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Pathogensis of Cell Injury

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ABSTRACT

When cells are injured, one of two patterns will generally results in reversible cell injury leading to adaptation of the cells and tissue, or irreversible cell injury leading to cell death and tissue damage. When cells adapt to injury, their adaptive changes can be atrophy, hypertrophy, hyperplasia, or metaplasia. Injured cells may also accumulate materials including fat, cholesterol, protein, glycogen, or pigment. Cell membrane diseases are life threatning disorders which are genetic in nature. They usually work against proteins in the body which are important for ion channels and receptors within the membrane. Ribosomopathies can arise from abnormalities of either rRNA or varios RPs. Abnormal ribosome biogenesis is linked to several human genetic disease. Different diseases are discuss related to pathogenesis of reversible and irreversible injury. Mitochondrial diseases are caused by mutations in the mitochondrial DNA. At other times they are caused by mutations in genes of nuclear DNA whose gene products are imported into the mitochondria as well as acquired mitochondrial conditions understanding pathogenesis of injury aspects is foundational to the understanding of disease processes and conditions.

Keywords: Cell death, Tissue damage, Irreversible injury, Pathogenesis.

I. INTRODUCTION

Cell injury is defined as a variety of stresses in cell that encounters as a result of changes in its internal and external environment. Cells of the body have inbuilt mechanism to deal with the changes in the environment[1].The cellular response to stress varies and depends upon the variables like the type of the cell and tissue involved and on extent and type of cell injury. Cellular responses to injury may be cellular adaptations if there is increased functional demand, the cell may adapt to the changes and then revert back to normal after the stress is removed[2]. In reversible cell injury, the stress is mild to moderate, the injured cells may recover and Irreversible cell injury, the stress is permanent or severe, the injured cells may be die[3].

1. Pathogenesis

Ischemia (interruption of blood supply) and hypoxia (impaired oxygen supply to the tissues) are the most common forms of cell injury[4].

1.1 Reversible cell injury:

If the ischemia or hypoxia is of short duration, the effects are reversible on rapid restoration of circulation[5]. E.g: Coronary artery occlusion, Myocardial infraction contractility, metabolism. The sequential changes are as under:

1.1.1 Decreased cellular ATP

ATP is derived from two sources i.e aerobic respiration and anaerobic respiration. Ischemia and hypoxia both limit the supply of oxygen to the cells thus causing decreased ATP generation[6].

1.1.2 Reduced intracellular pH

Due to low oxygen supply to the cell, aerobic respiration fails first-switch to anaerobic glycolytic pathway for energy (ATP) requirement which result in rapid decline in glycogen ad accumulation of lactic acid- lowering of intracellular pH- clamping of nuclear chromatin[7].

1.1.3 Damage to plasma membrane sodium pump

ATP dependent sodium pump (Na^+/K^+/ATPase) which operates at the plasma membrane allows active transport of sodium out of the cell and diffusion of K^+ into cell. ATPase activity interferes with this membrane regulated process[8]. Results in intracellular accumulation of Na^+ and diffusion of K^+ out of cell.increased in intracellular water to maintain iso-osmotic conditions (hydroid swelling).

1.1.4 Decrease in protein synthesis

As a result of continued hypoxia, ribosomes and detached from endoplasmic reticulum and polysomes are degraded to monosomes, thus causing decrease in protein synthesis.Ultrastructural involves endoplasmic reticulum in which Distension of cisternae by fluid deatachment of polyribosomes from surface of ER. In Plasma membrane there is Loss of microvilli and in Nucleolus segregation of granular and fibrillar components of nucleolus and reduced synthesis of ribosomal RNA[9].

1.2 Irreversible cell injury:

Persistent ischemia or hypoxia may results in irreversible changes in structure and function of cell (cell death)[10].

1.2.1 Mitochondrial dysfunction

As a result of continued hypoxia a large cytosolic influx of Ca^{++} ions occur which taken up by mitochondria and cause mitochondrial dysfunction[11].

1.2.2 Membrane damage

Defect in membrane function especially plasma membrane is the most important event in irreversible cell injury[12].

The mechanisms underlying membrane damage are:
Acclerated degradation of membrane phospholipid

i) Cytoskeletal damage
ii) Toxic oxygen radicals
iii) Breakdown products of lipids
iv) Reperfusion damage

Hydrolytic enzymes

Damage to cytosomal membranes is followed by liberation of hydrolytic enzymes (RNAase, DNAase, protease, glycosidase, phosphatase) which on acting activation cause enzymatic digestion of cellular components and induced nuclear change and hence cell death.

Serum estimation of liberated intracellular enzymes

Liberated enzymes just mentioned above leak across the abnormally permeable cell membrane into the serum. The estimation of these enzymes may used as parameter of cell death. E.g. In myocardial infraction, estimation of elevated serum SGPT and isoenzymes of creatinine kinase, cardiac troponins, are used guides for death of heart muscle[13-15].

1.3 Pathogenesis related to cell

1.3.1 Cell membrane damage

Cell membrane diseases are life threatning disorders which are genetic in nature. They usually work against proteins in the body which are important for ion channels and receptors within the membrane. These disease operate either by disrupting the normal functions of the cells or by simply affecting the cell membranes. Many of these disorders contain other components. Following are some of the important disorders related to cell membrane:

Hyaline membrane disease

It is commonly associated with pre-term infants. It affects the lungs at the time of birth causing respiratory distress. As a result, lungs require abnormal levels of oxygen and carbon dioxide exchange after birth.

Alzheimer's disease

It is a progressive disease that destroys memory and other important mental functions. The oxidative stress caused by Alzheimer's disease in the brain results in phospholipid alterations. These alterations disrupt functions of the brain cells.

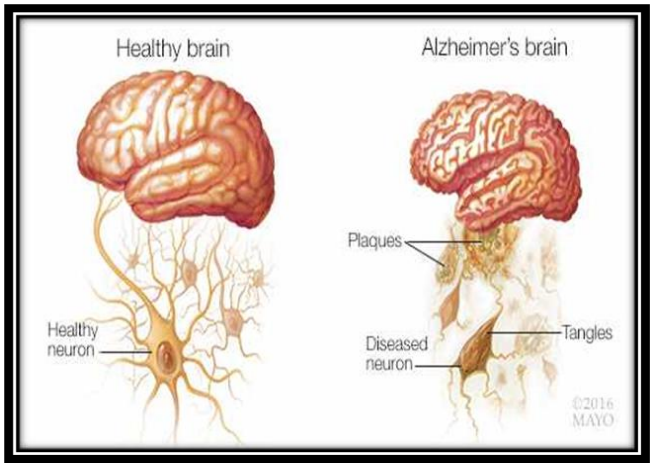

Fig 1. Alzheimer's Disease

Cystic fibrosis

It is a disease which brings about an excessive production of fluid in the lungs due to a defective calcium ion channel. When the channel mutate leading to alteration in proteins, it causes the mucus to build up in the lungs, creating difficulty in breathing.

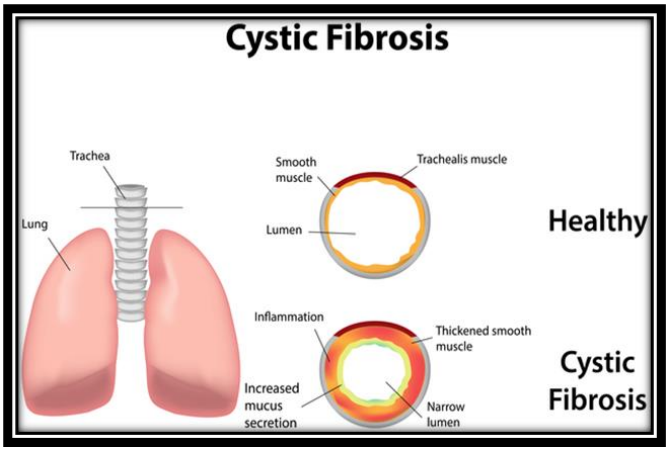

Fig 2. Cystic fibrosis

Duchenne muscular dystrophy

This disease affects dystrophin in the muscle cell. Dystrophin allows the muscle cell wall to connect with the intracellular section. In absence of dystrophin, the cell membrane is incapable of repairing itself, destroying it and causing muscular dystrophy[16-17].

1.3.2 Mitochondrial Damage

Mitochondrial damage can lead to diseases which are together termed as mitochondrial disease. Sometimes mitochondrial diseases are caused by mutations in the mitochondrial DNA.

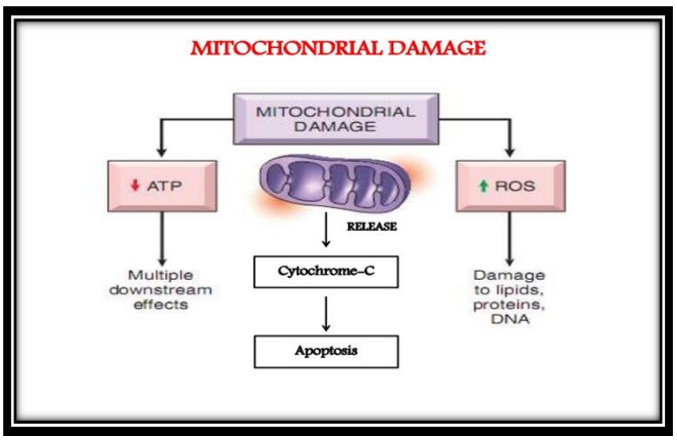

Fig 3. Mitochondrial Damage

At other times they are caused by mutations in genes of nuclear DNA whose gene products are imported

into the mitochondria as well as acquired mitochondrial conditions. Symptoms of mitochondrial disease includes: Poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological disorders and autonomic dysfunction. Following are the examples of mitochondrial diseases:

Diabetes mellitus and deafness (DAD)

It is subtype of diabetes which is caused from a point mutation at position 3243 in human mitochondrial DNA and it is characterized by diabtes and sensorineural hearing loss.

Leber's hereditary optic neuropathy (LHON)

It is a mitochondrially inherited (transmitted from mother to offspring) dengeration of retinal ganglion cells (RGCs) and their axons that leads to an acute or subacute loss of central vision; this affects predominantly young adult males.

Fig 3. Leber's hereditary optic neuropathy (LHON)

Leigh syndrome: Sub-acutesclerosing encephalopathy.
Neuropathy, ataxia, retinitis pigmentosa (NARP): A type of dementia.

Myoneurogenic gastrointestinal encephalopathy (MNGIE): A type of neuropathy[18].

1.3.3 Ribosomal damage

Damage to ribosomes can lead to diseases which termed as Ribosomopathy. Ribosomopathies are caused by alterations in the structure or function of ribosomal component proteins or rRNA genes whose products are involved in ribosomal biogenesis. Ribosomes are essential for protein synthesis in all living organisms. They contain scaffold of ribosomal RNA (rRNA) on which an extensive variety of ribosomal proteins(RP) are arrayed. Ribosomopathies can arise from abnormalities of either rRNA or varios RPs. Abnormal ribosome biogenesis is linked to several human genetic disease. Name of some these disease are listed below. Details including which chromosomes are affected genotype, phenotype, protein and the site of disruption are for the diseases.

Diamond-blackfan anemia

It is characterized normocytic or macrocytic anemia (low RBC counts) with decreased erythroid progenitor cells in the bone marrow.Affected individuals may also have an opening in the roof of the mouth (cleft palate) with or without a split in the upper lip (cleft lip). They may have a short, webbed neck; shoulder blades that are smaller and higher than usual; and abnormalities of their hands, most commonly malformed or absent thumbs.

Dyskeratosis congenital (DKC)

The entity was classically defined by the triad abnormal skin pigmentation, nail dystrophy and leukoplakia of the oral mucosa. It is characterized by short telomeres.

Shwachman-Diamond syndrome

It is characterized by bone marrow dysfunction, skeletal abnormalities and short stature.

5q-myelodysplastic syndrome

It is type of bone marrow disorder.

Treacher Collins syndrome

A inherited condition in which bones and tissues in face aren't developed.

Cartilage-hair hypoplasia

It is disorder of bone growth characterized by short stature with other skeletal abnormalities[19].

North American Indian childhood cirrhosis

The disorder worsens with age, progressively damaging the liver and leading to chronic, irreversible liver disease (cirrhosis) in childhood or adolescence.

Bowen-conradi syndrome

Affected individual have low birth weight, experiencing feeding problems, and grow very slowly[20].

1.3.4 Nuclear Damage

Following diseases are caused by damage to the cell nucleus:

Coronella de lange syndrome

It is a rare genetic disorder present from birth. It causes range of physical, cognitive and medical challenges and affects both sexes equally. Some of the important symptoms of the disease are as Low birth weight, Delayed growth and small stature, Development delay, Missing limbs or portions of limbs, Microcephaly: small head size, Excessive body hair, Hearing impairment and vision abnormalities, Partial joining of second and third toes, Seizures and heart defects.

Revesz syndrome

It is a fatal disease which causes exudative retinopathy and bone marrow failure.Other symptoms includessevere aplastic anemia, intrauterine growth retardation, fine sparse hair, fine reticulate skin pigmentation, ataxia due to cerebellar hypoplasia and cerebral calcification. It is genetic disease thought to be caused by short telomeres.

Schinzel-Giedion Syndrome

It is congenital, neurogenerative terminal syndrome. It exhibits severe midface retraction, skull abnormalities, renal anomalies. Babies with the syndrome have severe mental retardation, growth retardation and global development delay.

Spinal muscular atrophy

It is characterized by loss of motor neurons and progressively muscle wasting, often leading to early death. It is caused by a genetic defect in the SMN1 gene, which encodes SMN, a protein which is needed for survival of motor neurons. It causes loss of function of neuronal cells in the anterior horn of spinal cord leading to atrophy of skeletal muscles. Muscular atrophy first affects proximal muscles and lung muscles[21].

Treacher Collins syndrome

It is an autonomal dominant congenital disorder characterized by craniofacial deformities, typically involving the ears, eyes, cheek bones and jaw bones. The typical physical features include downward-slanting eyes, microganthia i.e. a smaller lower jaw, conductive hearing loss, under developed zygomotic bones, drooping part of lateral lower eyelids and malformed or absence of ears[22-23].

Triple-A syndrome

It is a rare autosomal recessive congenital disorder. AAA stands for achalasia-addisonian-alacrima. It is progressive disorder taking years to develop. The patient with adrenal insufficiency/addison's disease due to ACTH resistance, alacrima i.e. absence of tear secretion and achalasia i.e. failure of a ring of muscle fibers to relax to the lower esophageal sphincter which delays food going to stomach. It is associated with mutations of the AAAS gene, which encodes a protiens known as ALADIN[24].

II. CONCLUSION

Cell injury induced by free radicals. Several types of process can increase the production of free radical. Some of the reversibly injured cells include mitochondria densities, cellular swelling, cytoskeletal

disruption and in irreversibly damaged involves incresead eosinophilia in cells, great big mitochondria densities and nuclear changes such as pyknosis, karyolysis and karyorrhexis. As due to damges of cell part like cell membrane, mitochondrial, ribosomal nuclear damage results into different diseases like alzheimer, cystic fibrosis disease and cancer etc.

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