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Review

Apoptosis signaling and BCL-2 pathways provide opportunities for novel targeted therapeutic strategies in hematologic malignances

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ABSTRACT

Apoptosis is an essential biological process involved in tissue homeostasis and immunity. Aberrations of the two main apoptotic pathways, extrinsic and intrinsic, have been identified in hematological malignancies; many of these aberrations are associated with pathogenesis, prognosis and resistance to standard chemotherapeutic agents. Targeting components of the apoptotic pathways, especially the chief regulatory BCL-2 family in the intrinsic pathway, has proved to be a promising therapeutic approach for patients with hematological malignances, with the expectation of enhanced efficacy and reduced adverse events. Continuous investigations regarding the biological importance of each of the BCL-2 family components and the clinical rationale to achieve optimal therapeutic outcomes, using either monotherapy or in combination with other targeted agents, have generated inspiring progress in the field. Genomic, epigenomic and biological analyses including BH3 profiling facilitate effective evaluation of treatment response, cancer recurrence and drug resistance. In this review, we summarize the biological features of each of the components in the BCL-2 apoptotic pathways, analyze the regulatory mechanisms and the pivotal roles of BCL-2 family members in the pathogenesis of major types of hematologic malignances, and evaluate the potential of apoptosis- and BCL-2-targeted strategies as effective approaches in anti-cancer therapies.

1. Introduction

Apoptosis is an important process involved in organism development, tissue homeostasis, metabolic regulation immunity, and elimination of damaged, infected and unwanted cells, contributing to the overall health of cells. Apoptosis is mediated by the extrinsic and intrinsic pathways. The extrinsic pathway, also designated as the death-receptor pathway, is mediated by the binding of cell-surface death receptors and their natural ligands. The intrinsic pathway, also known as the mitochondrial pathway and a major focus of this review, is strictly regulated by BCL-2 family proteins. Cell killing also can occur via a substitute pathway, a cytotoxic T-cell and natural killer cell-mediated and perforin-granzyme-dependent killing pathway, in which granzyme A and granzyme B are involved, but this pathway is not discussed in this review.

Numerous experiments have proven that deregulation of apoptosis is a common and causative event in hematologic malignances and is associated with tumor development, prognosis and resistance to chemotherapeutic agents [1–5]. Components of the extrinsic pathway and BCL-2 family are targets for anti-cancer therapies currently in development. These anti-cancer agents have been proved efficient with enhanced efficacy and reduced side-effects in patients with hematological malignancies, especially in refractory and relapsed cases. ABT-199, a selective inhibitor of the anti-apoptotic protein BCL-2, was recently awarded a 'Breakthrough Therapy Designation' from the United States Food and Administration (FDA) in recognition of its promise as a treatment for patients with relapsed/refractory chronic lymphocytic leukemia (CLL) [6]. This advance in therapy is evidence of the successful investigation of apoptosis and BCL-2 family proteins in recent years.

In this review, we address recent advances in regard to the structure, function and regulatory mechanisms of the BCL-2 family in the apoptotic pathway, and we highlight the biological role of BCL-2 family proteins in hematological malignancies. Potential strategies for targeting components of the apoptotic pathways and BCL-2 members for the treatment of patients with hematological malignances in preclinical and clinical trials are discussed. The principles, dose schedules, adverse events, efficacies, limitations and some response-predicted laboratorial parameters associated with these trials are presented.

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2. Apoptotic pathways

2.1. Extrinsic pathway

The extrinsic pathway is triggered when cell-surface death receptors (DRs) are bound by their natural ligands [7]. DRs are members of the tumor-necrosis factor receptor (TNFR) family and are characterized by intracellular death domains. The group of DRs includes Fas (CD95), tumor necrosis factor α receptor 1 (TNFR1), tumor necrosis factor α ligand-receptor 1(TRAIL-R1, DR4), tumor necrosis factor α ligand-receptor 2 (TRAIL-R2, DR5), DR3, and DR6. Death-inducing ligands can be soluble factors or cell surface molecules on T lymphocytes, including FasL/CD95 ligand (CD95L), tumor necrosis factor α ligand (TNFα) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Upon ligand binding, DRs attract the adaptor protein FADD (Fas-associated death domain protein, also known as MORT1), which, in turn, recruits inactive forms of certain members of the caspase protease family, forming a “death-inducing signaling complex” (DISC), and resulting in activation of caspases 8 and 10, thus triggering apoptosis [8]. BID, a pro-apoptotic member in the intrinsic apoptotic pathway, is cleaved by active caspase-8 and translocates to mitochondria.

2.2. Intrinsic pathway

The intrinsic pathway is tightly regulated by the balance of pro-apoptotic and anti-apoptotic BCL-2 family proteins within mitochondria. Intrinsic apoptotic signals from the intracellular microenvironment include toxins, drugs, viral infections, free radicals, hypoxia, hyperthermia, calcium flux, loss of growth factors, cytokines or hormones, and elimination of apoptotic suppression [9,10]. These intrinsic stimuli initiate activation and interactions between BCL-2 family proteins (Fig. 2B–C), forming the mitochondrial outer membrane permeabilization (MOMP) complex. These molecular events result in release of cytochrome *c* and other factors from the mitochondrial inter-membrane space, inducing the formation of the apoptosome (caspase activation complex) which in turn activates caspase 9. The interaction between the anti-apoptotic and pro-apoptotic members can inhibit or activate MOMP and determine the fate of a cell. Activation of apoptotic caspase-9 leads to the activation of downstream “executioner” caspases.

The extrinsic and intrinsic apoptotic pathways converge into a common downstream pathway that includes the “executioner” caspases 3, 6 and 7. These caspases cleave each other, activate cytoplasmic endonuclease, degrade cytoskeletal proteins and polymerase ADP ribosylstransferase (PARP), thereby triggering various biochemical and morphological alterations in apoptotic cells. The last component of apoptosis is their phagocytic uptake.

2.3. Inhibitors of apoptosis proteins

Inhibitors of apoptosis proteins (IAPs) are a family of molecules that are pivotally involved in inhibition of the extrinsic and intrinsic pathways. The human IAP superfamily consists of nine members: NAIP, MLIAP, XIAP, cIAP1, cIAP2, ILP2, survivin, livin and BRUCE [11]. Each member of this family has a common domain composed of 70 amino-acid baculovirus repeats (BIR) that can suppress caspase function by facilitating protein-protein interactions, thus inhibit apoptosis. IAPs have been proven to be dysregulated in a variety of hematological malignances and can potentially serve as targets of anti-cancer therapies (Fig. 1) [12].

3. BCL-2 family

3.1. Classification of BCL-2 family members

BCL-2 is highly expressed and its structure is highly conserved in many hematologic cancers, and constitutes an essential component of the BCL-2 family in cell death regulation. Since its discovery in follicular lymphoma (FL), BCL-2 has been recognized as a new class of oncogene that does not affect cell proliferation but instead promotes tumorigenesis by preventing cells from undergoing apoptosis. BCL-2 can also protect cells from a broad range of cytotoxic stimuli, including anti-cancer drugs [13,14]. Through three decades of research effort, it has been confirmed that BCL-2 plays a crucial role in apoptosis, heralding a new era in our understanding of cell survival pathways. Currently, > 25 BCL-2 family members have been identified, that are categorized into three main subtypes according to their structural and sequence homology: anti-apoptotic members (for which BCL-2 is the prototype), multi-domain pro-apoptotic members, and BH3-only members.

Anti-apoptotic members share four BCL-2 homology (BH1-4) domains. These anti-apoptotic members include: BCL-2, BCL-X_L (also known as BCL2L1), MCL-1, BCL-W (also known as BCL2L2), A1 (known as BCL2Al or BFL1 in human), and BCL-B (also known as DIVA, BOO and BCL2L10 in mouse) [15]. Multi-domain pro-apoptotic BCL-2 family members include: BAK, BAX and BOK. BH3-only members include BID, BIM, PUMA, BAD, NOXA (also known as PMAIPI), HRK, BIK, BMF, BNIP3 and NIX [16,17].

The multi-domain pro-apoptotic members BAX and BAK are identified as “effectors”. Upon activation, these molecules directly induce conformational changes, leading to the MOMP complex and thus initiate apoptosis. BH3-only members can be divided into two subtypes according to the functions they play in pro-apoptosis: “activators” and “sensitizer/derepressors”. “Activators”, include tBID, BIM, and PUMA, and can directly interact with the “effectors” BAK, BAX and anti-apoptotic proteins. “Sensitizer/derepressor” molecules including BAD, BIK, BMF, HRK and NOXA, and cannot directly combine with “effectors”, but instead interact with anti-apoptotic members and then free “activators” to combine with BAX and BAK (Fig. 2).

Anti-apoptotic members reside on the outer mitochondrial membrane (OMM), the endoplasmic reticulum membrane and the nuclear envelop [16,18]. These proteins preserve OMM integrity by directly inhibiting pro-apoptotic proteins. BAX and BAK are important due to their critical roles in the formation of the MOMP complex (Fig. 2B–C). BID is induced by caspase 8, and thus connects the extrinsic and intrinsic apoptotic pathways [19].

The complex network of interactions between pro- and anti-apoptotic BCL-2 family proteins tightly regulates the mitochondrial apoptotic response, allowing for a swift response to specific stimuli to prevent deleterious cell death during normal cellular homeostasis. Interruption of the stoichiometric balance between anti- and pro-apoptotic BCL-2 family proteins can lead to a variety of human diseases including cancers and inflammatory or autoimmune disorders.

3.2. Structure of BCL-2 family

The BH domain is the homologous sequence shared by BCL-2 family proteins. All anti-apoptotic and some pro-apoptotic family members (BAX, BAK) share multiple BH1-4 domains. BH3-only proteins, as elucidated above, are a special group of pro-apoptotic members. The BH3 domain is constructed of 9 to 15 amino acids that are required to enable a protein to bind to anti-apoptotic BCL-2. The BH4 domain, a conserved structure-sequence motif which can stabilize BH1-3 domains, is essential for the anti-apoptotic activity of BCL-2 proteins. The highly conserved BH4 domain is located on the native N-terminal domain of BCL-2 and is composed of a stretch of 20 amino acids (residues 10–30) organized in a helical structure f1-f2-X-X-f3-f4. In this structure, X represents amino acids, f1, f2, f4 are aliphatic residues, and f3 is an aromatic residue. The loss of the BH4 domain completely eliminates the anti-apoptotic activity of BCL-2 without influencing the ability of BCL-2 to bind BH3-only proteins [20]. Most BCL-2 members have a transmembrane (TM) domain that anchors the molecule to the membrane of organelles, most notably the mitochondrial membrane.