Dentistry & Dental Practices Journal

Chembio Publishers
Right Choice for Researchers

Opinion *Volume 1; Issue 1*

Cell Injury, Death and Adaptation

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Received Date: September 06, 2018; **Published Date:** September 24, 2018

Pathology

Pathology is the study of disease. The pathologist attempts to determine the etiology (cause) and pathogenesis (the mechanism of the development of disease) by identifying changes in the gross (morphologic) or microscopic (histologic) appearance.
Many techniques are used by pathologists are used to classify diseases:

i. Immunohistochemistry – specific monoclonal antibodies directed at tumor cells.
ii. In-situ hybridization – use of DNA probes.

This information is used to guide therapy and determine prognosis (the likely outcome).

Gross Alterations

Gross alterations changes in size, shape, color, or consistency that is recognizable to the naked eye.

a. Atrophy (Hypertrophy: Hyperplasia: Necrosis (dead tissue): An organ or a portion of an organ dies and becomes soft and pale.
b. Calcifications: Pale, firm, granular deposits are seen in a tissue or organ. Amorphous calcifications can partially or completely ossify (become bone).
c. Pigmentation: Brown (melanin from melanocytes or Hemosiderin from erythrocytes) or yellow (deposition of lipid in cells).

Cellular Adaptations of Growth and Differentiation

Physiologic adaptation

Physiologic Adaptation Response of cells to normal stimulation by hormones or endogenous chemical mediators (e.g., enlargement of breasts and the induction of lactation by pregnancy).

Pathologic adaptation

Pathologic Adaptation helps cells to modulate their environment to escape injury.

Cellular adaptations to stress

Hypertrophy: Hypertrophy organ or structure becomes bigger because the constituent cells enlarge.

a. Physiologic (growth of uterus during pregnancy stimulated by estrogen).
b. Adaptive (skeletal muscle enlargement in a weight lifter or cardiac enlargement in a patient with chronic hypertension).

Hyperplasia: Hyperplasia organ or structure gets bigger because there is an increase in the number of cells.

a. Physiologic
   i. Hormonal hyperplasia (proliferation of the female breast during puberty or pregnancy).
   ii. Compensatory hyperplasia occurs when a portion of tissue is removed or diseased (stimulated by growth factors, the liver regenerates after a portion is removed).
b. Pathologic

Usually due to excessive hormonal or growth factor stimulation (endometrial hyperplasia), which also provides a fertile soil in which a cancerous proliferation may arise (endometrial cancer).

Atrophy (shrinkage): Atrophy organ or structure becomes smaller because the constituent cells shrink.

a. Decreased workload
b. Loss of innervation

Citation: Osama Johnson. Cell Injury, Death and Adaptation. Dentistry & Dent Pract J 2018, 1(1): 180005.

c. Diminished blood supply, inadequate nutrition,
d. Loss of endocrine stimulation (menopause), and aging.
e. Often accompanied by marked increases in the number of autophagic vacuoles.

Metaplasia: Metaplasia reversible change in which there is the substitution of one adult cell type for another
a. Better withstand the adverse environment; however, important protective mechanisms or normal functions are lost.
b. Increased propensity for malignant transformation.
c. Examples
i. Squamous change in respiratory epithelium in habitual cigarette smokers (loss of ciliary clearance).
ii. Gastric or intestine-type mucosa replacing stratified squamous epithelium in chronic gastric reflux. (e.g., Barrett's esophagus).

Major Causes of Cellular Injury (overview)

Hypoxia

Hypoxia deprives the cell of aerobic respiration
a. Cellular systems, which require a constant supply of ATP, fail.
b. Ischemia, the loss of blood supply, is the most common cause of hypoxia.
c. Also CO poisoning, hypo-oxygenation of blood.

Chemical agents

Many chemicals cause primary injury to cell membranes, or to the membranes of critical cell organelles.
a. Free radical injury.
b. Direct covalent binding to the cell membrane or by combining with a critical molecular component.
c. O_2, CO, pollutants, asbestos, alcohol.

Infectious agents

a. Bacteria release enzymes or toxins (which act as chemicals) to injure cells.
b. Viruses may produce direct cytopathic injury or may elicit an immune response, which injures cells.
c. Fungi, rickettsiae, protozoa, tapeworms, etc.

Immunologic agents (Chapter 5)

a. Allergic/anaphylactic reactions.
b. Autoimmune diseases.

Genetic defects

a. From chromosomal to single base pair mutation.
b. Accumulation of damaged or mis-folded proteins.
c. Deficiency of enzymes, etc.
d. Accumulation of damaged DNA.

Nutritional imbalances

a. Protein-calorie insufficiency.
b. Vitamin deficiencies.
c. Excess nutrition/obesity.
d. Excess animal fat.

Physical Agents

a. Trauma, extremes of temperature, radiation, electric shock, etc.

Aging

a. Alterations in replication and repair.

Morphology of Cell and Tissue Injury

Cellular function may be lost long before cell death
Morphologic changes after injury happen far later than injury or loss of function
Reversible Injury
a. Cellular swelling: Small clear vacuoles are seen in the cytoplasm.
i. Grossly, organs may exhibit pallor, increased weight and rigidity
ii. Seen in acute viral hepatitis
b. Fatty change (steatosis): Appearance of lipid vacuoles in the cytoplasm.
i. Alcohol induced hepatocellular injury
c. Ultra structural changes
i. Plasma membrane alterations (blebs)
ii. Mitochondrial swelling
iii. Dilation of the ER
iv. Nuclear alterations

Irreversible cell injury - Necrosis

a. Coagulative necrosis: Characteristic of hypoxic death of cells in all tissues except the brain.
i. Preservation of the basic structural outline of the cell or tissue is seen for several days.
ii. Common for infarcts (ischemic necrosis) (e.g., Myocardial infarction).
b. Liquefactive necrosis: Usually associated with the presence of large amounts of hydrolytic enzymes and is particularly prevalent in bacterial infections. The enzymes rapidly digest the cells so that no structural evidence of the cell remains (Abscess formation).
c. Gangrenous necrosis: Ischemic injury followed by bacterial infection (Coagulative necrosis with

superimposed Liquefactive changes (e.g., gangrene of a limb).

d. Caseous necrosis: Seen most often in a focus of tuberculosis infection.
   i. "Cheesy" white gross appearance.
   ii. Microscopically, the necrotic focus is composed of amorphous granular debris with a distinctive ring of granulomatous inflammation.
   iii. Tissue architecture is obliterated.
e. Enzymatic fat necrosis: Focal areas of fat destruction
   i. In pancreatic injury, pancreatic enzymes (lipases) are released and digest abdominal adipose tissue. Fatty acids are released and complex with calcium to form grossly visible chalky-white areas ("soaps").
f. Fibrinoid Necrosis
   i. Usually in immune reactions involving blood vessels.
   ii. Ag-Ab complexes plus fibrin.
   iii. Look bright pink on H&E (fibrin-like).

Sub-cellular Responses to Injury

Autophagy

Primary lysosomes are intracellular organelles containing hydrolytic enzymes, which are involved in the breakdown of phagocytosed material

a. Heterophagy: Cells engulf material through *endocytosis* (phagocytosis or pinocytosis). These endocytosed vacuoles fuse with a lysosome (phagolysosome) resulting in the degradation of the engulfed material.
b. Autophagy: The removal of damaged or senescent organelles. The intracellular organelles are sequestered in a sac of RER (autophagosome), which fuses with a primary lysosome (autophagolysosome).

Induction (hypertrophy) of smooth ER

a. Smooth Endoplasmic Reticulum: Contains enzyme systems, which are vital in detoxifying drugs. The taking of barbiturates causes hepatocytes to produce more SER. Therefore, as the amount of SER increases, the patient will develop tolerance to the drug.

Mitochondrial alterations

a. During cellular hypertrophy, mitochondria increase in number; and decrease in number during cellular atrophy.

Cytoskeletal abnormalities

a. Cytoskeletal components
   i. Microtubules (20-25nm)
   ii. Thick (myosin) filaments (15nm)
   iii. Thin (actin) filaments (6-8nm)
   iv. Intermediate filaments (10nm)
b. Abnormalities may be reflected in defects in cell function (leukocyte migration and phagocytosis, sperm motility, respiratory clearance, etc.) or intracellular accumulations of fibrillar material ("alcoholic hyaline") of the liver and the neurofibrillary tangle found in the brain of Alzheimer's disease).

Mechanisms of Cell Injury

Cellular response depends of the type of injury, duration, and severity

The consequences depend on cell type, cell status, cell adaptability, and genetic makeup

Can result from

a. Depletion of ATP
b. Damage to Mitochondria
c. Influx of Calcium
d. Accumulation of Oxygen-derived free radicals
e. Defects of Membrane permeability
f. Damage to DNA and Proteins

Depletion of ATP

a. Electron transport in mitochondria. ADP to ATP
b. Causes of decrease
c. Reduced oxygen
d. Nutrients
e. Exposure to toxins
f. Depletion to 5-10% of normal levels may lead to:
   i. Decreased membrane sodium pump, thus gain of fluid in cell
   ii. Increase in anaerobic glycolysis; decreased pH
   iii. Failure of calcium pump
   iv. Disruption of protein synthesis apparatus (RER)

Damage to mitochondria

a. Major consequences of damage
   i. Loss of membrane potential and pH change, leading to failure of oxidative phosphorylation, thus less ATP
   ii. Leakage of proteins out of mitochondrion, leading to cell apoptosis

Influx of calcium

a. Normal relations are ATP-dependent.
b. Increased Ca^{++} activates some deleterious enzymes.

Accumulation of oxygen-derived free radicals

a. Oxidative Stress
b. Chemical species with a single unpaired electron
c. Generated by
a. Enzymatic metabolism of exogenous chemicals (e.g., CCl_4)

b. "Oxygen toxicity" during therapeutic oxygen administration
c. Ultraviolet light produces radiolysis of water
d. Inflammation, produced by leukocytes
e. Nitric oxide (NO)
d. ROS can lead to
a. Lipid per oxidation of membranes
i. ROS attack double bonds
ii. Get an autocatalytic chain reaction
b. Cross-linking of proteins
i. Sulfhydryl-mediated cross-linking, leading to degradation or loss of function
c. DNA fragmentation
i. SS-breaks
e. Protective
a. Superoxide dismutase
b. Glutathione peroxidase
c. Catalase
d. Endogenous and exogenous anti-oxidants (e.g., Vit E, A, C, β-carotene)
f. Defects of Membrane permeability
a. Common feature in most cell injury
b. Contributors
i. Decreased phospholipid synthesis
ii. Increased phospholipid breakdown
iii. ROS
iv. Cytoskeletal abnormalities
v. Lipid breakdown products
c. Most important sites
i. Mitochondrial membranes
ii. Plasma membrane
a) Osmotic balance, ions, proteins
b) Leaking metabolites
iii. Lysosomal membranes
a) May lead to auto digestion
g. Damage to DNA and Proteins
a. DNA damage may lead to apoptosis.
b. Protein damage may lead to improper folding, also leading to apoptosis.

Examples of Cell Injury and Necrosis

Ischemic and hypoxic injury (Reversible or Irreversible)

a. Example: myocardial ischemia from coronary occlusion.
i. Heart stops contractions after 60 seconds, but this is reversible.
ii. Duration of ischemia resulting in cell death (~30 minutes).
iii. Ultra structural changes characteristic of irreversible injury (30-40 minutes).
iv. Elevation of serum enzymes characteristic of myocardial cell death (~6 hours) Cardiac muscle enzymes and the other proteins that leak from dead cells are useful for diagnosis of cardiac muscle death. (Creatine kinase, Troponin).
v. Light microscopic evidence of cell death (Coagulative necrosis) (~12 hours).

Ischemia-reperfusion injury

a. Can get increase in cell injury with reperfusion of ischemic tissues.
i. New damage from ROS.
ii. Inflammation may increase with increase in blood flow and WBC's.
iii. Complement system may also become activated.

Chemical (toxic) injury

a. Two general mechanisms
i. Act directly by combining with a critical molecular component or organelle.
a) E.g. cancer chemotherapy drugs.
ii. Are converted to reactive toxic substances.
a. P-450 oxidase of SER.
b. Most are formed into ROS, (e.g., CCl_4, acetaminophen).

Apoptosis – "Programmed Cell Death"

Examples of normal cell death

a. Destruction of embryonic structures.
b. Involution of the lactating breast after weaning.
c. Cell deletion in a proliferating population.
d. Death of cells after they have served their purpose (neutrophils and lymphocytes in inflammation).
e. Elimination of potentially harmful self-reactive lymphocytes.
f. Cell death induced by cytotoxic T-lymphocytes.

Pathologic apoptosis

a. DNA damage
b. Accumulation of misfolded proteins
c. Cell injury from certain infections (usually viral)
d. Pathologic atrophy in organs after duct obstruction (pancreas, parotid, kidney)

Histologically appears as

a. Single cell death (individual cells drop out)
b. Condensation of nuclear chromatin
c. Karyorrhexis – nuclear fragmentation
d. Cytoplasm buds and fragments into pieces
e. Cell fragments degrade or are phagocytosed
f. No inflammatory response is seen

Intracellular Accumulations

Materials can abnormally accumulate in a cell if

a. Synthesis of a normal endogenous substance is normal or increased, but metabolism is inadequate to remove it (steatosis, fatty liver).
b. Defective protein, folds incorrectly or cannot be transported.
c. Normal or abnormal endogenous substance accumulates because it cannot be metabolized due to an enzymatic defect (lysosomal storage disease).
d. Exogenous material accumulates because it cannot be degraded or transported (carbon, silica).

Different accumulations

h. Fatty Change (Steatosis)
i. Abnormal accumulation of triglycerides in the cells
ii. Caused by toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia.
iii. Most often seen in the liver (fatty liver).
i. Cholesterol and cholesteryl esters
i. Macrophages become filled with minute, membrane-bound vacuoles of lipid to form xanthoma (foam) cells.
j. Proteins
i. Accumulations of immunoglobulins in the RER of plasma cells results in rounded, eosinophilic Russell bodies.
ii. Cytoplasmic inclusion of proteins in alcoholic liver disease (Mallory bodies).
iii. Neurofibrillary tangles of Alzheimer disease
k. Glycogen
i. Deposits are seen with abnormalities in the metabolism of glucose or glycogen and are seen as vacuoles within the cell. Glycogen (a carbohydrate) stains pink with periodic acid-Schiff (PAS).
ii. Glycogen Storage Diseases - A group of closely related genetic disorders in which there is an enzymatic defect in the synthesis or breakdown of glycogen.
l. Pigments
i. Exogenous
a) Carbon or coal dust. Accumulates in macrophages in pulmonary parenchyma or lymph nodes.
b) Foreign bodies. e.g., shrapnel, bullets, amalgam, graphite
ii. Endogenous pigments
a) Lipofuscin: "Wear and tear" pigment; a brownish-yellow granular material formed when free radicals stimulate per oxidation or membrane lipids.
b) Melanin: Synthesized only by melanocytes when tyrosinase oxidizes tyrosine to DOPA (dihydroxyphenylalanine) and acts as a screen against harmful UV radiation. May be seen in basal keratinocytes or dermal melanophages.
c) Hemosiderin: A hemoglobin-derived granular pigment (golden-yellow to brown). Iron is stored with the protein apoferritin. Results from local excesses of iron (from hemorrhage or systemic overload).

Pathologic Calcification

An abnormal deposition of calcium salts
a.Dystrophic calcifications form when mitochondria in dead cells act as a nucleus upon which calcium phosphate is deposited. These appear as an amorphous granular basophilic deposit Histologically.
i. Calcific aortic stenosis.
ii. Atherosclerosis.
b. Metastatic calcifications occur in normal tissues whenever there is hypocalcaemia which can be caused by any of the following:
i. Hyperparathyroidism (primary or secondary).
ii. Myeloma or metastatic carcinoma (destruction of bone).
iii. Vitamin D-related disorders (D intoxication, sarcoidosis).
iv. Renal failure (phosphate retention, leading to secondary hyperparathyroidism).

Cellular Aging

a. Mechanisms
i. DNA damage.
ii. Decreased cellular replication.
a) Telomere shortening.
iii. Reduced regenerative capacity of tissue stem cells.
iv. Accumulation of metabolic damage.
v. Some growth factors.
b. Morphologic alterations
i. Irregular and abnormally lobed nuclei.
ii. Pleomorphic and vacuolated mitochondria.
iii. Decreased endoplasmic reticulum
iv. Distorted Golgi apparatus.
v. Accumulation of lipofuscin pigment, indicating past membrane damage and lipid per oxidation.