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Commentary

Bcl-2 family members as molecular targets in cancer therapy

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ABSTRACT

Escape from apoptosis is often a hallmark of cancer cells, and is associated to chemotherapy resistance or tumor relapse. Proteins from the Bcl-2 family are the key regulators of the intrinsic pathway of apoptosis, controlling the point-of no-return and setting the threshold to engage the death machinery in response to a chemical damage. Therefore, Bcl-2 proteins have emerged as an attractive target to develop novel anticancer drugs. Current pharmacological approaches are focused on the use of peptides, small inhibitory molecules or antisense oligonucleotides to neutralize antiapoptotic Bcl-2 proteins, lowering the threshold and facilitating apoptosis of cancer cells. We discuss here recent advances in the development of Bcl-2 targeted anticancer therapies.

1. Introduction

The bcl-2 oncogene was first described in 1984 in an acute B-cell leukemia cell line carrying the t(14;18) chromosome translocation [1]. In contrast with other oncogenes, bcl-2 was shown to favor cell survival through inhibition of apoptosis, rather than inducing cell proliferation [2,3]. With the completion of whole-genome sequence and progress in bioinformatics, more than 25 members of the bcl-2 gene family have been identified in humans [4]. All members of this family are involved in the regulation of cell death, with some of them being antiapoptotic, like Bcl-2 itself, and others being proapoptotic. Antiapoptotic members of the Bcl-2 family, except for Mcl-1, contain all the four Bcl-2 homology (BH) domains, whereas the proapoptotic proteins contain three (Bax and Bak, multidomain) or only the BH3 domain (the BH3-only subfamily) (Fig. 1). The Bnip subfamily is usually included into the BH3-only group based on its limited homology with BH3 domains [4]. Beclin-1 [5], a Bcl-2 binding protein that promotes autophagy, and the citosolic fragment of Erbb4 (4ICD) [6] have also been proposed to be BH3-only proteins. The antiapoptotic viral proteins F1L and M11L, could also be included in the Bcl-2 family based in its Bcl-2-like fold [7]. The antiapoptotic proteins Bcl-2, Bcl-XL and Mcl-1 are overexpressed in many tumor cells, contributing to tumorigenesis by inhibition of apoptosis. Overexpression of antiapoptotic members of the Bcl-2 family could also be implicated in chemotherapy resistance [8].

Bcl-2 family proteins are key regulators of the mitochondrial or intrinsic apoptotic pathway, inducing or preventing the release of apoptogenic proteins such as cytochrome c, apoptosis inducing factor (AIF), Smac/DIABLO, EndoG and Omi/HtrA2 that reside in the intermembrane space of mitochondria in healthy cells (Fig. 2). This event seems to determine the fate of the cell after receiving a physical or chemical insult [9,10]. Moreover, many apoptosis inducers activate one or more of the BH3-only proteins and the participation of at least a multidomain proapoptotic protein (Bak or Bak) is imperative for the intrinsic cell death pathway [11]. Because of this central role in the intrinsic pathway, mitochondria and Bcl-2 proteins are now viewed as potential drug targets for antitumor therapy. In the last years, small

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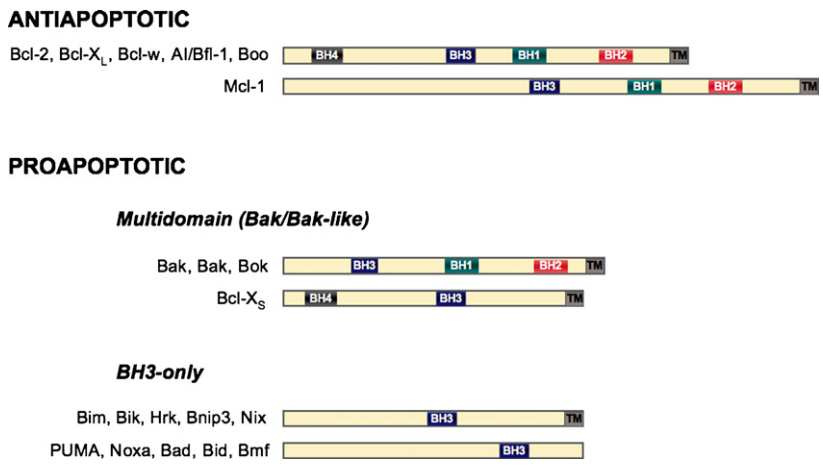

Fig. 1 – Bcl-2 family of proteins. BH, Bcl-2 homology domain; TM, transmembrane domain.

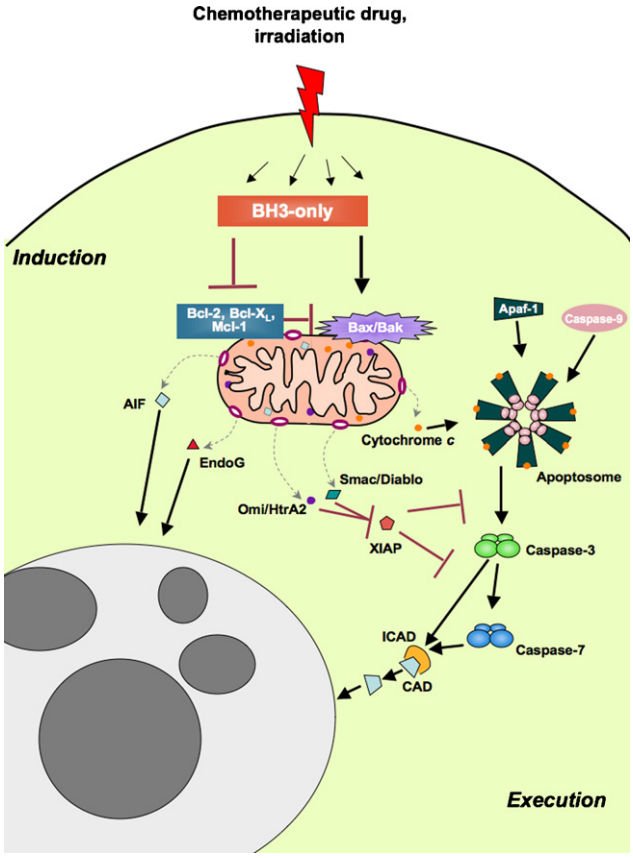

Fig. 2 – The intrinsic pathway of apoptosis. In response to a chemical insult or irradiation, BH3 proteins act as damage sensors and induce mitochondrial permeabilization either by freeing Bax/Bak from antiapoptotic Bcl-2 proteins, or by direct activation of Bax/Bak. Apoptogenic proteins cytochrome c, AIF and EndoG, Omi/HtrA2 and Smac/Diablo are released from mitochondria. Cytochrome c forms a complex with Apaf-1 and procaspase-9 leading to apoptosome formation and caspase-9 activation that triggers a caspase activation cascade. Caspases, AIF and EndoG carry on the execution of apoptosis. Bcl-2 targeted therapies seek to block the antiapoptotic members of the family, thus provoking or facilitating the mitochondrial release of apoptogenic proteins.

compounds, peptides and antisense oligodeoxynucleotides targeting Bcl-2 proteins have been evaluated in preclinical studies or even reached clinical assays.

2. Synthetic BH3-mimetics

According to the "displacement model", BH3-only members of the Bcl-2 family bind to antiapoptotic members, counteracting their protective effect by freeing multidomain proapoptotic members Bax and Bak. It has also been proposed that some BH3-only proteins can also directly activate Bax and/or Bak, although this is still a matter of controversy in the field. Irrespective of the mechanism, direct or by displacement, BH3-only proteins seem to be crucial for the intrinsic pathway of apoptosis, acting as damage sensors that determine cell fate and overexpression of BH3-only proteins induce apoptosis in different cell types [11–17].

Emulation of the proapoptotic activity of BH3-only proteins has become an attractive strategy for the development of new anticancer therapies. First, recent advances in the knowledge of the structure of complexes between BH3 domains and prosurvival members of the Bcl-2 family have opened the opportunity for rational design of anticancer drugs. Second, BH3 domains are relatively small (14–24 amino acids) making possible the synthesis of peptides or small molecules pharmacologically active that reproduce their proapoptotic function in cells.

2.1. *Peptides*

Overexpression of BH3 domains induces apoptosis and soluble BH3-peptides produce cytochrome c release from isolated mitochondria [11]. For their potential use in cancer therapy, these peptides must be modified in order to increase cell uptake and stability. Stapled BH3 peptides with enhanced stability, like the *BID-SAHB* peptide derived form Bid, have been shown to induce apoptosis in Jurkat cells and to inhibit the growth of leukemia xenografts [18]. Wang et al. synthesized a Bad-BH3 peptide with a cell permeable moiety (*cpm-1285*) that induced apoptosis in HL-60 leukemia cells in a caspase-dependent way and delayed myeloid leukemia growth in mice [19]. These reports indicate that BH3 peptides