and other parasites.

Immunological agents:

Immunity is a 'double edged sword'—it protects the host against various injurious agents but it may also turn lethal and cause cell injury. e.g. hypersensitivity reactions, anaphylactic reactions; and autoimmune diseases.

Nutritional derangements:

A deficiency or an excess of nutrients may result in nutritional imbalances.Nutritional deficiency diseases may be due to overall deficiency of nutrients (e.g. starvation), of protein calorie (e.g.marasmus, kwashiorkor), of minerals(e.g.anaemia), or of trace elements. Nutritional excess is a problem of affluent societies resulting in obesity, atherosclerosis, heart disease and hypertension.

Aging:

Cellular aging or senescence leads to impaired ability of the cells to undergo replication and repair, and ultimately lead to cell death culminating in death of the individual.

Psychogenic diseases:

There are no specific biochemical or morphologic changes in common acquired mental diseases due to mental stress,

strain, anxiety, overwork and frustration. However, problems of drug addiction, alcoholism, and smoking result in various organic diseases such as damage, chronic bronchitis, lung cancer, peptic ulcer, hypertension, ischaemic heart disease etc.

Idiopathic cause:

Idiopathic means “of unknown cause”. Finally, although so much is known about the etiology of diseases, there still remain many diseases for which exact cause is undetermined.
For example, most common form of hypertension(90%) is idiopathic (or essential) hypertension.

PATHOGENESIS OF CELL INJURY

The following principles apply in pathogenesis of most forms of cell injury by various agents:

1. Type, duration & severity of injurious agent

The extent of injury depend upon type (living/nonliving), duration (how much time it contact to the cell)& severity (how much injurious agent is severe) of stimulus agents.
Ex. Small dose of chemical toxin or short duration of ischemia causes cell injury, whereas a large dose of same chemical persistent ischemia causes cell death. irreversible cell injury after 20-30minutes of persistent ischemia.

2. Type, status & adaptability of target cell

The type of cell as regards its susceptibility to injury, its nutritional and metabolic status, and adaptation of the cell to hostile environment determine the extent of cell injury e.g. skeletal muscle can withstand hypoxic injury for
long-time while cardiac muscle suffers. Ischaemia and hypoxia are the most common forms of cell injury. Although underlying intracellular mechanisms and ultrastructural changes involved in reversible and irreversible cell injury by hypoxia and ischaemia depending upon extent of hypoxia and type of cells involved, they are a continuation of the
process.

Reversible cell injury:

If the ischaemia or hypoxia is of short duration, the effects may be reversible on rapid restoration of circulation.
The sequential biochemical and ultrastructural changes in reversible cell injury are as under:
Decreased generation of cellular ATP: Damage by ischaemia versus hypoxia from other causes.
Intracellular lactic acidosis:Nuclear clumping.
Damage to plasma membrane pumps: Hydropic swelling and other membrane changes.
Failure of sodium-potassium pump. - Failure of calcium pump.
Reduced protein synthesis: Dispersed ribosomes

Irreversible cell injury:

Continuation of ischaemia or hypoxia results in irreversible damage to the structure and function of the cell (cell death). The stage at which this point of no return or irreversibility is reached from reversible cell injury is unclear but the sequence of events is a continuation of reversibly injured cell.
Two essential phenomena distinguish irreversible from reversible cell injury: Inability of the cell toreverse mitochondrial dysfunction on reperfusion orreoxygenation.
Disturbance in cell membrane function in general, and in plasma membrane in particular. In addition, there is further reduction in ATP, continued depletion of proteins, reduced intracellular pH, and leakage of lysosomal enzymes into the cytoplasm. These biochemical changes have effects on the ultrastructural components of the cell.

1. Calcium influx: Mitochondrial damage

Mitochondrial Damage: Mitochondria are important targets for all types of injury, including hypoxia and toxins.

Mitochondrial changes are seen as vacuoles in the mitochondria and deposit of amorphous calcium salts in mitochondrial matrix.

Mitochondria can be damaged by :

A- Increases of cytosolic Ca2+

B Oxidative stress

C- Breakdown of phospholipids, andby

D- Lipid breakdown products.

Mitochondrial damage results in the formation of a high-conductance channel, called mitochondrial permeability transition, present in the inner mitochondrial membrane. In the initial phase it is reversible but once mitochondrial permeability transition is irreversble it becomes a deathblow to the cell. Mitochondrial damage can also be associated with leakage of cytochrome c into the cytosol.

2. Activated phospholipases: Membrane damage.

Damage to membrane function in general, and plasma membrane in particular, is the most important event in irreversible cell injury in ischaemia. As a result of sustained ischaemia, there is increased cytosolic influx of calcium in the cell. Increased calcium activates endogenous phospholipases. These in turn degrade membrane phospholipids

progressively which are the main constituent of the lipid bilayer membrane. Besides, there is also decreased replacement-synthesis of membrane phospholipids due to reduced ATP. Other lytic enzyme which is activated is ATPase which causes further depletion of ATP.

3. Intracellular proteases: Cytoskeletal damage

The normal cytoskeleton of the cell (microfilaments, microtubules and intermediate filaments) which anchors the cell membrane is damaged due to degradation by activated intracellular proteases or by physical effect of cell

swelling producing irreversible cell membrane injury.

4. Activated endonucleases: Nuclear damage

The nucleoproteins are damaged by the activated lysosomal enzymes such as proteases and endonucleases. Irreversible damage to the nucleus can be in three forms:

i) Pyknosis: Condensation and clumping of nucleus which becomes dark basophilic.

ii) Karyorrhexis: Nuclear fragmentation in to small bits dispersed in the cytoplasm.

iii) Karyolysis: Dissolution of the nucleus

5. Lysosomal hydrolytic enzymes: Lysosomaldamage,cell death and phagocytosis.

The lysosomal membranes are damaged and result in escape of lysosomal hydrolytic enzymes. These enzymes are activated due to lack of oxygen in the cell and acidic pH. These hydrolytic enzymes (hydrolase, RNAase, DNAase, protease, glycosidase, phosphatase, lipase, amylase, cathepsin etc) which on activation bring about enzymatic digestion of cellular components and hence cell death.