CELL INJURY

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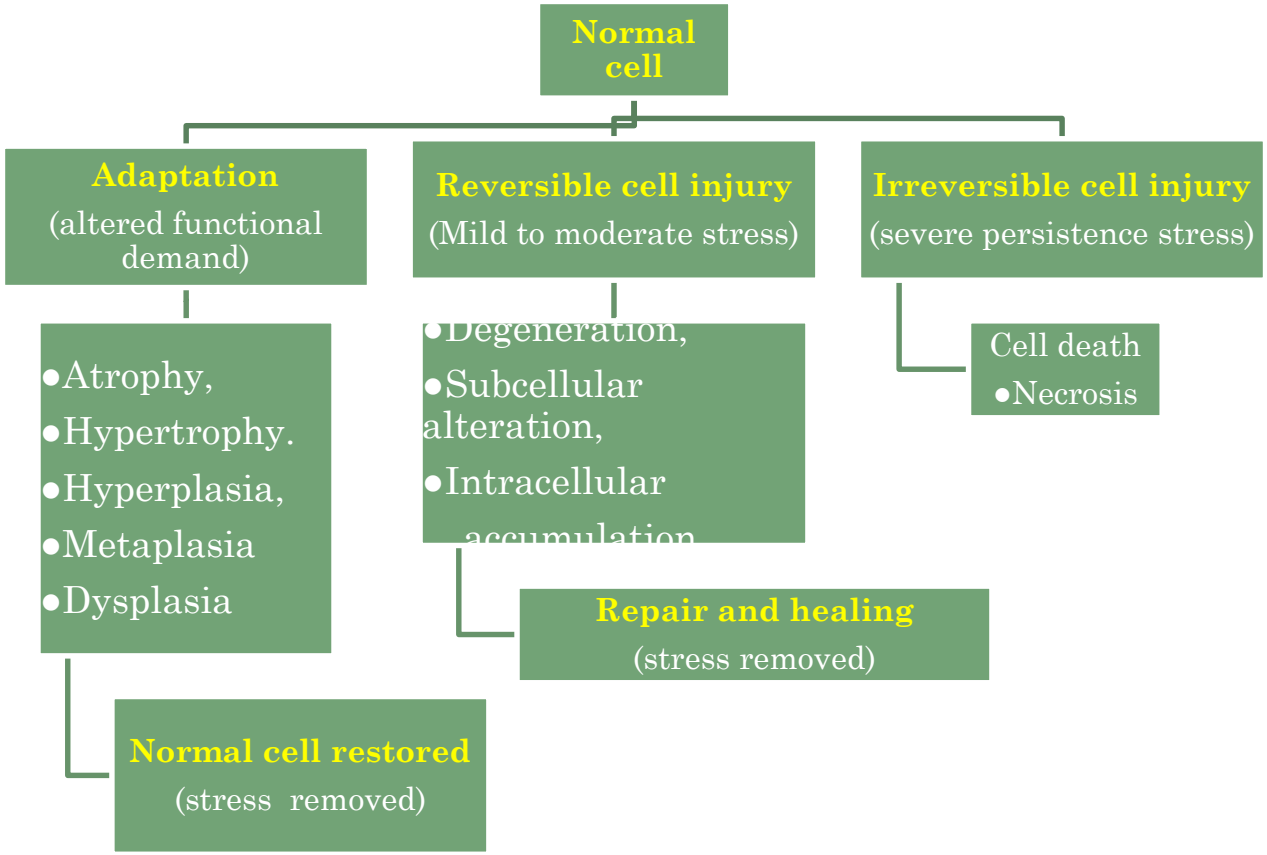
DEFINITION

- It is functional and morphological effects of a variety of stress due to etiological agents a cell encounter resulting in change in the internal and external environment.


Normal cell
Adaptation
(altered functional demand)
Reversible cell injury
(Mild to moderate stress)
Irreversible cell injury
(severe persistence stress)
•Atrophy,
•Hypertrophy.
•Hyperplasia,
•Metaplasia
•Dysplasia
•Degeneration,
•Subcellular alteration,
•Intracellular
Cell death
•Necrosis
Repair and healing
(stress removed)
Normal cell restored
(stress removed)

Etiological factors

A) Genetic causes

B) Acquired cause

1. Hypoxia and ischaemia
2. Physical agents
3. Chemical agents and drugs
4. Immunological agents
5. Nutritional factors: PEM , obesity
6. Agening
7. Psychogenic disease
8. Microbial agents
9. Iatrogenic factors
10. idiopathic

Pathogenesis of cell injury

- Irrespective of the etiological factors and type of the cell injury following features are common :

1. Factors pertaining to etiological agents and host:
   - Type,duration and severity of injurious agent
   - Type ,status and adaptability of the target cell
2. Common underlying mechanism:
   - Mitochondrial damage lead to decrease ATP
   - Cell membrane damage
   - Release of toxic free radicals
3. Usual morphological changes: Reversible and irreversible cell injury changes.
4. Function implication and disease outcome

Pathogenesis of ischaemic and hypoxic cell injury

- Reversible cell injury:

1. Decrease generation of cellular ATP:

- Aerobic
- Anaerobic
- In interruption of the blood supply both oxygen and glucose is not available ,so it leads to more severe form of injury as compared to hypoxia.

2. Intracellular lactic acidosis leads to nuclear clumping

3. Damage to plasma membane:

- Decrease ATP lead to - decrease synthesis of phospholipid
  - failure of Na-K ATPase pump
  - failure of Ca pump
- Because of all these Na and water accumulated which lead to swelling of the cell and accumulation of calcium lead to swelling of the mitochondria which again disturb the function of mitochondria.

4. Reduced protein synthesis: because of swelling of ER and golgi apparatus ,detachment of ribosomes from the ER lead to decrease protein synthesis.

Morphology of reversible cell injury

- Loss of microvilli
- Swelling of the cell
- Blebs and intramembranous particle formation
- Swelling of the mitochondria
- Formation of myelin figures in the cytoplasm
- Reversible clumping of the chromatin

Pathogenesis of irreversible cell injury

- Two mechanisms will decide the type of injury:

1. Inability of the cell to reverse mitochondrial dysfunction on reperfusion
2. Disturbance of the cell membrane function .

1. Calcium influx leads to mitochondrial damage
2. Activation of phospholipase will lead to further damage to the cell membrane
3. Activation of proteases lead to damage to the cytoskeleton
4. Activation of endonuclease enzyme lead to damage to the nucleus:

- **Pyknosis:** condensation and clumping of nucleus
- **Karyorrhexis:** nuclear fragmentation in to small bits
- **Karyolysis:** dissolution of the nucleus

5. Activation of Lysosomal hydrolytic enzymes will lead to phagocytosis.

Morphology of irreversible cell injury

- Swelling of the mitochondria with vaccuoles
- Breakdown of cell membrane
- Lysis of the ER and disappear Golgi apparatus
- Rupture of lysosome
- Disruption of cytoskeleton
- Pyknosis
- Karyorrhexis
- Karyolysis

Ischaemia –Reperfusion injury

- Depending upon the duration of ischaemia-hypoxia,restoration of blod flow results in following consequences:

1. From ischaemia to reversible injury- when period of ischaemia is very short.
2. From ischaemia to irreversible injury- much longer period of ischaemia.
3. From ischaemia to reperfusion injury- when ischaemia is for somewhat longer duration.

Mechanism of reperfusion injury

1. Calcium overload:on already injured cell leads to lipid peroxidation of membrane causing further membrane damage.
2. Excessive generation of free radicals
3. Subsequent inflammatory reaction

Generation of free radicals

- During normal cell metabolism reduction –oxidation reaction takes place with ATP generation by oxidative process in which O2 combine with H atom and in the process H2O is formed.
- This reaction involves four electron donation in four step involving transfer of one electron in each step.
- Free radicals have unpaired electron in its outer orbit.
- Generated within mitochondrial inner membrane.
- Free radicals are: Superoxide oxygenO'2

  Hydrogen peroxide(H2O2)

  Hydroxyl radical(OH -)

- Other free radicals :
- Nitric oxide(NO) and peronitrite (ONOO)- chemical mediator formed by endothelial cells, neurons, macrophages etc.
- Halide reagent(chlorine or chloride)-released in leucocytes reacts with superoxide and forms hypochlorous acid(HOCl)
- Exogenous sources- some environmental agents like tobacco and industrial pollutants.

Cytotoxicity of free radicals

- Oxygen free radicals are very unstable and destroyed spontaneously that depends on catalytic action of certain enzymes such as superoxide dismutase, catalase and glutathione peroxidase.
- If not destroyed then these free radicals can bind to all molecules of the cell because they have electron free residue –called oxidative stress.
- Cause damage to cell by following mechanism:

1. Lipid peroxidation of membrane fatty acid-form lipid hydroperoxy radicals and lipid hypoperoxides.Cause widespread membrane damage and destruction of organelles.
2. Oxidation of proteins-leads to degradation of cytosolic neutral proteases and cell destruction.
3. DNA damage
4. Cytoskeletal damage-interfere in mitochondrial aerobic phosphorylation and thus cause ATP depletion.

- Conditions with free radical injury:
  - Ischaemic reperfusion injury
  - Ionising radiation
  - Chemical toxicity
  - Chemical carcinogenesis
  - Hyper oxia- oxygen therapy
  - Cellular agening
  - Killing of microbial agents
  - Inflammatory damage
  - Destruction of tumour cells
  - Atherosclerosis
- Antioxidants are: Vitamin E,A C , sulphydryl containing compounds (cysteine, glutathione) ,serum proteins(ceruloplasmin , transferrin).

THANK YOU