PTB Domains of IRS-1 and Shc Have Distinct but Overlapping Binding Specificities

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Wolf, Gert, Thomas Trüb, Elizabeth Ottinger, Lori Groninga, Ann Lynch, Morris F. White, Masaya Miyazaki, Jongsoon Lee, and Steven E. Shoelson. 1995. “PTB Domains of IRS-1 and Shc Have Distinct but Overlapping Binding Specificities.” Journal of Biological Chemistry 270 (46). American Society for Biochemistry & Molecular Biology (ASBMB): 27407–10. doi:10.1074/jbc.270.46.27407.

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:41555766

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Insulin binding to the insulin receptor activates it as a substrate kinase, leading to tyrosine phosphorylation of at least two cytoplasmic proteins, IRS-1 and Shc (1, 2). IRS-1 is phosphorylated at many tyrosine positions (3), whereas Shc is phosphorylated predominantly at one site in cells (4). Since SH2 domain proteins bind specifically with phosphoryseryl sites in proteins (5, 6), IRS-1 is capable of multiple interactions with SH2 proteins, including phosphatidylinositol 3-kinase, the phosphatase SH-PTP2, and Grb2, a linker protein upstream of Ras. In contrast, when Shc is phosphorylated in cells, it interacts primarily with Grb2 (7).

The phosphotyrosine binding (PTB) domain (also called PID or SAIN domain) was recently found to provide a mechanism for protein binding with phosphoryseryl sequences, distinct from SH2 domains (8–11). Perhaps related to the phosphorylation of Shc by many tyrosine kinases, in addition to the insulin receptor, its PTB domain appears to interact with multiple phosphoryseryl proteins (8–12). The specificity of the Shc PTB domain can be analyzed by methods analogous to those used previously for SH2 domains. The Shc PTB domain binds with \( \beta \) turn-forming motifs frequently containing phosphorylated NPXY sequences (13–15), in contrast with SH2 domains that bind extended phosphopeptide sequences carboxyl-terminal to phosphotyrosine (pTyr) (5, 6). Since efficient IRS-1 phosphorylation in cells also depends on the phosphorylation of a \( \beta \) turn-forming NPXY motif in insulin receptors (16), IRS-1 might contain a related PTB domain (even though IRS-1 and Shc show no extended sequence homology). In yeast two-hybrid experiments, the amino-terminal ~500 residues of IRS-1 direct an interaction between the insulin receptor and IRS-1 that is functionally related to Shc PTB domain interactions (11, 17). The recent cloning of the IRS-2 gene revealed two regions of deduced protein sequence homology with IRS-1 (18), suggesting that one might function as a PTB domain.

We now show that a 174-residue region from the amino terminus of human Shc (33–206) and a 173-residue region from human IRS-1 (144–316) bind similarly with activated insulin receptors. While both domains bind \( \beta \) turn-forming motifs amino-terminal to pTyr, their specificities differ in detail.

**MATERIALS AND METHODS**

Recombinant Proteins and Synthetic Peptides—Fragments of the human IRS-1 and human Shc cDNAs were subcloned into a pGEx-4T vector using polymerase chain reactions. Escherichia coli strains DH5\( \alpha \) or XL-1 blue were transformed with vectors encoding glutathione S-transferase (GST) fusion proteins GST/IRS-1(144–316), GST/IRS-1(108–516), GST/IRS-1(144–316), GST/Shc(1–196), GST/Shc(1–206), GST/Shc(1–238), GST/Shc(1–474), GST/Shc(20–206), GST/Shc(33–206), and GST/Shc(46–206), (13), where numbers in parentheses refer to residues of human IRS-1 (19) and human Shc p52 (20), respectively. Proteins were expressed and isolated as usual using glutathione-agarose affinity chromatography and elution with glutathione (13, 21). Phosphopeptides were synthesized and purified as described (22).

Direct Binding between Native and Mutated Insulin Receptors and IRS-1 and Shc Proteins—Wild-type insulin receptors were isolated from transfected NIH-3T3 cells and purified by wheat germ agglutinin affinity chromatography. Mutated Y960F receptors were isolated following similar protocols from transfected Chinese hamster ovary cells (23). The receptors were autophosphorylated by sequential incubation with 100 \( \mu \)M insulin (16 h) and 50 \( \mu \)M ATP plus 5 \( \mu \)M Mn\(^{2+}\) as described (24). Phosphorylated receptors were incubated with glutathione-agarose-bound fusion proteins (5 \( \mu \)g) in the presence and absence of competing ligands. Bound proteins were eluted from the glutathione-agarose, separated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membranes, and identified by blotting with anti-insulin receptor antibodies.

**Binding Assays between Phosphopeptides and IRS-1 and Shc Proteins—PTB-phosphopeptide assays are operationally similar to previously described assays for SH2 domain interactions (13, 21, 22). Phosphopeptides derived from the sequence surrounding Tyr-960 of the IRS-1 protein were synthesized and purified as described (22).**
binding. We previously showed that the Shc PTB domain could be pared down to residues 1–206 of human Shc p52 without loss of function. Further truncation at the COOH terminus (1–196) led to complete loss of function, whereas initiation at Met-46 rather than Met-1 (corresponding to the start site of Shc p46) led to ~20-fold reduction in binding affinity (13). We have since found that the Shc PTB domain can be truncated at its amino terminus (20–206 and 33–206) without loss of binding affinity (13). The mixtures were incubated overnight and radioactivity associated with the unwashed glutathione-agarose was determined.

RESULTS AND DISCUSSION

Delineation of Shc and IRS-1 PTB Domains—We previously showed that the Shc PTB domain could be pared down to residues 1–206 of human Shc p52 without loss of function. Further truncation at the COOH terminus (1–196) led to complete loss of function, whereas initiation at Met-46 rather than Met-1 (corresponding to the start site of Shc p46) led to ~20-fold reduction in binding affinity (13). We have since found that the Shc PTB domain can be truncated at its amino terminus (20–206 and 33–206) without loss of binding affinity (13). Therefore, a stably folded, functional Shc PTB domain is encompassed by a maximum of 174 residues (33–206).

Experiments with the yeast two-hybrid system have suggested that the amino-terminal one-third of IRS-1 might contain a functionally related domain (11, 17). Therefore, GST/IRS-1 fusion proteins expressed in E. coli were constructed for use in binding experiments with intact insulin receptors and peptides derived from sequences surrounding insulin receptor Tyr-960 and IL4 receptor Tyr-497 (both NPXY motifs). IRS-1(4–516) and IRS-1(108–516) proteins exhibited binding in the peptide assay (Fig. 1, A and C). Since the former protein contains an intact PH domain, and the latter does not, the IRS-1 PH domain appears to be irrelevant for this interaction. An independently expressed PH domain (1–134) shows no function in this assay. We were interested in further delimiting the domain, although since IRS-1 and Shc share negligible sequence homology, it was not possible to align putative PTB domains. Comparisons between rat IRS-1 and IRS-2 proteins reveal only two regions of deduced sequence homology: their PH domains and an additional region carboxy-terminal to it (18). The second region of human IRS-1 (residues 144–316) expressed as a GST fusion protein binds in the peptide assays (Fig. 1, A and C) and with the intact insulin receptor (Fig. 2). Shc and IRS-1 PTB Domain Interactions with the Insulin Receptor—Insulin receptors phosphorylated in vitro were precipitated by Shc(1–238) and IRS-1(144–316) PTB domain GST-fusion proteins (Fig. 2). Precipitation of the receptor occurred only in the presence of the fusion protein (Fig. 2A) and insulin activation (Fig. 2B). Moreover, both interactions were inhibited by phosphotyrosine, consistent with both proteins being classified as “phosphotyrosine binding domains” (Fig. 2B). Although the insulin receptor contains at least six sites for tyrosine autophosphorylation (25), efficient endogenous substrate phosphorylation requires phosphorylation specifically at Tyr-960 (16). When Tyr-960 is mutated to Phe, the bulk of insulin receptor phosphorylation remains intact (23). We now show that the Tyr-960→Phe mutation blocks association of the insulin receptor with both PTB domains (Fig. 2C) to demonstrate that this site interacts with both domains. Tyr-960 of the insulin receptor is within an NPXY motif, and related sequences have recently been shown to be important for interactions with the Shc PTB domain (8, 13–15). However, a hydrophobic residue at the Xaa-3 position is also important for Shc PTB domain binding (12, 13), and this is lacking in the insulin receptor.2 Peptide competition assays were used to compare sequence requirements for binding by the Shc and IRS-1 PTB domains. At 1.0 μM concentrations, NPXY phosphopeptides derived from the mT antigen (mT pY250/8) and IL4 (IL4 pY497/11) and insulin receptors (IR pY960/15) all blocked the association between the insulin receptor and the Shc PTB domain (Fig. 2D). Identical studies with the IRS-1 PTB domain showed inhibition with the IL4 and insulin receptor sequences but no effect by the mT peptide. No inhibition with either PTB domain occurred with unphosphorylated peptide controls.

Comparative PTB Domain Binding Specificities—To analyze the determinants of IRS-1 PTB domain binding and compare IRS-1 and Shc PTB domain specificities, direct binding assays were developed similar to those used previously for SH2 domains (13, 21, 22). For example, the Shc PTB domain binds the mT peptide with highest affinity (1D50 = 1.2 μM) and IL4 and

2 References to peptide and protein positions are relative to pTyr.
insulin receptor-derived sequences with 25–32-fold lower relative affinities (Fig. 3). In contrast, the IRS-1 PTB domain binds the IL4 receptor sequence with highest affinity (ID$_{50} = 6.2$ μM), the native insulin receptor sequence with intermediate affinity (ID$_{50} = 170$ μM), and not at all with the mT-derived sequence. These findings clearly demonstrate significant differences in binding specificities between these domains. In the remainder of this study, we have analyzed determinants of Shc versus IRS-1 PTB domain specificity in detail, using native and modified peptide sequences derived from the mT antigen and the insulin, IL4, TrkA, ErbB4, and EGF receptors.

Previously we showed that the hexapeptide, mT-derived sequence LSNPTpY binds the Shc PTB domain with high affinity (13). Phosphorylation is required, whereas substitution of Leu$^\text{5}$, Asn$^\text{5}$, Pro$^\text{2}$, or Thr$^\text{5}$ with Ala significantly reduced affinity. These findings suggested that: (i) a hexapeptide sequence is sufficient for high affinity interaction, (ii) a hydrophobic residue at Xaa$^\text{5}$ is important, (iii) the N and P positions of the NPXY motif are critical, and (iv) the residue at the X position influences affinity. Similar modes of binding with the Shc PTB domain are observed for the TrkA (IENPQpYFS), ErbB4 (AKKAFDNPDpYWN), and EGF receptor (HSTAVGN-PEpYLN) sequences (Table I). All have hydrophobic residues at Xaa$^\text{5}$ positions relative to pTyr. We now show that the IRS-1 PTB domain does not bind with the mT, TrkA, ErbB4, or EGF receptor peptides (Table I).

However, both IRS-1 and Shc PTB domains bind directly with insulin and IL4 receptor sequences (Figs. 2 and 3), which lack hydrophobic residues at Xaa$^\text{5}$. Therefore, the insulin and IL4 receptor sequences were used to compare binding specificities (the corresponding sequence of the IGF-1 receptor was found to be too similar to that of the insulin receptor to warrant independent analysis). Phosphorylation of tyrosine is crucial for binding both peptide sequences (Table I), consistent with the requirements for insulin activation and Tyr-960 phosphorylation required for PTB interaction with the intact insulin receptors (Fig. 2). Removal of residues from the amino termini of the insulin and IL4 receptor peptide sequences revealed the importance of residues at the Xaa$^\text{8}$ and Xaa$^\text{7}$ positions, relative to pTyr, for binding with both PTB domains. Carboxyl-terminal truncations were tolerated, providing pTyr

![Fig. 3. Competition assays with Shc and IRS-1 PTB domains.](http://www.jbc.org/)

**Table 1** Specificities of Shc versus IRS-1 PTB domains

| Peptide source | Sequence | Shc PTB | IRS-1 PTB |
|---------------|----------|---------|-----------|
|               | ID$_{50}$ ± S.E. | Relative affinity | Assay no. | ID$_{50}$ ± S.E. | Relative affinity | Assay no. |
| IR-pY960/15  | LYASSNPEpYLSASDV | 30 ± 5.3 | 4.0 | 10 | 170 ± 53 | 3.6 | 6 |
| IR-pY960/14  | YASSNPEpYLSASDV | 80 ± 13 | 1.5 | 4 | >300 | <2.0 | 2 |
| IR-pY960/13  | ASSNPEpYLSASDV | >300 | <0.4 | 4 | >300 | <2.0 | 2 |
| IL4R-pY497/11| LVIAIGNAPYRS | 38 ± 5.5 | 3.0 | 14 | 6.2 ± 0.3 | 100 | 14 |
| IL4R-pY497/10| VIGNAPYRS | 31 ± 3.9 | 3.9 | 4 | 114 ± 38 | 5.4 | 6 |
| IL4R-pY497/9  | AIGNAPYRS | >300 | <0.4 | 6 | >300 | <2.0 | 4 |
| IR-pY960/15  | LYASSNPEpYLSASDV | 30 ± 5.3 | 4.0 | 10 | 170 ± 53 | 3.6 | 6 |
| IR-Y960/15   | LYASSNPEpYLSASDV | >1000 | <0.12 | 2 | >1000 | <0.6 | 2 |
| IR-pY960A-1  | LYASSNPEpYLSASDV | 8.4 ± 0.6 | 14 | 6 | 6.5 ± 0.5 | 95 | 8 |
| IR-pY960A-2  | LYASSNPEpYLSASDV | 68 ± 12 | 0.6 | 2 | >300 | <2.0 | 2 |
| IR-pY960A-3  | LYASSNPEpYLSASDV | >300 | <0.4 | 2 | >300 | <2.0 | 2 |
| IR-pY960A-4  | LYASSNPEpYLSASDV | 71 ± 15 | 1.7 | 2 | 115 ± 30 | 5.4 | 4 |
| IR-pY960A-5  | LYASSNPEpYLSASDV | 68.7 ± 0.7 | 18 | 4 | 266 ± 58 | 2.3 | 4 |
| IR-pY960V-6  | LYASSNPEpYLSASDV | 52 ± 6.2 | 2.3 | 4 | 57.6 ± 6.7 | 11 | 6 |
| IR-pY960A-7  | LVIAIGNAPYRS | 194 ± 37 | 0.6 | 2 | >300 | <2.0 | 4 |
| IR-pY960A-8  | AIGNAPYRS | 124 ± 35 | 0.8 | 2 | >300 | <2.0 | 3 |
| IL4R-pY497/11| LVIAIGNAPYRS | 38 ± 5.5 | 3.0 | 14 | 6.2 ± 0.3 | 100 | 14 |
| IL4R-pY497/11| LVIAIGNAPYRS | >1000 | <0.4 | 2 | >300 | <2.0 | 2 |
| IL4R-pY497A-2 | LVIAIGNAPYRS | 34 ± 6.7 | 2.0 | 4 | 8.8 ± 0.4 | 70 | 4 |
| IL4R-pY497A-1 | LVIAIGNAPYRS | 152 ± 42 | 0.5 | 4 | 12 ± 1.2 | 52 | 3 |
| IL4R-pY497E-1 | LVIAIGNAPYRS | 151 ± 13 | 0.8 | 6 | >300 | <2.0 | 4 |
| IL4R-pY497A-2 | LVIAIGNAPYRS | 157 ± 57 | 0.5 | 4 | >300 | <2.0 | 4 |
| IL4R-pY497A-3 | LVIAIGNAPYRS | >1000 | <0.12 | 2 | >300 | <2.0 | 4 |
| IL4R-pY497A-4 | LVIAIGNAPYRS | 26 ± 5 | 4.6 | 4 | 2.4 ± 0.1 | 258 | 6 |
| IL4R-pY497A-6 | LVIAIGNAPYRS | 93 ± 30 | 0.7 | 4 | 24 ± 2.2 | 26 | 4 |
| IL4R-pY497A-7 | LVIAIGNAPYRS | 144 ± 15 | 0.5 | 4 | 52 ± 6.6 | 12 | 4 |
| IL4R-pY497A-8 | LVIAIGNAPYRS | 124 ± 50 | 0.7 | 4 | 28 ± 2.7 | 22 | 4 |

| mT-pY250/8 | LSNPTpYSV | 1.2 ± 0.1 | 100a | 12 | >300 | <2.0 | 2 |
| TrkA-pY490/8 | IFNpYFS | 6.3 ± 0.5 | 19 | 6 | >1000 | <0.6 | 2 |
| ErbB4-pY1242/12 | AKKAFDNPpYWN | 1.4 ± 0.2 | 86 | 4 | >300 | <2.0 | 2 |
| EGF-pY1114/2 | HSTAVGNPEpYLN | 2.5 ± 0.7 | 48 | 2 | >300 | <2.0 | 2 |

a Relative affinities for Shc and IRS-1 PTB domain assays were determined versus mT-pY250/8 and IL4R-pY497/11, respectively.
Substitution studies were conducted with both sequences to further probe binding mechanisms. Ala substitutions of hydrophobic residues at the Xaa-8 and Xaa-7 positions diminished binding with both PTB domains. Moreover, Ile→Ala within the IL4 receptor reduced binding with both domains, whereas Ala→Val substitution of the insulin receptor peptide increased binding affinity. These findings suggest that hydrophobic side chains at all three positions influence binding. Substitutions at the Xaa-8 and Xaa-7 positions of the insulin and IL4 receptor sequences were generally tolerated. Substitution of Asn→Thr within the NPXY motif abrogates binding by both PTB domains. For the Shc PTB domain, Pro→substitution leads to reduced but not abolished binding; for the IRS-1 PTB domain, substitution of Pro→ with Ala abolishes binding.

Substitutions at Xaa-1 (the X of NPXY) are particularly interesting. Glu→Ala substitution in the insulin receptor sequence leads to 30-fold gain of function for binding with the IRS-1 PTB domain (ID50 = 6.5 μM). The IL4 receptor contains Ala-1 naturally, and the corresponding peptide binds with high affinity (ID50 = 6.2 μM), equivalent to that of the Ala-substituted insulin receptor sequence. Consistent with these findings, Ala-1→Glu substitution in the IL4 receptor sequence leads to >50-fold loss of affinity for the IRS-1 PTB domain. Although the effects are in the same direction for interactions with the Shc PTB domain, their magnitudes are much smaller. These studies imply that biological systems may have evolved a means of using this position for selectively modulating affinities of PTB domain interactions. Along with its PTB domain, the PH domain of IRS-1 may participate in insulin receptor-catalyzed substrate phosphorylation (26), and a proper balance of affinities for both domains may be required for normal signaling.

Using all available data, consensus sequences for PTB domain binding can be constructed. The Shc PTB domain binds with highest affinity with sequences having a hydrophobic residue at the Xaa-8 position and an NPXY motif (this study and Refs. 12 and 13). Asn-3 within the NPXY motif appears to be critical, whereas Pro-2 can be substituted (e.g. Ala in the Ala scan or Leu of c-ErbB2; Ref. 14). Ala-1 appears to be preferred over Glu-1 (Table I), and in combination the residues within this region should be able to adopt a β-turn (13). The consensus motif: P-Ψ-X-N-β1-β2-pY, where Ψ is hydrophobic (Leu, Ile, Val, Phe) and β are β-turn forming residues, is present in the polyclonal virus mT antigen, TrkA, TrkB, TrkC, ErbB2, ErbB3, and the IL2 and EGF receptors. However, when Xaa-5 is not hydrophobic, as in the insulin, IL4, and IGf-1 receptors, then the Shc PTB domain will bind with sequences having hydrophobic Xaa-6, Xaa-7, and Xaa-8 residues in the motif P-Ψ-X-N-β1-β2-pY.

The IRS-1 PTB domain binds with the insulin and IL4 receptor peptides, but not mT, TrkB, ErbB4, or EGF receptor peptides, to imply that the isolated domains faithfully recapitulate biological substrate specificities. Some combination of hydrophobic residues at Xaa-6, Xaa-7, and Xaa-8 positions are important, Asn-3 and Pro-2 are crucial for high affinity binding, and substitutions at Xaa-1 module affinity. Thus the IRS-1 PTB domain binds preferentially with the sequence P-Ψ-X-N-β1-β2-pY, where Ψ sites are generally hydrophobic and β indicates a β-turn-forming residue (β1 = P; β2 < A ≥ E). The PTB domain specificities are summarized below.

Shc

P-Ψ-X-N-β1-β2-pY

IRS-1 or Shc

Ψ-Ψ-X-N-β1-β2-pY

Conclusion—PTB domains of similar length and function exist in Shc and IRS-1. Since the sequences of these domains have low homology, it is not yet possible to know whether they represent distinct or related elements of protein structure. The binding interactions mediated by PTB domains of Shc and IRS-1 are closely related to analogous SH2 domain interactions in that binding affinities are similar, phosphorylation serves as the on-off switch, and surrounding sequence provides specificity. However, both PTB domains show a reversal in the orientation of required peptide interactions compared to SH2 domains, since residues amino- and carboxyl-terminal to pTyr play a major role in determining specificity. Peptide sequences recognized by the two PTB domains are similar to one another, as both bind β-turn forming NPXY motifs. However, their specificities also differ since the Shc PTB domain binds with highest affinity to motifs having a hydrophobic Xaa-5 residue, relative to pTyr, while both IRS-1 and Shc PTB domains bind motifs having some combination of hydrophobic residues at Xaa-6, Xaa-7, and Xaa-8 positions. Differences in PTB domain specificity may be useful in targeting particular pathways for drug design, as has been proposed previously for SH2 domains. Distinct specificities of these PTB domains correlate with and may account for some biological differences between these two classes of phosphotyrosine binding peptides.

REFERENCES

1. Sun, J. X., Rothenberg, P., Kahn, C. R., Backer, J. M., Araki, E., Wilden, P. A., Cahill, D. A., Goddijn, B. J., and White, M. F. (1991) Nature 352, 73–77

2. Pronk, G. J., McGlade, J., Pelicci, G., Pawson, T., and Bos, J. L. (1991) J. Biol. Chem. 266, 5748–5753

3. Sun, J. X., Crimmins, D. L., Myers, M. G., Jr., Miralpeix, M., and White, M. F. (1993) Mol. Cell. Biol. 13, 7418–7428

4. Salini, A. E., McGlade, J., Pelicci, G., Nicotti, J., Pawson, T., and Pelicci, P. G. (1994) Oncogene 9, 2827–2836

5. Pawson, T. (1995) Nature 373, 573–580

6. Cohen, G. B., Rein, R., and Baltimore, D. (1995) Cell 80, 237–248

7. Rozakis-Adod, M., McGlade, J., Mambalou, G., Pelicci, G., Daly, R., Li, W., Batzer, A., Thomas, S., Brugge, J., Pelicci, G. P., Schlessinger, J., and Pawson, T. (1992) Nature 360, 689–692

8. Kavanaugh, W. M., and Williams, L. T. (1994) Science 266, 1862–1865

9. Blakie, P., Immanuel, D., Wu, J., Li, N., Yajnik, V., and Margolis, B. (1994) J. Biol. Chem. 269, 32031–32034

10. van der Geer, P., Wiley, S., Lai, V. K. M., Olivier, J. P., Gish, D. G., Stephens, R., Kaplan, D., Shoelson, S. E., and Pawson, T. (1995) Curr. Biol. 5, 404–412

11. Gustafson, T. A., He, W., Craparo, A., Schaub, C. D., and O’Neill, T. J. (1995) J. Biol. Chem. 270, 2541–2548

12. O’Neill, T. J., Pratap, A., and Gustafson, T. A. (1994) Mol. Cell. Biol. 14, 7433–7442

13. Feener, E. P., Backer, J. M., and Kahn, C. R. (1988) Cell 54, 641–649

14. O’Neill, T., Craparo, A., and Gustafson, T. A. (1994) Mol. Cell. Biol. 14, 753–760

15. White, M. F., Livingston, J. N., Backer, J. M., Lauris, V., Dull, T. J., Ullrich, A., and Kahn, C. R. (1988) Cell 54, 641–649

16. O’Neill, T. J., Pratap, A., and Gustafson, T. A. (1994) Mol. Cell. Biol. 14, 7433–7442

17. O’Neill, T., Pratap, A., and Gustafson, T. A. (1994) Mol. Cell. Biol. 14, 7433–7442

18. Sun, X. J., Wang, L.-M., Zhang, Y., Yenush, L., Myers, M. G., Glasheen, E. M., and White, M. F. (1995) Nature 377, 173–177

19. Araki, E., Sun, J. X., Haag, B. L., Jr., Chang, L.-M., Zhang, Y., Yang-Feng, T. L., White, M. F., and Kahn, C. R. (1993) Diabetes 42, 1041–1054

20. Pelicci, G., Lanfrancone, L., Grignani, F., McGlade, J., Cavallio, F., Forini, G., Nicotti, J., Pawson, T., and Pelicci, P. G. (1992) Cell 70, 93–104

21. Case, R. D., Piccione, E., Wolf, G., Bennett, A. M., Lechleider, R. J., Neel, B. G., and Shoelson, S. E. (1994) J. Biol. Chem. 269, 10467–10474

22. Piccione, E., Case, R. D., Domchek, S. M., Hu, P., Chauhduri, M., Backer, J. M., Schlessinger, J., and Shoelson, S. E. (1993) Biochemistry 32, 3197–3202

23. Backer, J. M., Shoelson, S. E., Weiss, M. A., Hua, X. Q., Cheatham, B., Haring, E. F., Cahill, D. C., and White, M. F. (1992) J. Biol. Chem. 267, 831–839

24. Lee, J., O’Hare, T., Pilch, P. F., and Shoelson, S. E. (1993) J. Biol. Chem. 268, 4092–4098

25. Feener, E. P., Backer, J. M., King, G. L., Wilden, P. A., Sun, J. X., Kahn, C. R., and White, M. F. (1993) J. Biol. Chem. 268, 11256–11264

26. Myers, M. G., Grammer, T. C., Brooks, J., Gilish, E. M., Wang, L.-M., Sun, X. J., Blenis, J., and White, M. F. (1995) J. Biol. Chem. 270, 11715–11718
PTB Domains of IRS-1 and Shc Have Distinct but Overlapping Binding Specificities
Gert Wolf, Thomas Trüb, Elizabeth Ottinger, Lori Groninga, Ann Lynch, Morris F. White, Masaya Miyazaki, Jongsoo Lee and Steven E. Shoelson

J. Biol. Chem. 1995, 270:27407-27410.
doi: 10.1074/jbc.270.46.27407

Access the most updated version of this article at http://www.jbc.org/content/270/46/27407

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 26 references, 16 of which can be accessed free at http://www.jbc.org/content/270/46/27407.full.html#ref-list-1