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Review

Regulation of pro-apoptotic BH3-only proteins and its contribution to cancer progression and chemoresistance

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ABSTRACT

The BH3-only members of the Bcl-2 protein family function as damage sensors in the cell and initiate the apoptotic cascade. Apoptosis is the primary mechanism by which the body gets rid of genetically defective cells and is critical for preventing the accumulation of cells with tumorigenic potential. BH3-only proteins have evolved to respond to distinct forms of cellular stress or DNA damage by inactivating the protective function of the prosurvival members of the Bcl-2 family. Therefore, a downregulated expression or activity of these proteins may favour tumor development. Moreover, the pro-apoptotic proteins are required for the success of most cancer treatments, including chemotherapy. Resistance to chemotherapy, a common feature of cancer, often reflects an inability of tumor cells to undergo apoptosis. Deciphering the regulation and activity of the BH3-only proteins may provide the basis for novel therapeutic strategies aimed at promoting tumor cell death or enhancing susceptibility to chemotherapeutic agents. This review summarizes the current knowledge of BH3-only proteins and their contribution to tumorigenesis and chemoresistance.

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1. Introduction to apoptosis

Apoptosis is a tightly regulated and highly efficient cell death system that requires the interaction between multiple factors. This cell death program can be triggered by a number of stimuli from outside or inside the cell including ligation of cell death receptors, growth factor withdrawal, DNA damage as a result of defects in DNA repair mechanisms, and treatment with cytotoxic drugs or irradiation. All these signals appear to activate a common cell death machinery leading to the characteristic features of apoptosis. The biochemical activation of classical apoptosis occurs mainly through the extrinsic or the intrinsic pathways. The first originates through the activation of cell membrane-anchored death receptors such as Fas, tumor necrosis factor (TNF) receptors and TNF-related apoptosis-inducing ligand (TRAIL) receptors, and results in the activation of caspase-8 or caspase-10. On the other hand, the intrinsic pathway originates from mitochondrial release of cytochrome *c* that leads to activation of caspase-9 [1]. A less well-known pathway originates from the endoplasmic reticulum and also results in the activation of caspase-9 [2]. In the best characterized model of the extrinsic pathway, binding of Fas to its ligand results in the recruitment of Fas-associated death domain protein (FADD) which in turns recruits the zymogen form of caspase-8. Existing data suggests that this apical caspase is activated by adaptor-mediated clustering of the inactive enzyme and recently it has been proposed a unified model for apical caspase activation based

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on dimerization of monomeric zymogens [3]. On the other hand, the intrinsic pathway relies on caspase-9, which is activated in a protein complex known as apoptosome that contains the adaptor apoptotic protease activating factor 1 (Apaf-1) and cytochrome *c* released from the mitochondria. A model similar to that proposed for the extrinsic pathway has also been suggested to explain the activation caspase-9. According to this, caspase-9 can be activated simply by directing their zymogens to the apoptosome, ruling out the requirement for allosteric activation and supporting an induced proximity dimerization model for apical caspase activation [4]. These active caspases can still be held in check by inhibitor of apoptosis proteins (IAPs) which may function as direct inhibitors of caspases and as E3 ligases that mediate caspase degradation [5]. The susceptibility of cells to undergo apoptosis is largely determined by the balance between anti-apoptotic and pro-apoptotic members of the Bcl-2 family that controls the intrinsic pathway. The anti-apoptotic proteins such as Bcl-2, Bcl-x_L, Bcl-w, A1 and Mcl-1, which all possess the Bcl-2 homology (BH) domains BH1, BH2, BH3 and BH4, counteract the action of pro-apoptotic proteins, and thus can inhibit mitochondrial apoptotic events. Amongst the pro-apoptotic proteins, Bax and Bak contain BH1-3 domains and can permeabilize mitochondrial outer membrane, whereas those containing exclusively the BH3 domain (referred as to BH3-only proteins) play a key role in sensing apoptotic stimuli and initiating apoptosis by activation of Bax or Bak [6]. Furthermore, one of these BH3-only proteins, Bid, connects the extrinsic and intrinsic pathways as it is activated by caspase-8. Permeabilization of the mitochondrial membrane by Bax or Bak releases the apoptogenic proteins cytochrome *c* and SMAC (which acts by inhibiting the IAPs from blocking caspase activity) into the cytosol initiating the activation of the caspase cascade [7].

2. Transcriptional and post-translational control of BH3-only proteins

In *C. elegans*, a single BH3-only protein, Egl-1, is required for the initiation of all developmentally programmed deaths of somatic cells, whereas at least eleven BH3-only proteins have been described in mammals (Bik, Bim, Bid, Bad, Hrk, Puma, Noxa, Bmf, Bnip3, Bnip3L, Bcl-gS). The pro-apoptotic activities of these proteins are stringently controlled by a variety of mechanisms, including transcriptional pathways and post-translational modifications (Fig. 1).

2.1. Transcriptional regulation

The tumor suppressor p53 is one of the main transcription factors involved in the regulation of pro-apoptotic Bcl-2 family members. This protein plays a pivotal role in the decision of whether the outcome of DNA damage will be growth arrest or apoptosis, and this choice is based, at least in part, on its transcriptional capacity. Among the BH3-only genes, puma, noxa and bik have been shown to be induced by the p53 pathway [8–10]. Although these three genes can be transcriptionally regulated by p53, current data suggest that puma is the principal mediator of p53-induced apoptosis [11].

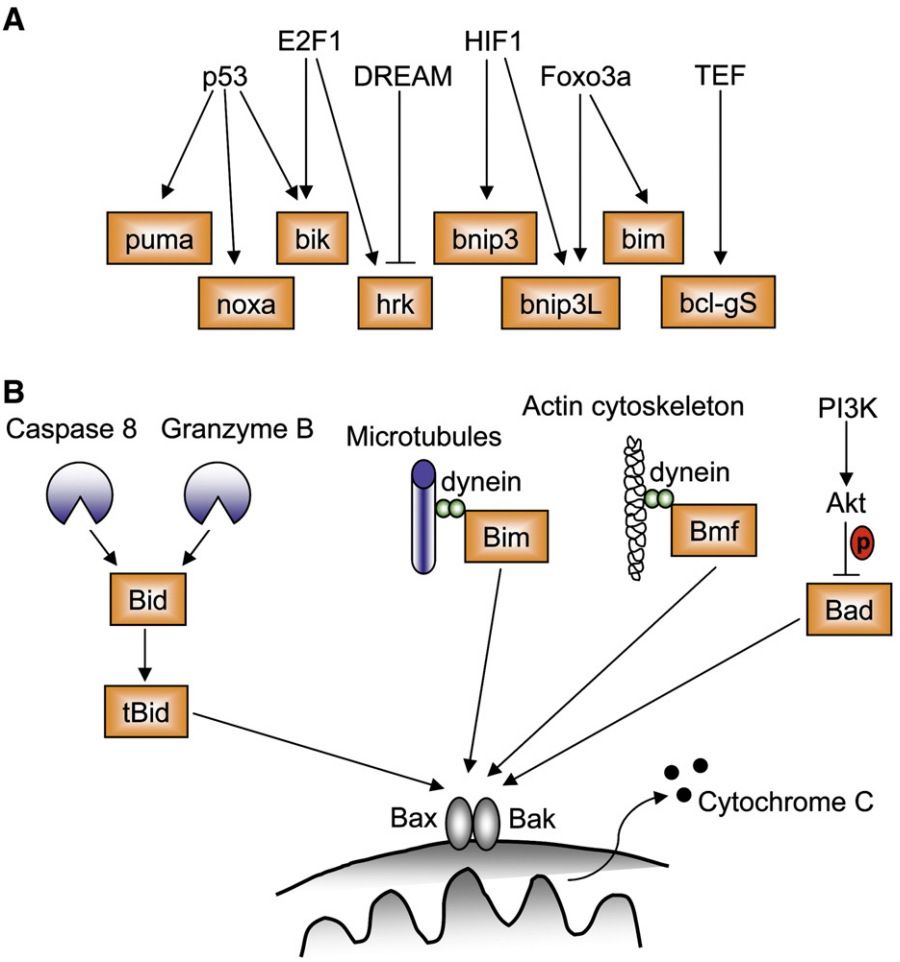

Fig. 1. Transcriptional (A) and post-translational (B) control of BH3-only members of the Bcl-2 family. All transcriptional regulators but DREAM promote the expression of different BH3-only genes. Phosphorylation, binding to dynein or proteolytic cleavage is the most common post-translational regulation of BH3-only proteins. Following activation, these proteins trigger Bax and Bak to cause cytochrome *c* release and subsequent activation of the caspase cascade.