Pathology

3rd Stage
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Lecture 4

Mechanisms of cell injury and cell death

2.Disturbances in calcium homeostasis: Injury (specially by ischemia and certain toxins) can increase intracellular calcium concentration, causing:

1.Activation of enzymes (phospholipase causing membrane damage, protease breaks down membrane and cytoskeleton proteins, endonuclease causing DNA and chromatin fragmentation and ATPase (adenosine triphosphatase) speeding ATP depletion).

2.Apoptosis initiation (by direct activation of caspases or increasing mitochondrial permeability).

3. Membrane Damage

***Is a consistent feature of most forms of cell injury that end in necrosis**

***Several mechanisms may contribute to membrane damage:**

1. ROS production 2. Decreased phospholipid synthesis (due to decrease ATP production) 3. Increased phospholipid breakdown (probably due to activation of phospholipase) 4. Cytoskeletal abnormalities (proteases activation)

***Membrane damage may affect all cellular membranes:**

1. Mitochondria membrane damage leading to decreased ATP generation and release of proteins that trigger apoptosis.

2. Plasma membrane damage results in loss of osmotic balance and influx of fluids and ions, as well as loss of cellular contents.

3. Injury to lysosomal membranes results in leakage of their enzymes into the cytoplasm and activation of lysosomal hydrolases (RNases, DNases, proteases, phosphatases and glucosidases, which degrade RNA, DNA, proteins, phosphoproteins, and glycogen, respectively).

4. Damage to DNA and proteins

Cells have a repair mechanism to correct DNA damage. If the damage is too severe to be corrected i.e. DNA damage is beyond repair, cell initiates apoptosis

(abnormal DNA has the potential to induce malignant transformation).Similar reaction is triggered by accumulation of improperly folded protein.

Hypoxia and Ischemia: **Persistent or severe hypoxia and ischemia eventually lead to failure of ATP generation, mitochondrial damage and ROS accumulation.**

ATP depletion results in:

- **Reduced activity of plasma membrane ATP-dependent pumps causing cell swelling, ER dilation and influx of ca^{2+}.**
- **Compensatory increase in anaerobic glycolysis leads to lactic acid accumulation, decreased intracellular pH and decreased activity of many enzymes.**
- **Prolonged or worsening depletion of ATP causes structural disruption of the protein synthetic apparatus with reduction in protein synthesis.**
- **Finally, there is irreversible damage to mitochondrial and lysosomal membranes and necrosis occurs.**

●Apoptosis is a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins (programmed cell death {suicide program}). Fragments of the apoptotic cells break off (apoptosis=falling off).

***The plasma membrane of the apoptotic cell remains intact, but is altered in such a way that the fragments (apoptotic bodies) will undergo rapid consumption by phagocytes, so dead cells are rapidly cleared before the leakage of cellular contents thus, apoptosis does not produce an inflammatory reaction. Apoptosis is an ATP dependent process.**

Causes of Apoptosis: Apoptosis could be *physiological or pathological.

***Physiological apoptosis occurs in many normal situations (to eliminate cells no longer needed and to maintain constant number of cells in tissues)**

1. **Programmed destruction of cells during embryogenesis (during normal development of an organism, some cells die and are replaced by new ones).**
2. **Involution of hormone-dependent tissues on hormone withdrawal, such as endometrial cell breakdown during the menstrual cycle.**

3. Cell loss in proliferating cell populations (e.g., intestinal epithelium) to maintain a constant cell number.

4. Elimination of cells that have served their useful purpose, e.g. neutrophils in acute inflammation and lymphocytes at end of the immune response.

5. Elimination of potentially harmful lymphocytes to prevent reactions against the body's own tissues (autoimmune diseases).

***Pathological apoptosis (when cells are damaged beyond repair).**

1. Severe DNA damage, e.g. after exposure to radiation and cytotoxic drugs, and repair mechanism cannot repair the injury

2. The accumulation of misfolded proteins e.g. due to mutations in the encoding genes

3. Certain infections, particularly some viruses, in which apoptosis of the infected cell is induced by the virus (human immunodeficiency virus), or by the host immune response (e.g. viral hepatitis).

Mechanisms of Apoptosis

***The main event in apoptosis is activation of enzymes called caspases which eventually activate enzymes that degrade the cells' proteins and nucleus.**

***Two distinct pathways end in caspase activation: the mitochondrial (intrinsic) pathway and the death receptor (extrinsic) pathway.**

Morphology of apoptotic cells

Apoptotic cells form shrunken masses with intensely eosinophilic cytoplasm and condensed chromatin. The nucleus eventually undergoes karyorrhexis. The apoptotic cells fragment into apoptotic bodies that are rapidly phagocytosed without provoking an inflammatory response

GOOD LUCK