APOPTOSIS - A REVIEW

Arun Singh ** Bastian T.S *** Ceena Denny E * V. Ipe Varghese**

**P.G. Student , **Professor and H.O.D. Department of Oral & Maxillofacial Pathology,*

Sardar Patel Post Graduate Institute of Dental & Medical Sciences, Lucknow

**** Reader, MCODS, Mangalore*

***** Controller of Examinations, Kerala University of Health & Allied Sciences.*

Abstract:

Apoptosis is a process of controlled cellular death whereby the activation of specific death-signaling pathways leads to deletion of cells from tissue. Apoptosis is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death.

Keywords:- Apoptosis, p53, Bcl-2 & Caspases.

Introduction:-

In addition to cell-cycle arrest and repair machinery, the damaged cells, where damage is beyond repair, may induce an apoptotic (programmed cell death - PCD) response that is highly cell-specific and is the most common form of physiologic cell death in multicellular forms.[4] Apoptosis is a process of controlled cellular death whereby the activation of specific death-signaling pathways leads to deletion of cells from tissue. These death-signaling pathways can

be activated in response to receptor–ligand interactions, environmental factors such as ultraviolet light and redox potential, and internal factors that are encoded in the genome ("programmed cell death").[1]

HISTORICAL OVERVIEW:-

Apoptosis has long been identified as an evolutionarily conserved process of active cell elimination during development. Its phenotypic features include DNA fragmentation and chromatin condensation, cell shrinkage, and formation of apoptotic bodies, which are cleared by phagocytosis without initiating a systemic inflammatory response. The execution of apoptosis requires novel gene expression and protein synthesis. Apoptosis has evolved as an intricate and critical mechanism for balancing cell proliferation and for the active remodelling of tissues during development.

The identification of apoptosis under pathological settings dates back to the 1960s, when John FR Kerr was studying ischemic liver damage. He observed a novel cell death phenotype that was morphologically distinct from classical necrosis. Dying hepatocytes in the ischemic penumbra were found to have shrunk to form small round masses of cytoplasm containing condensed nuclear chromatin. These dying cells were taken up by neighbouring hepatocytes and phagocytes without initiating a broader inflammatory response. This phenomenon was also recognized in normal rat livers. This distinct type of cell death, temporarily named 'shrinkage necrosis', was also found to occur in cancer and during normal development. The term 'apoptosis' was subsequently coined to replace shrinkage necrosis, and has later been used interchangeably with programmed cell death, albeit loosely, because of similar requirements for genetic programming and new protein synthesis, as well as morphological similarities.[7]

Cell death, along with differentiation and growth, is a fundamental aspect of the life cycle of a eukaryotic cell, the control of cell number is the result of the balance between cell loss and gain. The molecular mechanisms leading to the controlled removal of cells in tissues by apoptosis are not fully understood. It is clear that under physiological conditions the process is active, requires energy and the induction/activation of specific genes have led to the identification of several genes needed for the completion of the cell death program. These genes have been classified

into specific functional groups that play distinct roles within the cell death program. The first group of genes includes permissive elements which specify which cells will undergo apoptosis. The second group comprises elements whose induction or down-regulation initiates the apoptosis pathway. A third set of genes includes effector elements required for killing and the subsequent disposal and degradation of cellular remnants. Genes with functional homology to some of those defined in C. elegans have been described in mammals: Bcl-2 and ted-9, caspases and ted-3. These genes, grown into families of homologous genes, together with additional important regulatory elements, are at the centre of intense research efforts to dissect the molecular mechanisms of the death machinery.[5]

Some cells express Fas or TNF receptors that can lead to apoptosis via ligand binding and protein cross-linking. Other cells have a default death pathway that must be blocked by a survival factor such as a hormone or growth factor. There is also the issue of distinguishing apoptosis from necrosis, two processes that can occur independently, sequentially, as well as simultaneously. In some cases it's the type of stimuli or the degree of stimuli that determines if cells die by apoptosis or necrosis. At low doses, a variety of injurious stimuli such as heat, radiation, hypoxia and cytotoxic anticancer drugs can induce apoptosis but these same stimuli can result in necrosis at higher doses. Finally, apoptosis is a coordinated and often energy-dependent process that involves the activation of a group of cysteine proteases called "caspases" and a complex cascade of events that link the initiating stimuli to the final demise of the cell.[6]

MECHANISMS OF APOPTOSIS:

Mainly two types of apoptotic pathways such as intrinsic and extrinsic (or death receptor) have been well described that involve a number of proteins.

Extrinsic apoptosis pathways of type I and type II-

Extrinsic apoptosis signalling is mediated by the activation of so called "death receptors" which are cell surface receptors that transmit apoptotic signals after ligation with specific ligands. Death receptors belong to the tumor necrosis factor receptor (TNFR) gene superfamily, including TNFR-1, Fas/CD95, and the TRAIL receptors DR-4 and DR-5. All members of the TNFR family consist of cysteine rich extracellular subdomains which

allow them to recognize their ligands with specificity, resulting in the trimerization and activation of the respective death receptor. Subsequent signalling is mediated by the cytoplasmic part of the death receptor which contains a conserved sequence termed the death domain (DD). Adapter molecules like FADD or TRADD themselves possess their own DDs by which they are recruited to the DDs of the activated death receptor, thereby forming the so-called death inducing signalling complex (DISC). In addition to its DD, the adaptor FADD also contains a death effector domain (DED) which through homotypic DED-DED interaction sequesters procaspase-8 to the DISC. As described above, the local concentration of several procaspase-8 molecules at the DISC leads to their autocatalytic activation and release of active caspase-8. Active caspase-8 then processes downstream effector caspases which subsequently cleave specific substrates resulting in cell death. Cells harboring the capacity to induce such direct and mainly caspase-dependent apoptosis pathways were classified to belong to the so called type I cells.

In type II cells, the signal coming from the activated receptor does not generate a caspase signalling cascade strong enough for execution of cell death on its own. In this case, the signal needs to be amplified via mitochondria-dependent apoptotic pathways. The link between the caspase signalling cascade and the mitochondria is provided by the Bcl-2 family member Bid. Bid is cleaved by caspase-8 and in its truncated form (tBID) translocates to the mitochondria where it acts in concert with the proapoptotic Bcl-2 family members Bax and Bak to induce the release of cytochrome c and other mitochondrial proapoptotic factors into the cytosol. Cytosolic cytochrome c is binding to monomeric Apaf-1 which then, in a dATP-dependent conformational change, oligomerizes to assemble the apoptosome, a complex of wheel-like structure with 7-fold symmetry, that triggers the activation of the initiator procaspase-9. Activated caspase-9 subsequently initiates a caspase cascade involving downstream effector caspases such as caspase-3, caspase-7, and caspase-6, ultimately resulting in cell death.[2,3]

Intrinsic pathway of apoptosis:-

Following DNA damage, there is an increase in level of Bax and decrease in level of Bcl-2, which causes mitochondria to release pro-apoptotic factors, such as cytochrome-c. These factors cause activation of procaspase-9, followed by

downstream apoptotic effectors. Recently, it has been found that in response to DNA damage, activation of caspase-2 is required before mitochondrial permeabilization and release of cytochrome-c. Expression of cyclin-D3 and caspase-2 in human cells potentially induces apoptosis. After releasing cytochrome-c, it binds to apoptotic protease activating factor Apaf-1 and forms a 7-span symmetrical active complex 'apoptosome' in nucleotide dATP/ATP dependent manner. The apoptosome subsequently recruits procaspase-9 into its central region to form an active holoenzyme, which further activates downstream executioner caspases, such as caspase-3/7 that leads to PCD (programmed cell death). In mammalian cells, caspase activity is also stimulated by one of the pro-apoptotic mitochondrial proteins Smac/Diablo, and Omi/HtrA2, They interfere with the action of inhibitor of apoptosis(IAP) family protein (e.g., survivin) and promote apoptosis. In addition to caspase activator proteins, some other molecules such as AIF (apoptosis inducing factor) and Endo G (endonuclease G) has also been found to be released from mitochondria that cause apoptosis by DNA fragmentation and subsequent chromosomal condensation. Recent evidence suggests that Bax/Bak can also be localized in the endoplasmic reticulum (ER) and gets activated in response to ER stress, leading to calcium depletion and murine caspase-12 activation.

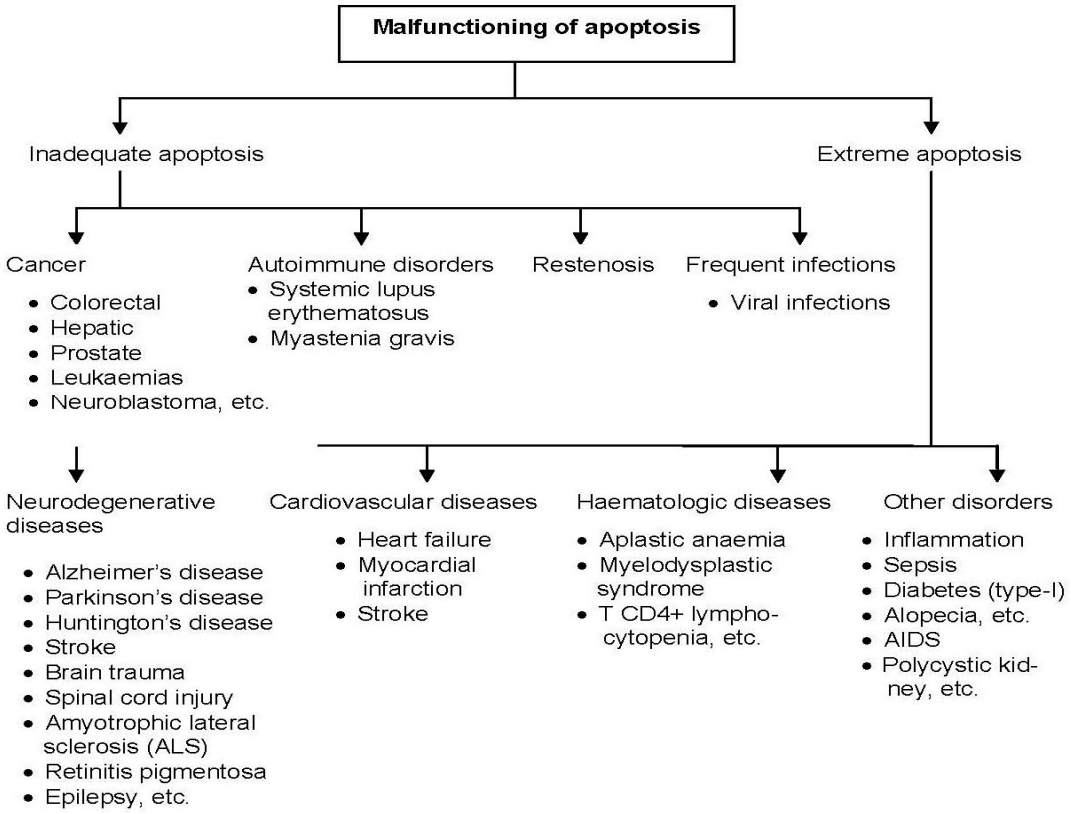
In addition to other organisms, PCD has also been suggested in various phytoplankton species such as cyanobacteria (e.g., Trichodesmium sp., Anabaena flos-aquae), green algae (e.g., Dunaliella tertiolecta) and dinoflagellates (e.g., Peridinium gatunense). However, it is not very clear how PCD is operating in phytoplankton. The presence of key apoptotic enzymes such as paracaspase (in bacteria), metacaspase (in plant/fungi) and caspases (in animals) that share common active sites are considered to be highly conserved across taxa, although, the presence of animal cell death regulator, such as Bcl-2 family and p53 in all the life forms is still in dispute.[2,3,4]

MALFUNCTIONING OF APOPTOSIS:-

Improper apoptosis or malfunctioning of individual apoptotic machinery may cause several human diseases like cancer, neurodegenerative as well as several types of autoimmune disorder. It has been found that unnecessary cell death and unsound regulation of caspase activity are associated with certain diseases

such as Alzheimer's disease, Parkinson's disease and Huntington's disease. Augmented activities of caspases-8 and -9 have been observed in peripheral blood mononuclear cells of Alzheimer's disease patients and in brain tissues of Alzheimer's as well as Parkinson's disease patients. Huntington's disease, a neurodegenerative disorder, has also been found to be caused by increased activity of caspase-10 in a manner similar to caspase-8. Mutations on Fas and Fas ligand (Fas-L) in humans may cause a complicated immune disorder like autoimmune lymphoproliferative syndrome (ALPS), a semblance of murine lymphoproliferation (lpr) and generalized lymphoproliferative disorder (gld).

The three autosomal dominant diseases such as Muckle Wells syndrome, familial cold auto-inflammatory syndrome and chronic infantile neurological cutaneous and articular (CINCA) syndrome caused by missense mutations in the NACHT domain of NALP3 protein are closely related to autoinflammatory syndromes distinguished by periodic fever, skin rashes, amyloidosis and development of neurological complications. It has been suggested that loss of caspase-14 expression is associated with progression of ovarian cancer and the mutation in p53 gene may cause neoplastic diseases. Thus it seems that apoptotic pathway is associated with several biological processes and plays a vital role in regulating various diseases.[4]



Conclusion:

Apoptosis is a energy-dependent flow of molecular events and triggered by certain stimuli such as UV radiation, oxidative stress, genotoxic chemical with in biological system. It course through two types of pathways such as intrinsic and extrinsic that involves the activation of a set of cysteine proteases known as "caspases". Apoptosis plays a significant role in survival by maintaining the homeostasis in multicellular organisms as well as in the management of many diseases. Malfunctioning of apoptotic pathway may cause several human diseases like cancer, neurodegenerative as well as several types of autoimmune disorder. Certain photosensitizing drugs are being employed in photodynamic therepy to induce apoptosis for the treatment of cancer and non cancer cells.

Reference:-

1. *Gustavo Matute-Bello and Thomas R Martin. Science review: Apoptosis in acute*

lung injury. Critical Care. 2003; 7: 355-358.

2. *Ivan Damjanov, James Linder, W. A. D. Anderson. Anderson's Pathology; 10th edition.*
3. *Kumar V, Abbas A K, Fausto N. Robbins and Cotran Pathologic Basis Of Disease; 7th edition.*
4. *Rajesh p. Rastogi, richa and rajeshwar p. Sinha. Apoptosis: Molecular mechanisms and pathogenicity. Excli journal 2009; 8: 155-181.*
5. *Shigekazu Nagata. Apoptosis by Death Factor. Cell. 2007; 88: 355–365.*
6. *Susan Elmore. Apoptosis: A Review of Programmed Cell Death. Toxicol Pathol. 2007; 35(4): 495–516.*
7. *Xiaopeng Zhang, Yaming Chen, Larry W Jenkins, Patrick M Kochanek and Robert SB Clark. Bench-to-bedside review: Apoptosis/programmed cell death triggered by traumatic brain injury. Critical Care 2005, 9:66-75.*