**Apoptosis**

Apoptosis is a pathway of cell death induced by tightly regulated intracellular proteins in which cell is destined to die by activating some enzymes that damage DNA and nuclear and cytoplasmic proteins.

* Pathway of cell death
* Programmed and suicidal cell death
* Apoptosis occurs by activating some enzymes that damage DNA and nuclear and cytoplasmic proteins.
* In apoptosis cell membrane remans intact while in necrosis cell membrane is damaged.

**Causes of apoptosis:**

Apoptosis occurs in physiological and pathological condition:-

**1 .Physiological condition:**

**Embryogenesis:** During embryogenesis which include implantation, organogenesis and metamorphosis, in all stages of development a lot of cells that are not needed are died via apoptosis.

**Hormonal dependent apoptosis**: When mother stops breast feeding breast regress in size this occurs via apoptosis.

In prostate, after castration testosterone level is reduced resulted in apoptosis and reduction in size of prostate gland occurs.

Endometrial cell breakdown occurs during menstruation through apoptosis.

**Apoptosis in proliferating cells**: It is a common phenomena in multicellular organs. When number of cells exceed their normal level, apoptosis occurs to reduce number of cells to a normal level. e.g in intestinal crypts epithelium.

**Apoptosis of host cells that have useful purposes**: Neutrophils take part in acute inflammation. Acute inflammation is a protective mechanism against infection. When neutrophils have done their job they are died through apoptosis. Similarly, elimination of lymphocytes after immune response.

**Death of self-reactive T-lymphocytes**: Lymphocytes are mature to become highly reactive. Apoptosis occurs to eliminate the highly reactive lymphocytes against self-antigen in order to prevent autoimmune disease.

**2 .Pathological condition**:

**Injurious substances**: Apoptosis occurs due to various injurious substances like UV radiations and cytotoxic drugs etc. Both of these damage DNA. If cells are unable to repair this damaged DNA it is necessary to kill that cells because mutated DNA can translocate into other positions and will cause carcinoma.

**Viral Infection** : Apoptosis also occurs in viral infections. e.g In viral hepatitis, virus induced apoptosis.

**Tumor cells**: Apoptosis occurs in tumor cells. When tumor regress in size, they became smaller may be due to exposure of cytotoxic drugs that induce apoptosis.

**Atrophy of cells**: When duct is obstructed, parenchymal cells reduce in their size and ultimately death of parenchymal cells occurs via apoptosis.

**Morphological changes in apoptosis**

In apoptosis, cells are observed under microscope and following changes occur:

1. Cell shrinkage
2. Cytoplasm becomes dense
3. Organelles are tightly packed

Chromatin condensation occurs and these chromatin fragments just beneath the nuclear membrane, this fragmentation damage the nucleus. Formation of buds occur around plasma membrane. They become separated and result in formation of apoptotic bodies.

**Apoptotic bodies:** These apoptotic bodies contain dense cytoplasm, tightly packed organelles and may or may not have nucleus.

**Biochemical Changes**

Following biochemical changes occur :-

1. Protein cleavage
2. DNA damage
3. Phagocytosis

**Protein cleavage:**

An important family of enzymes in cells is caspases. It is protease enzyme with cysteine group. It is also called cysteine protease or caspases. They cause destruction of cytoskeletal proteins and nuclear proteins.

**DNA damage:**

Due to action of enzyme, fragments of DNA can be separated by using a technique of gel electrophoresis that separate DNA fragments into 50-300kilo base pairs. These DNA fragments appear like a ladder.

**Phagocytosis:**

On the apoptotic cell membrane, there are special proteins called phosphotidyl serine. There are some adhesive molecules on the apoptotic cell membrane like adhesive glycoproteins.

This phagocytosis is performed by tissue macrophages.

These adhesive glycoproteins facilitate the binding of phagocytes with apoptotic bodies that cause removal of apoptotic bodies. This process occurs very rapidly and no inflammation occurs.

**Mechanism of apoptosis**

Two phases of apoptosis are:-

1. Initiation phase
2. Execution phase

**Initiation Phase:**

In initiation phase, caspases are activated whereas in execution phase cell death occurs.

**Types of initiation phase**:

Initiation phase is sub-divided into two types:-

1. Extrinsic pathway
2. Intrinsic pathway

**Extrinsic pathway:**

Many cells have a death receptor on their surface e.g receptors for tumor necrosis factor, and receptor for FAS.

T-lymphocytes have a special protein called FAS ligand or TNF recognize the target expressing their receptors. When these ligand bind to their receptors, there is cross-linkage between three or more receptors that induce adapter molecule to bind with death domain e.g

FAS associated death domain.

These adapter molecule will attract the inactive form of caspases known as pro caspases 10 that further attract another procaspases and convert into active form that are called caspases known as caspases 8 and caspases 9 which are active form. These two induce apoptosis.

**Intrinsic pathway:**

In intrinsic pathway, there is no activation of death receptors. In intrinsic pathway, there is increase in mitochondrial permeability. Every cell has a growth factor. When any growth factor binds to the cell surface receptors, there is formation of antu-apoptotic bodies on the surface of mitochondrial membrane that prevent apoptosis.

BCL2 or BCL-X are anti-apoptotic bodies. Due to any radiation or no growth signal, there is no formation of BCL2 and BCL-X \. Absence of anti-apoptotic bodies result in conversion or replacement of anti-apoptotic bodies into pro-apoptotic bodies that damage mitochondrial membrane. As a result increase in mitochondrial permeability causes cell death.

In mitochondrial membrane, there is cytochrome C enzyme. Due to destruction of mitochondrial membrane, cytochrome C enzyme is released and cause APAF1( apoptosis activating factors).

**Execution phase:**

Caspases8 and caspases 9 activate caspases 3 and caspases 6 enzymes that cause destruction of nuclear and cytoskeletal proteins and results in blebs formation.