CELL DEATH

Death is the ultimate event in the life of all organisms. Death and degradation of cells takes place at particular times. Death of cells is also induced in cases of acute injury and infection, DNA damage, toxicity and trauma or when cells turn cancerous. Cell death may occur through 'cellular suicide' with the help of the intracellular organelles called lysosomes (autophagy); or when induced by acute injury or infection (necrosis); or through programmed cell death (apoptosis) Apoptosis is genetically controlled through a pre-designated pathway. Autophagy and Necrosis cause cell death through alternate pathways.

Apoptosis

Apoptosis was a term coined in 1972 for the process of active cell death resulting in the orderly breakdown of cellular structures. This is also known as programmed cell death since apoptosis is triggered by the expression of specific genes and blockage of mRNA or protein synthesis. It was best understood in the nematode C elegans where out of a total of 1090 somatic cells 131 undergo programmed death during development. This number of dying cells in invariant in the species. Since then the significance of programmed cell death was established in developmental biology of other species for genetically determined elimination of cells. Apoptosis occurs normally during development and aging as a homeostatic mechanism to maintain cell populations in tissues and as a defence mechanism in immune reactions and diseased conditions. Apoptosis is often initiated by removal of growth factors from cells and sometimes as an active response to a signal during the developmental process. For example, it is the process responsible for elimination of tissues during finger and toe formation in limbs of vertebrates, and loss of the tail in tadpoles during metamorphosis.

Some of the major events of apoptosis include chromatin condensation and nuclear fragmentation. As apoptosis proceeds, individual cells or clusters of cells become increasingly round and undergo pyknosis (the reduction of cell volume), the membrane bulges out in small portions known as blebs and organelles undergo modifications. However the cell does not lose its membrane integrity and the cells contents are not released in to the intercellular spaces and no inflammatory responses occur. The dying cells are usually phagocytosed typically by macrophages to prevent secondary necrocis. Apoptosis is an energy-dependent process. Three major biochemical events occur during apoptosis:

i) **DNA and protein breakdown**: Early apoptosis is characterized by the breakdown of DNA into 50-300kb fragments that are then cut into oligonucleotides by endonucleases. This results in DNA fragments of a range of lengths.

ii) **Activation of caspases**: Late apoptosis is characterized by the activation of cysteine proteases known as caspases that break down the protein and cytoskeletal components of the cell and activates the enzyme DNase, which continues the degradation of the cell's DNA. Caspases breakdown about 100 cellular proteins which bring about changes in the cell which are characteristic of programmed cell death or apoptosis, for example out of a family of a dozen caspases, one is inhibitor of DNA and causes DNA fragmentation; another called nuclear lamin brings about nuclear fragmentation. A cascade of caspases breaks the cell into small membrane-covered vesicles by folding the cell inwards. The cell membrane remains intact during the process despite vesicle or blebs budding on the cell surface. As apoptosis progresses, these cells will lose the cell-to-cell adhesions and will separate from the neighboring cells (Fig 11.12).

iii) **Membrane modifications**: In which an intracellular transmembrane protein, is exposed on the surface by which phagocytes recognise the dying cell.

The process of apoptosis is divided into two pathways: the intrinsic pathway if the apoptosis is initiated in the mitochondria and the extrinsic pathway which is started by the binding of signaling molecules or ligands to transmembrane receptors that involve death receptors domains on the intracellular side and these lead to a cascade of reactions that start the apoptotic process.

Necrosis

Necrosis another cell death process is different from apoptosis. It can happen simultaneously or independently of programmed cell death. Necrosis is accidental death induced by an acute injury or a deadly disease or DNA damage as opposed to programmed cell death. Necrosis, therefore, is not a naturally occurring phenomenon but is induced by serious injury. In Greek necrosis means death.

Necrosis is considered to be a toxic process which is uncontrolled and passive that is, it does not require an energy source to take place. It affects a large field of cells and is mediated by two main mechanisms- injury to the cell membrane and interference with the supply of the energy to the cells. Some of the major morphological changes that occur with necrosis include cell swelling;

formation of cytoplasmic vacuoles; disruption of ribosomes and organelle membranes; swollen and ruptured mitochondria and lysosomes; and eventually disruption of the cell membrane. This loss of cell membrane structure results in the release of the cytoplasmic contents into the surrounding tissue (Fig.11.12).

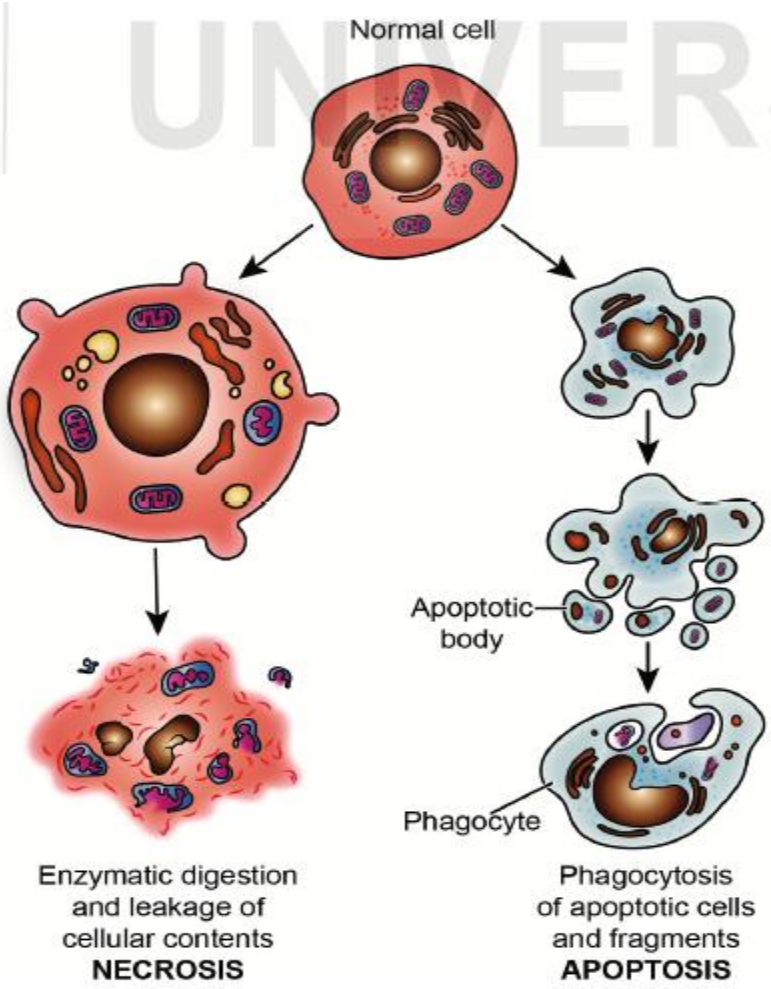

Fig. 11.12: Cell death by necrosis and apoptosis.

The unregulated release of products of cell death to the outside, initiates inflammatory response in the surrounding tissue. Leucocytes and nearby phagocytes eliminate the dead cells through phagocytosis. Damaging substance from leucocytes can cause damage to surrounding tissues and if untreated, necrosis results in building up decomposing dead tissue and cell debris at or near site of necrotic cell death (e.g. gangrene). Often necrotic tissue needs surgical removal.