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Supplemental Information

The BCL-2 Family Reunion

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Table S1. Signaling to the BCL-2 family

Protein	Stimulus/Inducer	Regulation	Regulating Factor	Effect	Reference
BH3-only proteins					
BAD	Growth factor	Phosphorylation	Akt	Anti-apoptotic	del Peso et al., 1997; Datta et al., 1997
	Cytokine	Phosphorylation	p70S6k	Anti-apoptotic	Harada et al., 2001
	Growth factor	Phosphorylation	PKA	Anti-apoptotic	Datta et al., 2000
	Growth factor	Phosphorylation	p90RSK	Anti-apoptotic	Tan et al., 1999
	Growth factor	Phosphorylation	PIM kinases	Anti-apoptotic	Fox et al., 2003; Yan et al., 2003
	Cytokine	Phosphorylation	PAK	Anti-apoptotic	Schürmann et al., 2000; Cotteret et al., 2003
	Growth factor withdrawal	Phosphorylation	JNK	Pro-apoptotic	Donovan et al., 2002
	Suppression of neuronal activity	Phosphorylation	Cdc2	Pro-apoptotic	Konishi et al., 2002
	Glucose/Growth factor	Phosphorylation		Glucose/Insulin metabolism	Danial et al., 2003; Danial et al., 2008
	Calcium	Dephosphorylation	Calcineurin	Pro-apoptotic	Wang et al., 1999
	Cytokine withdrawal	Dephosphorylation	PP2A and PP2C	Pro-apoptotic	Chiang et al., 2001; Klumpp et al., 2003
	Cytokine withdrawal	Dephosphorylation	PP1	Pro-apoptotic	Ayllón et al., 2000
	BAD phosphorylation	Sequestration	14-3-3	Anti-apoptotic	Zha et al., 1996; Datta et al., 2000
BID	Fas/TNFα/TRAIL	Cleavage	Caspase 8	Pro-apoptotic	Li et al., 1998 Luo et al., 1998
	Heat shock	Cleavage	Caspase 2	Pro-apoptotic	Bonzon et al., 2006
	Cytotoxic T cell	Cleavage	Granzyme B	Pro-apoptotic	Sutton et al., 2000; Heibein et al., 2000
	Ischemia / cisplatin	Cleavage	Calpain	Pro-apoptotic	Chen et al., 2001; Mandic et al., 2002
	Lysosome permabilization	Cleavage	Cathepsin	Pro-apoptotic	Stoka et al., 2001; Reiners et al., 2002
	BID cleavage	N-myristoylation (C-BID)		Pro-apoptotic	Zha et al., 2000
	BID cleavage	Ubiquitination (N-BID)		Pro-apoptotic	Tait et al., 2007
	TNFα	Phosphorylation	JNK	Pro-apoptotic	Deng et al., 2003
		Phosphorylation	Casein kinase	Anti-apoptotic	Desagher et al., 2001; Degli Esposti et al., 2003
	DNA damage	Phosphorylation	ATM	S phase arrest	Zinkel et al., 2005; Kamer et al., 2005
BIM	Cytokine withdrawal	Transcription	FOXO3a	Pro-apoptotic	Dijkers et al., 2000; Gilley et al., 2003
	ER stress	Transcription	CHOP-C/EBPα	Pro-apoptotic	Puthalakath et al., 2007
	Growth factor withdrawal	Transcription	c-Jun, FOXO and Myb	Pro-apoptotic	Biswas et al., 2007
	Glucocorticoid	Transcription	Glucocorticoid receptor	Pro-apoptotic	Erlacher et al., 2005; Ploner et al., 2008
	TGF-β	Transcription	Smad	Pro-apoptotic	Ramjaun et al., 2007
		Transcription	E2F1	Pro-apoptotic	Hershko and Ginsberg, 2004
		mRNA stability	miR-17-92	Anti-apoptotic	Xiao et al., 2008
	Growth factor	Phosphorylation	ERK1/2 and RSK1/2	Anti-apoptotic	Ley et al., 2003; Dehan et al., 2009
	DNA damage / Trophic factor withdrawal	Phosphorylation	JNK	Pro-apoptotic	Lei and Davis, 2003; Putcha et al., 2003
	ER stress	Dephosphorylation	PP2A	Pro-apoptotic	Puthalakath et al., 2007
	Growth factor	Ubiquitination	βTrCP	Anti-apoptotic	Akiyama et al., 2003; Dehan et al., 2009
		Sequestration	DLC1	Anti-apoptotic	Puthalakath et al., 1999
BIK	DNA damage	Transcription	P53	Pro-apoptotic	Mathai et al., 2002
	TGF-β	Transcription	Smad	Pro-apoptotic	Spender et al., 2009
		Transcription	E2F1	Pro-apoptotic	Real et al., 2006
	Proteasome inhibition			Pro-apoptotic	Nikrad et al., 2005; Zhu et al., 2005
		Cleavage	RHBDD1	Anti-apoptotic	Wang et al., 2008
		Phosphorylation	Casein kinase	Pro-apoptotic	Verma et al., 2001; Li et al., 2003
BMF	TGF-β	Transcription	Smad	Pro-apoptotic	Ramjaun et al., 2007
		Sequestration	DLC2	Anti-apoptotic	Puthalakath et al., 2001

Table S1 continued

HRK	Potassium deprivation	Transcription	c-Jun	Pro-apoptotic	Ma et al., 2007
		Transcription	E2F1	Pro-apoptotic	Hershko and Ginsberg, 2004
	Cytokine	Transcription inhibition	DREAM	Anti-apoptotic	Sanz et al., 2001
NIX	Hypoxia	Transcription	HIF1-α	Pro-apoptotic	Sowter et al., 2001
Noxa	DNA damage	Transcription	p53	Pro-apoptotic	Oda et al., 2000
	DNA damage	Transcription	p73	Pro-apoptotic	Flinterman et al., 2005
	Hypoxia	Transcription	HIF1-α	Pro-apoptotic	Kim et al., 2004
		Transcription	E2F1	Pro-apoptotic	Hershko and Ginsberg, 2004
	Proteasome inhibition	Transcription	cMyc	Anti-apoptotic	Nikiforov et al., 2007
		Transcription inhibition	ΔNp63	Anti-apoptotic	Rocco et al., 2006
		Transcription inhibition	Bmi1	Anti-apoptotic	Yamashita et al., 2008
PUMA	DNA damage / Growth factor withdrawal	Transcription	p53	Pro-apoptotic	Nakano and Vousden, 2001; Yu et al., 2001
	DNA damage / Growth factor withdrawal	Transcription	p73	Pro-apoptotic	Melino et al., 2004; Ming et al., 2008
	Cytokine withdrawal	Transcription	FOXO3a	Pro-apoptotic	You et al., 2006
	Glucocorticoid	Transcription	Glucocorticoid receptor	Pro-apoptotic	Erlacher et al., 2005
	ER stress	Transcription	CHOP and p53	Pro-apoptotic	Li et al., 2006; Kieran et al., 2007
		Transcription	E2F1	Pro-apoptotic	Hershko and Ginsberg, 2004
		Transcription inhibition	ΔNp73	Anti-apoptotic	Melino et al., 2004
		Transcription inhibition	ΔNp63	Anti-apoptotic	Rocco et al., 2006
		Transcription inhibition	Slug	Anti-apoptotic	Wu et al., 2005
Anti-apoptotic BCL-2 proteins					
A1	TNFα	Cleavage	Calpain	Pro-apoptotic	Kucharczak et al., 2005
BCL-2		mRNA stability	miR-15/miR-16	Pro-apoptotic	Cimmino et al., 2005
		Phosphorylation	ERK1/2	Anti-apoptotic	Deng et al., 2000; Deng et al., 2004
		Phosphorylation	JNK	Pro-apoptotic	Yamamoto et al., 1999; Xiao et al., 2004
	Nutriment deprivation	Phosphorylation	JNK	Induction of Autophagy	Wei et al., 2008
		S-nitrosylation	nitric oxide	Anti-apoptotic	Chanvorachote et al., 2006; Azad et al., 2006
BCL-xL	DNA damage	Phosphorylation	JNK	Pro-apoptotic	Kharbanda et al., 2000; Basu and Haldar, 2003
	DNA damage	Deamidation			Deverman et al., 2002; Zhao et al., 2007
MCL-1	Oxydative stress	Phosphorylation	JNK	Pro-apoptotic	Inoshita et al., 2002
	Cytokine withdrawal	Phosphorylation	GSK-3	Pro-apoptotic	Maurer et al., 2006
		Phosphorylation	ERK-1/2	Anti-apoptotic	Domina et al., 2004
	DNA damage	Ubiquitination	MULE	Pro-apoptotic	Nijawan et al., 2003; Zhong et al., 2005; Warr et al., 2005
	DNA damage	Ubiquitination	NOXA binding	Pro-apoptotic	Willis et al., 2005; Czabotar et al., 2007
		Ubiquitination	β-TrCP	Pro-apoptotic	Ding et al., 2007
		Deubiquitination	USP9X	Anti-apoptotic	Schwickart et al., 2010
Pro-apoptotic effectors					
BAX	DNA damage	Transcription	P53	Pro-apoptotic	Miyashita et al., 1995
	Growth factor, Nicotine	Phosphorylation	Akt	Anti-apoptotic	Gardai et al., 2004; Xin and Deng, 2005
	Nicotine	Phosphorylation	PKCζ	Anti-apoptotic	Xin et al., 2007
	Cytokine	Phosphorylation	ERK1/2	Anti-apoptotic	Shen et al., 2009
	DNA damage	Phosphorylation	JNK and p38	Pro-apoptotic	Kim et al., 2006
	Trophic factor withdrawal	Phosphorylation	GSK3-β	Pro-apoptotic	Linseman et al., 2004
		Dephosphorylation	PP2A	Pro-apoptotic	Xin and Deng, 2006
	Cytokine withdrawal	Cleavage	Calpain	Pro-apoptotic	Toyota et al., 2003; Shen et al., 2009

Table S2. Mammalian BCL-2 family protein data bank (PDB) structures
The X-ray and NMR structures are colored in black and red, respectively; species are indicated by h = human, m = mouse or r = rat; h-r denotes human-rat chimeric proteins; *denotes NMR models derived using docking algorithms.

Free Protein / Complex	PDB	Reference
mA1 + mBAK BH3	2VOH	Smits et al., 2008
mA1 + BID BH3	2VOI	Smits et al., 2008
hA1 + hBIM BH3	2VM6	Herman et al., 2008
mA1 + mBMF BH3	2VOG	Smits et al., 2008
mA1 + mPUMA BH3	2VOF	Smits et al., 2008
hBAK (native)	2IMT	Moldoveanu et al., 2006
hBAK (Se-Met derivative)	2IMS	Moldoveanu et al., 2006
hBAK	2YV6	Wang et al., 2009
hBAX	1F16	Suzuki et al., 2000
hBAX + hBIM SAHB	2K7W*	Gavathiotis et al., 2008
hBCL-2 (isoform 1)	1G5M	Petros et al., 2001
hBCL-2 (isoform 2)	1GJH	Petros et al., 2001
hBCL-w	1O0L	Hinds et al., 2003
hBCL-w	1MK3	Denisov et al., 2003
hBCL-w + mBID BH3	1ZY3*	Denisov et al., 2006
hBCL-xL	1MAZ	Muchmore et al., 1996
hBCL-xL	1LXL	Muchmore et al., 1996
rBCL-xL	1AF3	Aritomi et al., 1997
mBCL-xL	1PQ0	Liu et al., 2003
hBCL-xL	1R2D	Manion et al., 2004
hBCL-xL + hBAD BH3	1G5J	Petros et al., 2000
hBCL-xL + hBAK BH3	1BXL	Sattler et al., 1997
hBCL-xL + hBCL-xL	2B48	O'Neill et al., 2006
hBCL-xL + hBeclin BH3	2P1L	Oberstein et al., 2007
mBCL-xL + mBeclin BH3	2PON	Feng et al., 2007
mBCL-xL + mBIM BH3	1PQ1	Liu et al., 2003
hBCL-xL + hBIM BH3	3FDL	Lee et al., 2009
hBID	2BID	Chou et al., 1999
mBID	1DDB	McDonnell et al., 1999
mMCL-1	1WSX	Day et al., 2005
h-rMCL-1 + hBIM BH3	2NL9	Czabotar et al., 2007
mMCL-1 + mNoxa BH3 A	2ROD	Day et al., 2008
mMCL-1 + mNoxa BH3 B	2JM6	Czabotar et al., 2007
h-rMCL-1 + hNoxa BH3 B	2NLA	Czabotar et al., 2007
mMCL-1 + mPUMA BH3	2ROC	Day et al., 2008

Table S3. BCL-2 family mouse model phenotypes

Gene	Mutation	Phenotype	Combination Phenotype	Reference
Anti-apoptotic BCL-2 proteins				
a1	Knockout	Neutrophils display enhanced spontaneous apoptosis and lack LPS-induced apoptosis inhibition	-NA-	Hamasaki et al., 1998 Orlofsky et al., 2002
bcl-2	Knockout	Increased postnatal mortality, polycystic kidneys, apoptotic involution of thymus and spleen, graying of hair follicles, reduced numbers of neurons, small size	**with *bik-/-* :** No additional phenotype **with *bim-/-* :** Heterozygous knockout rescues pigment defect; homozygous knockout further rescues kidney phenotype (see below)	Coultas et al., 2004 Veis et al., 1993 Boulliet et al., 2001
bcl-w	Knockout	Male sterile due to spermatogenesis defects	-NA-	Print et al., 1998
bcl-x	Knockout	Lethal at embryonic day E13.5 due to massive apoptosis of hematopoietic and neuronal cells	-NA-	Motoyama et al., 1995
mcl-1	Knockout	Embryonic lethal due to failure of the blastocyst to implant	-NA-	Rinkenberger et al., 2000
Pro-apoptotic effectors				
bak	Knockout	None	**with *bax-/-* :** Pre-/peri-natal lethality; interdigital webbing; behavioral, hematopoetic, homeostatic, immune, nervous system and reproductive defects; cells resistant to apoptosis **with *bim-/-* :** Increased white blood cells	Lindsten et al., 2000 Hutcheson et al., 2005
bax	Knockout	B and T cell hyperplasia; abnormal germ cells and gonad morphology; prolonged ovarian lifespan; reduced CNS and PNS cell death	**with *bak-/-* :** See above **with *bim-/-* :** Inter-digital webbing; male infertility; increased white blood cells (see below)	Hutcheson et al., 2005 Knudson et al., 1995 Wei et al., 2001
BH3-only proteins				
bad	Knockin (3S→3A)	Growth factor-dependent survival is reduced in immune and nervous cells	-NA-	Datta et al., 2002
	Knockin (S155A)	Abnormal insulin secretion	-NA-	Danial et al., 2008
	Knockout	Animals develop diffuse large B cell lymphoma	-NA-	Ranger et al., 2003
bid	Knockout	Animals are resistant to anti-Fas ligation	**with *bim-/-* :** No additional phenotype (see below)	Yin et al., 1999 Willis et al., 2007
bik	Knockout	None	**with *bcl-2-/-* :** See above **with *bim-/-* :** Male infertility	Coultas et al., 2005
bim	Knockout	Accumulation of lymphoid and myeloid cells; development of autoimmune kidney disease; females display imperforated vaginas	**with *bak-/-* :** See above **with *bax-/-* :** See above **with *bid-/-* :** See above **with *bik-/-* :** See above **with *bcl-2-/-* :** See above **with *noxa-/-* :** Abnormal NK cell morphology	Bouillet et al., 1999 Huntington et al., 2007
bmf	Knockout	Lymphocytes protected from apoptosis induced by glucocorticoids or histone deacetylase inhibitors; mice develop B-cell restricted lymphadenopathy; increased rate of gamma-irradiation-induced thymic lymphomas	-NA-	Labi et al., 2008
bnip3L/nix	Knockout	Abnormal morphology, lack of mitochondrial clearance, decreased numbers and increased fragility of reticulocytes and erythcrocytes	-NA-	Diwan et al., 2007 Schweers et al., 2007
hrk	Knockout	Motorneurons are protected from cell death induced by resection of the hypoglossal nerve; delayed cell death of superior cervical ganglia neurons triggered by nerve growth factor withdrawal	-NA-	Imaizumi et al., 2004 Coultas et al., 2007
noxa	Knockout	MEFs and thymocytes display mild resistance to etoposide	**with *bim-/-* :** see above	Villunger et al., 2003
puma	Knockout	Lymphocytes protected from apoptosis; thymocytes, neurons and MEFs resistant to DNA-damage induced apoptosis	-NA-	Jeffers et al., 2003 Villunger et al., 2003

Table S4. Non-BCL-2 family regulators of MOMP

Protein	Putative BH3?	Binding Partner(s)	Mechanism	MOMP Description	Reference
14-3-3θ	No	BAX	Inhibitor	Blocks BAX translocation and MOMP	Nomura et al., 2003
2-5 (A) Synthetase 9-2	Yes	BCL-2, BCL-xL	De-repressor	Over-expression induces apoptosis; mutation of the putative BH3 domain abolishes interaction with BCL-2 and BCL-xL and abolishes apoptosis induction	Ghosh et al., 2001
Apolipoprotein L6	Yes	Unknown	Unknown	MOMP and apoptosis induced by overexpression is dependent on the BH3 domain	Liu et al., 2005
ASC/TMS1/PYCARD	No	BAX	Direct activator	Knockdown of ASC inhibits BAX translocation	Ohtsuka et al., 2004
ATG5	No	BCL-xL	De-repressor	Calpain-cleaved Atg5 translocates from the cytosol to mitochondria and associates with BCL-xL	Yousefi et al., 2006
BRCC2	Yes	Unknown	Unknown	Over-expression induces apoptosis, which can be blocked by BCL-xL. Deletion of a BH3-like domain abolishes apoptosis-inducing activity	Broustas et al., 2004
G0S2	No	BCL-2	De-repressor	Prevents BCL-2:BAX association	Welch et al., 2009
Histone H1.2	No	Unknown	Unknown	MOMP induction is dependent on BAK	Konishi et al., 2003
Humanin	No	BAX, BID, BIM	Inhibitor	Inhibits BAX, BID and BIM	Guo et al., 2003 Luciano et al., 2005 Zhai et al., 2005
Ku-70	No	BAX	Inhibitor	Inhibits BAX in the cytosol	Amsel et al., 2008
MAP-1	Yes	BAX	Direct activator	Interacts with BAX following apoptotic stimuli; siRNA-mediated knockdown reduces apoptosis induced by BAX over-expression and BAX translocation to the mitochondria during apoptosis	Tan et al., 2001 Tan et al., 2005
Nucleophosmin	No	BAX	Direct activator	Binds active BAX during apoptosis	Kerr et al., 2007
Nur77/TR3	No	BCL-2	Direct activator/De-repressor	Induces MOMP, requires BCL-2 over-expression	Lin et al., 2004
p53	No	BAK, BAX, BCL-xL	Direct activator/De-repressor	Induces MOMP via BAK/BAX	Mihara et al., 2003 Chipuk et al., 2004 Leu et al., 2004 Chipuk et al., 2005
RAD9	Yes	BCL-2, BCL-xL	De-repressor	Deletion of BH3 domain abolishes ability to induce apoptosis and interact with BCL-2 and BCL-xL	Komatsu et al., 2000
SPIKE/CMP5	Yes	Bap31	De-repressor	Prevents formation of a complex between Bap31 and BCL-xL	Mund et al., 2003
Tissue Transglutaminase	Yes	BAX	Direct activator	Sensitizes cells to staurosporine in a BH3-dependent manner; co-IPs BAX from purified mitochondria	Rodolfo et al., 2004
VDAC2	No	BAK	Inhibitor	Maintains BAK in a monomeric, inactive conformation	Cheng et al., 2003

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