

TUMOROGENESIS : EVASION OF APOPTOSIS BY THE CANCER CELLS

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ABSTRACT

Evasion of apoptosis is one of the hall marks of cancer. The overwhelming ability of tumor cells to increase in number is influenced not only by un-limited replicative potential but also to a great degree by their ability to evade apoptosis. Apoptosis is the programmed cell death that ensures the removal of old and genetically altered cells that can not be repaired. So the process is very important for continued preservation of genetic information in all body cells. Cancer cells acquire the overwhelming ability to evade apoptosis, thereby the genetic mutations necessary for carcinogenic phenotype start accumulating. The cancer cell thus becomes immortalized, this genetically mutated, immortalized cell then divides and reproduces genetically mutated daughter cells, and thus tumorigenesis develops. Apoptosis is brought about by a family of proteases, called as caspases. The principal function of caspases is proteolysis of specific substrates which facilitates the occurrence of various morphological and biochemical characteristics of apoptosis. They also act as critical signaling molecules in the apoptotic pathway and serve to amplify the signal during caspase cascade.

There are a variety of ways by which cells can evade apoptosis. This article looks at a variety of strategies acquired by the cells to evade apoptosis and to become immortalized. A thorough and complete understanding of these strategies can enable us to maximize the benefits of the apoptosis inducing agents, which are often included in the chemotherapeutics of carcinomas. Infact many of the conventional combination therapies utilize apoptosis inducing agents along with radiotherapy.

Key words: Apoptosis, Caspases, Tumorigenesis, Bcl-2 family

APOPTOSIS

The demise of cells by programmed cell death is characterized by a well defined sequence of morphologic changes which are collectively termed as apoptosis.¹ The characteristic morphologic changes of apoptosis that serve to distinguish it from other forms of cell death are;

- a. Apoptotic cell shrinks in size and condenses.
- b. Chromatin becomes highly condensed within the nucleus and appears to be concentric with the nuclear membrane.
- c. The cytoplasmic organelles remain intact and their integrity is preserved, apart from some swelling of the endoplasmic reticulum.
- d. The mitochondrial wall loses its integrity and cytochrome C leaches out.
- e. Externally the membrane becomes convoluted referred to as blebbing.
- f. Cell then sheds apoptotic bodies which are membrane bound vesicles containing cytoplasmic organelles and sometimes chromatin.
- g. Phagocytic cell secrete cytokines like IL-10 and TGF- β which inhibit inflammation.²

Apoptotic bodies are then phagocytized; however some times apoptotic cells become phagocytized before the shedding of apoptotic bodies. (Fig 1) Cells can enter apoptosis and be phagocytized within an hour, rendering their appearance very transient indeed.¹

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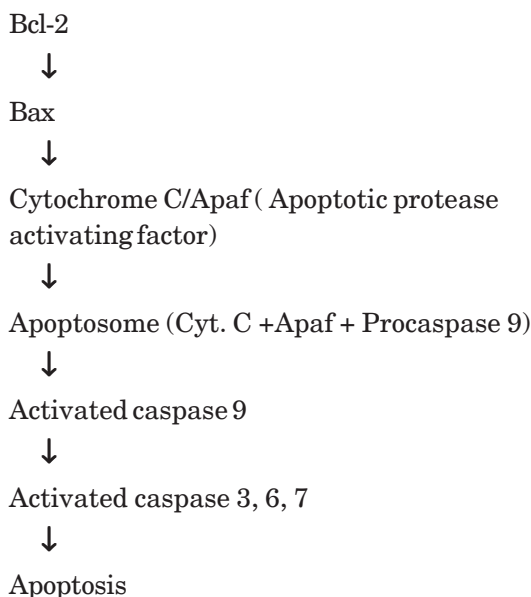
MECHANISMS OF APOPTOSIS

There are three mechanisms which can bring about apoptosis in a cell. These are:

- Intrinsic or mitochondrial pathway.
- Extrinsic or death receptor pathway.
- AIF induced pathway.²

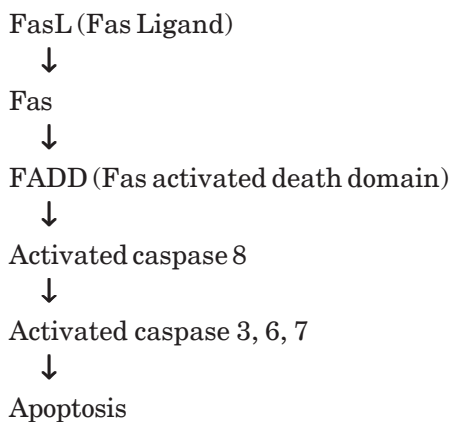
INTRINSIC OR MITOCHONDRIAL PATHWAY

In a normal healthy cell the outer membrane of the mitochondria displays a protein called as Bcl-2. Any internal damage to the cell will cause inhibition of this protein that will lead to the activation of Bax protein encoded by a family of pro-apoptotic genes. Thus the process of apoptosis will be activated.²



EXTRINSIC OR DEATH RECEPTOR PATHWAY

Extrinsic or death receptor pathway is mediated by Fas and TNF receptors present on the cell membrane of target cell. Any external stimulus in the form of ligand binds to them, thus activating them and initiating a cascade of caspase cleavages leading to apoptosis.



AIF INDUCED PATHWAY

This is the mechanism of apoptosis which does not use caspases and is initiated by an effector molecule released by the mitochondria called as AIF or apoptosis inducing factor. It is released by the mitochondria when ever cell is signaled to die. AIF migrates to the nucleus, passes through the membrane, binds to DNA and triggers the characteristic chromatin condensation which is the hallmark of apoptosis resulting in cell death.²

ROLE OF CASPASES

Caspases are a family of aspartate specific cysteine proteases, which exist as single chain inactive zymogens in proapoptotic cells. The principal function of caspases is proteolysis of specific substrates which facilitates the occurrence of various morphological and biochemical characteristics of apoptosis. They also act as critical signaling molecules in the apoptotic pathway and serve to amplify the signal during caspase cascade. There can be two types of caspases:

- Initiator caspases or up-stream caspases like caspase 2, 8, 9, 10, 11 and caspase 12.
- Effector caspases or down-stream caspases like caspase 3, 6 and 7.¹

Caspase 3 is a major effector caspase which is expressed in a wide range of tissues with high turn over rates. This clearly indicates that caspase 3 is expressed exclusively in tissues which have a great inclination for apoptosis^{2,3} and hence can be used as a very effective marker for apoptosis. Fig 2 shows all the different pathways involved in apoptosis and the roles of initiator and effector caspases in initiation and progression of this process.

APOPTOSIS IN CANCER

Developing resistance towards apoptosis is one of the most important factors in the survival of the malignant cell. Cells that escape apoptosis grow faster and live longer than normal cells.⁴ These cells thus develop a malignant potential. Thus an understanding of the mechanisms involved in the evasion of apoptosis play an important role in perceiving cancer.

MECHANISM OF EVASION OF APOPTOSIS

Evasion of apoptosis can be acquired by the cells using a variety of strategies, some of them less clearly understood than the others. These can be explained as following:

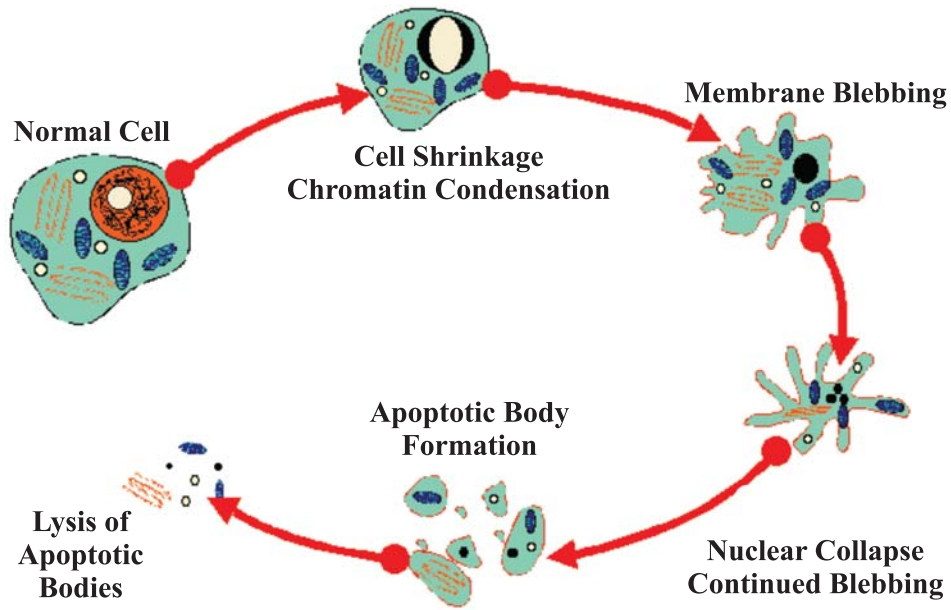


Fig 1: APOPTOSIS. Adapted from www-micro.msb.le.ac.uk.....⁹

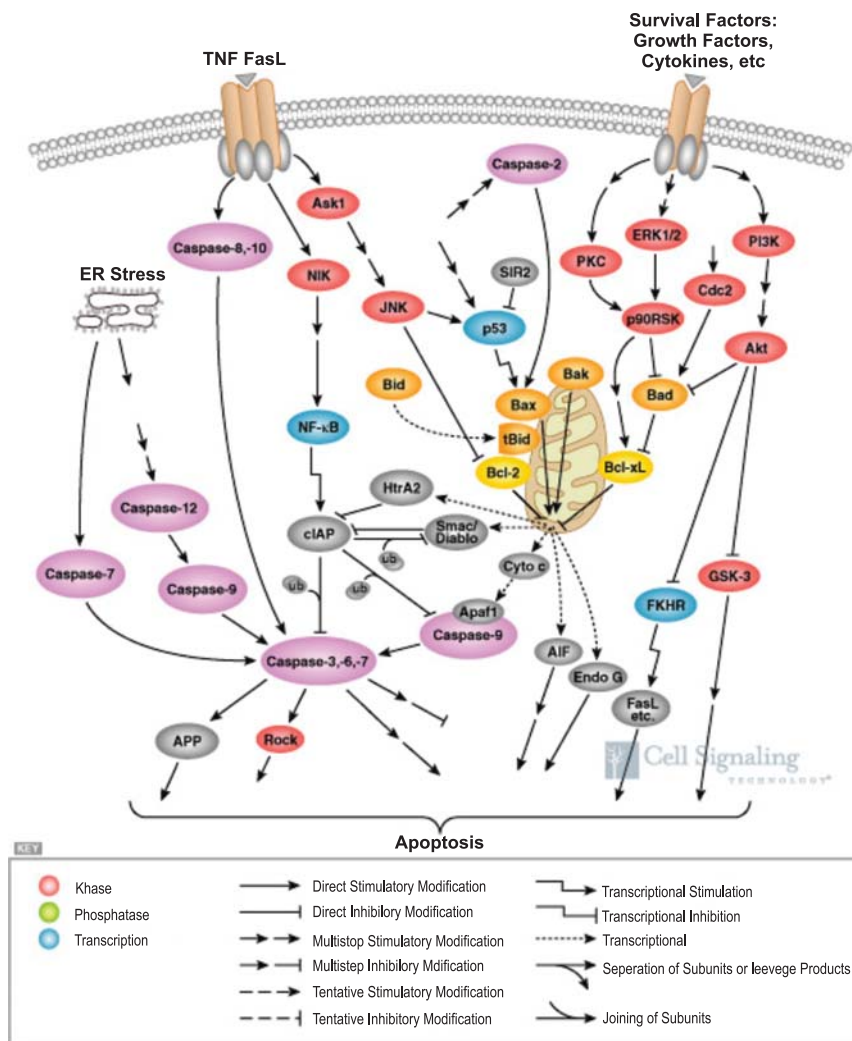
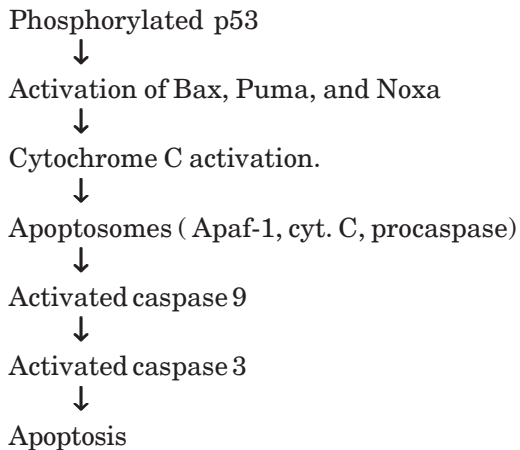


Fig 2: APOPTOTIC. Pathways adapted from www.web.books.com.....⁹

- P53 gene, dubbed as the guardian of the genome, is one of the most commonly mutated tumor suppressor gene. The resultant inactivation of p53 protein is responsible for giving 50% of the tumors apoptosis evasive characteristics. The pathway that p53 follows in a normal cell to induce apoptosis is:



- Another pathway involved is P13 Kinase-AKT/ PKB pathway, which is concerned with the anti-apoptotic survival signals. This survival signaling circuit is found to be up-regulated either by extracellular factors such as IGF-1 and IL-3, or by intracellular signals involving RAS, thus leading to evasion of apoptosis.
- Recently a new mechanism of apoptosis evasion has been observed in lung and colon carcinoma cell lines, which involves an up-regulation of non-signaling decoy receptor for FAS ligand, thus decreasing the intensity of death inducing signal and moving most of it away from FAS death receptor.⁵
- Many cells employ the activation of the transcription factor NF- κ B, which may be caused by TNF activation. Such cells are resistant to stimuli that can induce apoptosis. Inhibition of NF- κ B nuclear translocation enhances cell death by apoptosis in these cells.⁶

Cancer cells involve an amalgamation of these different mechanisms to evade apoptosis. (Fig 2) The evasion of apoptosis when combined with telomerase activation, which gives the cells unlimited proliferative potential, leads to the expression of a highly malignant phenotype.

CONCLUSIONS

Improved understanding of the biology of apoptosis can not only aid in understanding the behavior of

malignant cells but can also lead to the identification of novel therapeutic targets. Studies have shown a synergistic interaction between radiotherapy and apoptosis inducing chemotherapy, probably mediated by radiation-induced up-regulation of certain death receptors. One such receptor has been identified as TRAIL (Tumor necrosis factor-related apoptosis-inducing ligand). TRAIL is an effective endogenous activator of the cell death pathway and mainly activates the cell surface death receptors 4 and 5 also designated as DR4 and DR5. Therefore a combined therapeutic approach can be employed with radiotherapy and apoptosis inducing chemotherapy enhancing the effects of each other.⁷ Furthermore the development of multidrug resistance in tumour cells has also been attributed to the resistance to apoptosis because most of these drugs induce apoptosis in the target malignant cells.⁸ It is therefore mandatory to understand the biologic pathways involved in imparting resistance to apoptosis, as this can not only enhance the effects of combination treatments but also aid in understanding the problems of multidrug resistance development in malignant cells.

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