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Role of Apoptosis in Various Human Diseases

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1.0 Abstract

Committing suicide by a cell itself is astonishing, though every cell participates in such a controlled death program for several physiological processes including embryonic development, immune system regulation, and protection of cells in response to any kind of tissue injury and other stresses. Apoptosis, a form of programmed cell death, is classified as recognizable morphological changes; ultimately leading to the cell's death in a regulated fashion. However, the deregulation of the apoptotic pathway could cause severe human maladies such as many neurodegenerative diseases, cancers, and also autoimmune disorders by hampering the cell cycle and different cell signaling cascades. This article reviews the basic underlying mechanisms of apoptosis and its relation with several human pathologies. It also focuses on how such a minor or huge change in apoptosis could cause severe to fatal human diseases.

Keywords: Apoptosis, cancer, caspase, extrinsic pathway, intrinsic pathway

2.0 Introduction

Cell death is a crucial and chief controlled mechanism to maintain the normal plant and animal cell development cycle and to remove undesired cells starting from the beginning of a cell to its ultimate maturation. Apoptosis, such an intracellular regulated death program, was first published in a renowned paper that opened a new horizon to the field of biological research (Kerr et al., 1972). The participating cells in apoptosis show several morphological attributes, differentiating them from other nonapoptotic cells. The apoptotic program activated by many physiological and pathological factors can be divided into two distinct stages. The first stage begins with the shrinkage and condensation of the cytoskeleton. The disintegration of the nuclear envelope and condensation of nuclear chromatin gradually breaks up the cell into many membranes bound fragments. Consequently, the cell surface blebs and cleaving into membrane-enclosed components called apoptotic bodies. The second step is the recognition and engulfment of the apoptotic body by surrounding phagocytes, enabling the intracellular degradation in phagosome by various hydrolytic enzymes, thus preventing the spilling of contents to the

neighboring healthy cells avoiding inflammation. (Elmore, 2007; Häcker, 2000; Kerr et al., 1972).

Apoptosis plays a critical function between cell survival and cell death in a regulated manner. In the case of a cell with damaged DNA, the cell cycle halts at the checkpoints to repair the DNA damage. If the damage is irreparable, the accumulation of the tumor suppressor protein p53 will activate many transcription factors, turning on apoptosis. When p53 activity is downregulated, the apoptotic program will be hampered leading to tumorigenesis and the development of carcinoma (Wong, 2011). The dysregulation of apoptosis could also exert a devastating effect on many neurodegenerative disorders. Many neuronal cells die in a controlled manner via apoptosis during central and peripheral nervous system development. Neurotrophic factors from target cells provide signals, ultimately determining the fate of the survival of neuronal cells. In response to tissue damage, neurons undergo excessive uncontrolled apoptosis that develops into severe disorders (Mattson, 2000). Alzheimer's disease is such a kind of disease that results in apoptotic death of hippocampal and cortical neurons. Damage of the hippocampal neurons makes a person unable to remember new and fresh memories and forget what they recently learn or hear something from a source(Mattson, 2000). Parkinson's disease, another type of neurodegenerative disorder, happens due to the loss of dopaminergic neurons undergoing excessive apoptosis (Mattson, 2000; Venderova & Park, 2012). Huntington's disease is the result of the loss of neurons in the striatum that alters the body movement to very severe conditions (Mattson, 2000). Here, we focus on the apoptosis mechanism and its relation with different neurodegenerative disorders and carcinoma in a sequential manner.

3.0 Mechanism of Apoptosis:

The apoptotic program is facilitated by a type of proteases, known as, caspases. Caspases have cysteine residue at their active site and cleave their targets on aspartic acid residues. Caspases are first synthesized as inactive enzymes called procaspases which then undergo proteolytic cleavage to make active caspases. Once, the initiator caspases are synthesized they activate other executioner caspases thus, amplifying the apoptotic signal. The caspases participating in inflammation include caspases 1,4 and 5. Initiator caspases include caspase 2,8,9,10. Executioner caspases are caspase 3,6,7(Cohen, 1997; Elmore, 2007). An amazing fact may hit our mind that how an apoptotic cell is easily recognized by surrounding phagocytes. The phosphatidylserine, an important component of the cell plasma membrane is present in the inner leaflet of a normal cell membrane. But when a normal cell is converted into an apoptotic cell, the phosphatidylserine comes into the outer leaflet, marking a cell as an apoptotic cell. Surrounding phagocytes can recognize this marker and rapidly engulf them. Annexin V can bind to the phosphatidylserine present outer leaflet of the cell membrane and thereby using in the identification of apoptotic cells. Apoptosis can progress through two major pathways: extrinsic and intrinsic pathways. The extrinsic pathway involves extracellular ligand for death signal whereas intrinsic pathway, as the name suggests, occurs within the cell and involves mitochondria and other intracellular factors for continuing the death process (Elmore, 2007).

3.1 Extrinsic pathway:

The extrinsic pathway of apoptosis involves interaction between extracellular ligand and cell surface death receptor. Death receptors under the Tumor Necrosis Factor receptor (TNF) family contain an extracellular domain to which ligand interacts, the transmembrane domain, and an intracellular cytoplasmic domain comprising about 80 amino acids, called the death domain that mediates the amplification of apoptotic signal (Walczak & Krammer, 2000). The death receptors are CD95 (Apo1/Fas), TNFR1, TNF-related apoptosis-inducing ligand receptor 1 (TRAIL – R1), and TRAIL – R2. Death ligands include CD95 ligand (CD95L), TNFα (Fulda & Debatin, 2006; Walczak & Krammer, 2000). CD95 and CD95L are type 1 and type 2 transmembrane receptors respectively, expressed on activated

lymphocytes and killer lymphocytes (Walczak & Krammer, 2000). Upon binding of CD95L on the CD95 death receptor's extracellular domain the death receptor becomes trimerized. After binding of the ligand, the cytoplasmic domain of the death receptor recruits the adaptor protein such as FADD. This FADD then facilitates the binding of initiator procaspase 8 and form death inducing signaling complex (DISC). Within DISC oligomerization of procaspase 8 occurs that undergo proteolytic cleavage to activate itself. After activation procaspase 8 activates executioner caspase 3 thus amplifying the death signal (Elmore, 2007; Fulda & Debatin, 2006; Walczak & Krammer, 2000).

3.2 Intrinsic Pathway:

The intrinsic pathway is a mitochondrial-dependent cell death program, operated totally within the cells. Cells with irreparable DNA, hypoxia, oxidative stress can act as the stimuli for activation of the intrinsic pathway (Elmore, 2007). The intrinsic pathway is regulated by the Bcl2 family of proteins consisting of anti-apoptotic proteins such as Bcl2 itself and Bcl-xL and pro-apoptotic proteins such as Bak, Bax. Bak and Bax activate apoptosis by forming pores on the mitochondrial outer membrane, stimulating the liberation of cytochrome C and other proteins from the mitochondria to cytosol. Within the cytosol, cytochrome C recruits adaptor proteins called Apaf 1 which in turn facilitates the binding of initiator procaspase 9 forming apoptosome. Within apoptosome procaspase 9 undergoes proteolytic cleavage to activate itself forming caspase 9. Once activated it turns on the activation of executioner caspase 3, continuing the apoptotic signal (Elmore, 2007; Fulda & Debatin, 2006).

3.3 The Ending Mechanism Common to both extrinsic and intrinsic pathway:

The extrinsic and intrinsic pathway finally meets up to the similar ending executioner caspase, caspase 3, which ultimately progresses a cell towards death. Caspase 3 activates the protein complex that facilitates the release of endonuclease, cleaving the DNA. In normal healthy cells, Caspase Activated DNase (CAD) is normally inactivated by binding to its inhibitor ICAD. In a cell destined to apoptosis, caspase 3 cleaves ICAD which releases CAD, breaking the chromosomal DNA into fragments (Elmore, 2007). Caspase 3 also mediates cytoskeletal condensation, breakdown of the nuclear lamina, and various cell signaling cascades which help in the formation of apoptotic bodies.

4.0 Apoptosis in Development of Cancer:

Cancer, uncontrolled cell division, is one of the devastating effects of the dysregulation of apoptosis. Apoptosis is a tightly regulated mechanism controlled by many genes whose improper balance in synthesis can give rise to the tumor, which might be benign, that upon achieving invasive properties can become malignant tumors, ultimately leading to cancers. Several major factors that alter the proper functioning of the extrinsic and intrinsic pathway of apoptosis include the delicate balance of the Bcl2 family of proteins, p53 tumor suppressor protein, altered death signaling cascade which is described as follows (Wong, 2011).

4.1 Improper Balance of Bcl2 Family Proteins:

Bcl2 was recognized from its identification as an oncogene in human follicle lymphoma of B cell Origin (Tsujimoto, 1998). Bcl2 family of proteins consists of two subfamilies – pro-apoptotic proteins (promoting apoptosis) and anti-apoptotic proteins (inhibiting apoptosis). Anti-apoptotic proteins share the sequence homology through BH-1, BH-2, BH-3, and BH-4 domains and include Bcl2 itself and Bcl-xL and Bcl-W. Pro-apoptotic proteins include Bax, Bak that share homology from BH-1 to BH-3 but they do not have BH-4 domain(Tsujimoto, 1998). Another kind of proapoptotic protein is activated in response to many stress conditions including DNA damage, ER stress, etc. These proteins are called BH3 proteins involving Bid, Puma, Noxa, Bad, Bik, etc. (Wong, 2011). The pro-apoptotic and anti-apoptotic Bcl2 proteins can interact with

each other forming heterodimers. This heterodimerization can inhibit each other's function. This binding occurs by the insertion of the BH3 region of the pro-apoptotic protein within the hydrophobic pocket of BH-1, BH-2, and BH-3 domain of anti-apoptotic proteins. It should be noted that besides BH-1, BH-2 and BH-3 domains BH-4 is responsible mainly for antiapoptotic activity whereas BH-3 regulates pro-apoptotic activity(Tsujimoto, 1998). It has been already discussed that the intrinsic pathway of apoptosis is mitochondria dependent where the permeability of mitochondrial outer membrane proteins triggers the release of cytochrome-C from the intermembrane space of mitochondria into the cytosol. Within cytosol cytochrome-C binds with Apaf-1 and then recruits initiator procaspase 9 forming apoptosome, activating initiator procaspase, and amplifying the signal (Plati et al., 2008). This pathway is tightly modulated by the ratio of pro-apoptotic and anti-apoptotic proteins. If this ratio is somehow altered, it leads to the development of many cancers. The overexpression of Bcl-xL is linked with Kaposi's sarcoma, colorectal adenocarcinoma, and multiple myeloma (Plati et al., 2008). In the colorectal adenocarcinoma overexpression of Bax is mainly observed (Wong, 2011). BH-3 domain performs pro-apoptotic function by interacting with other pro-apoptotic proteins via with other their BH-3 domain. The binding of Bax and Bak with other BH-3 domain-containing proteins induces conformational changes that facilitate the killing of the cell (Tsujimoto, 1998). Bid functions as a linker between extrinsic and intrinsic pathways. When the extrinsic pathway is turned on by binding of death ligand to a death receptor, initiator caspase 8 cleaves Bid and forms activated C terminal Bid fragment called t Bid. This t Bid then translocates into the mitochondria and induces the release of cytochrome C from mitochondria to cytosol activating the intrinsic pathway (Plati et al., 2008). It has been observed that Bad is regulated by phosphorylation and dephosphorylation. Under normal conditions Bad is phosphorylated by Akt. This phosphorylated Bad can't bind to Bak or Bax thus they do not induce apoptosis. But when death signal is present, the phosphate group pf Bad is removed, it, therefore, goes to interact with Bax or Bak, activating apoptosis (Tsujimoto, 1998).

4.2 p53 in Apoptosis:

p53, a tumor suppressor protein, regulates a key point in inducing apoptosis, cell cycle arrest, DNA repair processes. If a cell with a condition of irreparable DNA damage arises, p53 is activated and promotes cell cycle arrest, and induces the apoptotic death of the cell cycle checkpoint proteins, thereby preventing the damage to be passed onto the daughter generations. It has been observed that in most of the 50% of human cancers the p53 gene is mutated thus unable to turn on the apoptotic program and hence, the devastating effect of cancer appears. To participate in such processes, p53 itself should be tightly regulated. The overexpression of p53 is observed in many degenerative diseases such as sclerosis, arthritis and is also involved in stroke or cardiac arrest(Fridman & Lowe, 2003; Hassan et al., 2014). p53 shows its activity by transcribing many of its target genes. Structurally p53 contains three domains – an NH2 terminal acidic transactivation domain (TA domain), DNA binding domain, and COOH terminal oligomerization domain. The DNA binding domain is responsible for binding to its target gene for its transcription. The homo-tetramerization form of p53 is a functionally activated form that is achieved by oligomerization of the COOH domain of p53 (Ozaki & Nakagawara, 2011). p53 has a huge impact most importantly on apoptosis, regulation of cell cycle checkpoints. In normal cell conditions, p53 activity is lowered due to its binding to another ubiquitin-protein ligase MDM2. This MDM2 causes the destruction of p53 which set the lower level of p53 in the cell. When such abnormal condition i.e. DNA damage by ionizing radiation rises, ATM kinase recognizes this and phosphorylates p53. This phosphorylated p53 can't bind to MDM2 and thus can easily activate the transcription of its targets including DNA repair genes. After the completion of repair process the cell is now able to move further into the cell cycle. This activated form of p53

activates the transcription of p21 gene that mediates the destruction of G1/s cyclins inhibiting the cell cycle progression, thus providing the time of repairing the damage of the cell and preventing the accumulation of mutation leading to cancer (Elmore, 2007; Ozaki & Nakagawara, 2011). If the damage can't be repaired, p53 performs another function i.e. to induce the apoptosis of the damaged cell. p53 mainly stimulates pro-apoptotic proteins that include Bax and BH-3 domain-containing proteins Puma, Noxa, and Bid. In other words, it can be said that p53 increases the ratio of pro and anti-apoptotic proteins thereby, enhancing apoptosis. These genes contain p53 response elements to which the DNA binding domain of p53 can easily bind and begin its function (Fridman & Lowe, 2003). In the case of extrinsic pathway, p53 can directly activate the death receptor loci i.e. Fas or CD95 death receptor loci, and also the genes encoding Fas ligand. This makes the cell more sensitive to death receptor-ligand interaction, thus increasing the possibility of cell death. As it has been noticed that p53 can activate Bid it increases the connection between extrinsic and intrinsic pathways by acting as a linker. In addition to this p53 can activate the effector gene which transcribes Apaf1 that helps in the formation of apoptosome complex, initiating the intrinsic pathway cascade (Fridman & Lowe, 2003). Being a transcriptional activator p53 must be translocated into the nucleus for activating its targets. They contain nuclear pore complexes which bind to importin α/β, facilitating its entry inside the nucleus. If the α portion is removed or mutated somehow, p53 remains within the cytoplasm. Therefore, mainly importin α is necessary for translocation of p53 into the nucleus. It's very obvious to have an export signal when its function is over within the nucleus. This export signal is provided by Leu rich nuclear export signal recognized by Chromosomal region maintenance 1 (CRM1). Homo tetramers of p53 mask this export signal site that helps it to stay within the nucleus as long as it is functioning. The ubiquitination by MDM2 at the COOH terminal Lys rich region altered the tetramer complex, thereby unmasking the NES site and exporting it from the nucleus (Ozaki & Nakagawara, 2011).

4.3 Inhibitors of Apoptosis Proteins:

Apoptosis is also regulated by an important class of proteins called Inhibitors of Apoptosis proteins or IAPs. IAPs contain Baculovirus IAP repeat domain (BIR) by which they can interact with caspases. This interaction destroys caspases, so they are unable to amplify the death signal. There are different types of IAPs such as NAIP (BIRC1), c-IAP1 (BIRC2), c-IAP2 (BIRC3), etc. (Wong, 2011). In much human cancer overexpression of IAPs takes place that blocks unwanted cell death, promoting malignancy. Many types of IAPs bind to caspase 3, caspase 7 and block the pathways (Plati et al., 2008). In pancreatic cancer altered expression of IAP occurs and it makes the cancer cells resistant to chemotherapy. One IAP called Livin is overexpressed in melanoma and lymphoma. Another IAP called Survivin overexpressed in many cancers including breast, colon, lung, prostrate interact with caspase 3 and caspase 7, restricting their functions (Plati et al., 2008). In non-small cell lung carcinomas (NSCLCs) surviving and another IAP i.e. XIAP are overexpressed which ultimately blocks apoptosis machinery.

4.4 Alteration of Death Signaling Cascade:

The interaction of the death ligand with the death receptor generates a signaling cascade, destined to the death of the cell sequentially. CD95 (FAS/Apo1) death receptor and its CD95L belonging to the Tumor Necrosis Factor family is considered to initiate the death signaling mechanism mainly T cell receptor triggered apoptosis. Apart from that they also take part in the removal of virus-infected cells and cancer cells. So, they are very suitable for cancer therapy. Since they are all overexpressed in cells but their ex (Peter et al., 2015; Walczak & Krammer, 2000)pression is higher in the thymus, liver, kidney, and heart (Peter et al., 2015; Walczak & Krammer, 2000). Death receptors attached to membrane attract to death ligand present on cytotoxic T lymphocytes, killing each other. Dimerization of CD95 can't induce apoptosis. The conversion into trimeric form is

the only functional state of CD95 in the apoptotic pathway. Like other death receptors, CD95 also contains 80 amino acids long death domain that amplifies the death signal(Walczak & Krammer, 2000). When CD95L binds to the CD95 death receptor, the death domain of the death receptor recruits the adaptor protein FADD which in turn recruits procaspase 8 forming a death-inducing signaling complex (DISC). The procaspase is now activated within DISC and interacts with other executioner caspases and finally impart its effect on targets leading to death of the cell. Cancer cells become resistant to this CD95 death signaling. They have modified themselves in such a way that constant expression of CD95 on the membrane surface of cell fail to provide any death inducing effect on them (Peter et al., 2015). One mechanism includes the overexpression of c-FLIP (FLICE inhibitory protein). the c-FLIP expression can block the binding of procaspase 8 to DISC. In addition, this also causes reduced expression of procaspase 8 or FADD. Thus, cells are prevented from undergoing death. A higher amount of cFLIP is present in many colon cancers and also many prostate cancer cell lines PC-3 and DU-145 (Peter et al., 2015; Plati et al., 2008). In many cancer cells, the under-expression of Fas is also observed. In germinal center-derived B cell lymphomas, somatic mutation of Fas or silencing of Fas gene is recognized. Various tumor epithelium cells of many human cancers express CD95L which has an effect of upregulating cancer formation (Plati et al., 2008). Through IL10, prostaglandin E2 vascular endothelial growth factor A the overexpression of membrane-bound CD95L is present on many tumor cells CD95 can be in two forms. one is soluble and another one is membrane-bound. Membrane-bound is generally considered for apoptotic activity and soluble form is known for anti-apoptotic activity (Peter et al., 2015). Based on the activities CD95 is involved in many therapeutic strategies. Different strategies that induce the expression of procaspase 8 can again transform the cancer cells to become sensitive to death-inducing apoptosis. Many metabolic inhibitors are also used to lower the expression of cFLIP that make the therapeutic strategies to respond to cancer cells. Demethylation, gene transfer, interferon-mediated transcriptional activation can cause the expression of procaspase 8 to rise which can enhance the sensitization of cancer cells towards death receptors and apoptosis (Plati et al., 2008).

5.0 Apoptosis in Lung Cancer:

Lung cancer is one of the major threats occurring worldwide. About more than 1 million deaths occur due to lung cancer per year and 1.4 million people are diagnosed every year (Pore et al., 2013). Human lung cancer comprises two types small cell lung cancer (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC is again divided into subgroups – adenocarcinoma, squamous cell carcinoma, and large cell lung cancer. Non-smokers usually suffer from adenocarcinoma and smoking is mainly linked with SCLC. SCLC are neuroendocrine tumors and the difference in biology, response to therapy, and prognosis exist between SCLC and NSCLC (Pore et al., 2013; Shivapurkar et al., 2003). In most cases, it has been reported that without symptoms or very few symptoms of lung cancers appear. So the patients are in a very advanced stage for diagnosis of cancer which increases the risk of death (Pore et al., 2013). Caspase 8 and caspase 10 are not expressed in SCLC meaning that the alteration of the death receptor signaling extrinsic pathway is responsible for developing lung cancer. Promoter methylation, point mutation, and also homozygous deletion affect the reduced expression of tumor suppressor genes. In many cases, the p53 gene is mainly inactivated due to point mutation but in some recent studies, it has been noted that gene inactivation takes place by methylation of prompter genes that are normally unmethylated in normal cases. CpG sites of CpG islands of most of the cancers are primary targets for methylation that results in transcriptional silencing. Methylation does not cause the changes of the nucleotide sequences and by applying demethylating agent methyl groups can be removed from the methylated nucleotide sequences making it reversible. Various pro-apoptotic genes such as apaf1, caspase 8 , death associated protein kinase (DAP) and components of the p53 pathway are downregulated by

methylation (Shivapurkar et al., 2003). In high grade and low-grade neuroendocrine SCLC caspase 8 expression is absent but not in NSCLC that lack the neuroendocrine characteristics. Methylation is mainly involved for gene silencing in SCLC, although other methods also exist. But methylation and gene silencing are not present in NSCLC (Shivapurkar et al., 2003).Another important regulator in lung cancer is death-associated protein kinase or DAP kinase. DAP kinase belonging to the serine-threonine protein kinase family has the pro-apoptotic activity consisting of five types. The N terminal region of these kinases share the homology to all the family members but the difference exists in the C terminal region that links each kinase to each signal transduction pathway. DAP kinases are involved in both death receptor and mitochondrial-dependent apoptotic pathways. In many cancer loss of expression of DAP kinase causes reduced expression in p53 dependent pathways. DAP kinases having multidomain structures have specific tissue localization such as DAP kinase is linked with actin filaments pf cytoskeleton. In lung cancer, DAP kinase is inactivated by methylation and other approaches are also involved. In NSCLC methylation is associated with advanced tumor size and lymph node development without any exposure to tobacco. From the bronchial epithelium of smokers methylation can be detected (Shivapurkar et al., 2003). Bcl2 family proteins are another regulator of apoptosis. Bcl2 is expressed higher in SCLC than in NSCLC and squamous cell carcinoma shows higher expression of these proteins than adenocarcinoma of NSCLC type. Bax. Family of Bcl2 protein show pro-apoptotic activity which indicates that a ratio of Bcl2:Bax destines the fate of the cell from tumor resistance to apoptosis. In the case of neuroendocrine lung tumors, an inverse relationship is followed in the ratio of low-grade and high-grade tumors with predominant expression of Bax in the first type and predominant expression in the second type. The highest level of Bcl2: Bax ratio is observed in p53 mutant type (Shivapurkar et al., 2003). IAPs are considered as another mediator of lung cancer. The interaction of IAPs with initiator and effector caspase inhibits the proteolytic maturation of caspases specially caspase 3 and caspase 7. So, the apoptotic pathways are never initiated. Survivin, an IAP, is thought to be responsible for lung cancer. Survivin contains a single BIR domain and is localized to components of the mitotic spindle. It is highly expressed in fetal and embryonic tissue and is not present in an adult differentiated tissue. Its expression is greatly observed in the NSCLC type (Shivapurkar et al., 2003). Smoking is one of the risk factors for lung cancers. Many studies revealed that tobacco-taking patients have a high frequency of p53 mutation than non-tobacco-taking patients. P53 mutation provides a risk factor because it acts as a tumor suppressor gene preventing cancer development (Pore et al., 2013). G: C to T: A transversion mutation is present greatly in smokers whereas it is rarely found in non-smokers. It has been reported that transversion and deletion account for 80% of smoking women while transition mutations are observed about 80% in tobacco-free adenocarcinoma women (Liu et al., 2017). p53 mutation appears around 50% in NSCLC and about 70% in SCLC (Shivapurkar et al., 2003).

6.0 Apoptosis in Breast Cancer:

Breast cancer is one of the most common types of cancer in women found worldwide. About 18% of cancers in a woman are breast cancer-related. Over the past few years the mortality rate has been decreased to about 25% due to the extensive research concerned with chemotherapy, treatment, resistance to various treatments in breast cancer patients (Parton et al., 2001). The mammary gland is such a kind of organ system in mammals that achieves its complete maturation and morphological development in two physiological states, puberty, and pregnancy. Normal breast development is simply a balance between cell proliferation and cell death. Excessive cell proliferation and reduced apoptosis cause tumor growth which often gets to become malignant. The growth and maturation of the mammary gland comprise sequential stages which are regulated by many steroid hormones and other growth factors. The imbalance of apoptotic

regulatory proteins Bcl2 may be influenced by regulatory hormones estrogen and progesterone (Kumar et al., 2000; Parton et al., 2001).Terminal cells of the developing mammary duct remain in a quiescent stage until pregnancy begins. At the onset of pregnancy epithelial cells start to proliferate rapidly giving additional ductal branching and lobuloalveolar growth. During pregnancy and lactation, these alveoli become fully matured and form terminal end bud that is the major site of milk production at lactation. After lactation stops, a massive restructuring and apoptosis help the gland back to its primary ductal structures. A repeated cycle of resting-state with menstruation is followed in the absence of pregnancy until a gradual senile involution with menopause begins (Kumar et al., 2000; Parton et al., 2001). Therefore, proliferation and apoptosis are essential for normal mammary gland development. If the apoptotic activity is upregulated or downregulated, mutations accumulate gradually, developing into tumorous growth (Parton et al., 2001). The pro-apoptotic and anti-apoptotic members of the Bcl2 family are critical components for mammary gland development. The ratio of Bax, pro-apoptotic protein, and Bcl-x, anti-apoptotic protein remain evenly distributed during mammary gland development. But, the expression of pro-apoptotic protein at the time of late pregnancy and lactation increases, and they remain expressed during rapid apoptotic involution. Another Bcl2 anti-apoptotic protein Bcl-w is expressed in pregnancy and lactation but they are downregulated at the onset of apoptosis (Kumar et al., 2000). In humans, Bcl2 is expressed in almost about 80% of cases and their function is also linked with estrogen and progesterone giving good prognostic features. This association between apoptosis inhibitor and good prognostic features is validated by the improved survival of patients with Bcl2 positive tumors compared with that of Bcl2 negative (Parton et al., 2001). p53 mutation is also associated with breast cancer. Loss of heterozygosity of the p53 gene is mainly responsible for the mutation and development of cancerous properties. Many studies revealed that p53 mutations are increasingly present in BRACA1 and BRAC2 mutation carriers of breast cancer. In medullary breast cancer, type p53 mutation is present in almost 100% of cases. BRACA 1 gene mutation is mainly associated with medullary breast cancer (Gasco et al., 2002). In these cases, BRACA 1 gets mutated due to the methylation-dependent gene silencing process. However, in addition to these genes, other genes are also mutated, leading to breast cancer. One of these genes is called ATM which provides a strong correlation with p53. Patients having ATM mutations are much more susceptible to breast cancer than the normal one. If ATM gets mutated, a lowering function of p53 is also observed, sometimes having loss of heterozygosity. Another gene responsible for p53 dysfunction is Chk2. If Chk2 is mutated, then upon ionizing radiation Chk2 can't phosphorylate p53 inhibiting its function. Another factor responsible for p53 mutation is Mdm2. Overexpression of Mdm2 also correlates with the reduced activity of p53. But this case rarely occurs in breast cancer cells. A completely different class of proteins acting as the cofactor for p53 function is apoptosis stimulating protein of p53 (ASPP). There are two classes of this proteins designated as ASPP1 and ASPP2 encoded by separate genes. Expression of either ASPP1 or ASPP2 stimulates the apoptosis inducing activity of p53 thereby enhancing the expression of pro-apoptotic proteins such as Bax but it has very little effect on p21 gene. In primary breast cancer lacking p53 mutation the activity of ASPP1 and ASPP2 are greatly reduced (Gasco et al., 2002). One IAP called Survivininteracts with caspase 3 and caspase 7 and inhibit their function thus, leading to block the apoptotic machinery. On the other hand, nitric oxide induces the activity of caspase 1, 3 and 6, mitochondrial pathway and inducing the rate of apoptosis. Flavopiridol is used in breast cancer therapy that induces the apoptosis and blocks the tumor growth. It actually activates Caspase 3 activity which is required to amplify the apoptosis signal (Gasco et al., 2002).

7.0 Apoptosis in Neurodegenerative Disorder:

While most of the cells in a body performs effective proliferative mechanism and undergoes

programmed cell death or apoptosis, neurons survive usually from this pathway throughout their lifetime because they play some crucial roles in neuronal cascade such as motor neurons connecting to the skeletal muscle and helps in the restoring long-lived memory to that region of the brain that have this kind of function, so that they have to survive through death signals (Mattson, 2000). During the development of the central and peripheral nervous system, many neurons undergo death program. Whether a neuron lives or is dead is determined by many signals that also include competition between a limited amount of neurotrophic factors secreted from target cells and the activated receptor for excitatory neurotransmitter glutamate (Mattson, 2000). In the case of overproduction of neurons, some neurons may undergo death which is considered a normal process and it also provides enough neurons that can easily comprise a neuronal circuit. But if this program is somehow altered i.e. if the huge amount of cells undergo apoptosis then people may survive from many neurodegenerative injuries and also diseases such as Alzheimer's disease, Parkinson's, Huntington's diseases, etc. In neuronal cells, apoptosis can be induced by many signals. One of such signals includes the absence or low level of neurotrophic factors that can trigger neuronal cell death during nervous system development and also in neurodegenerative disorders. Another factor includes the overactivation of excitatory neurotransmitter receptor i.e. the receptor for glutamate which is associated with many neurodegenerative conditions such as stroke, trauma. Oxidative damage that includes the excess presence of free radicals may damage protein, lipids, nucleic acids, presenting another signal for neurodegenerative diseases. Some environmental toxins can also cause apoptosis affecting brain damage and behavioral disturbances (Mattson, 2000). Bcl2 proteins also regulate apoptosis in neuronal cells like other cells of an organism. Overexpression of Bcl2 protein makes a cell resistant against apoptosis that is linked with Alzheimer's, stroke, and other disorders. In many cases, the absence of Bax can also enhance apoptosis.

7.1 Alzheimer's Disease:

One of the most common types of human neurodegenerative disorder is Alzheimer's disease characterized by the inability of proper recognition and emotional and behavioral disturbances which are associated with synaptic degeneration and neuronal death in limbic structures i.e. hippocampus and amygdala and the associated region of the cerebral cortex (Mattson, 2000). The presence of senile plaques and neurofibrillary tangles (NFTs) are prominent features of Alzheimer's disease. Senile plaques comprise extracellular amyloid β protein, dystrophic neuronal processes, and reactive glia and NFTs contain intracellular lesions of filamentous aggregates of the microtubule-associated protein tau (Dickson, 2004). The disease is defined by the accumulation of amyloid β plaques formed by the accumulation of amyloid β peptides that are processed by proteolytic cleavage of amyloid precursor protein (APP).

Excessive DNA damage, altered caspase function, disrupted the balance of apoptosis regulatory Bcl2 family members in neuronal regions are associated with amyloid deposition in this disease.Peroxidation of membrane lipid by amyloid β sensitizes the neuronal cells to death cascade. This causes the impairment of ion motive ATPase and glucose and glutamate transporter which finally has an effect on membrane depolarization, ATP depletion, abnormally controlled calcium influx and mitochondrial dysfunction. Therefore antioxidants that have the function of reducing lipid peroxidation and drugs that helps in the stabilization of calcium homeostasis can be used in protecting the neuronal cells from apoptosis (Mattson, 2000) . Caspase 3 is involved in APP cleavage and it, in turn, mediates the cleavage of tau at its C terminal domain which results in the formation of tau-hyperphosphorylation and accumulation of NFTs. Caspase 3 can be induced by amyloid β which again causes the abnormal processing pattern of tau protein (Favaloro et al., 2012). γ secretase cleavage of APP produces membrane-associated carboxy-terminal fragments that can induce apoptosis by APP-binding protein

called APP BP1, driving neurons into the mitotic cycle and ending into apoptosis (Mattson, 2000). Alzheimer's disease can also be inherited in an autosomal dominant manner if the mutation occurs in three critical genes- one gene encoding APP and another two encoding presenilins 1 and 2. When a mutation in APP encoded gene occurs, alteration of processing of APP takes place. This causes the increasing level of amyloid β, characteristics of this disease. Presenilin mutation causes the increasing γ secretase cleavage of APP which results in the accumulation of amyloid β that ultimately destines a cell towards death(Mattson, 2000). APP can also be cleaved by caspase 6 and this N terminal APP fragments acts as a substrate for death receptor 6. When this death receptor 6 becomes activated it mediates axonal degeneration (Favaloro et al., 2012).

7.2 Parkinson's Disease:

Parkinson's disease is another kind of neurodegenerative disorder that is characterized by a movement disorder, tremors, and rigidity. This disease condition begins due to a lack of neurotransmitter dopamine caused by the damage of dopaminergic neurons in the substantia nigra region of the brain. It is an age-related and sporadic disease and in about 5% of cases it is familial (Favaloro et al., 2012; Lev et al., 2003). Oxidative stress generated by toxic metabolites of the domain is considered as the basic death sensitivity of dopaminergic neurons. Exposure to dopamine, 6-hydroxydopamine, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) involve biochemical, morphological changes that are typical characteristics of neuronal apoptosis cell death. The oxidative stress occurs due to the generation of ROS during normal dopamine metabolism either by autooxidation or by the action of monoamine oxidase in many culture studies domains induced apoptosis can be blocked by applying many antioxidants such as N-acetyl-L-cysteine and dithiothreitol. This protection is associated with decreased function of Caspase 3 and Caspase 9 though to involve in dopamine-induced apoptosis by producing ROS (Lev et al., 2003). 6-OHDA is another type of dopaminergic neurotoxin that causes the activation of caspases and also induces the activity of pro-apoptotic members of Bcl2 family such as Bax. The degeneration of dopaminergic neurons also takes place by MPTP neurotoxin. The function of MPTP is determined by many factors such as administration mode, age of the animal, and dosage. It has been observed that in young mice MPTP causes the damage of dopaminergic terminals in the stratum but the degeneration of dopaminergic neurons in the substantia nigra occurs due to the chronic administration of MPTP. MPTP is a mitochondrial toxin that achieve its destructive feature by converting into MPP+ by the action of the enzyme monoamine oxidase. MPP+ then is taken up by dopamine transporter for entry into the dopaminergic neurons in the substantia nigra. It then kills these cells by inhibiting mitochondrial complex 1 activity thereby inducing the initiation of the apoptotic program (Lev et al., 2003).

8.0 Conclusion

Apoptosis is considered an important regulatory death program cascade that is responsible for the proper development of an organism and characterized by morphological and biochemical changes of cells where caspases play a critical role. It is a highly controlled process dependent upon various factors such as Bcl2 proteins, p53, IAPs and so on which if gets altered, leads to many severe situations. This fascinating feature of apoptosis grabs the attention of scientists and prolonged research clarifies many aspects of this cell death program. Lung cancer, prostate cancer, breast cancer, etc. are one of the resultant effects of dysregulation of apoptosis. The alteration of the apoptotic pathway, as well as the imbalance of regulatory molecules, can generate severe to fatal neurodegenerative disorders such as Alzheimer's, Parkinson's and even stroke, and many more. The death signaling cascade performs the primary factor for a cell destined to become an apoptotic cell. In cancer cells, maintenance of apoptosis is very much crucial because it helps to remove the unwanted cells preventing the development of tumors. In cancer cells targeting apoptosis is a new treatment strategy that further needs to be improved by extensive research in the coming

years. Understanding the basic mechanism of apoptosis at the molecular level provides the proper identification of the cause of the diseases and enhances the therapeutic strategy.

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