Cell injury essay sample

Cell injury

cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Injury may progress through a reversible stage and culminate in cell death Reversible cell injury.

In early stages or mild forms of injury, the functional and morphologic changes are reversible if the damaging stimulus is removed.

Cell injury

The hallmarks of reversible injury are reduced oxidative phosphorylation with resultant depletion of energy stores in the form of adenosine triphosphate (ATP), and cellular swelling caused by changes in ion concentrations and water influx. In addition, various intracellular organelles, such as mitochondria and the cytoskeleton, may also show alterations. Causes of Cell Injury

Oxygen Deprivation.

Hypoxia is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative respiration. Hypoxia is an extremely important and common cause of cell injury and cell death. Causes of hypoxia include ischemia, cardiorespiratory failure, and decreased oxygen-carrying capacity of the blood, after severe blood loss. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die.

Causes of Cell Injury

Physical Agents.

Physical agents capable of causing cell injury include mechanical trauma,

extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock. Chemical Agents and Drugs.

From simple chemicals such as glucose and salt or oxygen to poisons and environmental chemicals can cause cell injury. Causes of Cell Injury
Infectious Agents.
Virus to large helminthes cause cell injury.
Immunologic Reactions.
Immune reaction and autoimmunity can cause cell injury
Genetic Derangements. chromosomal anomaly, enzyme defects in inborn errors of metabolism, accumulation of damaged DNA or misfolded proteins can cause cell injury. Nutritional Imbalances.
Nutritional imbalances continue to be major causes of cell injury. Malnutrition (under nutrition and over nutrition

Mechanisms of Cell Injury
The mechanisms responsible for cell injury are complex.
There are, however, several principles that are relevant to most forms of cell injury: The cellular response to injurious stimuli depends on the nature of the injury, its duration, and its severity. The consequences of cell injury depend on the type, state, and adaptability of the injured cell. The cell’s nutritional and hormonal status and its metabolic needs are important in its response to injury.

Mechanisms of Cell Injury
When the striated muscle cell in the leg is deprived of its blood supply, it can

be placed at rest and preserved; not so the striated muscle of the heart. Exposure of two individuals to identical concentrations of a toxin, such as carbon tetrachloride, may produce no effect in one and cell death in the other. This may be due to genetic variations affecting the amount and activity of hepatic enzymes that convert carbon tetrachloride (CCl_4) to toxic by-products.

Mechanisms of Cell Injury

With the complete mapping of the human genome, there is great interest in identifying genetic polymorphisms that affect the responses of different individuals to injurious agents. Cell injury results from different biochemical mechanisms acting on several essential cellular components.

Mechanisms of Cell Injury

The cellular components that are most frequently damaged by injurious stimuli include mitochondria, cell membranes, the machinery of protein synthesis and packaging, and the DNA in nuclei. Any injurious stimulus may simultaneously trigger multiple interconnected mechanisms that damage cells. This is one reason why it is difficult to ascribe cell injury in a particular situation to a single or even dominant biochemical derangement.

Mechanisms of Cell Injury

DEPLETION OF ATP

ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and chemical (toxic) injury. ATP is produced in two ways. The major pathway in mammalian cells is oxidative phosphorylation of adenosine

diphosphate, in a reaction that results in reduction of oxygen by the electron transfer system of mitochondria.

Mechanisms of Cell Injury

The second is the glycolytic pathway, which can generate ATP in the absence of oxygen using glucose derived either from body fluids or from the hydrolysis of glycogen. The major causes of ATP depletion are reduced supply of oxygen and nutrients, mitochondrial damage, and the actions of some toxins (e. g., cyanide). Tissues with a greater glycolytic capacity (e. g., the liver) are able to survive loss of oxygen and decreased oxidative phosphorylation better than are tissues with limited capacity for glycolysis (e. g., the brain). Mechanisms of Cell Injury

High-energy phosphate in the form of ATP is required for virtually all synthetic and degradative processes within the cell. These include membrane transport, protein synthesis, lipogenesis, and the deacylation-reacylation reactions necessary for phospholipid turnover. Depletion of ATP to 5% to 10% of normal levels has widespread effects on many critical cellular systems:

Mechanisms of Cell Injury

The activity of the plasma membrane energy-dependent sodium pump (ouabain-sensitive Na+, K+-ATPase) is reduced. Failure of this active transport system causes sodium to enter and accumulate inside cells and potassium to diffuse out. The net gain of solute is accompanied by isosmotic gain of water, causing cell swelling, and dilation of the ER.

Mechanisms of Cell Injury

Cellular energy metabolism is altered.

If the supply of oxygen to cells is reduced, as in ischemia, oxidative phosphorylation ceases, resulting in a decrease in cellular ATP and associated increase in adenosine monophosphate. These changes stimulate phosphofructokinase and phosphorylase activities, leading to an increased rate of anaerobic glycolysis, which is designed to maintain the cell's energy sources by generating ATP through metabolism of glucose derived from glycogen. Mechanisms of Cell Injury

As a consequence glycogen stores are rapidly depleted. Anaerobic glycolysis results in the accumulation of lactic acid and inorganic phosphates from the hydrolysis of phosphate esters. This reduces the intracellular pH, resulting in decreased activity of many cellular enzymes Failure of the Ca2+ pump leads to influx of Ca2+, with damaging effects on numerous cellular components.

Mechanisms of Cell Injury

With prolonged or worsening depletion of ATP, structural disruption of the protein synthetic apparatus occurs, manifested as detachment of ribosomes from the rough ER and dissociation of polysomes, with a consequent reduction in protein synthesis. In cells deprived of oxygen or glucose, proteins may become misfolded, and misfolded proteins trigger a cellular reaction called the unfolded protein response that may culminate in cell injury and even death.

Mechanisms of Cell Injury

Ultimately, there is irreversible damage to mitochondrial and lysosomal

membranes, and the cell undergoes necrosis. MITOCHONDRIAL DAMAGE Mitochondria are the cell’s suppliers of life-sustaining energy in the form of ATP, but they are also critical players in cell injury and death. Mitochondria can be damaged by increases of cytosolic Ca2+, reactive oxygen species, and oxygen deprivation, and so they are sensitive to virtually all types of injurious stimuli, including hypoxia and toxins.

Mechanisms of Cell Injury

In addition, mutations in mitochondrial genes are the cause of some inherited diseases. There are two major consequences of mitochondrial damage. Mitochondrial damage often results in the formation of a high-conductance channel in the mitochondrial membrane, called the mitochondrial permeability transition pore. The opening of this conductance channel leads to the loss of mitochondrial membrane potential, resulting in failure of oxidative phosphorylation and progressive depletion of ATP, culminating in necrosis of the cell.

Mechanisms of Cell Injury

One of the structural components of the mitochondrial permeability transition pore is the protein cyclophilin D, which is a target of the immunosuppressive drug cyclosporine (used to prevent graft rejection). In some experimental models of ischemia, cyclosporine reduces injury by preventing opening of the mitochondrial permeability transition pore—an interesting example of molecularly targeted therapy for cell injury (although its clinical value is not established).

Mechanisms of Cell Injury

The mitochondria also sequester between their outer and inner membranes several proteins that are capable of activating apoptotic pathways; these include cytochrome c and proteins that indirectly activate apoptosis inducing enzymes called caspases. Increased permeability of the outer mitochondrial membrane may result in leakage of these proteins into the cytosol, and death by apoptosis. Mechanisms of Cell Injury

INFLUX OF CALCIUM AND LOSS OF CALCIUM HOMEOSTASIS

The finding that depleting calcium protects cells from injury induced by a variety of harmful stimuli indicates that calcium ions are important mediators of cell injury. Cytosolic free calcium is normally maintained at very low concentrations (-0. 1 µmol) compared with extracellular levels of 1. 3 mmol, and most intracellular calcium is sequestered in mitochondria and the ER.

Mechanisms of Cell Injury

Ischemia and certain toxins cause an increase in cytosolic calcium concentration, initially because of release of Ca2+ from intracellular stores, and later resulting from increased influx across the plasma membrane. Increased intracellular Ca2+ causes cell injury by several mechanisms. The accumulation of Ca2+ in mitochondria results in opening of the mitochondrial permeability transition pore and, failure of ATP generation.

Mechanisms of Cell Injury

Increased cytosolic Ca2+ activates a number of enzymes, with potentially deleterious cellular effects. These enzymes include phospholipases (which

cause membrane damage), proteases (which break down both membrane and cytoskeletal proteins), endonucleases (which are responsible for DNA and chromatin fragmentation), and ATPases (thereby hastening ATP depletion). Increased intracellular Ca2+ levels also result in the induction of apoptosis, by direct activation of caspases and by increasing mitochondrial permeability Mechanisms of Cell Injury

ACCUMULATION OF OXYGEN-DERIVED FREE RADICALS (OXIDATIVE STRESS)
Cell injury induced by free radicals, particularly reactive oxygen species, is an important mechanism of cell damage in many pathologic conditions, such as chemical and radiation injury, ischemia-reperfusion injury (induced by restoration of blood flow in ischemic tissue), cellular aging, and microbial killing by phagocytes. Free radicals are chemical species that have a single unpaired electron in an outer orbit.

Mechanisms of Cell Injury

Mechanisms of Cell Injury

Energy created by this unstable configuration is released through reactions with adjacent molecules, such as inorganic or organic chemicals—proteins, lipids, carbohydrates, nucleic acids—many of which are key components of cell membranes and nuclei. Moreover, free radicals initiate autocatalytic reactions, whereby molecules with which they react are themselves converted into free radicals, thus propagating the chain of damage. Reactive oxygen species (ROS) are a type of oxygen-derived free radical whose role in cell injury is well established.

Mechanisms of Cell Injury

ROS are produced normally in cells during mitochondrial respiration and energy generation, but they are degraded and removed by cellular defense systems. Thus, cells are able to maintain a steady state in which free radicals may be present transiently at low concentrations but do not cause damage. When the production of ROS increases or the scavenging systems are ineffective, the result is an excess of these free radicals, leading to a condition called oxidative stress.

Mechanisms of Cell Injury

Oxidative stress has been implicated in a wide variety of pathologic processes, including cell injury, cancer, aging, and some degenerative diseases such as Alzheimer disease. ROS are also produced in large amounts by leukocytes, particularly neutrophils and macrophages, Act as mediators for destroying microbes, removal of dead tissue, and other unwanted substances. Therefore, injury caused by these reactive compounds often accompanies inflammatory reactions, during which leukocytes are recruited and activated Mechanisms of Cell Injury

Pathologic Effects of Free Radicals.

The effects of ROS and other free radicals are wide-ranging, but three reactions are particularly relevant to cell injury: Lipid peroxidation in membranes. In the presence of O2, free radicals may cause peroxidation of lipids within plasma and organellar membranes. Oxidative damage is initiated when the double bonds in unsaturated fatty acids of membrane lipids are attacked by O2-derived free radicals, particularly by H.

Mechanisms of Cell Injury

The lipid–free radical interactions yield peroxides, which are themselves unstable and reactive, and an autocatalytic chain reaction ensues (called propagation), which can result in extensive membrane damage. Oxidative modification of proteins.

Free radicals promote oxidation of amino acid side chains, formation of protein-protein cross-linkages (e. g., disulfide bonds), and oxidation of the protein backbone.

Mechanisms of Cell Injury

Oxidative modification of proteins may

Damage the active sites of enzymes,

Disrupt the conformation of structural proteins,

Enhance proteasomal degradation of unfolded or misfolded proteins, Raising havoc (mess) throughout the cell.

Mechanisms of Cell Injury

Lesions in DNA.

Free radicals are capable of causing

single- and double-strand breaks in DNA,

cross-linking of DNA strands, and

formation of adducts.

Oxidative DNA damage has been implicated in cell aging and in malignant transformation of cells. Mechanisms of Cell Injury

DEFECTS IN MEMBRANE PERMEABILITY

Membrane damage may affect the functions and integrity of all cellular membranes Plasma membrane damage results in loss of osmotic balance

and influx of fluids and ions, as well as loss of cellular contents. The cells may also leak metabolites that are vital for the reconstitution of ATP, thus further depleting energy stores.

Mechanisms of Cell Injury

The plasma membrane can also be damaged directly by

various bacterial toxins,

viral proteins,

lytic complement components,

and a variety of physical and chemical agents.

Several biochemical mechanisms may contribute to membrane damage

Mechanisms of Cell Injury

Decreased phospholipid synthesis.

Increased phospholipid breakdown.

Severe cell injury is associated with increased degradation of membrane phospholipids, probably due to activation of endogenous phospholipases by increased levels of cytosolic and mitochondrial Ca2+. Phospholipid breakdown leads to the accumulation of lipid breakdown products, including unesterified free fatty acids, acyl carnitine, and lysophospholipids, which have a detergent effect on membranes.

Mechanisms of Cell Injury

They may also either insert into the lipid bilayer of the membrane or exchange with membrane phospholipids, potentially causing changes in permeability and electrophysiologic alterations. Cytoskeletal abnormalities.

Cytoskeletal filaments serve as anchors connecting the plasma membrane to the cell interior. Activation of proteases by increased cytosolic calcium may cause damage to elements of the cytoskeleton.

Mechanisms of Cell Injury

In the presence of cell swelling, this damage results, particularly in myocardial cells, in detachment of the cell membrane from the cytoskeleton, rendering it susceptible to stretching and rupture

Mechanisms of Cell Injury

Consequences of Membrane Damage.

Injury to lysosomal membranes results in leakage of their enzymes into the cytoplasm and activation of the acid hydrolases in the acidic intracellular pH of the injured (e. g., ischemic) cell. Lysosomes contain RNases, DNases, proteases, phosphatases, glucosidases, and cathepsins. Activation of these enzymes leads to enzymatic digestion of proteins, RNA, DNA, and glycogen, and the cells die by necrosis Mechanisms of Cell Injury

When reversible injury becomes irreversible and progresses to cell death. The “ point of no return,” at which the damage becomes irreversible, is still largely undefined, and there are no reliable morphologic or biochemical correlates of irreversibility.

Mechanisms of Cell Injury

Two phenomena consistently characterize irreversibility—the inability to reverse mitochondrial dysfunction (lack of oxidative phosphorylation and ATP generation) even after resolution of the original injury, and profound disturbances in membrane function.

Injury to lysosomal membranes results in the enzymatic dissolution of the injured cell that is characteristic of necrosis.

Mechanisms of Cell Injury

Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a means of detecting tissue-specific cellular injury and necrosis using blood serum samples. Cardiac muscle, for example, contains a specific isoform of the enzyme creatine kinase and of the contractile protein troponin; liver (and specifically bile duct epithelium) contains an isoform of the enzyme alkaline phosphatase; and hepatocytes contain transaminases.

Mechanisms of Cell Injury

Irreversible injury and cell death in these tissues are reflected in increased levels of such proteins in the blood Measurement of these biomarkers is used clinically to assess damage to these tissues. Morphologic Alterations in Cell Injury reversible cell injury .

Morphology. Cellular swelling is the first manifestation of almost all forms of injury to cells. It may be more apparent at the level of the whole organ. When it affects many cells, it causes some pallor, increased turgor, and increase in weight of the organ. On microscopic examination.

Difficult morphologic change to appreciate with the light microscope;

Morphologic Alterations in Cell Injury

Morphologic Alterations in Cell Injury

Morphologic Alterations in Cell Injury

small clear vacuoles may be seen within the cytoplasm; these represent

distended and pinched-off segments of the ER. This pattern of nonlethal injury is sometimes called hydropic change or vacuolar degeneration. Swelling of cells is reversible.

Cells may also show increased eosinophilic staining, which becomes much more pronounced with progression to necrosis.

Morphologic Alterations in Cell Injury

The ultrastructural changes of reversible cell injury include: Plasma membrane alterations, such as blebbing, blunting, and loss of microvilli Mitochondrial changes, including swelling and the appearance of small amorphous densities Dilation of the ER, with detachment of polysomes; intracytoplasmic myelin figures may be present. Nuclear alterations, with disaggregation of granular and fibrillar elements. Morphologic Alterations in Cell Injury

Morphologic Alterations in Cell Injury

These morphologic changes are associated with

decreased generation of ATP,

loss of cell membrane integrity,

defects in protein synthesis,

cytoskeletal damage, and

DNA damage.

Within limits, the cell can repair these derangements and, if the injurious stimulus abates, will return to normalcy. Persistent or excessive injury, however, causes cells to pass the rather nebulous “ point of no return” into irreversible injury and cell death.

Morphologic Alterations in Cell Injury

Different injurious stimuli may induce death by necrosis or apoptosis. Severe mitochondrial damage with depletion of ATP and rupture of lysosomal and plasma membranes are typically associated with necrosis. Summary

Cell injury occurs when the cell is Unable to adapt

Mechanism

1. Depletion of ATP

Reduced energy dependent sodium pump

Influx of sodium V efflux of potassium

Gain of water – Cell swelling

Dilatation of ER

Altered cellular energy metabolism

Summary

Increased AMP – anaerobic glycolysis – depleted glycogen – increased lactic acid + inorganic phosphate – decreased PH – decreased enzyme activity

Influx of calcium

Detachment of ribosomes from ER – decreased protein synthesis Increased un/misfolded protein response – cell injury and death Summary

Summary

2. Mitochondrial damage by increased calcium, ROS and oxygen deprivation

Opening of mitochondrial permeability transition pore

Depletion of oxygen

Leakage of apoptotic activating proteins – apoptosis

Summary

3. Influx of calcium

Opening of mitochondrial permeability transition pore

Failure of ATP generation

Activation of enzymes (phospholipases, proteases, endonucleases, ATPase

Activation of caspases – apoptosis

Summary

4. ROS-autocatalytic

Lipid peroxidation

Oxidative damage of unsaturated FFA

Oxidative modification of proteins – damage active site of enzymes

Proteasomal degradation of un/misfolded proteins

Lesions of DNA

Accumulation of lipid breakdown products.

Summary

Cytoskeletal abnormalities

Lysosomal membrane damage

NB. Mitochondrial dysfunction and profound disturbance of membrane function are sure evidence of irreversible cell injury