

Apoptosis: It's Role in Colorectal Cancer

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Abstract: Programmed cell death type I (apoptosis) has been linked to the pathogenesis of cancers with reference to initiation, progression and persistence. Colorectal mucosa is the 5th commonest site for cancer involvement and its one of the sites with high cell turnover rate thus high rate of apoptosis. Colorectal cancer has a strong link to the pre-malignant adenomas which are usually asymptomatic and have a very slow growth rate. The rate of apoptosis in the colonic mucosa has been shown to have an inverse relationship with the amount of adenomatous changes in the colonic mucosa. This article seeks to review the contribution of apoptosis in colorectal cancer.

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I. Introduction

Apoptosis is a form of programmed cell death in which excess or unwanted cells and tissues are removed from the body via a well regulated physiological mechanism not characterized by inflammation(1-3). Apoptosis has been likened to the falling of leaves from trees in Autumn in Greek literature(4). Similarly, the unwanted cells get shed off through the body's normal physiological mechanisms. Apoptosis plays a major role in normal histomorphogenesis in intra-uterine and extra-uterine life as well as regulating the immune system by either generating a pulling force or acting as a biological blade(4). Normal tissue and cell homeostasis requires constant removal and replacement of senescent and damaged cells by new ones(5). This is achieved through apoptosis. Every day, an adult loses nearly 0.4% of the total body cellular mass i.e. approximately 150 billion cells through apoptosis(6).

Apoptosis (programmed cell death type I), as a form of programmed cell death, is quite distinct from necrosis. The major functional distinction is on whether the body will mount an inflammatory immune response or not. In apoptosis, the cell death is physiological and tightly regulated by the gene, in that, specific and precise signaling pathways are activated resulting in selection of cells to undergo 'suicide'. The signaling is intracellular and results in cell membrane blebbing, fragmentation and condensation of chromosomal DNA. These processes result in cell shrinkage and formation of apoptotic bodies that will later on be engulfed by phagocytic cells which include macrophages. The clearance of apoptotic bodies is quite efficient and results in no leakage of cytoplasmic contents which are bound to induce an inflammatory response(1,6,7). In contrast, necrosis involves death of a cell following an injurious stimulus. In this case, the cell membrane is unable to control movement of ions and water in and out of the cell with resultant swelling of the cell and its intracellular organelles which later burst into the surrounding environment. These products induce an inflammatory response by the body(4,7).

Research has shown that deranged apoptosis is one of the key players in establishment and progression of malignant tumors as well as development of resistance to cancer chemotherapeutic agents(8-11).

II. Molecular mechanisms in apoptosis

Mammals have been shown to exhibit two key apoptotic pathways i.e. intrinsic (mitochondrial dependent) and extrinsic (death receptor dependent) pathways. In the two pathways, caspases have been shown to be the main regulatory proteins(12,13). Caspases are intracellular cysteine proteases. 14 have been identified of which caspases 2,3,6,7,8,9 and 10 are involved in apoptosis. Each caspase is produced as a heterodimer having a larger sub-unit p20 and a smaller sub-unit p10. They are activated by proteolytic cleavage to become heterotetramers with two small and two large sub-units(11-14).

Caspases can either be initiator caspases(2,8,9,10), effector/executioner caspases(3,6,7) or inflammatory caspases(1,4,5). Effector caspases breakdown specific substrates to result in cellular changes seen in apoptosis whereas initiator caspases activate the effector caspases (15).

III. The extrinsic death receptor pathway

This pathway is dependent on signals that are coming from outside the cell(15). The apoptotic cascade begins following attachment of an extracellular ligand, either TNF, Fas ligand or TNF-related apoptosis inducing ligand to a transmembrane protein(death receptor) extracellular domain(13,15). Upon binding, the intracellular part of the transmembrane protein i.e the death domain, binds a counterpart protein e.g. Fas-associated death domain or TNF receptor associated death domain(13,14). The bound intracellular proteins as well contain another binding site called the Death Effector Domain(DED) which is also found in pro-caspase 8. DED interacts with DED of FADD. These interactions result in a Death Inducing Signalling Complex(DISC) that leads to activation of pro-caspase 8 which in-turn activates effector caspases that effect apoptosis(2,5,8,15).

IV. The intrinsic mitochondrial apoptosis pathway

In contrast to the extracellular death receptor pathway, the apoptotic signals in the intrinsic mitochondrial apoptosis pathway comes from within the cell itself upon identification of cell stressors by intracellular proteins(11). The intracellular proteins transmit signals to the mitochondria that result in Mitochondrial Outer Membrane Permeabilization(8,11). Mitochondrial Outer Membrane Permeabilization is dependent on the balance between B-cell lymphoma 2 protein family proteins i.e. anti-apoptotic proteins (MCL-1, A1/Bfl-1, Bcl-B/Bcl2L10, BCL-2) and pro-apoptotic proteins(BAX, BOK, BAK, BID, BIM, PUMA, NOXA, BIK, BAD, HRK, BMF). For MOMP to occur, there is usually a complex interaction between the mitochondrial membrane-protein and protein-protein interactions mediated by the BCL-2 protein family(8,16,17).

Following an intracellular apoptotic signal, the pro-apoptosis BCL-2 proteins BAX and BAK activate and insert into the outer mitochondrial membrane with resultant release of cytochrome c and other apoptosis mediator proteins(Apoptosis Inducing Factor, endonuclease G, Smac/DIABLO and serine protease Omi/HtrA2)(12,13). Upon release of cytochrome c into the cytoplasm, it interacts with apoptosis protease activator 1 to form an apoptosome resulting in activation of caspase 9(an initiator caspase). Caspase 9 activates the effector caspase 3 and the apoptotic cascade begins leading to cell death(3,4,10,16).

V. Apoptosis and cancer

Programmed cell death and survival is a highly regulated process by the gene. It requires a strict balance between apoptosis and survival. An offset of this balance is bound to result in disease. Recently, apoptosis has been shown to play a major role in causation, progression and persistence of cancer as well as an important target for cancer chemotherapeutic agents(4,6,7,11). It has also been shown that, through altering the apoptosis process, some cancers have become resistant to the old conventional cancer chemotherapeutic agents(16).

Activation of the apoptosis cascade is either through the extrinsic death pathway or through the intrinsic pathway. The intrinsic caspase activation pathway is dependent on the BCL-2 protein family. The BCL-2 protein family has been shown to possess proteins that are both pro-apoptosis and anti-apoptosis. A balance between the two protein groups plays a critical role in cell death and proliferation(11,16). The role of BCL-2 protein family in apoptosis has been explored in causation and progression of cancer as well as one of the sites upon which cancers can evade apoptosis thus gaining resistance to cancer chemotherapeutic agents. These facts have been used to develop drugs that target the BCL-2 family proteins for treatment of cancer(11–13,16,18). The BCL-2 protein family has 3 categories of proteins that participate in apoptosis i.e. pro-survival guardians(BCL-XL, BCL-W, MCL-L-1, A1/BFL-1, BCL-2, BCL-B), pro-apoptotic effectors(BAX and BOK) and pro-apoptotic initiators. An interaction between these proteins dictate whether a cell will die or survive.

VI. Apoptosis in colorectal cancer: cancer genesis

Colorectum is the 5th commonest site for cancer involvement. Abnormal apoptosis in the mucosa of the colon and rectum has been associated with development of colorectal cancer(8,9,11). This could be as a result of shutting down of genes that initiate apoptosis or mutations in genes that suppress cell death(21). The colon is lined with simple columnar epithelial cells that are sourced from stem cells found in the colonic crypts. These cells normally move from the base of the crypts to the luminal surfaces of the colonic mucosa and thereafter flecked off, thus, normal colonic epithelium maintenance involves a strict balance between apoptosis of epithelial cells next to the colonic lumen and multiplication of stem cells at the colonic crypt bases(18). Stem cells at the bases of colonic crypts undergo mitosis in which new DNA synthesis occurs. This DNA is passed on to new epithelial daughter cells which move towards the lumen of the colon with subsequent shedding off. The old DNA is usually retained in the stem cell which in this case, the cell has to undergo apoptosis to avoid

mutations(15,17,19). Epithelial cells, including those of the colonic mucosa have been shown to have a high potency of undergoing apoptosis in case of altered DNA. Some foods that are protective against colorectal cancer have been shown to have components that enhance apoptosis(21).

Nearly 90% of cases of colorectal cancer are sourced from the pre-malignant adenomas which are usually asymptomatic and have a very slow growth rate. Furthermore, the rate of apoptosis in the colonic mucosa has been shown to have an inverse relationship with the amount of adenomatous changes in the colonic mucosa(5,24). Due to this, asymptomatic patients with colorectal adenomas tend to accumulate huge numbers of mutant cells because of the reduced apoptotic rates(5,13,22). In colorectal cancer, genetic instability has been shown to play a major role in acquisition of the malignant cell phenotype(5,16,21,24). Several studies have shown a strong relationship between failure/abnormal apoptosis and development of colorectal cancer as well its resistance to conventional chemotherapeutic agents(5). Failure of apoptosis or abnormal apoptosis favors accumulation of DNA damaged cells thus propagating further the adenoma-carcinoma sequence(5,18,21).

The apoptotic index, which is the ratio of apoptotic events in relation to the total number of cells has been shown to increase through the adenoma carcinoma sequence and is associated with poor prognosis in terms of overall survival and disease free survival(5,24). These research findings are the special targets for novel cancer molecules.

The hallmark of colorectal cancer pathogenesis lies behind accumulation of gene mutations in genes that regulate epithelial cell growth and differentiation(25). Genome instability in colorectal cancer has been shown to take different forms ranging from mutations involving genes that regulate mitosis, tumor suppressor genes like p53 and Adenomatous Poliposis Coli-APC6(25). This instability creates an enabling environment for acquisition of cancer linked mutations(18,24,25).

Mutations involving the APC gene have been linked to up to 60% of colorectal carcinoma cases. APC is a protein manufactured by the epithelial cells as they transition to the top of the intestinal crypt. A mutation in this protein leads to impaired function since it is one of the tumor suppressor genes thus continued accumulation of APC mutant cells(5,21,25). APC protein has been associated with regulation of apoptosis, cell cycle as well as cell migration and differentiation(5). APC is found in normal cells as a complex of axin, glycogen synthase kinase 3b (GSK3b) and Beta-catenin

The lack of a normal functioning APC results in abnormal activation of the Wnt signaling pathway that plays a major role in the genesis of colorectal cancer. Activation of the Wnt signaling pathway overwhelms the phosphorylation of Beta catenin, an onco-protein leading to its stabilization and nuclear translocation. In conjunction with the T-cell factor/lymphocyte enhancer factor, Beta catenin leads to activation of TCF transcription target genes(c- myc, cyclin-D1, matrilysin, peroxisome proliferator-activated receptor delta and MDR1 (multidrug resistance). These genes have been implicated in cell proliferation and programmed cell death type I(apoptosis)(18,21,24).

The p53 gene, a tumor suppressor gene whose product is the p53 protein has been shown to lead to cell growth arrest in DNA damaged cells. This is a very crucial role in prevention of replication of damaged DNA thus avoiding accumulation of mutant cells(17,21,23,24). Despite the role of p53 gene and p53 protein in apoptosis, studies have shown that its mutant variant (mutant p53 gene and its products) do not have a major impact in development of colorectal cancer(21).

The bcl-2 family member proteins have been shown to play a vital role as pro-apoptotic and anti-apoptotic proteins. The bcl-2 protein resides in the lower half of the colonic crypts where basically the stem cells are found located. This location is thought to favour anti-apoptotic activity in the stem cells. In colorectal carcinoma, it has been shown that the location of the bcl-2 protein migrates to include the superficial parts of the colonic crypts thus cells in the involved regions have reduced apoptotic activity which is associated with colorectal carcinoma(21).

Dysregulated apoptosis with subsequent evasion of apoptotic pathways has been shown to be one of the key pathogenetic mechanisms in causation, progression and persistence of several cancers including colorectal cancer(25,26). Resistance to conventional cancer chemotherapeutic agents has been linked to deranged apoptotic pathways(18,24). Apoptosis has been shown to be dysregulated in cancer cells but maintained in normal cells. This finding paves way for target specific therapy unlike the old conventional cancer chemotherapeutic agents that also affect normal growing cells(25).

VII. Conclusion

Apoptosis plays a key role in normal tissue homeostasis as well as colorectal cancer pathogenesis. Alteration of the genes that regulate apoptosis have a strong link to the pathogenesis of apoptosis and drugs targeting these links have a great promise in the treatment of colorectal cancer.

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