

PIM serine/threonine kinases in the pathogenesis and therapy of hematologic malignancies and solid cancers

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References

- Xie Y, Xu K, Linn DE, Yang X, Guo Z, Shimelis H, et al. The 44-kDa Pim-1 kinase phosphorylates BCRP/ABCG2 and thereby promotes its multimerization and drug-resistant activity in human prostate cancer cells. *J Biol Chem.* 2008;283(6):3349-56.
- Zhang F, Beharry ZM, Harris TE, Lilly MB, Smith CD, Mahajan S, et al. PIM1 protein kinase regulates PRAS40 phosphorylation and mTOR activity in FDCCP1 cells. *Cancer Biol Ther.* 2009;8(9):846-53.
- Peng C, Knebel A, Morrice NA, Li X, Barringer K, Li J, et al. Pim kinase substrate identification and specificity. *J Biochem.* 2007;141(3):353-62.
- Yan B, Zemskova M, Holder S, Chin V, Kraft A, Koskinen PJ, et al. The PIM-2 kinase phosphorylates BAD on serine 112 and reverses BAD-induced cell death. *J Biol Chem.* 2003;278(46):45358-67.
- Aho TL, Sandholm J, Peltola KJ, Mankonen HP, Lilly M, Koskinen PJ. Pim-1 kinase promotes inactivation of the pro-apoptotic Bad protein by phosphorylating it on the Ser112 gatekeeper site. *FEBS Lett.* 2004;571(1-3):43-9.
- Fox CJ, Hammerman PS, Cinalli RM, Master SR, Chodosh LA, Thompson CB. The serine/threonine kinase Pim-2 is a transcriptionally regulated apoptotic inhibitor. *Genes Dev.* 2003;17(15):1841-54.
- Macdonald A, Campbell DG, Toth R, McLauchlan H, Hastie CJ, Arthur JS. Pim kinases phosphorylate multiple sites on Bad and promote 14-3-3 binding and dissociation from Bcl-XL. *BMC Cell Biol.* 2006;7:1.
- Koike N, Maita H, Taira T, Ariga H, Iguchi-Ariga SM. Identification of heterochromatin protein 1 (HP1) as a phosphorylation target by Pim-1 kinase and the effect of phosphorylation on the transcriptional repression function of HP1(1). *FEBS Lett.* 2000;467(1):17-21.
- Mochizuki T, Kitanaka C, Noguchi K, Muramatsu T, Asai A, Kuchino Y. Physical and functional interactions between Pim-1 kinase and Cdc25A phosphatase. Implications for the Pim-1-mediated activation of the c-Myc signaling pathway. *J Biol Chem.* 1999;274(26):18659-66.
- Bachmann M, Kosan C, Xing PX, Montenarh M, Hoffmann I, Moroy T. The oncogenic serine/threonine kinase Pim-1 directly phosphorylates and activates the G2/M specific phosphatase Cdc25C. *Int J Biochem Cell Biol.* 2006;38(3):430-43.
- Wang Z, Bhattacharya N, Mixter PE, Wei W, Sedivy J, Magnuson NS. Phosphorylation of the cell cycle inhibitor p21Cip1/WAF1 by Pim-1 kinase. *Biochim Biophys Acta.* 2002;1593(1):45-55.
- Morishita D, Katayama R, Sekimizu K, Tsuruo T, Fujita N. Pim kinases promote cell cycle progression by phosphorylating and down-regulating p27Kip1 at the transcriptional and posttranscriptional levels. *Cancer Res.* 2008;68(13):5076-85.
- Grundler R, Brault L, Gasser C, Bullock AN, Dechow T, Woetzel S, et al. Dissection of PIM serine/threonine kinases in FLT3-ITD-induced leukemogenesis reveals PIM1 as regulator of CXCL12-CXCR4-mediated homing and migration. *J Exp Med.* 2009;206(9):1957-70.
- Leverson JD, Koskinen PJ, Orrico FC, Rainio EM, Jalkanen KJ, Dash AB, et al. Pim-1 kinase and p100 cooperate to enhance c-Myb activity. *Mol Cell.* 1998;2(4):417-25.
- Zippo A, De Robertis A, Serafini R, Oliviero S. PIM1-dependent phosphorylation of histone H3 at serine 10 is required for MYC-dependent transcriptional activation and oncogenic transformation. *Nat Cell Biol.* 2007;9(8):932-44.
- Bajaj BG, Verma SC, Lan K, Cotter MA, Woodman ZL, Robertson ES. KSHV encoded LANA upregulates Pim-1 and is a substrate for its kinase activity. *Virology.* 2006;351(1):18-28.
- Gu JJ, Wang Z, Reeves R, Magnuson NS. PIM1 phosphorylates and negatively regulates ASK1-mediated apoptosis. *Oncogene.* 2009;28(48):4261-71.
- Bachmann M, Hennemann H, Xing PX, Hoffmann I, Moroy T. The oncogenic serine/threonine kinase Pim-1 phosphorylates and inhibits the activity of Cdc25C-associated kinase 1 (C-TAK1): a novel role for Pim-1 at the G2/M cell cycle checkpoint. *J Biol Chem.* 2004;279(46):48319-28.
- Hogan C, Hutchison C, Marcar L, Milne D, Saville M, Goodlad J, et al. Elevated levels of oncogenic protein kinase Pim-1 induce the p53 pathway in cultured cells and correlate with increased Mdm2 in mantle cell lymphoma. *J Biol Chem.* 2008;283(26):18012-23.
- Winn LM, Lei W, Ness SA. Pim-1 phosphorylates the DNA binding domain of c-Myb. *Cell Cycle.* 2003;2(3):258-62.
- Zhang Y, Wang Z, Li X, Magnuson NS. Pim kinase-dependent inhibition of c-Myc degradation. *Oncogene.* 2008;27(35):4809-19.
- Rainio EM, Sandholm J, Koskinen PJ. Cutting edge: Transcriptional activity of NFATc1 is enhanced by the Pim-1 kinase. *J Immunol.* 2002;168(4):1524-7.
- Bhattacharya N, Wang Z, Davitt C, McKenzie IF, Xing PX, Magnuson NS. Pim-1 associates with protein complexes necessary for mitosis. *Chromosoma.* 2002;111(2):80-95.
- Wang Z, Bhattacharya N, Meyer MK, Seimiya H, Tsuruo T, Tonani JA, et al. Pim-1 negatively regulates the activity of PTP-U2S phosphatase and influences terminal differentiation and apoptosis of monoblastoid leukemia cells. *Arch Biochem Biophys.* 2001;390(1):9-18.
- Nihira K, Ando Y, Yamaguchi T, Kagami Y, Miki Y, Yoshida K. Pim-1 controls NF-κappaB signalling by stabilizing RelA/p65. *Cell Death Differ.* 2010;17(4):689-98.
- Maita H, Harada Y, Nagakubo D, Kitaura H, Ikeda M, Tamai K, et al. PAP-1, a novel target protein of phosphorylation by pim-1 kinase. *Eur J Biochem.* 2000;267(16):5168-78.
- Chiocchetti A, Gibello L, Carando A, Aspesi A, Secco P, Garelli E, et al. Interactions between RPS19, mutated in Diamond-Blackfan anemia, and the PIM-1 oncogene. *Haematologica.* 2005;90(11):1453-62.
- Aho TL, Sandholm J, Peltola KJ, Ito Y, Koskinen PJ. Pim-1 kinase phosphorylates RUNX family transcription factors and enhances their activity. *BMC Cell Biol.* 2006;7:21.
- Chen XP, Losman JA, Cowan S, Donahue E, Fay S, Vuong BQ, et al. Pim serine/threonine kinases regulate the stability of Socs-1 protein. *Proc Natl Acad Sci USA.* 2002;99(4):2175-80.
- Peltola KJ, Paukku K, Aho TL, Ruuska M, Silvennoinen O, Koskinen PJ. Pim-1 kinase inhibits STAT5-dependent transcription via its interactions with SOCS1 and SOCS3. *Blood.* 2004;103(10):3744-50.
- Ishibashi Y, Maita H, Yano M, Koike N, Tamai K, Ariga H, et al. Pim-1 translocates sorting nexin 6/TRAF4-associated factor 2 from cytoplasm to nucleus. *FEBS.* 2001;506(1):33-8.

Online Supplementary Table S1.

Proposed cellular substrates of PIM serine/threonine kinases

Protein*	OMIM*	Full name	Alternative name(s)	Function	Recognition motif	Target residue(s)	Method(s)	Reference(s)
ABCG2	603756	ATP-binding cassette, sub-family G, member 2	ABCP, BCRP, MRPX	xenobiotic transporter protein	KKKKITV	T362	Y2H	1
AKT1S1	610221	Akt1 substrate proline-rich	PRAS40	cell signaling	RPRLNNTSDFQ	T246	in vitro kinase assay	2
AP15	609774	Apoptosis inhibitor 5	AC11	protein assembly, cell survival	n.d.	n.d. [PIM2]	motif-hypothesis	3
BAD	603167	Bcl2-antagonist of cell death	BCL2L8	cell survival	RGRHSSY...RGRSRSA...ELRRMSD	S75, S98, S118	GST-pulldown	4-7
CBX3	604477	Chromobox protein homolog 3	HP1 γ	chromatin regulation	KRKSLSDSESDDKSKS	S83(?)	Y2H	8
CDC25A	116947	Cell division cycle 25A	-	cell cycle control	n.d.	S118 (?)	GST-pull down	9
CDC25C	157680	Cell division cycle 25C	-	cell cycle control	n.d.	n.d.	GST-pulldown	10
CDKN1A	116899	Cyclin-dependent kinase inhibitor 1A	CIP1, WAF1, p21, KIP1, p27	cell cycle regulation	RKRRQTSM	T145	motif-hypothesis	11
CDKN1B	600778	Cyclin-dependent kinase inhibitor 1B	NPY3R, FUSIN	cell cycle regulation	RKRPAT...LRRRROT	T157, T195	pull-down/motif hypothesis	12
CXCR4	152843	Chemokine, CXC motif, receptor 4	SND1, p100	transcriptional regulator	RGGHSS	S339	motif hypothesis/in vitro kinase assay	13
EBNA2 COACTIVATOR p100	602181	EBNA coactivator p100	-	protein translation	ERHPSWR	n.d.	Y2H	14
EIF4B	603928	Eukaryotic translation initiation factor 4B	4E-BP1	translation	n.d.	S406 [PIM2]	motif-hypothesis	3
EIF4EBP1	602223	Eukaryotic translation initiation factor 4E-binding protein 1	FKHRL1, FOXO3	transcriptional regulator	RPRSTCT...RRRAVS,	T32, S253	S657 [PIM2], Immunoblot	6
FOXO3A	602681	Forkhead box O3A	H3FT, H3T	nucleosome	QTARKST	S10	pull-down/motif hypothesis	12
HIST3H3	602820	Histone H3	-	virus protein	RURRS	S205 and/or S206	GST-pulldown	15
KSHV-LANA1	-	Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen	ASK1	cell signaling	ATRGRCSSVG	S83	motif hypothesis/in vitro kinase assay	16
MAP3K5	602448	Mitogen-activated protein kinase kinase kinase 5	CTAK1	cell cycle regulation	n.d.	T70?	Y2H	17
MARK3	602678	MAP3K10/ubule affinity-regulating kinase 3	HDML	E3 ubiquitin ligase	R3RAIS...RKRHK...	S166, S186	motif hypothesis/in vitro kinase assay	19
MDM2	164785	Mouse double minute 2 homolog	AMV	transcriptional activator	n.d.	n.d.	GST-pull down	20
NYB	169980	ν -myb myeloblastosis viral oncogene homolog	-	transcriptional regulator	AKRAKLDSGR	S329	GST-pulldown/motif hypothesis	21
NYC	190080	ν -myc avian myeloblastosis viral oncogene homolog	NFATC, NFAT2	transcriptional activator	n.d.	n.d.	GST-pull down	22
NFATC1	600489	Nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 1	-	cell division	QIRKRV/SLE	S1981	motif-hypothesis	23
NUMA	164009	Nuclear mitotic apparatus protein 1	GLEPP1, PTPU2	signaling, tumor suppressor?	KRKITN	T95	motif-hypothesis	24
PTPRO	600579	Protein tyrosine phosphatase, receptor type, O	RELA, NFkB-65	transcriptional regulator	QLRRPSDREL	S276	expression cloning/in vitro kinase assay	25
REL-A/p65	164014	V-reil avian reticuloendotheliosis viral oncogene homolog A	PAP1	splicing factor	KHKAKGSSE	S204, S206	Y2H	26
RP9	607331	Retinitis pigmentosa 9, autosomal dominant	-	structural ribosome subunit	n.d.	n.d.	Y2H	27
RPS19	603474	Ribosomal protein S19 (Blackfan-Diamond anemia)	-	transcriptional regulator	n.d.	n.d.	Y2H	28
RUNX1	151385	Runt-related transcription factor 1	ANL1, CBF α 2, PEBP2AB	transcriptional regulator	n.d.	n.d.	Y2H	28
RUNX3	600210	Runt-related transcription factor 3	ANL2, CBF α 3, PEBP2AC	transcriptional regulator	n.d.	n.d.	Y2H/GST-pull down	29,30
SOCS1	603587	Suppressor of cytokine signaling 1	SS11, CIS1, JAB, TIP3	cell signaling	n.d.	n.d.	Y2H	29,30
SOCS3	604476	Suppressor of cytokine signaling 3	SS13, CIS3	-	n.d.	n.d.	Y2H	31
SNX6	606098	Sorting nexin-2	TFAF2,	cell transport	n.d.	n.d.	Y2H	

(*; www.ncbi.nlm.nih.gov/omim/)