

Apoptosis: Molecular Basis Of Programmed Cell Death And Its Role In Cancer

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Abstract

Our somatic cells are reproduced by the process of mitosis and nearly death of all of them will be by apoptosis, a physiological route of cellular suicide. Cancers can crop up when imbalance of this process occurs, by an increased cell proliferation or a decreased cell death. Our information about the mechanisms of apoptosis has improved perceptions about origin and progress of some cancers. In few cases resistance to apoptosis may explain the cause of failure of cancer therapies. With the knowledge of apoptotic mechanisms, the treatment plans are developing by promoting apoptosis of cancer cells and by limiting death of normal cells. The goal of this review is to propose a broad summary of current information on apoptosis, its role in cancer and role of some proteins like caspases, Bcl-2, IAP, p53 in apoptosis.

Keywords – Apoptosis, caspases, Bcl-2, IAP, p53, cancer.

INTRODUCTION

All Cell Deaths Are Not Physiological & All Cell Deaths Are Not Pathological.

Apoptosis, a programmed cell death.

Apoptosis was mainly described by its structural changes like cell shrinkage, membrane blebbing, chromatin condensation and nuclear fragmentation. (1-4) The recognition of apoptosis as a gene-mediated program & it is having importance in understanding the developmental biology and tissue homeostasis, that is number of cells regulated by the factors influencing cell division as well as those controlling survival, differentiation & programmed cell death. The genetic foundation for apoptosis implies that cell death can be disrupted by mutation. Defective apoptotic pathways are said to be having role in various diseases ranging from neurodegenerative diseases to malignant disorders. (5,6)

Expanded apoptosis was seen in tumor treated with radioactivity and those treated with cytotoxins, mentioned that therapies that expanded the pace of apoptosis could be utilized to treat malignancies.(7)

Recent information about the bcl-2 quality, which is frequently moved in follicular lymphoma, encoded as cell demise inhibitory protein. (8) When bcl-2 was added in cells in tissue culture, it not only protected them from apoptosis also help in opposing multidrug effect.(9,10) This shows that apoptosis inhibitory qualities of bcl-2. Thus it causes not only cell injury but also decides the reaction to treatment. Thus, when control of apoptosis, by Bcl-2 for instance, is joined with development of stimulatory oncogene like c-myc cancer grows very quickly.(11)

Apoptosis -- A Common Response To Cell Stress

Apoptosis is a commonly induced by cell stress. (12) Cell physiology is monitored by cell itself in many aspect. Any noxious agent, capable of killing a cell will cause physiological changes when given at certain dose. The cell after detecting it will undergo some kind of stress response. In such situation some protective responses, such as production of heat shock proteins may occur to protect the cell, but other responses such as initiation of the apoptotic process, enhances cell death process. So if the drug is having cytotoxic action, it can be utilized for therapeutic purpose in cancer by inducing apoptosis of cancer cells.

Not only drugs, but many other factors can disturb cell physiology and induce apoptotic response. Changes in genetic expression, overexpression of genes and expression of mutant genes are also responsible for apoptosis. The oncogene like c-*myc* can stimulate apoptosis both when it is overexpressed or when its expression is reduced causes cancer. (13,14,15)

Mechanisms Of Apoptosis

It is evident that demise of the cell is eminent if process necessary for their survival gets obliterated. Cell bear such mechanisms whose physiological role is to cause their own death. One such physiological mechanism is termed apoptosis or programmed cell death. Cells undergoing this process classically shows characteristic structural changes.

Generally, apoptotic cells shrink, their chromatin condenses around the margins of the nucleus later on cell is engulfed by another cell. Biochemical indicators of apoptosis include activation of proteases called as caspases, cleavage of proteins and DNA and exposure of phosphatidylserine on the cell surface. Though all these events helps in identification of apoptotic cells, it is essential to note that they may occur in some cells that have initiated the apoptosis process and are going to die may not show any of such changes. (16)

Although it is easy to identify dead cell, it is difficult to determine the living cell. The gold standard for this is loss of ability to reproduce, to regenerate similar cell.(17)

Important Biochemical Mechanisms In Apoptosis

The main event that causes programmed cell death is still a debatable topic. Some researchers are of opinion that caspase activation turn out to be the crucial event in apoptosis, some currently believe that the mitochondrial catastrophe due to loss of cytochrome c from the mitochondrial intermembrane space. (18,19)

The protein caspase 9 (*Cysteiny aspartate specific proteases*) can be activated by Apaf-1, an adaptor protein. Apaf-1 is activated by cytochrome c which is released from the mitochondria.(20) Apaf-1 proteins then form a multi-subunit complex with caspase 9 termed as 'apoptosome' in which caspase 9 becomes proteolytically active.(21) Caspase 9 can cleave and activate other caspases such as caspase 3, which cleaves many proteins within the cell, including ICAD, an inhibitor of an

endonuclease (CAD) that cleaves the cell DNA, (22) which can be spotted as the classical ladder pattern by electrophoresis. (23,24)

The other apoptotic pathway that is controlled by certain members of the tumor necrosis factor (TNF) receptor family, usually named as 'death receptors'. In this pathway, when receptors such as TNF receptor 2, CD95 (Fas/APO-1) and TRAIL receptors form ligand, their cytoplasmic domains recruit the adaptor protein FADD, which in turn recruits and activates caspase 8 and caspase 10. (25,26) Even though secondary damage to the mitochondria can be caused by activation of these caspases, apoptosis can occur independent of the mitochondria. (27,28)

Apoptosis Is Regulated By Bcl-2 Family Members

Cells having other apoptotic proteins, collectively called as the Bcl-2 family, but none of these proteins interacts directly with Apaf-1. (29) It is known that Bcl-2 family members, including Bcl-2 itself, Mcl-1, Bcl-x and Bcl-w can inhibit cell death but exact mode of action is not known. (30)

In addition to the anti-apoptotic Bcl-2 family associates and the pro-apoptotic family associates Bax and Bak, there is a third subfamily of Bcl-2-like proteins known as 'BH3-only' proteins. (31) These are pro-apoptotic proteins. BH3-only proteins such as Bim, PUMA, Bid and Bad can bind to anti-apoptotic Bcl-2 family members such as Bcl-2, Mcl-1, Bcl-w and Bcl-x, but exact mode of action leading to activation of Bax and Bak remains unknown.

The BH3-only proteins are organized by transcription, phosphorylation, sequestration and cleavage. For example, the tumor suppressor gene *p53* induces apoptosis by transcriptionally activating the gene for PUMA. (32,33) Bcl-2 and Bim are kept inactive in healthy cells by sequestration on microtubules and myosin, respectively. (34,35) Bid is activated following cleavage by caspase 8 and Bad is regulated by phosphorylation. (36,37)

Follicular Lymphoma And Bcl-2

The most common carcinoma of the blood cells is the follicular lymphoma (B cell neoplasia). Bcl-2 can check apoptosis of cells lack of cytokine and said to be the first oncogene that acts by inhibiting cell death rather than by stimulating cell proliferation. (8)

Research suggest that development of leukemia is extremely rapid when *bcl-2* transgene in the lymphoid compartment combined with a *c-myc* transgene. (11)

Regulation Of Apoptosis By Inhibitors Of Apoptotic Proteins (Iaps)

In addition to proteins such as Bcl-2 that inhibit cell death, there is another family of proteins termed IAPs that act after caspases become activated by binding to them and preventing them from cleaving their substrates. The well-characterized IAP can bind and inhibit caspases 3, 7 and 9. (38,39)

Apoptosis And P53

p53 is the gene that commonly gets mutated. *p53* can induce cell cycle arrest by transcriptionally activating the *p21* cyclin kinase inhibitor gene and also causes cell death by transcriptionally activating pro-apoptotic genes, especially for the BH3-only protein PUMA. These non-apoptotic activities of *p53*, like causing cell cycle arrest, may play important role in preventing the primary oncogenic mutation, also its capability to induce apoptosis may hamper subsequent transforming events. (40,41,42)

Recent studies suggest that p53 can act on its own for transcriptional regulation, direct binding and inhibition of Bcl-x at the mitochondria, leading to apoptosis. (43) As the gene for PUMA must be given by p53 following DNA damage and PUMA is required for p53-mediated apoptosis. (33)

Apoptosis And Iaps And Paracaspases

In mucosa-associated lymphoid tissue (MALT) lymphomas, translocation of genes for cIAP2 and paracaspase commonly occurs. (44,45,46) This translocation ends in synthesis of a fusion protein with an N-terminal half containing the BIR domains of cIAP2 and the C-terminal half containing the protease-like parts of paracaspase. (47) How it contributes to oncogenesis is not yet known but the possibilities include inhibition of apoptosis by the BIR domains or through activation of NF κ B p52 by the paracaspase region. Translocations causing expression of Bcl10 are associated with MALT lymphoma. (48,49) It seems that MALT lymphomas are caused by increased NF κ B signaling rather than direct inhibition of caspases by IAPs. (50)

CONCLUSION

There are correlative evidence that inhibition of programmed cell death can lead to cancer, this concept known by translocations in leukemia and lymphomas. Nearly all the studies of the pro- and anti-apoptotic proteins shows correlations between their expression and several types of cancer. For example, follicular lymphomas bear *bcl-2* translocations. Elevated Bcl-2 expression is linked with melanoma. Mcl-1 can be seen in certain myelomas. Elevated levels of XIAP have been detected in small cell carcinoma of the lungs. So various apoptotic proteins can be seen in cancer cells but further extensive research is required for conclusive statements, so that it will have vast impact on treatment and prevention of cancer.

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