

Table S3: Consensus binding motifs for SH2 domains. The experimentally determined consensus peptide binding motifs of a sub-set of SH2 domains.

SH2 Domain	Binding Motif	References
Abl	[pY] [E/T/M] [N/E/D] [P/V/L]	(Songyang et al., 1993)
Blnk	[pY] [D/Q] [D] [V]	(Kabak et al., 2002)
Cbl	[N] [X] [pY] [S/T] [X] [X] [P]	(Lupher et al., 1997)
Crk	[pY] [D/K/N] [H/F/R] [P/V/L]	(Songyang et al., 1993)
Csk	[pY] [T/A/S] [K/R/Q/N] [M/I/V/R]	(Songyang et al., 1994)
Fes	[pY] [E] [X] [V/I]	(Songyang et al., 1994)
Fgr	[pY] [E/Y/D] [E/N/D] [I/V]	(Songyang et al., 1993)
Fyn	[pY] [E/T] [E/D/Q] [I/V/M]	(Songyang et al., 1993)
	[V] [pY] [Q] [N] [W/F]	(Dente et al., 1997)
	[pY] [Q/Y/V] [N] [Y/Q/F]	(Songyang et al., 1994)
Grb2	[pY] [I/V] [N] [I/L/V]	(Rodriguez et al., 2004)
(SEM-5)	[pY] [L/V/I] [N] [V/P]	(Songyang et al., 1993)
Grb7	[F/Y] [pY] [E/T/Y/S] [N] [I/L/V/P/T/Y/S]	(Rodriguez et al., 2004)
Grb10	[F/Y] [pY] [E/T/Y/S] [N] [I/L/V/P/T/Y/S]	(Rodriguez et al., 2004)
Itk	[pY] [A/E/V] [Y/F/E/S/N/V] [P/F/I/H]	(Bunnell et al., 2000)
Lck	[pY] [E/T/Q] [E/D] [I/V/M]	(Songyang et al., 1993)
	[pY] [D/y] [d/e/l/y] [V]	(Jones et al., 2006)
Nck	[pY] [D] [E] [P/D/V]	(Songyang et al., 1993)
PI3KR_N (p85_N)	[pY] [M/I/V/E] [X] [M]	(Songyang et al., 1993)
PI3KR_C (p85_C)	[pY] [M/L/I] [X] [M]	(Songyang et al., 1993)
PLCG1_N	[pY] [V/I/L] [E/D] [L/I/V]	(Songyang et al., 1993)
PLCG1_C	[pY] [V/I/L] [E/D] [P/V/I]	(Songyang et al., 1993)
	[L] [Y/H] [pY] [M/F] [X] [F/M]	(Beebe et al., 2000)
PTPN6_N	[pY] [F] [X] [F/P/L/Y]	(Songyang et al., 1994)
	[V/I/L] [X] [pY] [A] [X] [L/V]	(Beebe et al., 2000)
PTPN6_C	[X] [X] [pY] [Y] [M] [K/R]	(Beebe et al., 2000)
	[pY] [I/V] [X] [V/I/L/P]	(Songyang et al., 1993)
PTPN11_N	[I/L/V/m] [X] [pY] [T/V/A] [X] [I/V/L/f]	(Sweeney et al., 2005)
	[I/L/V] [I/L/V] [I/F/V] [pY] [T/V] [I/L] [I/L/V/P]	(Rodriguez et al., 2004)
PTPN11_C	[T/V/I/y] [X] [pY] [A/s/t/v] [X] [I/v/I]	(Sweeney et al., 2005)
Rasa_N	[pY] [I/L/V] [X] [φ]	(Holland et al., 1997)
Rasa_C	[pY] [X] [X] [P]	(Holland et al., 1997)
	[T/S] [X] [X] [X] [X] [V/I]	(Hwang et al., 2002)
SH2D1A	[T] [I] [pY] [X] [X] [V/I]	(Poy et al., 1999)
SH2D1B	[T] [I] [pY] [X] [X] [V/I]	(Poy et al., 1999)
SH3BP2	[pY] [E/M/V] [N/V/I] [X]	(Songyang et al., 1994)
SHB	[pY] [T/V/I] [X] [L]	(Karlsson et al., 1995)
	[pY] [I/E/Y/L] [X] [I/L/M]	(Songyang et al., 1994)
	[N] [I/V] [pY] [E/G] [T] [I/V/L] [W/F]	(Dente et al., 1997)
Shc1	[pY] [I/E/T] [X] [I/L/M]	(O'Bryan et al., 1996)
Shc2	[pY] [I/M/T/D/L] [M/I] [M/F/I/Y/V]	(O'Bryan et al., 1996)
Shc3	[pY] [L/M/I/Q] [M/Y] [I/L/M/V]	(O'Bryan et al., 1996)
SHIP	[pY] [Y/S/T/v] [L/y/n/l/e/f] [L/N/l/e/l]	(Sweeney et al., 2005)
Src	[pY] [EDT] [ENY] [IML]	(Songyang et al., 1993)
STAT1	[pY] [D/E] [P/R] [R/P/Q]	(Wiederkehr-Adam et al., 2003)
STAT3	[pY] [X] [X] [Q]	(Stahl et al., 1995)
Syk_C	[pY] [Q/T/E] [E/Q] [L/I]	(Songyang et al., 1994)
	[pY] [D/E] [N] [I/F/V]	(Auger et al., 1996)
Tns	[pY] [E] [N] [F/I/V]	(Songyang and Cantley, 1995)
Vav1	[pY] [M/L/E] [E] [P]	(Songyang et al., 1994)

Table S3 References:

- Auger, K. R., Songyang, Z., Lo, S. H., Roberts, T. M., and Chen, L. B. (1996). Platelet-derived growth factor-induced formation of tensin and phosphoinositide 3-kinase complexes. *J Biol Chem* 271, 23452-23457.
- Beebe, K. D., Wang, P., Arabaci, G., and Pei, D. (2000). Determination of the binding specificity of the SH2 domains of protein tyrosine phosphatase SHP-1 through the screening of a combinatorial phosphotyrosyl peptide library. *Biochemistry* 39, 13251-13260.
- Bunnell, S. C., Diehn, M., Yaffe, M. B., Findell, P. R., Cantley, L. C., and Berg, L. J. (2000). Biochemical interactions integrating Itk with the T cell receptor-initiated signaling cascade. *J Biol Chem* 275, 2219-2230.
- Dente, L., Vetriani, C., Zucconi, A., Pelicci, G., Lanfranccone, L., Pelicci, P. G., and Cesareni, G. (1997). Modified phage peptide libraries as a tool to study specificity of phosphorylation and recognition of tyrosine containing peptides. *J Mol Biol* 269, 694-703.
- Holland, S. J., Gale, N. W., Gish, G. D., Roth, R. A., Songyang, Z., Cantley, L. C., Henkemeyer, M., Yancopoulos, G. D., and Pawson, T. (1997). Juxtamembrane tyrosine residues couple the Eph family receptor EphB2/Nuk to specific SH2 domain proteins in neuronal cells. *Embo J* 16, 3877-3888.
- Hwang, P. M., Li, C., Morra, M., Lillywhite, J., Muhandiram, D. R., Gertler, F., Terhorst, C., Kay, L. E., Pawson, T., Forman-Kay, J. D., and Li, S. C. (2002). A "three-pronged" binding mechanism for the SAP/SH2D1A SH2 domain: structural basis and relevance to the XLP syndrome. *Embo J* 21, 314-323.
- Jones, N., Blasutig, I. M., Eremina, V., Ruston, J. M., Bladt, F., Li, H., Huang, H., Larose, L., Li, S. S., Takano, T., *et al.* (2006). Nck adaptor proteins link nephrin to the actin cytoskeleton of kidney podocytes. *Nature* 440, 818-823.
- Kabak, S., Skaggs, B. J., Gold, M. R., Affolter, M., West, K. L., Foster, M. S., Siemasko, K., Chan, A. C., Aebersold, R., and Clark, M. R. (2002). The direct recruitment of BLNK to immunoglobulin alpha couples the B-cell antigen receptor to distal signaling pathways. *Mol Cell Biol* 22, 2524-2535.
- Karlsson, T., Songyang, Z., Landgren, E., Laverne, C., Di Fiore, P. P., Anafi, M., Pawson, T., Cantley, L. C., Claesson-Welsh, L., and Welsh, M. (1995). Molecular interactions of the Src homology 2 domain protein Shb with phosphotyrosine residues, tyrosine kinase receptors and Src homology 3 domain proteins. *Oncogene* 10, 1475-1483.
- Lupher, M. L., Jr., Songyang, Z., Shoelson, S. E., Cantley, L. C., and Band, H. (1997). The Cbl phosphotyrosine-binding domain selects a D(N/D)XpY motif and binds to the Tyr292 negative regulatory phosphorylation site of ZAP-70. *J Biol Chem* 272, 33140-33144.
- O'Bryan, J. P., Songyang, Z., Cantley, L., Der, C. J., and Pawson, T. (1996). A mammalian adaptor protein with conserved Src homology 2 and phosphotyrosine-binding domains is related to Shc and is specifically expressed in the brain. *Proc Natl Acad Sci U S A* 93, 2729-2734.
- Poy, F., Yaffe, M. B., Sayos, J., Saxena, K., Morra, M., Sumegi, J., Cantley, L. C., Terhorst, C., and Eck, M. J. (1999). Crystal structures of the XLP protein SAP reveal a class of SH2 domains with extended, phosphotyrosine-independent sequence recognition. *Mol Cell* 4, 555-561.
- Rodriguez, M., Li, S. S., Harper, J. W., and Songyang, Z. (2004). An oriented peptide array library (OPAL) strategy to study protein-protein interactions. *J Biol Chem* 279, 8802-8807.
- Songyang, Z., Blechner, S., Hoagland, N., Hoekstra, M. F., Piwnicka-Worms, H., and Cantley, L. C. (1994). Use of an oriented peptide library to determine the optimal substrates of protein kinases. *Curr Biol* 4, 973-982.
- Songyang, Z., and Cantley, L. C. (1995). Recognition and specificity in protein tyrosine kinase-mediated signalling. *Trends Biochem Sci* 20, 470-475.
- Songyang, Z., Shoelson, S. E., Chaudhuri, M., Gish, G., Pawson, T., Haser, W. G., King, F., Roberts, T., Ratnofsky, S., Lechleider, R. J., and *et al.* (1993). SH2 domains recognize specific phosphopeptide sequences. *Cell* 72, 767-778.
- Stahl, N., Farruggella, T. J., Boulton, T. G., Zhong, Z., Darnell, J. E., Jr., and Yancopoulos, G. D. (1995). Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors. *Science* 267, 1349-1353.
- Sweeney, M. C., Wavreille, A. S., Park, J., Butchar, J. P., Tridandapani, S., and Pei, D. (2005). Decoding protein-protein interactions through combinatorial chemistry: sequence specificity of SHP-1, SHP-2, and SHIP SH2 domains. *Biochemistry* 44, 14932-14947.
- Wiederkehr-Adam, M., Ernst, P., Muller, K., Bieck, E., Gombert, F. O., Ottl, J., Graff, P., Grossmuller, F., and Heim, M. H. (2003). Characterization of phosphopeptide motifs specific for the Src homology 2 domains of signal transducer and activator of transcription 1 (STAT1) and STAT3. *J Biol Chem* 278, 16117-16128.