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Letter to the Editor

Nomenclature of dynein light chain-linked BH3-only protein Bim isoforms

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Dear Editor,

Bcl-2 family members play pivotal roles in regulation of apoptosis. They functionally and physically associate with the mitochondrial membrane and regulate mitochondria-mediated apoptotic signals either positively or negatively. The proapoptotic Bcl-2 subfamily can be divided into two groups. One possesses multiple domains, that is, three Bcl-2 homology domains 1–3 (BH1–3) and the other possesses a BH3 domain alone.[1,2] To date, at least eight BH3-only protein members (Bad, Bid, Bik/Blk, Bim/Bod, Bmf, Hrk, PUMA and Noxa) have been identified and all of them strongly induce apoptosis. Their proapoptotic activity is strictly controlled by transcriptional or post-translational regulation. For example, transcription of Noxa and Puma is activated in a p53-dependent manner, whereas Bad, Bim and Bmf are regulated by phosphorylation. Although Bim and Bmf directly bind to DLC (dynein light-chain) proteins, which are components of both dynein and myosin V motor complexes, they are sequestered from DLC proteins when they are phosphorylated.[3–5] These unbound Bim and Bmf molecules are recruited to the mitochondrial membrane and interact with Bcl-2 or Bcl-XL, allowing inhibition of their antiapoptotic activity.[6]

There are a variety of Bim mRNA transcripts which are the products of alternative splicing.[7] These various isoforms differ in size and may have different apoptotic activity. Some of them lack the BH3 domain and the others lack DLC-binding domain. These isoforms may function as decoys of proapoptotic Bim products, probably representing a novel regulatory mechanism for BH3-only proteins. Originally, three different Bim isoforms (BimEL, BimL and BimS) were found[3] and thereafter a lot of other isoforms have been identified and the number is still expanding.[8,9] Indeed, reverse transcriptase-polymerase chain reaction (RT-PCR) technique and western blots clearly demonstrate that variable isoforms are abundantly expressed in a cell line (Figure 1a) and significant portions of Bim products other than BimEL, BimL and BimS isoforms were detected to exist variably in cell lines (Figure 1b), indicating that variable Bim transcripts are actually translated in cells. The biological functions of several novel Bim isoforms have already been characterized.[8–10] These data imply roles of variable Bim isoforms in regulating the life and death of cells. Owing to the independent isolation by several laboratories, a wide variety of names have been used in the literature to refer to them. To facilitate the dissemination of information concerning these isoforms, we propose the name changes that are shown in Figure 2. These names describe the domain structure of the isoforms, that is, BimD has no BH3 domain, and thus this isoform is a kind of decoy. BimDd has a dynein-binding domain while BimED has exon 3, which is a feature of BimEL. Determination of the exon numbers was carried out on the basis of a matching process between cDNA and the genomic sequences according to the BAC clone RP11-438K19 (Accession number AC096670).

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M Adachi[*,1,2], *X Zhao*[1,2] *and K Imai*[1]

[1] First Department of Internal Medicine, Sapporo Medical University School of Medicine, S1 W16, Sapporo 060-8543, Japan
[2] Division of Molecular Oncology and Molecular Diagnosis, Graduate School of Medicine, Sapporo Medical University School of Medicine, S1 W16, Sapporo 060-8543, Japan
* Corresponding author: M Adachi, Division of Molecular Oncology and Molecular Diagnosis, Graduate School of Medicine, Sapporo Medical University School of Medicine, S1 W16, Sapporo 060-8543, Japan. Tel: +81 11 611 2111; Fax: +81 11 611 2282; E-mail: adachi@sapmed.ac.jp

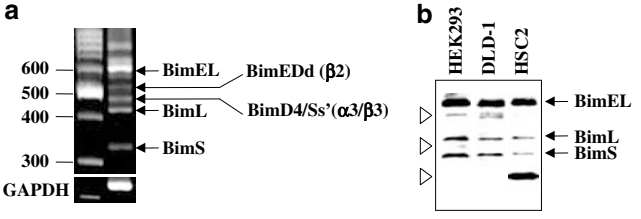

Figure 1 Expression of Bim isoforms in human cell lines. (**a**) Total RNA of HSC-2 cells was extracted with TRIzol (BRL Life and Technologies, MD, USA). Bim cDNAs were amplified and isolated from 0.5 μg of total RNA using M-MLV Reverse transcriptase (RT; Invitrogen, Carlsbad, CA, USA) with oligo $(dT)_{20}$ and TOPO TA Cloning Kit (Invitrogen). The following primer pairs were used for RT-PCR: GAPDH: 5′-cgaccactttgtcaagctca-3′ and 5′-aggggtctacatggcaactg-3′; Bim: 5′-atggcaaagcaaccttctga-3′ and 5′-tcaatgcattctccacacca-3′. PCR products were isolated from each band and cloned into the TA cloning vector to determine these Bim isoforms by sequencing. Molecular size marker is shown in base pairs. (**b**) Total cell lysates (20 μg/lane) from HEK293, DLD-1 and HSC-2 were subjected to western blot analysis using a polyclonal anti-Bim antibody (Santa Cruz Biotechnology). BimEL, BimL and BimS are indicated by arrows, and the other isoforms are indicated by open triangles

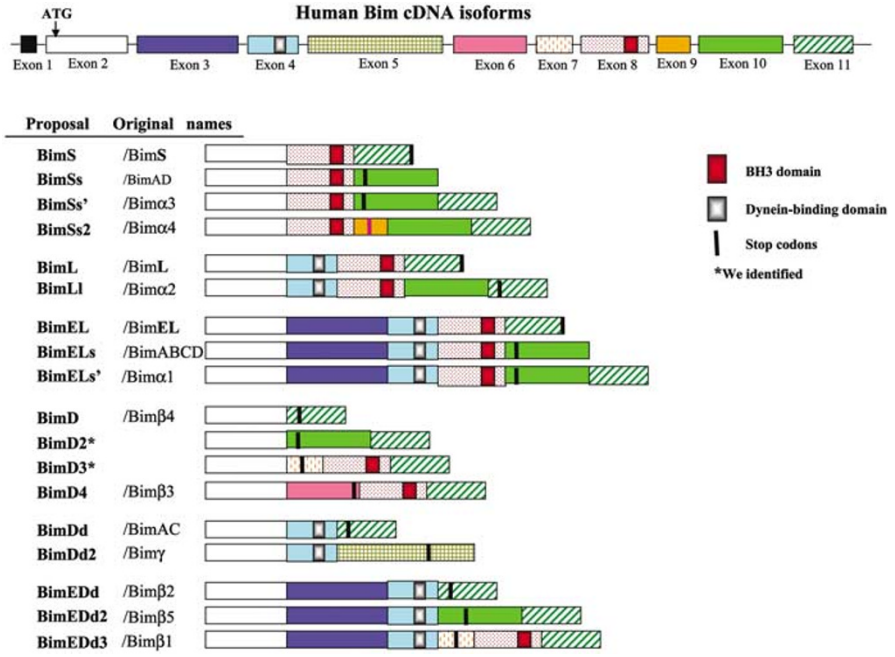

Figure 2 Alignment of Bim isoforms and their transcripts

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