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Review Article

BIM (BCL-2 INTERACTING MEDIATOR PROTEIN OR BCL-2-LIKE PROTEIN 11) AND CANCER

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ABSTRACT

BCL-2 (B-cell lymphoma-2) orBcl-2 was the first anti-death gene discovered, a milestone with far reaching implications for tumor biology.BCL-2, was discovered because of its involvement in t (14;18) chromosomal translocations observed in non-Hodgkin's lymphomas (Tsujimoto et al.) [1] in 1985. Multiple members of the human Bcl-2 family of apoptosis-regulating proteins have been identified. Bim (Bcl-2 Interacting Mediator of cell death), most important member of BH3-only proteins and a pro-apoptotic member of the BCL-2 protein family.Bim is a Bcl-2 homology 3 (BH3)-only protein that was discovered by O'Connor et al. [2] in 1998, while screening for proteins binding the anti-apoptotic Bcl-2 protein, giving raise to its name Bcl-2 interacting mediator of cell death. In the same year, Hsu et al. [3] discovered the same gene using Mcl-1 as a bait and termed the gene Bcl-2 related ovarian death agonist (BOD). Its official gene name is now Bcl-2-like 11 (Bcl-2L11/apoptosis facilitator). Defects in the expression of proapoptotic members of the BCL-2 family occusr in cancer, resulting in loss of the tumor suppressor function of these killer genes.In the issue of Cancer Discovery, Faber and colleagues demonstrate that the basal expression of BIM is positively correlated with the amount of apoptosis induced by the corresponding tyrosine kinase inhibitor treatment within the same subtype of several oncogene-addicted cancer cell types. [4]. Their results suggest that pre-treatment assessment of BIM levels can identify patients who would benefit from molecularly targeted therapies even after biomarker-based patient selectio. In the past few years, the pro-apoptotic molecule Bim has abstracted increasing attention as a plausible target for tumor therapy. A variety of normal and pathological systems regulated by Bim dependent on cell type, apoptotic stimulation and chemotherapeutic agent has been

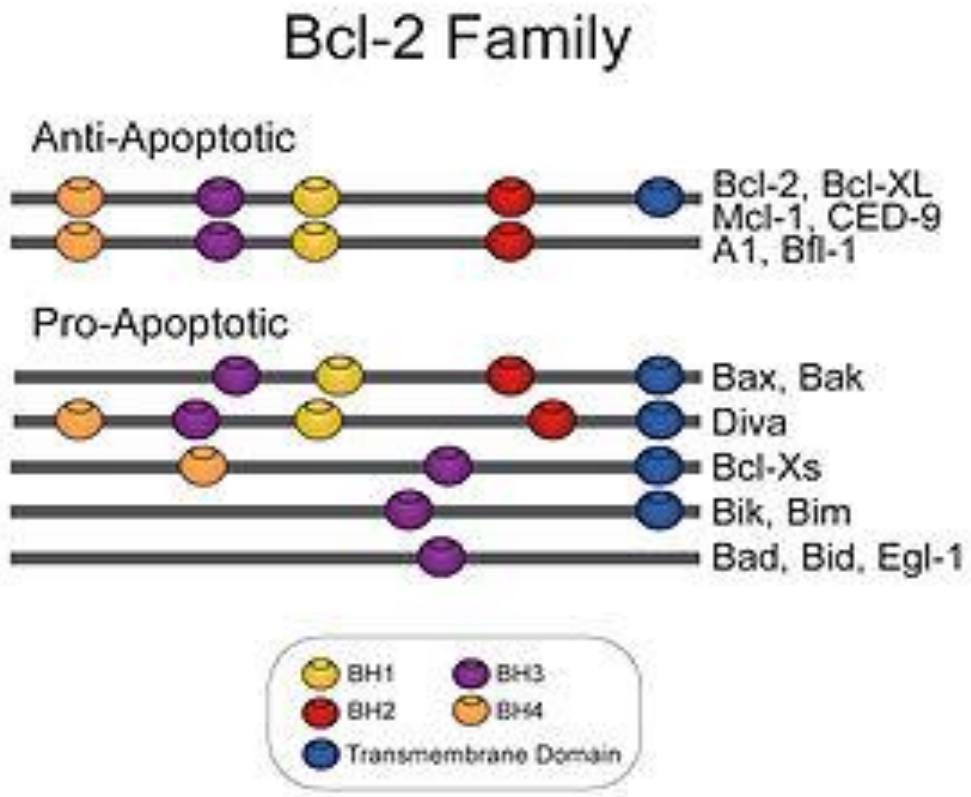
documented. Bim promotes anoikis of many tumor cells, such as lung cancer, breast cancer, osteosarcoma and melanoma. [5]. Various chemotherapeutic agent use Bim as a mediating executioner of cell death. Hence, Bim suppression supports metastasis and chemoresistance. The potential benefits of Bim targeted therapies are selectivity of treatment for tumor cells and reduction in tumor associated phenomena such as metastasis and chemoresistance. A fine balance in the intracellular expression levels of Bim and its regulatory proteins is crucial for properly regulating apoptosis. This review will take us into a journey through the fascinating world of Bim.

Keywords: BCL-2, non-Hodgkin's lymphomas, chromosomal translocations, pro-apoptotic, Bcl-2 related ovarian death agonist (BOD), tyrosine kinase inhibitor, oncogene, anoikis, metastasis,chemoresistance

INTRODUCTION

The average adult human produces and in parallel eradicates ~60 billion cells daily, with new cells formed by cell division and old cells eliminated principally by apoptosis, thus striking a balance under normal circumstances. The ability to control cell numbers at both the points of entry and exit allows flexibility to more rapidly respond to stress, injury and physiological cues. However, it also creates a liability in terms of neoplasia, as genes that normally suppress or induce physiological cell death often become dysregulated in cancers. Bcl-2-family proteins regulate all major types of cell death, including apoptosis, necrosis and autophagy, thus operating as nodal points at the convergence of multiple pathways with broad relevance to oncology. Experimental therapies targeting Bcl-2-family mRNAs or proteins are currently in clinical testing, raising hopes that a new class of anticancer drugs may soon be available.BH3-only proteins constitute major proportion of pro-apoptotic members of Bcl-2 family of apoptotic regulatory proteins and participate in embryonic development, tissue homeostasis and immunity.The members of the Bcl-2 family share one or more of the four characteristic domains of homology entitled the Bcl-2 homology (BH) domains (named BH1, BH2, BH3 and BH4). The BH domains are known to be crucial for function, as deletion of these domains via molecular cloning affects survival/apoptosis rates. The BH3-only members play a key role in promoting apoptosis and participate in vital biological processes, their absence contributes to autoimmunity and tumorigenesis. The BH3-only family members are Bim, Bid, BAD and others. Bim (Bcl-2 Interacting Mediator of cell death), most important member of BH3-only proteins, shares a BH3-only domain (9-16 aa) among 4 domains (BH1-BH4) of Bcl-2 family proteins and highly pro-apoptotic in nature. Bim may promote apoptosis by both acting as a death agonist and as well as a survival antagonist.

Keywords: cell division, neoplasia, apoptosis, necrosis, autophagy, autoimmunity, tumorigenesis



The Role of Bim as a Guardian of Tissue Homeostasis:

In response to apoptotic signals, various enzymes are activated in a pathway-specific manner and the classical caspase activation chain reaction is set in motion [6]. Mammals have mainly two distinct apoptosis signaling pathways, the death receptor pathway and the mitochondrial pathway. In the mitochondrial pathway, the B-cell lymphoma-2 (Bcl-2)-family of proteins have a crucial role. The Bcl-2 family comprises three subfamilies, namely, an anti-apoptotic family, pro-apoptotic multidomain family, and pro-apoptotic BH3-only protein family. The Bcl-2-homology domain 3 only (BH3-only) proteins share only the short BH3 domain with members of the BCL-2 family. BH3-only proteins are strictly regulated through both transcription and post-transcription mechanisms [7]. They are essential for initiation of various physiological apoptotic situations, including developmentally programmed cell death and stress-induced apoptosis [8]. So far, at least eight BH3-only proteins have been discovered in mice and humans. Bim is one of these BH3-only proteins. Bim upregulation triggers cytochrome c release from mitochondria, which consequentially induces a chain reaction that entails the formation of the apoptosome and the activation of its effector, caspase-9. Thus, Bim upregulation induces apoptosis (Fig. 1).

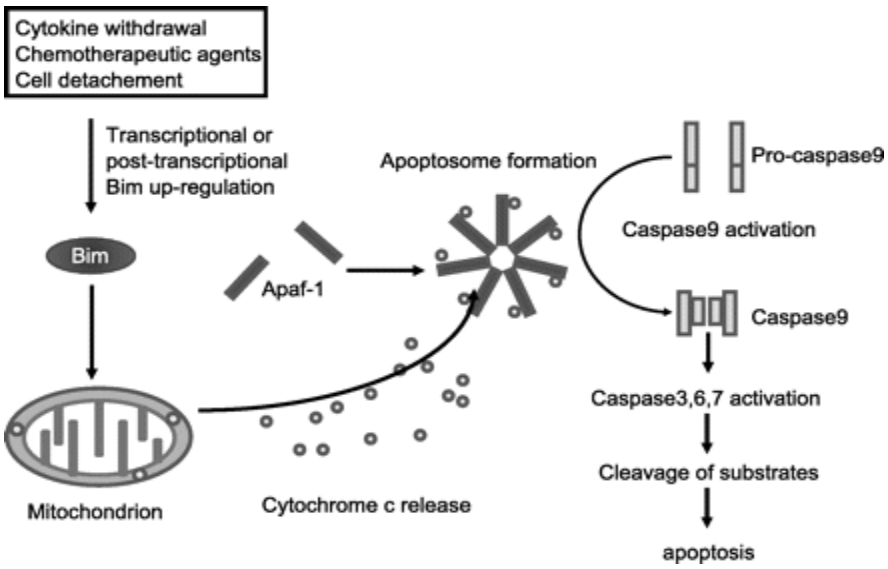


Figure 1: A mechanistic scheme of how Bim activation can act to promote apoptosis. Cytokine withdrawal, chemotherapeutic agents, and cell detachment trigger apoptosis by upregulation of Bim. Bim upregulation leads to disruption of the outer mitochondrial membrane, resulting in release of cytochrome c. Released cytochrome c promotes apoptosome-mediated caspase-9 activation. The apoptosome is composed of Apaf1 (apoptotic-protease-activating factor 1) and released cytochrome c. Once activated, caspase-9 cleaves executioner caspase-3, -6, and -7 and leads to apoptosis in the stimulated cell.

Regulation of Bim:

The BH3-only Bim protein is a major determinant for initiating the intrinsic apoptotic pathway under both physiological and pathophysiological conditions. Tight regulation of its expression and activity at the transcriptional, translational and post-translational levels together with the induction of alternatively spliced isoforms with different pro-apoptotic potential, ensure timely activation of Bim. A coordinated expression and activity of Bim shape immune responses, and ensure tissue integrity. Under physiological conditions, Bim is essential for shaping immune responses where its absence promotes autoimmunity, while too early Bim induction eliminates cytotoxic T cells prematurely, resulting in chronic inflammation and tumor progression. Enhanced Bim induction in neurons causes neurodegenerative disorders including Alzheimer's, Parkinson's and Huntington's diseases [9] [10] Moreover, type I diabetes is promoted by genetically predisposed elevation of Bim in β-cells. On the contrary, cancer cells have developed mechanisms that suppress Bim expression necessary for tumor progression and metastasis.

Keywords: Bim, expression, apoptosis, cancer, transcriptional, post-translational, isoform, cytotoxic

ROLE OF BIM IN APOPTOSIS

Indirect and Direct Apoptosis Induction by Bim:

Bim has been implicated in the regulation of intrinsic cell death induced by a large number of stimuli, including growth factor or cytokine deprivation, calcium flux, ligation of antigen receptors on T and B cells, loss of adhesion (anoikis), glucocorticoids, microtubule perturbation and tyrosine kinase inhibitors. It has been shown to be critical for apoptosis in B and T lymphocytes, macrophages and granulocytes. The pioneer studies by O'Connor et al. [2] and Hsu et al. [3], showed that over expression of Bim in Chinese hamster ovary (CHO) cells or 293T human embryonic kidney cells led to apoptosis

Bim-induced apoptosis:

The pro-apoptotic effect of Bim depends on Bak and Bax [11], as do most apoptotic stimuli. A constitutively active form of Bim induces apoptosis in cells derived from either Bax−/− or Bak−/− animals, but failed to do so in Bax−/−Bak−/− double KO (knock out) cells [11]. Activation of Bak and Bax leads to homo-oligomerization and assembly within the mitochondrial outer membrane (MOM) followed by MOM permeabilization (MOMP), cytochrome C release, and initiation of the intrinsic apoptotic pathway [12, 13]. Bim also leads to uncoupling of mitochondrial respiration and the subsequent increase in the cellular levels of reactive oxygen species (ROS) [14].

Involvement of Bim in Cancer (Bim and Tumorigenesis):

Experimental evidence shows that a single oncogene can be critical to tumorigenesis or that tumors become addicted to the oncogene for their tumorigenesis [15]. The latter is an “oncogene addiction” hypothesis. Naturally, these addicted genes pose as suitable targets for tumor control. Bim is one such possible candidate of an addicted oncogene.

Reduced Bim expression is a hallmark for carcinogenesis. Tumor cells have evolved different mechanisms to suppress Bim expression and/or activity thereby overcoming the apoptotic barrier that else would have led to their eradication. The efficacy of many anti-cancer drugs depends on Bim, and insufficient Bim induction or Bim function is often an underlying cause of therapy failure. Many cancer cells have developed one or more mechanisms for preventing Bim from acting, intervention of which may result in the reactivation of the apoptotic process. Determination of the specific survival dependency pathway in each cancer case is important for choosing the right targeting drug therapy.

The breakdown of tissue homeostasis leads to various pathological situations including tumor formation. Thus Bim plays important roles for tomorigenesis and tumor treatment. Baby mouse kidney epithelial (BMK) cells transformed byE1A and dominant negative p53 (p53DD) form tumors in nude mice. The formation and growth of tumors in nude mice are supported by Bim deficiency (16). This data suggest that Bim

is possibly a key regulator of epithelial tumors as well. However, the absence of Bim plays a more important role for the formation of tumor metastasis and the acquisition of resistance to chemotherapy.

The Role of Bim in Tumor metastasis:

The acquisition of anchorage independence is an indispensable step for tumor metastasis. Cells are normally dependant on anchorage and undergo apoptosis after their loss of attachment with their neighboring cells or their extracellular matrix. So, apoptosis induced by cell detachment (anoikis) is a crucial barrier against metastases [18]. Anoikis stimuli can activate both the death receptor and mitochondrial pathways which recruit or suppress several molecules including Bim. Bim play a key role in the anoikis of a variety of tumor cells such as breast cancer, lung cancer, osteosarcoma etc[17,19]. These tumor cells have to bypass or abrogate Bim mediated cell death as well as in order to metastasize. [20]

The Bim Status as a Prognostic Criterium:

Usually cancer cells with high basal Bim expression show better response to Bim-dependent chemotherapy than those with low Bim expression, which can be explained by the rapid available pre-made Bim, a state termed “primed for apoptosis”. When Bim is expressed at relative high basal levels, the cancer cells have often developed a mechanism (e.g., concomitant Mcl-1 or Bcl-2 upregulation) that antagonizes the pro-apoptotic function of Bim.[21] As the cancer cells become dependent on the anti-Bim mechanism for survival, targeting this mechanism will induce Bim-dependent cancer cell death. For instance, it was sufficient to reduce Mcl-1 levels to induce Bim-dependent apoptosis in c-Myc positive HER-positive breast cancer cells [22]. Not only the basal Bim level account for better prognosis, but also the ability of the cancer cells to elevate Bim expression in response to chemotherapy is important for the clinical response. This has been demonstrated for glucocorticoid susceptibility of pediatric acute lymphoblastic leukemia (ALL).

A Tumor Suppressive Function of Bim:

Several studies suggest that Bim functions as a tumor suppressor. In mice, inactivation of one allele of Bim accelerates Myc-induced B cell leukemia. In this experimental system, Bim is induced by Myc, and inactivation of one Bim allele was sufficient for Myc-induced tumor development. Whereas the p19Arf/p53 pathway is frequently mutated in tumors arising in Bim+/+ Eμ-Myc mice, it was unaffected in most Bim-deficient tumors, indicating that Bim reduction is an effective alternative to loss of p53 function [23]. Similarly, Bim deficiency in mice overexpressing the Eμ-vAbl oncogene accelerated the development of plasmacytomas . The v-Abl-expressing plasmacytomas frequently harbor a rearranged c-Myc gene [24]. Another example is the formation and growth of tumors derived from baby mouse kidney epithelial (BMK) cells transformed by E1A and dominant negative p53, that is facilitated by simultaneous Bim deficiency [25], suggesting a role for Bim in preventing epithelial cancer cell formation. These authors [25] also showed that Bim-deficiency led to

paclitaxelresistant tumor cells. An interesting study by Merino et al. [26] showed that Bim deficiency in PyMT (MMTV-Polyoma Middle-T) female mice didn't affect primary breast tumor growth, but rather increased the survival of metastatic cells within the lung. These data suggest a role for Bim in the suppression of breast cancer metastasis. Bim is frequently eliminated in human cancer, providing a growth advantage to the tumor cells. For instance, homozygous deletions of the Oncotarget cancers through Cox2/PGE2 signaling that activates the c-Raf/MEK/ERK1/2 pathway [27]. Treatment of Cox2- expressing colorectal carcinoma with selective Cox2 inhibitors induced Bim expression [27]. Downregulation of Bim expression was associated with tumor progression towards an anchorage-independent phenotype [27]. This might be due to upregulation of Bim by oncogenic stress stimuli. BimEL and BimL were also found to be expressed at higher levels in prostate cancer cells than normal prostate tissue [28].

Apoptosis and autophagy: BIM as a mediator of tumour cell death in response to oncogene-targeted therapeutics.

The BCL-2 homology domain 3 (BH3)-only protein, B-cell lymphoma 2 interacting mediator of cell death (BIM) is a potent pro-apoptotic protein belonging to the B-cell lymphoma 2 protein family. In recent years, advances in basic biology have provided a clearer picture of how BIM kills cells and how BIM expression and activity are repressed by growth factor signalling pathways, especially the extracellular signal-regulated kinase 1/2 and protein kinase B pathways. In tumour cells these oncogene-regulated pathways are used to counter the effects of BIM, thereby promoting tumour cell survival. In parallel, a new generation of targeted therapeutics has been developed, which show remarkable specificity and efficacy in tumour cells that are addicted to particular oncogenes. It is now apparent that the expression and activation of BIM is a common response to these new therapeutics. Indeed, BIM has emerged from this marriage of basic and applied biology as an important mediator of tumour cell death in response to such drugs. The induction of BIM alone may not be sufficient for significant tumour cell death, as BIM is more likely to act in concert with other BH3-only proteins, or other death pathways, when new targeted therapeutics are used in combination with traditional chemotherapy agents. [29]

Keywords: Cytokine deprivation, calcium flux, ligation, antigen receptors,anoikis, perturbation, double KO(knock out) cells, MOMP,ROS

BH3-only protein BIM: An emerging target in chemotherapy:

Bim initiates the intrinsic apoptotic pathway under both physiological and patho-physiological conditions. Reduction in Bim expression was found to be associated with tumor promotion and autoimmunity, while over expression inhibited tumor growth and drug resistance as cancer cells suppress Bim expression and stability. Apart from its role in normal homeostasis, Bim has emerged as a central player in regulation of tumorigenesis, therefore gaining attention as a plausible target for chemotherapy. Regulation of Bim

expression and stability is complicated and regulated at multiple levels viz. transcriptional, post-transcriptional, post-translational (preferably by phosphorylation and ubiquitination), epigenetic (by promoter acetylation or methylation) including miRNAs. Furthermore, control over Bim expression and stability may be exploited to enhance chemotherapeutic efficacy, overcome drug resistance and select anticancer drug regimen as various chemotherapeutic agents exploit Bim as an executioner of cell death. Owing to its potent anti-tumorigenic activity many BH3 mimetics e.g. ABT-737, ABT-263, obatoclax, AT-101and A-1210477 have been developed and entered in clinical trials. It is more likely that in near future strategies commanding Bim expression and stability ultimately lead to Bim based therapeutic regimen for cancer treatment. [30] [31] [32] [33]

Keywords: Apoptosis; Bcl-2 family; Cell signaling; Mitochondria, tumorigenesis, chemotherapy, BH3 mimetic

Future directions in Developing Bim targeted tumor treatments:

Various tumors are immortalized and transformed with over expression of anti-apoptotic Bcl-2 family proteins. Recently, plenty of BH3 mimetics has been developed some of which show successful outcome in both in vitro and clinical trials. Bim can abrogate the functions of all of the anti-apoptotic Bcl2 family protein. [34] Interestingly, in some tumors, Bim expression is inversely correlated to Mcl-1 expression [35] [36]. Thus, Bim protein injection into cells is a potent candidate of Bim-targeted tumor treatment, especially for tumors resistant to BH3 mimetics. Bim downregulation is crucial not only for chemotherapy resistance but also for metastasis. The effects of some Bim-targeted agents can be restricted to the restitution of anchorage-dependence or chemotherapy sensitivity. This restriction can reduce side effects and provide possible new cocktail regimens of chemotherapeutic agents. On the other hand, the strong pro-apoptotic ability of Bim can abrogate all of the anti-apoptotic Bcl-2 molecules. This ability can make Bim-targeted agents act only as strong cytotoxins without tumor selectivity, and is a significant disadvantage. [37] [38] Nevertheless, tumor-selective kill is a distinct possibility with Bim-targeted therapies. The diversity of Bim regulatory systems provides researchers tumor-selective Bim-targeted agents. Accordingly, correction of abnormal Bim-regulation systems abrogates tumorigenesis, metastatic ability, and chemoresistance. As previously explained above, Bim down-regulation is mainly promoted by ERK phosphorylation and subsequent proteasomal degradation, although Bim is rigorously regulated by various transcriptional and post-transcriptional systems in normal mammalian cells. Thus, a restitution of the ubiquitination-proteasome Bim degradation system is the key to furnishing tumor selectivity. Furthermore, proteasome inhibitors such as bortezomib cannot target all Bim-downregulated tumors. This phenomenon suggests that the Bim proteasome degradation system is a cell-specific target. However, the search for proper targets in the ubiquitin-proteasome system is relatively young, and much more work needs to be done to furnish better options for therapy.

Keywords: Abrogate, in vitro

CONCLUSION

Physiologically, the pro-apoptotic BH3-only protein Bim plays a key role in induction of apoptosis of various type cells and development of some organs. Recently, the knowledge pertaining to the importance of Bim in cancer is increasing. Current reports suggest that Bim downregulation is important for tumorigenesis, especially for metastatic ability. The ERK-mediated proteasomal degradation system is frequently used for Bim downregulation in order for cancer cells to obtain metastatic ability. Chemotherapeutic agents, such as imatinib, gefitinib, and bortezomib activate Bim in order to kill tumor cells. [39] These agents are, as it were, primitive Bim-targeted agents. Bim downregulation contributes to chemoresistance as well. A direct Bim protein transduction system is a potent candidate of tumor treatment because BH3 mimetics show successful tumor treatment data. [40] Furthermore, Bim protein transduction may possibly overcome tumor resistance to BH3 mimetics.

A possible disadvantage of the application of drugs targeting Bim is the potential for a strong and broad range apoptosis induction. However, this point can be easily turned into an advantage, if Bim selectivity could be engineered into the candidate molecule. The potent advantage of Bim-targeting therapy is tumor cell selectivity because of the diversity of Bim controlling systems within cells. Furthermore, targeting of the Bim ubiquitination-proteasome degradation system, which is frequently used by tumor cells as an escape route from chemotherapeutic agents or anoikis, can provide tumor selectivity. Bim suppression is important not only for chemotherapy resistance but also for metastasis. The effects of some Bim-targeted agents are more a restitution of anchorage-dependence or chemotherapy sensitivity than as direct tumor killers. This potent feature may provide a new combination recipe for chemotherapeutic agents clinically. The area of Bim-targeted cancer treatment is really in an early phase of development. Further critical analysis of the Bim regulatory system is required in order to genuinely test the boundaries for such a not-so-novel concept.

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