CELLULAR REACTIONS TO INJURY

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Cell injury underlies all diseases. When a cell is exposed to an injurious agent the possible outcomes are:

1. The cell may adapt to the situation or

2. They cell may acquire a reversible injury or

3. The cell may obtain an irreversible injury & may die. The cell may die via one of two ways: either by necrosis or by apoptosis.

Which of these outcomes occur depends on both the injurious agent & on cellular factors. In other words, the result depends on the type, severity, & duration of the injury & on the type of the cell.

Types of cellular adaptation

Hypertrophy

Hypertrophy is increase in the size of cells. Increased workload leads to increased protein synthesis & increased size & number of intracellular organelles which, in turn, leads to increased cell size.

The increased cell size leads to increased size of the organ. Examples: the enlargement of the left ventricle in hypertensive heart disease & the increase in skeletal muscle during strenuous exercise.

Hyperplasia

Hyperplasia is an increase in the number of cells. It can lead to an increase in the size of the organ. It is usually caused by hormonal stimulation.

It can be physiological as in enlargement of the breast during pregnancy or it can pathological as in endometrial hyperplasia.

Atrophy

Atrophy is a decrease in the size of a cell. This can lead to decreased size of the organ. The atrophic cell shows autophagic vacuoles which contain cellular debris from degraded organelles. Atrophy can be caused by:

1. Disuse
2. Under nutrition
3. Decreased endocrine stimulation
4. Denervation
5. Old age

Metaplasia

Metaplasia is the replacement of one differentiated tissue by another differentiated tissue. There are different types of metaplasia. Examples include:

1. Squamous metaplasia

This is replacement of another type of epithelium by squamous epithelium. For example, the columnar epithelium of the bronchus can be replaced by squamous epithelium in cigarette smokers

2. Osseous metaplasia

This is the replacement of a connective tissue by bone, for example at sites of injury.

Reversible cellular changes & accumulations

Even though there are many different kinds of reversible cellular changes & accumulations, here we will only consider fatty change & accumulation of pigments.

Fatty change

This is accumulation of triglycerides inside parenchymal cells. It is caused by an imbalance between the uptake, utilization, & secretion of fat.

Fatty change is usually seen in the liver, heart, or kidney. Fatty liver may be caused by alcohol, diabetes mellitus, malnutrition, obesity, & poisonings.

These etiologies cause accumulation of fat in the hepatocytes by the following mechanisms:

a. Increased uptake of triglycerides into the parenchymal cells.

b. Decreased use of fat by cells.

c. Overproduction of fat in cells.

d. Decreased secretion of fat from the cells.

The accumulations of pigments

Pigments can be exogenous or endogenous. Endogenous pigments include melanin, bilirubin, hemosiderin, & lipofuscin. Exogenous pigments include carbon.

These pigments can accumulate inside cells in different situations.

Melanin

Melanin is a brownish-black pigment produced by the melanocytes found in the skin. Increased melanin pigmentation is caused by sun tanning & certain diseases e.g. nevus, or malignant melanoma.

Decreased melanin pigmentation is seen in albinism & vitiligo

Bilirubin

Bilirubin is a yellowish pigment, mainly produced during the degradation of haemoglobin. Excess accumulation of bilirubin causes yellowish discoloration of the sclera, mucosae, & internal organs. Such a yellowish discoloration is called jaundice.

Jaundice is most often caused by

Haemolytic anaemia

Haemolytic anaemia is characterized by increased destruction of red blood cells.

Biliary obstruction

This is obstruction of intrahepatic or extra hepatic bile ducts. It can be caused by gallstones.

Hepatocellular disease

This is associated with failure of conjugation of bilirubin.

Hemosiderin

Hemosiderin is an iron-containing pigment derived from ferritin. It appears in tissues as golden brown amorphous aggregates & is identified by its staining reaction (blue 18 colour) with the Prussian blue dye.

Hemosiderin exists normally in small amounts within tissue macrophages of the bone marrow, liver, & spleen as physiologic iron stores.

It accumulates in tissues in excess amounts in certain diseases. This excess accumulation is divided into 2 types:

Hemosiderosis

When accumulation of hemosiderin is primarily within tissue macrophages & is not associated with tissue damage, it is called hemosiderosis.

Hemochromatosis

When there is more extensive accumulation of hemosiderin, often within parenchymal cells, which leads to tissue damage, scarring & organ dysfunction, it is called hemochromatosis.

Cell death

Cells can die via one of the following two ways:

1. Necrosis
2. Apoptosis

Necrosis

In necrosis, excess fluid enters the cell, swells it, & ruptures its membrane which kills it. After the cell has died, intracellular degradative reactions occur within a living organism.

Necrosis does not occur in dead organisms. In dead organisms, autolysis & heterolysis take place.

Necrosis occurs by the following mechanisms:

A. Hypoxia

B. Free radical-induced cell injury

C. Cell membrane damage

D. Increased intracellular calcium level

Hypoxia

Hypoxia is decreased oxygen supply to tissues. It can be caused by:

1. Ischemia

Ischemia is decreased blood flow to or from an organ. Ischemia can be caused by obstruction of arterial blood flow – the most common cause, or by decreased perfusion of tissues by oxygen-carrying blood as occurs in cardiac failure, hypotension, & shock.

2. Anaemia

Anaemia is a reduction in the number of oxygen-carrying red blood cells.

3.Carbon monoxide poisoning

CO decreases the oxygen-capacity of red blood cells by chemical alteration of hemoglobin

4. Poor oxygenation of blood due to pulmonary disease. The cell injury that results following hypoxia can be divided into early & late stages

Early (reversible) stages of hypoxic cell injury

At this stage, hypoxia results in decreased oxidative phosphorylation & ATP synthesis. Decreased ATP leads to:

a) Failure of the cell membrane Na – K pump, which leads to increased intracellular Na & water, which cause cellular & organelle swelling. Cellular swelling (hydropic change) is characterized by the presence of large vacuoles in the cytoplasm. The endoplasmic reticulum also swells.

The mitochondria show a low amplitude swelling. All of the above changes are reversible if the hypoxia is corrected.

b) Disaggregation of ribosomes & failure of protein synthesis.

Late (irreversible) stages of hypoxic cell injury.

This is caused by severe or prolonged injury. It is caused by massive calcium influx & very low pH, which lead to activation of enzymes, which damage the cell membrane& organelle membranes.

Irreversible damage to the mitochondria, cell membranes, & the nucleus mark the point of no return for the cell, that is after this stage, the cell is destined to die.

Release of aspartate aminotransferase (AST), creatine phosphokinase(CPK), & lactate dehydrogenase (LDH) into the blood is an important indicator of irreversible injury to heart muscle following myocardial infarction.

Free radical-induced injury

Free radical is any molecule with a single unpaired electron in the outer orbital. Examples include superoxide & the hydroxyl radicals. Free radicals are formed by normal metabolism, oxygen toxicity, ionizing radiation, & drugs & chemicals, & reperfusion injury.

They are degraded by spontaneous decay, intracellular enzymes such as glutathione peroxidase, catalase, or superoxide dismutase, & endogenous substances such as ceruloplasmin or transferrin.

When the production of free radicals exceeds their degradation, the excess free radicals cause membrane pump damage, ATP depletion, & DNA damage. These can cause cell injury & cell death.

Cell membrane damage

Direct cell membrane damage as in extremes of temprature, toxins, or viruses, or indirect cell membrane damage as in the case of hypoxia can lead to cell death by disrupting the homeostasis of the cell.

Increased intracellular calcium level

Increased intracellular calcium level is a common pathway via which different causes of cell injury operate. For example, the cell membrane damage leads to increased intracellular calcium level.

The increased cytosolic calcium, in turn, activates enzymes in the presence of low pH. The activated enzymes will degrade the cellular organelles.

Types of necrosis

The types of necrosis include:

1. Coagulative necrosis
2. Liquefactive necrosis
3. Fat necrosis
4. Caseous necrosis
5. Gangrenous necrosis

Coagulative necrosis

Cogulative necrosis most often results from sudden interruption of blood supply to an organ, especially to the heart. It is, in early stages, characterized by general preservation of tissue architecture.

It is marked by the following nuclear changes: Pyknosis (which is chromatin clumping & shrinking with increased basophilia), karyorrhexis (fragmentation of chromatin), & karyolysis (fading of the chromatin material).

Liquefactive necrosis

Liquefactive necrosis is characterized by digestion of tissue. It shows softening & liquefaction of tissue.

It characteristically results from ischemic injury to the CNS. It also occurs in suppurative infections characterized by formation of pus.

Fat necrosis

Fat necrosis can be caused by trauma to tissue with high fat content, such as the breast or it can also be caused by acute hemorrhagic pancreatitis in which pancreatic enzymes diffuse into the inflamed pancreatic tissue & digest it.

The fatty acids released from the digestion form calcium salts (soap formation or dystrophic calcification).

In addition, the elastase enzyme digests the blood vessels & cause the haemorrhage inside the pancreas, hence the name haemorrhagic pancreatitis.

Caseous necrosis

Caseous necrosis has a cheese-like (caseous, white) appearance to the naked eye. And it appears as an amorphous eosinophilic material on microscopic examination. Caseous necrosis is typical of tuberculosis.

Gangrenous necrosis

This is due to vascular occlusion & most often affects the lower extremities & the bowel. It is called wet gangrene if it is complicated by bacterial infection which leads to superimposed liquefactive necrosis.

Whereas it is called dry gangrene if there is only coagulative necrosis without liquefactive necrosis.

Necrosis can be followed by release of intracellular enzymes into the blood, inflammation or dystrophic calcification.

Apoptosis(programmed cell death)

Apoptosis is the death of single cells within clusters of other cells. (Note that necrosis causes the death of clusters of cells.) In apoptosis, the cell shows shrinkage & increased acidophilic staining of the cell. This is followed by fragmentation of the cells. These fragments are called apoptotic bodies.

Apoptosis usually occurs as a physiologic process for removal of cells during embryogenesis, menstruation, etc… It can also be seen in pathological conditions caused by mild injurious agents.

Apoptosis is not followed by inflammation or calcification. The above mentioned features distinguish apoptosis from necrosis.

Pathologic calcification

Pathologic calcification is divided into 2 types:

1. Metastatic calcification

This is caused by hypercalcemia, resulting from hyperparathyroidism, milk-alkali syndrome, sarcoidosis etc

2. Dystrophic calcification

This occurs in previously damaged tissue, such as areas of old trauma, tuberculous lesions, scarred heart valves, & atherosclerotic lesions. Unlike metastatic calcification, it is not caused by hypercalcemia. Typically, the serum calcium level is normal.