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Apoptosis as Therapeutic Target for Anticancer Drugs

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Abstract

Cancer is a disease characterized by an uncontrolled increase of cells caused by a mismatch between cell growth and programmed cell death. This review focuses on both extrinsic and intrinsic apoptotic pathways, a mechanism of programmed cell death with particular relevance to Tumor cells and Malignancy. The BCL-2 family of proteins controls cell death primarily by direct binding interactions that regulate mitochondrial outer membrane permeabilization (MOMP) leading to the irreversible release of intermembrane space proteins, subsequent caspase activation and apoptosis. Loss of apoptotic regulation permits cancer cells to live longer, allowing more time for mutations to accumulate, which can increase tumor invasiveness, induce angiogenesis, deregulate cell proliferation, and interfere with differentiation. Future research will focus on developing drug combinations that preferentially cause apoptosis in cancer cells.

Keywords: BCL-2, Mitochondria, Apoptosis, Cancer

Introduction

Apoptosis is the method of modified cell passing. It is utilized amid early improvement to dispense with undesirable cells; for illustration, those between the fingers of a creating hand. In grown-ups, apoptosis is utilized to free the body of cells that have been harmed past repair. Apoptosis moreover plays a part in preventing cancer. There are two distinct pathways of apoptosis: the intrinsic (or mitochondrial) and extrinsic (or death receptor) pathways. Although they share the end result of activating caspases, the mechanisms by which this occurs are quite distinct. This review focuses on pathways of apoptosis. It discusses the molecular biology of the regulation of apoptosis, and the relevance to cancer [1, 2].

Extrinsic pathway of apoptosis

Extrinsic pathway pathways include those activated by death ligands. Death Receptors (DRs) are cell surface receptors that transmit apoptotic signals initiated by specific ligands and play a central role in instructive apoptosis (see also the Death Receptor Pathway). These receptors activate Death Caspases (DCs) within seconds of ligand binding, causing an apoptotic demise of the cell within hours. DRs belong to the superfamily of TNFR (Tumor Necrosis Factor Receptor), which are characterized by a Cys-rich extracellular domain and a homologous intracellular domain known as the Death Domain (see also TNF Superfamily Pathway). Adapter-molecules like FADD (Fas-Associated via Death Domain), TRADD (Tumor Necrosis Factor Receptor-1-

Associated Death Domain), or Daxx contain Death Domains so that they can interact with the DRs and transmit the apoptotic signal to the death-machinery. The best characterized Death Receptors are Fas and TNFR1 (Tumor Necrosis Factor Receptor-1) [3, 4].

FasL (Fas Ligand), a homotrimeric protein, acts as ligand for Fas and causes oligomerization of its receptor upon binding (see also the Fas Pathway). Associated with this is the clustering of the Death Domains and binding of co-factor FADD. The FADD protein binds via its DED (Death Effector Domain) motif to a homologous motif in Procaspase-8. The complex of Fas, FADD and ProCaspase-8 is called the DISC (Death Inducing Signaling Complex). The co-factor function of FADD, in turn, is blocked by interaction with the regulator FLIP (FLICE Inhibitory Protein). Upon recruitment by FADD, Procaspase-8 oligomerization drives its activation through self-cleavage. Active Caspase-8 then activates downstream caspases (Caspase-3 and -7), committing the cell to apoptosis. The Caspase-3 cleaves DNA fragmentation factor ICAD (Inhibitor of Caspase-Activated DNase) in a heterodimeric form consisting of CAD and cleaved ICAD. Cleaved ICAD dissociates from CAD, inducing oligomerization of CAD that has DNase activity. The active CAD oligomer causes the internucleosomal DNA fragmentation, which is an apoptotic hallmark indicative of chromatin condensation [4].

Intrinsic pathway of apoptosis

The intrinsic apoptosis pathway begins when an injury occurs within the cell. Intrinsic stresses such as oncogenes, direct DNA damage, hypoxia, and survival factor deprivation, can activate the intrinsic apoptotic pathway. P53 is a sensor of cellular stress and is a critical activator of the intrinsic pathway (See the p53 Pathway for Apoptosis Signaling). The DNA checkpoints proteins, ATM (Ataxia Telangiectasia Mutated protein), and Chk2 (Checkpoints Factor-2), directly phosphorylate and stabilize p53 and inhibit MDM2 (Mouse Double Minute-2 Homolog)–mediated ubiquitination of p53. MDM2 binds p53 and mediates the nuclear export. When bound to MDM2, p53 can no longer function as an activator of transcription. p53 initiates apoptosis by transcriptionally activating pro-apoptotic Bcl2 family members and repressing anti-apoptotic Bcl2 proteins and CIAPs. Other p53 targets include BAX, Noxa, PUMA (p53-Upregulated Modulator of Apoptosis), and the most recently identified, BID. P53 also trans activates other genes that may contribute to apoptosis, including PTEN (Phosphatase and Tensin Homolog Deleted on Chromosome-10), APAF1, Perp, p53AIP1 (p53-regulated Apoptosis-Inducing Protein-1), and genes that lead to increases in ROS (Reactive Oxygen Species) [5]. These ROS lead to generalized oxidative damage to all mitochondrial components. Damage to mitochondrial DNA disrupts mitochondrial oxidative phosphorylation, contributing to a number of human diseases [6].

Other proteins released from damaged mitochondria, such as SMAC (Second Mitochondria-Derived Activator of Caspase), Diablo, Arts, and Omi/HTRA2 (High Temperature Requirement Protein-A2), counteract the effect of IAPs (Inhibitor of Apoptosis Proteins), which normally bind and prevent activation of Caspase-3. The interaction between Bcl family members IAPs, SMAC, and Omi/HTRA2 is central to the intrinsic apoptosis pathway. Recent studies demonstrate that another nuclease, EndoG (Endonuclease-G), is specifically activated by apoptotic stimuli and is able to induce nucleosomal fragmentation of DNA independently of Caspase and DFF (DNA-Fragmentation Factor)/CAD

(Caspase-Activated DNAse). EndoG is a mitochondrion-specific nuclease that translocate to the nucleus and cleaves chromatin DNA during apoptosis. Another protein, AIF (Apoptosis Inducing Factor), has also been attributed a role in apoptosis, becoming active upon translocation from mitochondria to nuclei, where it initiates chromatin condensation and large-scale DNA fragmentation [6, 7, 8, 9, 10].

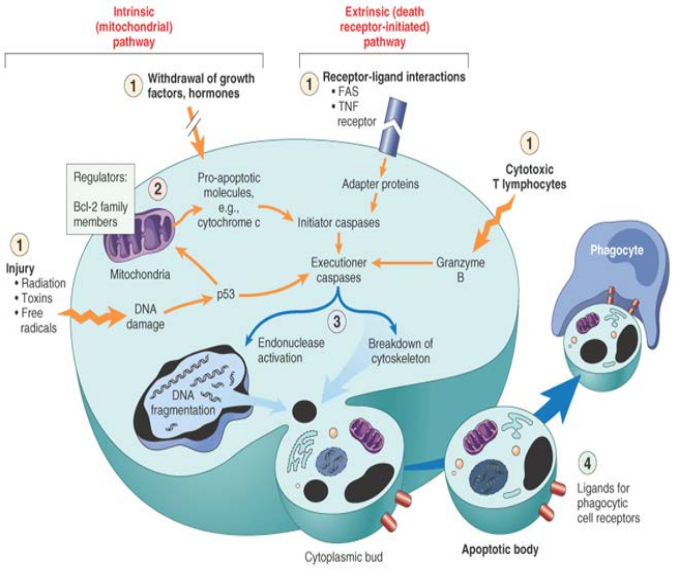

Figure 1: Extrinsic and Intrinsic pathways in Apoptosis

Cancer and Apoptosis

Cancer refers to any one of a large number of diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Cancer often has the ability to spread throughout your body. Cancer is the second-leading cause of death in the world. Cancer is caused by changes (mutations) to the DNA within cells. The DNA inside a cell is packaged into a large number of individual genes, each of which contains a set of instructions telling the cell what functions to perform, as well as how to grow and divide. Errors in the instructions can cause the cell to stop its normal function and may allow a cell to become cancerous. The hallmarks of cancer are present in all cancer cells regardless of the cause or type; these include uncontrolled growth, angiogenesis and apoptosis evasion. The prevention of cancer is one of the main functions of apoptosis. The loss of apoptotic control gives more time for the accumulation of mutations which can increase deregulate cell proliferation and interfere with differentiation [11, 12].

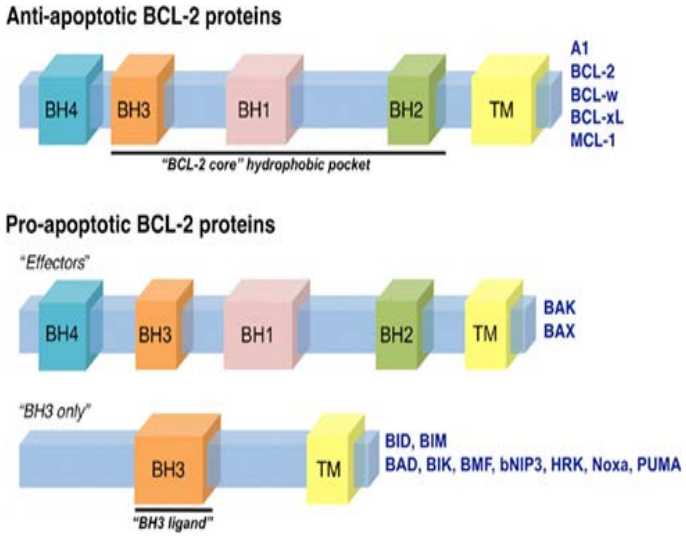

Figure 2: Bcl-2 family proteins

Targeting apoptosis is also effective for all types of cancer. There are many anticancer drugs that target various stages in both the intrinsic and extrinsic pathways. Two common strategies for therapeutic targeting are stimulation of proapoptotic molecules and inhibition of antiapoptotic molecules [12].

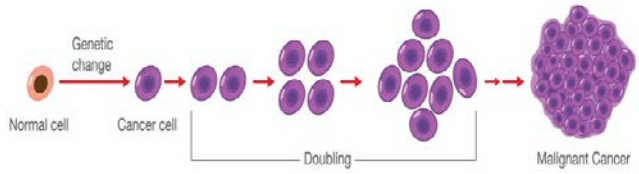

Figure 3: Cancer Cell development

Anticancer by induction of apoptosis

1. Anticancer through Activating Reactive Oxygen Species ROS is oxygen-derived species including superoxide, hydrogen peroxide singlet oxygen, and hydroxyl radical and plays a crucial role in cancer

development and apoptosis. It is well known that anticancer agents can generate ROS to mainly accumulate ROS in the mitochondria of cancer cells for activating apoptotic signaling pathways [13].

2. Anticancer through Affecting Bcl-2/Bax Pathway

The Bcl-2/Bax pathway plays a key role in intrinsic apoptotic pathway, which is dependent on the ratio of Bcl-2 and Bax in the mitochondria. Specifically, Bcl-2 protein can block the efflux of Cyt-c from cytosol to mitochondria to prevent caspase activation, then further inhibiting apoptosis. Bax protein acts as apoptosis promoter while Bcl-2 protein as apoptosis suppressor [14].

3. Anticancer through Activating Caspase Proteases

Caspases belong to the cysteinyl aspartate-specific proteases family, which is closely involved with apoptotic cell death. Dysregulation of caspases may cause various diseases in humans such as cancer and inflammatory disorders [15]. Caspase family was categorized as the initiator caspases such as caspases-8, -9, and 10 and the effector caspases such as caspases-3, -6, and -7. The activation of caspases-3 and -7 is essential for inducing downstream DNA cleavage molecules, which is involved with both extrinsic and intrinsic apoptotic pathways. The development of novel anticancer agents through the activation of caspases is one of the effective strategies in the treatment of cancer [16, 17].

4. Anticancer through The energy supply since cancer cells display a high energy demand, drugs that can directly perturb mitochondrial respiration and glycolysis could lead to an extensive depletion of ATP, sensitizing cancer cells to death. High metabolic rates and mitochondrial dysfunction has been shown to lead to elevated intracellular ROS levels in cancer cells. Thus anti- cancer compounds that push the cellular ROS levels past the threshold for cancer cells are potent inducers of apoptosis [18].

Conclusion

Cancer is one of the leading causes of death in the world. If upregulation of the antiapoptotic proteins is halted or disrupted, then the proapoptotic proteins can trigger apoptosis. Several reports have suggested that anticancer drugs kill susceptible cells by inducing expression of death receptor ligands, especially Fas ligand (FasL). Other reports have indicated that chemotherapeutic agents trigger apoptosis by inducing release of cytochrome c from mitochondria and causing cancer cell undergoing programmed cell death.

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