International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 04 Issue: 09 | Sept -2020 ISSN: 2582-3930

Review: Cancer and Programmed Cell Death (PCD)

Zafer Ansari[1], Medha Petkar[2]

[1]*Biotechnology Department, Kolhapur Institute of Technology, College of engineering (Autonomous), Kolhapur, Maharashtra*

[2]*Biotechnology Department, Kolhapur Institute of Technology, College of engineering (Autonomous), Kolhapur, Maharashtra*

Abstract:

Cancer is the result of disruption in the rule or process that a normal cell generally follows regulated cell division, differentiation and apoptosis, and this rule is not followed by a cancer or tumor cell. When a cell lost its control over regulated division and differentiation, escapes apoptosis and becomes cancerous in nature as it has the ability to disrupt the normal balance of the body or a particular area of the body. Depending on the property of a tumor cell it can be benign or malignant. Programmed cell death (PCD) is the key to overcome the benign or malignant tumor in the body of a human being. A normal human body generates 10-100 billion of cells everyday and same numbers of cells die accordingly to maintain the homeostasis of our body. The cells that are replaced by new ones are mostly damaged, infected (bacterial or viral), & senescent. This replacement of cells is done by a programmed mechanism of action that leads to the death of the cells and is known as "programmed cell death (PCD)"

Key words: Cancer, Apoptosis, Programmed cell death, senescent

INTRODUCTION:

Cancer can be described as a mass of cells that are undifferentiated, lost their normal cellular functions and results in uncontrollable growth of cells. This uncontrollable growth starts from a single normal body cell that lost its normal functions that is resulted due to genetic mutations in normal cells [2]. Mutation leads to overexpression of certain proto-oncogenes that leads to its overexpression and continuous cell division [1]. Cancer development starts from single cell that leads to invasion of surrounding tissues and organs and further leads to organ failure and health issues. This undifferentiated mass of cells is termed as 'tumor', resulted due to continuous cell division [2]. Tumors can be harmful and non-harmful as well to some extent, based on this tumors are classified. There are two types of tumors depending upon their physiological state:

Classification of tumors:

i. Benign tumor:
It's a mass of cells that does not invade surrounding tissues and organs, harmless and can be removed by surgery easily. They are slow dividing,

encapsulated and do not metastasize. These are non-cancerous in nature and termed as 'only tumor' [1].

ii. Malignant tumor:
These are fast dividing cells and invade surrounding tissues and organs that further leads to organ failure. These are harmful tumors, cancerous in nature and very rapidly dividing. They cannot be cured or treated easily, because they are malignant and metastasize so cannot be removed by multiple surgeries as well [2]

The length of a tumor ranges from millimeter (mm) to centimeter (cm) and the weight of it ranges from milligram (mg) to kilogram (kg) [2].

Normal cell proliferation is density dependent and stops when reaches to a certain density, whereas the cancer cell does not show the characteristic. Normal cell would die after certain number of cell division. Cancer cell can divide infinitely and thus does not undergo apoptosis. Cancer cell can synthesize its own growth factor and can regulate its own proliferation. Cancer cell also has the ability to promote new blood vessels for the developing tumor and is called angiogenesis. The genes that are involved in causation of cancer by genetic or epigenetic changes are called cancer-critical genes. This gene contributes to the transformation of normal cell into cancerous cell [1]. These genes are mainly control function like cell cycle progression, cell cycle arrest, DNA repair, cell death, etc. Cancer genes arise from a gain of function of a gene, or loss of function of a gene. When a gain of mutation transforms a cell toward cancer, it is called proto-oncogene and when a loss of function mutation transforms a cell toward cancer is called tumor [2]. Proto-oncogene control cell growth, cell division and accelerates it in cancer cell by involving growth factors, growth factor receptors, transcription factors, etc. and reduces the sensitivity to cell death. Increase in expression of proto-oncogene results in oncogene [1].

Cancer is one of the most leading lethal diseases in the world. Lung cancer and Breast cancer are the most common cancer found, followed by colorectal cancer. Lung cancer is very common and lethal to men, whereas breast cancer is common in women [1]. Major cause of cancer is genetic mutation that leads to activation of proto-oncogenes; mutation is majorly caused by exposure to UV radiation, cellular stress, bacterial infection and viral infection. Most common type of viral infection is Human papillomavirus (HPV) that causes cervical cancer mostly in females [2]. Cancer can be treated by radiation therapy, chemotherapy, surgery, hormonal therapy and gene therapy. Radiation therapy is one of the most common type of cancer treatment in which the patient is exposed to x-rays that kills cancerous cells, while during chemotherapy it is a chemical process also used to inhibit cellular division using drugs in appropriate dosage by targeting cellular growth receptors like Tyrosine Kinase Receptor (TKR) or proteins involved in cell division like P53 and Cyclin Dependent Kinase (CDK). Surgery for cancer removal always a better option but accompanied by greatest chance of spreading to other parts of the body. There are total four stages of cancer, till 1st and 2nd stages it is curable but during 3rd stage the percentage of cure is less than 50% and at 4th stage the percentage of cure is 5-10% because it's the last stage of cancer [1].

1. Programmed cell death (PCD):

During embryo development when the body is shaping itself many cells undergo cell death [5]. This cell death is mediated with the help of macrophages that engulf the dead cells by phagocytosis. This eradication in humans is done by two phenomena: necrosis and apoptosis. Both of these mediate cell death under stress but by distinguish mechanism of action. Necrotic cells are referred to as damaged/injured cells which undergo autolysis, a condition in which the cells undergo complete destruction carried out by their own cellular enzymes stored in lysosomes, it is an inflammatory process [3]. Necrosis occurs by bacterial or viral infection to the cells which leads to autolysis, after autolysis the cells swell, plasma membranes ruptures, and the cellular components are released outside and these results in activation and response of immune system followed by phagocytosis through macrophages [4]. This activation of immune system involves production of white blood cells in bulk amount. Whereas on the other hand, in apoptosis the cell shrinks, the cell structure is abnormal and the chromosome is condensed and fragmented [7]. The cell death under physiological conditions is mainly mediated by apoptosis by activation of caspase cascade. After apoptosis, dead cells are phagocytosed by macrophage; it is a non-inflammatory process, because it does not release any inflammatory factors and engulfs the cell completely. The dead cell is engulfed swiftly and this process is silent and referred as 'clean cell death'. Sometimes the cell is not engulfed completely by macrophages, so they undergo secondary necrosis, hence the intracellular materials are released outside which act as a signal for activation and response of immune system [5].

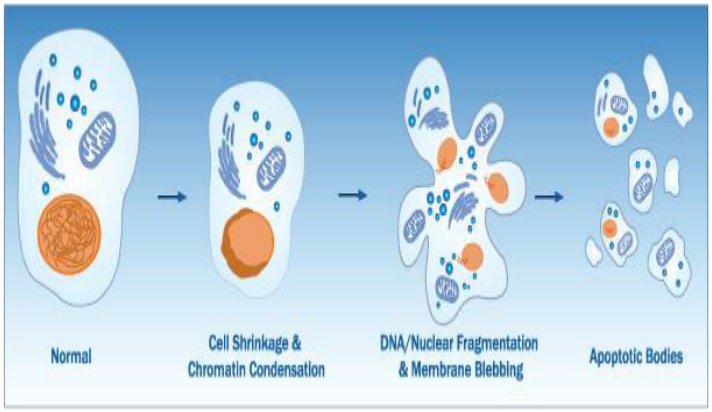

Fig 1: Schematic representation of a cell undergoing apoptosis

Diagram shows the steps of a normal cell undergoing apoptosis

1.1 Intrinsic pathway (IP):

Intrinsic pathway is also known mitochondrial mediated apoptosis, because mitochondrion is the target organelle during intrinsic pathway. This pathway is activated in many conditions such as DNA damage, upregulation of oncogenes, DNA-damaging molecules, drugs targeting cytoskeleton, loss of growth factor, etc. Activation of intrinsic pathway could be because of positive stimuli (toxins, viral invasions, and radiations) or negative stimuli (loss of growth signals or dysregulation of hormones) [6]. The process is overall upregulated by BCL-2 family member proteins. BH3-only protein is proapoptotic effector molecule that is upregulated transcriptionally during this pathway, this upregulated proteins activate Bax & Bak proteins which are inhibited by bcl-2 protein. Activated Bax & Bak oligomerize, and forms mitochondrial outer membrane permeabilization (MOMP). MOMP conducts permeabilization to mitochondria and results in release of cytochrome

c, SMAC and omi (HtrA2) [5], [6]. Free cytochrome c binds to Apaf-1 (apoptotic protease activating factor-1) that leads to formation of 'apoptosome' complex. SMAC and HtrA2 are a group of proapoptotic protein molecules that cleaves XIAP (X-linked inhibitor of apoptosis), XIAP is a member of IAPs (inhibitor of apoptosis) family, that inhibits the activation of caspase cascade. Further the apoptosome interacts with caspase-9, which activates itself by autocatalysis and followed by activation of caspase cascade. While HtrA2 after cleaving XIAP; starts cleaving cytoplasmic and cytoskeleton proteins, this result in complete shutdown of cellular metabolism and collapse of cytoskeleton [7]

1.2 Extrinsic pathway (EP):

As the name suggest, the extrinsic pathway is primarily mediated by cell death signaling from outside the cell through cellular transmembrane death receptors that belongs to the tumor necrosis factor (TNF), super-family of receptors. The induction of cell death signaling starts from the interaction between the ligands such as Fas ligand (Fas L) and TNF apoptosis inducing ligand (TRAIL) R1 to the transmembrane death receptors such as Fas receptor (Fas R) and TNF receptor (TNFR) respectively. This interaction of Fas ligand to its Fas receptor leads to assembly of death domain and is known as Fas associated death domain (FADD), while interaction with tumor necrosis factor receptor (TNFR) is followed by TNFR associated death domain (TRADD): both of these binding leads to pro-caspase-8 activation [6], [7]. Caspase-8 is activated autocatalytically by the formation of death inducing signal complex (DISC). Caspase-8 activation is followed by activation of caspase-3 which further activates inhibited endonuclease by cleaving the inhibitor molecule; cleavage of inhibitor leads to DNA fragmentation by endonuclease. Once caspase-8 is activated, simultaneously it also interacts with bid, this result in tbid (active form of bid), tbid is an intermediate molecule between extrinsic and intrinsic pathway and tbid further leads to activation of Bax and Bak to induce intrinsic pathway as well. But in some cases, cell death by extrinsic pathway is terminated by activation of pro-caspase-8 to caspase-8, further the triggered caspase-8 directly interacts with bid to induce intrinsic pathway, this is dependent and can be distinguished by the presence of X-linked inhibitor of apoptosis (XIAP) protein [8]. Extrinsic pathway can be blocked either by interaction of cFLIP to FADD, cFLIP is an apoptotic inhibitory protein that binds to FADD and blocking its activity, or the binding of toso protein to the activated caspase-8 [6].

2. Capsases:

ICE (IL-1β converting enzyme) is a protease that is responsible for the maturation of IL-1β (interleukin-1β). IL-1β is cytokines released by active macrophages that are processed to active form by proteolytic activity of caspase-1. CED-3 (cell death abnormal 3) is involved in programmed cell death in *C.elegans*, which is a homolog of human ICE [3]. ICE is a protease with histidine and cysteine residues in its active site, thus it is a cysteine protease and known as caspases. These proteases recognize at least five amino acid residues on its target protein and cleave the peptide bonds after aspartate [5]. Caspases are proteolytically inactive, but by the removal of two prodomains at the N-terminal generates an active form of caspase consisting of

two large and two small subunits [10]. Some caspases have same and some have different recognition sequences, but both cleave by different efficiency. Caspases in humans are classified in two groups: 1) caspases that mediate pyroptosis, are caspases 1, 4 & 5. 2) Caspases that participate in apoptosis are caspases 2, 3 & 6-10.

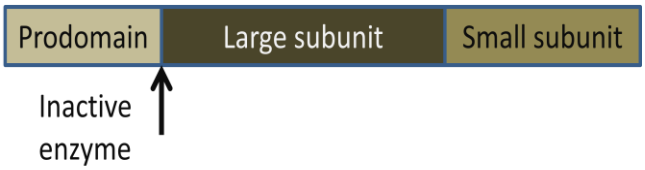

Fig 2: Domain organization of pro-caspase

Diagram represents the domain organization of pro-caspase. Pro-domain of pro-caspase is cleaved off by autocatalysis and activated to mediate apoptosis

3. DNA fragmentation:

The terminal process or wrapping up of cell death mechanism is done by DNA degradation. DNA fragmentation in apoptosis is processed by several endonucleases such as endonuclease G (Endo G), DNA fragmentation factor (DFF), and Apoptosis inducing factor (AIF). Only DFF is localized in nucleus, while AIF and Endo G are localized in mitochondria [9].

3.1 Caspase-dependent pathway:

DFF consist of two subunits: a 40kDa caspae-3 activated DNase CAD/DFF40 and a 45kDa inhibitor of CAD as ICAD/DFF45, and forms an ICAD/CAD complex (inactive form). During apoptosis caspase-3 cleaves ICAD from ICAD/CAD complex, which liberates CAD (active form) [10]. Active CAD breaks the double-stranded DNA by cleaving the linker regions and results in release of nucleosomes which can be characterized as 'DNA ladder' during Agarose gel electrophoresis (AGE). ICAD/CAD complex forms heterodimer and located in nucleus due to existence of nuclear localization signal at the C-termini of ICAD and CAD. ICAD act as a chaperone during synthesis of CAD and post translation forms heterodimer with CAD that inhibits its endonuclease activity [8].

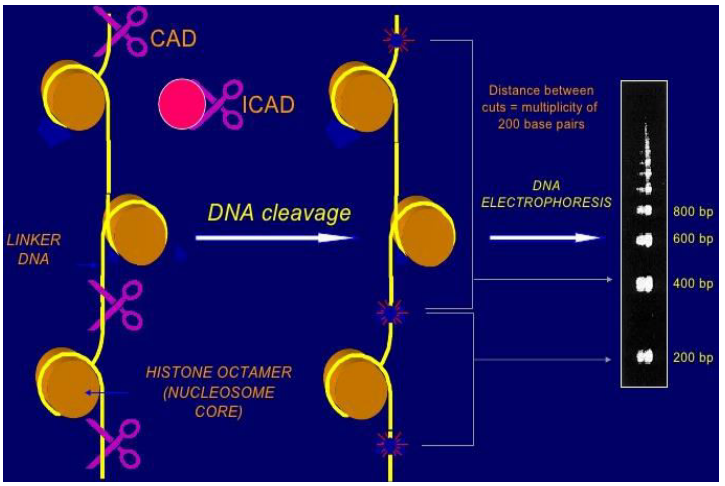

Fig 3: Caspase-dependent DNA fragmentation

The diagram represents the formation of nucleosomes from chromosomes by CAD endonucleases

3.2 Caspase-independent pathway:

Endo G is a pro-apoptotic protein that is situated in the inter-membrane space of mitochondria. It is located in mitochondria due to the presence of mitochondrial localization signal at their N-termini. By studies, most probably the N-terminal region is embedded in the inter-membrane space of mitochondria. During oxidative stress, it is cleaved from N-terminal and released by mitochondria and translocated to nucleus, where it

degrades the chromosomes by cleaving the linker DNA to generate nucleosomes. AIF is a mitochondrial falvoprotein, plays an essential role for oxidoreductase in a non-apoptotic cell [8]. AIF also escapes from mitochondria and transferred to nucleus, where it influences chromatin condensation and induces DNA cleavage into high molecular mass band fragments through other nucleases and does not take part in DNA fragmentation. Endo G and DFF mediate DNA fragmentation is a counter attack to oxidative stress only and carried out strictly in a caspase-independent manner. Simultaneously, HtrA2 is released from mitochondria and enters cytosol, there it activates transcription factor P73, further this leads to activation of pro-apoptotic genes such as Bax and Bak [6]. Once Bax and Bak are activated, they oligomerize to form mitochondrial outer membrane permeabilization (MOMP) complex, MOMP releases cytochrome c [7]. While Endo G and AIF mediate DNA fragmentation and complete shutdown of cellular metabolism.

CONCLUSION:

Cancer is one of the most leading and lethal disease all around the world, especially USA. Lung cancer and breast cancer is the most types of cancer all around the world in men and women respectively. In this review we have been trying to enlighten few hallmarks of cancer since it s becoming leading lethal disease worldwide. Simultaneously we have been trying to highlight some important points of Programmed cell death (PCD), PCD is a type of immune response against senescent, damaged & mutated cells of the body, before a normal cell is converted to cancerous cell due to mutation caused by DNA damage, viral infection, bacterial infection, activation of proto-oncogene, etc. Therefore, it can be concluded that cancer is one of the most concerning disease and programmed cell death has to be studied in details to generate a response against tumors

ACKNOWLEDGEMENT:

I would like to thank my batch mates Mr. Mayur Desai, Mr. Prathamesh Suryawanshi and Mrs. Apurva Karve (Department of Biotechnology, KIT's college of Engineering (Autonomous), Kolhapur, Maharashtra, India). I am grateful to my institution's faculty and HOD (Department of Biotechnology, KIT's college of Engineering (Autonomous), Kolhapur, Maharashtra, India) for their proper step by step guidance throughout.

REFERENCES:

1. Hanahan, D. and Weinberg, R.A., 2000. The hallmarks of cancer. *cell*, *100*(1), pp.57-70.
2. Dhama, K., Chauhan, R.S. and Singhal, L., 2005. Anti-cancer activity of cow urine: current status and future directions. *International Journal of Cow Science*, *1*(2), pp.1-25.
3. Pantsar, T., 2019. The current understanding of KRAS protein structure and

dynamics. *Computational and Structural Biotechnology Journal*.

4. Boland, M.L., Chourasia, A.H. and Macleod, K.F., 2013. Mitochondrial dysfunction in cancer. *Frontiers in oncology*, *3*, p.292.
5. Strasser, A., O'Connor, L. and Dixit, V.M., 2000. Apoptosis signaling. *Annual review of biochemistry*, *69*(1), pp.217-245.
6. Reed, J.C., 2000. Mechanisms of apoptosis. *The American journal of pathology*, *157*(5), pp.1415-1430.
7. Nagata, S., 2018. Apoptosis and clearance of apoptotic cells. *Annual review of immunology*, *36*, pp.489-517.
8. Kiraz, Y., Adan, A., Yandim, M.K. and Baran, Y., 2016. Major apoptotic mechanisms and genes involved in apoptosis. *Tumor Biology*, *37*(7), pp.8471-8486.
9. Pfeffer, C.M. and Singh, A.T., 2018. Apoptosis: a target for anticancer therapy. *International journal of molecular sciences*, *19*(2), p.448.
10. Kitazumi, I. and Tsukahara, M., 2011. Regulation of DNA fragmentation: the role of caspases and phosphorylation. *The FEBS journal*, *278*(3), pp.427-441.
11. Nowsheen, S. and Yang, E.S., 2012. The intersection between DNA damage response and cell death pathways. *Experimental oncology*, *34*(3), p.243.
12. Liu, X., Li, P., Widlak, P., Zou, H., Luo, X., Garrard, W.T. and Wang, X., 1998. The 40-kDa subunit of DNA fragmentation factor induces DNA fragmentation and chromatin condensation during apoptosis. *Proceedings of the National Academy of Sciences*, *95*(15), pp.8461-8466.
13. Nagata, S., 2000. Apoptotic DNA fragmentation. *Experimental cell research*, *256*(1), pp.12-18.
14. Hui, H., Dotta, F., Mario, U.D. and Perfetti, R., 2004. Role of caspases in the regulation of apoptotic pancreatic islet beta-cells death. *Journal of cellular physiology*, *200*(2), pp.177-200.