A Novel Phosphotyrosine-binding Domain in the N-terminal Transforming Region of Cbl Interacts Directly and Selectively with ZAP-70 in T Cells*

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The protooncogene product Cbl has emerged as a novel signal transduction protein downstream of a number of cell surface receptors coupled to tyrosine kinases. Recently, we and others have reported the activation-dependent association of Cbl with the Syk and ZAP-70 tyrosine kinases through presently undefined mechanisms. Potential Src homology 2 and 3 domain binding sites within the C-terminal half of Cbl mediate in vivo interactions with several signaling proteins; however, the N-terminal transforming region (Cbl-N) lacks recognizable catalytic or protein interaction motifs. Here, we show that in vitro Cbl-N (amino acids 1–357) but not Cbl-C (amino acids 358–906) binds to ZAP-70 in a T cell-activation-dependent manner. A point mutation in Cbl-N, G306E, corresponding to a loss-of-function mutation in the Caenorhabditis elegans Cbl homologue, SLI-1, severely compromised Cbl-N/ZAP-70 binding. Cbl-N/ZAP-70 binding was direct and phosphotyrosine-dependent, thus identifying a phosphotyrosine-binding domain within the transforming region of Cbl. In vivo, Cbl-N expressed in T cells selectively associated with the ZAP-70/Cbl complex. These results identify a novel mechanism for the direct participation of the N-terminal region of Cbl in ZAP-70 signal transduction, and suggest a biochemical mechanism for the leukemogenicity of the oncogene v-cbl through potential interaction with proliferation-related phosphotyrosyl proteins.

Engagement of the T lymphocyte antigen receptor (TCR),† together with the appropriate costimulatory signals, triggers a cascade of biochemical events that culminates in lymphocyte activation (for reviews see Refs. 1 and 2). An early and obligatory such event is tyrosine phosphorylation of the immunoreceptor tyrosine-based activation motifs of the TCR-associated ζ and CD3 chains by TCR-associated Src family tyrosine kinases Fyn and Lck. These phosphotyrosine residues provide docking sites for the tandem Src homology (SH) 2 domains of ZAP-70 and Syk, leading to membrane localization, tyrosine phosphorylation and concomitant activation of these tyrosine kinases (1, 2). Activation of ZAP-70/Syk kinases is required for propagating signals downstream of the Src kinases (1, 2). Furthermore, genetic evidence demonstrates that ZAP-70 is required for functional T cell development in both man and mouse (2).

In an effort to elucidate and characterize the immediate targets of T cell tyrosine kinases, we previously identified a Fyn/Lck SH3 domain-binding protein, p120/Cbl, which served as one of the earliest tyrosine kinase substrates upon TCR stimulation and which was present in preformed complexes with Fyn and Lck in unstimulated T cells (3–5). Analysis of the primary structure of Cbl, the product of the c-cbl proto-oncogene, revealed no obvious catalytic domains or SH2 or SH3 domains; however, Cbl possesses multiple proline-rich motifs and potential tyrosine phosphorylation sites, concentrated within the C-terminal half of the protein, which could mediate concurrent associations with SH3 and SH2 domain-containing proteins, respectively (6–8). Indeed, SH3-dependent constitutive interaction of Cbl with Grb2 and Nck adapters as well as its SH2-dependent activation-induced association with phoshatidylinositol 3-kinase and Crk adapter proteins has been observed following stimulation through T and B cell antigen receptors, as well as a number of other receptors (5, 9–13). Interestingly, an activation-dependent association of Cbl with Syk tyrosine kinase in B cells and myeloid cells, and of ZAP-70 in T cells has been observed, although the mechanism of these associations remains unclear (10, 13, 14). These studies clearly suggest a role for Cbl in signaling downstream of a number of cell surface receptors.

In this study we show that the N-terminal region of human Cbl (Cbl-N), equivalent to the portion of Cbl that forms the transforming v-Cbl protein (8, 15–17) contains a phosphotyrosine-binding domain (PTB) that interacts directly and relatively specifically with the T cell tyrosine kinase ZAP-70. Since the interaction between ZAP-70 and Cbl-N is abrogated by a single point mutation (G306E), corresponding to a mutation that inactivates the Caenorhabditis elegans homologue, suppressor of lineage defect-1 (SLI-1) (18), our studies suggest a novel, evolutionarily conserved PTB-dependent role for Cbl in signaling pathways.

**EXPERIMENTAL PROCEDURES**

T Cells and Activation—Jurkat-JMC, herein referred to as Jurkat, was maintained as described (12). JMC-T, a SV40 T antigen-expressing derivative of Jurkat-JMC, was maintained with 1 mg/ml G418 (Life Technologies, Inc.). For activation, 10⁶ cells/ml in RPMI 1640 medium...
with 20 ml HEPES and 2 ml sodium orthovanadate were incubated at 37 °C for 5 min in vitro. A monoclonal anti-human v-erbA SPV-T3 antibody (19) was added for 2–5 min (or as indicated). Cells were lysed by adding four volumes of cold lysis buffer (0.5% Triton X-100 (Fluka), 50 mM Tris, pH 7.5 (at room temperature), 150 mM sodium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM sodium orthovanadate, and 10 mM sodium fluoride).

**EGF Activation of Mammary Epithelial Cells—** MPI-PIII cells, derived by mutant p53de229-induced immortalization of a normal human mammary epithelial cell strain, were maintained in DFCI-1 medium, as described (20). Cells were deprived of EGF for 3 days prior to activation with EGF (100 ng/ml) for 10 min (21).

**Antibodies**—The monoclonal antibodies used in this work are as follows: 4G10 (anti-Tyr(P); IgG2a) (22), SVF-T3b (anti-CD5; IgG2a) (19), anti-ZAP-70 (ZAP-70; Santa Cruz Biotechnology, Santa Cruz, CA), anti-Erk2 (anti-phospho-tyrosine; Santa Cruz Biotechnology), and anti-Grb2 (anti-Grb2; Santa Cruz Biotechnology). The anti-Grb2 antibody was characterized by an immunoprecipitation and Western blot analysis of Jurkat cells stimulated with anti-CD3 mAb. The anti-Erk2 antibody was characterized by an immunoprecipitation and Western blot analysis of Jurkat cells stimulated with anti-CD3 mAb.

**RESULTS AND DISCUSSION**

**Recent reports have demonstrated in vivo associations between Cbl and several proteins involved in T lymphocyte signal transduction. These are mediated by Cbl’s tyrosine-phosphorylated residues and its proline-rich region which interact with SH2 and SH3 domains, respectively (5, 9, 12). However, the biochemical functions of Cbl’s N-terminal region, corresponding to the v-cbl oncogene, in T cell signal transduction remain unknown. To address the potential functions of the Cbl-N segment, we assessed its ability to interact with T cell proteins that undergo rapid tyrosine phosphorylation upon TCR stimulation. For this purpose, we carried out in vitro binding reactions using GST-Cbl-N (amino acids 1–357) or GST-Cbl-C (amino acids 358–906) and lysates from unstimulated or anti-CD3-stimulated Jurkat cells (Fig. 1A). Bound polypeptides were detected by anti-Tyr(P) immunoblotting. As expected, no phosphoproteins bound to GST in lysates of unstimulated cells or cells stimulated for 2 min with anti-CD3 mAb (lanes 1 and 2). Furthermore, GST-Cbl-C prominently bound to pp36/38 in lysates from anti-CD3-stimulated cells (lane 6). pp36/38 interacts with Grb2’s SH2 domain and thus was expected to indirectly interact with the Cbl-C fusion protein, which includes the Grb2 SH3-binding proline-rich region (5, 27). Consistent with this mechanism, anti-Grb2 immunoblotting (data not shown) demonstrated prominent and equivalent binding of Grb2 to GST-Cbl-C in lysates from both unstimulated and anti-CD3-stimulated cells, but not to GST-Cbl-N or GST alone. Unexpectedly, GST-Cbl-N, which lacks any proline-rich region, tyrosine phosphorylation (protein was made in bacteria), or a recognizable SH2 domain, showed substantial binding to a number of tyrosine-phosphorylated polypeptides (71, 69, 59, 55–57, 47, 45, 40, and 20 kDa) in lysates of anti-CD3-stimulated Jurkat cells (lane 4), with the 69-kDa polypeptide representing the most prominent band. The 69-kDa polypeptide was also detected at a low level in lysates of unstimulated cells (lane 3) correlating with the level of tyrosine phosphorylation of this protein in resting Jurkat cells. When Jurkat cells were stimulated with anti-CD3 mAb for different time points, a time-dependent binding to GST-Cbl-N, correlating with the extent of tyrosine phosphorylation at each time, was observed (Fig. 1B and data not shown).

Although a number of phosphoproteins were observed in GST-Cbl-N binding reactions, these polypeptides represented only a subset of those present in lysates of activated Jurkat cells (Fig. 1C, lane 12). The SDS-PAGE mobility of the prominent 69-kDa GST-Cbl-N binding phosphoprotein suggested that it might be the T cell-specific protein tyrosine kinase ZAP-70 (3, 28). Consistent with this possibility, GST-Cbl-N binding reactions included a 20-kDa protein of the approximate size of (P). Concurrent analysis of GST-Cbl-N binding reactions and anti-ZAP-70 immunoprecipitations (IPs) demonstrated that the GST-Cbl-N-binding 69-kDa phosphoprotein comigrated with ZAP-70 (Fig. 1C, compare lanes 3 and 4 with lanes 7 and 8, upper panel), and anti-ZAP-70 reprofiling of the blot identified the 69-kDa protein as ZAP-70 (lanes 3 and 4, lower panel).

Genetic studies of the vulval developmental pathway in the nematode C. elegans have provided evidence for the negative regulatory role of the Cbl homologue, SLI-1, in LET-23 (EGF receptor homologue) signaling (18). The N-terminal regions of the SLI-1 protein (residues 58–447) and mammalian Cbl (residues 45–434) are 55% identical, indicating an evolutionary conservation possibly due to conserved function (18). Indeed, the N-terminal region of Cbl directly interacted with phosphorylated hum EGF receptor in vitro (29). Significantly, a single point mutation, G315E, within the conserved N-terminal region of SLI-1 resulted in a loss-of-function allele (18). The corresponding glycine residue in human Cbl is located within a 21-amino acid stretch that shows 80% identity between C. elegans and man (18). To assess if the critical importance of this conserved region might be related to the phosphotyrosyl protein binding that we observed, we generated a GST-Cbl-N fusion protein with an analogous (G306E) mutation. The
G306E mutation drastically reduced or abolished the ability of GST-Cbl-N to bind to phosphotyrosyl proteins including ZAP-70 (Fig. 1C, lanes 5 and 6). Thus, the N-terminal transforming region of Cbl interacts with T cell phosphoproteins through a mechanism that requires the integrity of evolutionarily conserved sequences.

Interestingly, comparison of the anti-Tyr(P) and ZAP-70 immunoblots of GST-Cbl-N-binding reactions and ZAP-70 IPs (Fig. 1C, lanes 4 and 8, top to bottom panels) revealed that the stoichiometry of tyrosine phosphorylation on the Cbl-N-bound ZAP-70 was much greater. Taken together with the activation-dependence of the in vitro Cbl-N-ZAP-70 binding (lanes 4 and 8, bottom panel) and the in vivo Cbl/ZAP-70 or Cbl/Syk associations (10, 13, 14), these data suggested that the binding of Cbl-N to ZAP-70 was dependent on an activation-induced conformational change or post-translational modification. Since binding of Cbl-N to EGF receptor correlated with tyrosine phosphorylation of the latter (29), we assessed the role of tyrosine phosphorylation in Cbl-N/ZAP-70 interactions. First, we investigated the ability of GST-Cbl-N to bind to ZAP-70 in lysates prepared in the absence of the phosphatase inhibitors sodium fluoride and sodium orthovanadate (Fig. 2A). When phosphatase inhibitors were absent during lysis, Tyr(P) signals were undetectable in anti-ZAP-70 IPs or Cbl-N-binding reactions (lanes 1–6, upper panel). Anti-ZAP-70 blotting showed a severe reduction in binding of GST-Cbl-N to ZAP-70 (compare lanes 4 and 10) and a complete loss of the activation-dependence of this binding (compare lanes 3 and 4 with lanes 9 and 10, bottom panel).

To determine the type of phosphorylation required for the association of ZAP-70 with Cbl-N, we performed in vitro binding reactions in the presence of increasing concentrations of Tyr(P), Ser(P), or Thr(P) (Fig. 2B). As a control, we also carried out binding reactions with GST-Lck-SH2 (3, 5). Binding of ZAP-70 to both Lck-SH2 and Cbl-N was greatly reduced by 50 mM Tyr(P) but not by equivalent concentrations of Ser(P) or Thr(P) (lanes 6 and 11); the inhibition was detectable to a lesser extent with 10 mM Tyr(P) (lane 10, upper panel). Since, the bacterially expressed GST fusion proteins lack Tyr(P), the Tyr(P) competition must reflect binding of Cbl-N to phosphorylation sites induced upon T cell activation on either ZAP-70 or putative adapter molecules. This conclusion is consistent with the inability of tandem SH2 domains of ZAP-70 to bind to tyrosine-phosphorylated p120/Cbl (14, 30).

In view of the Tyr(P)-dependent interaction between Cbl-N and ZAP-70, it was of considerable significance to determine if this interaction was mediated by an intermediate protein, as suggested by Fournel et al. (14), or whether this interaction was direct. To assess direct binding, anti-Tyr(P) IPs from unstimulated and anti-CD3-stimulated Jurkat cell lysates were resolved on SDS-PAGE, transferred to PVDF membranes, and immunoblotted with anti-Tyr(P) antibody, followed by PA-HRPO and detection by ECL.

**Fig. 1.** Preferential binding of a 69-kDa phosphoprotein to GST fusion protein of the N-terminal oncogenic region of Cbl and its identity as ZAP-70 tyrosine kinase. A, phosphotyrosyl protein binding to GST fusion proteins of the N-terminal (GST-Cbl-N) and C-terminal (GST-Cbl-C) regions of Cbl. Binding reactions from lysates of unstimulated (−) or anti-CD3-stimulated (+) Jurkat cells (see “Experimental Procedures”) were subjected to SDS-PAGE, transferred to PVDF membranes, and blotted with anti-Tyr(P) antibody, followed by PA-HRPO and detection by ECL. B, effects of activation for various time points on phosphotyrosyl protein binding to GST-Cbl-N. Binding reactions were carried out as in A. Time points indicate incubation time at 37 °C in the absence (−) or presence (+) of anti-CD3 stimulating antibody prior to lysis. C, identification of the GST-Cbl-N-bound 70-kDa phosphoprotein as ZAP-70 and the effect of G306E mutation in Cbl-N. Binding reactions and IP were carried out as described under “Experimental Procedures.” Whole cell lysate was from 10⁶ cells; anti-ZAP-70 IP was from 10⁵ cells; all other IPs and binding reactions were from 2.5 × 10⁶ cells. Immunoblotting with anti-Tyr(P) (top panel) and with anti-ZAP-70 (bottom panel) was carried out as in A.
probed with purified GST fusion proteins (Far-Western blotting) followed by serial immunoblotting with anti-ZAP-70 and anti-Tyr(P) mAb (Fig. 3, A and B). GST-Cbl-N, but neither its loss of function mutant, Cbl-N/G306E, nor GST alone, could bind directly to a 69-kDa protein immunoprecipitated by anti-Tyr(P) antibody from activated cell lysates. Anti-ZAP-70 immunoblotting showed this protein to be ZAP-70. We have confirmed these results by assessing direct binding to ZAP-70 isolated by anti-ZAP-70 IPs (data not shown). Interestingly, direct binding of Cbl-N was highly specific for ZAP-70 even though other tyrosine-phosphorylated proteins were present in the lane, as seen by anti-Tyr(P) immunoblotting (Fig. 3A, compare lane 2 with lane 6). However, very weak binding to an ~55–57-kDa polypeptide can be detected after overexposure of the blot (Fig. 3A, lane 8). The relative dominance of phospho-ZAP-70 in the anti-Tyr(P) IPs (Fig. 3A, lane 6) is unlikely to account for the selective binding since the amounts of other proteins were clearly sufficient to allow direct binding to Lck-SH2 (Fig. 3B, lane 2). It is more likely that Cbl-N binding to additional polypeptides is indirect via ZAP-70 (except p55–57), since polypeptides of similar sizes are detectable in anti-ZAP-70 IPs (Figs. 1 and 2).

A direct phosphotyrosine-dependent binding between unphosphorylated Cbl-N and tyrosine-phosphorylated ZAP-70 strongly suggests the presence of a hitherto unidentified PTB domain within the transforming N-terminal region of Cbl, functionally analogous to PTB domains identified within the Shc adapter protein (31–33) and subsequently in insulin receptor substrate 1 (25). However, the primary sequence of Cbl-N is distinct from the sequences of Shc and IRS-1 PTB domains (8, 25). This is not surprising, in view of the lack of conserved primary structural features between PTB domains of Shc and IRS-1, even though they appear to share a binding motif of NPxPY (see Ref. 33 and references therein). Interestingly, the NMR data of the Shc PTB domain and recent crystallography data of the IRS-1 PTB domain demonstrate that their three-dimensional structures show only general conservation in the orientation of peptide binding, whereas the contact residues are different (34, 35). It therefore remains possible that Cbl's PTB domain recognizes a novel motif, consistent with the fact that neither of the known in vivo phosphorylation sites of
ZAP-70 (Tyr\(^{292}\) and Tyr\(^{492/493}\)) contain an NPXpY motif (36), although one in vitro phosphorylation site (NGT\(p\)Y\(^{495}\)) is similar. Interestingly, Cbl's PTB domain selectively binds to Syk in activated T and B cells,\(^a\) and both the Tyr\(^{492/493}\) and Tyr\(^{487}\) sites are conserved between ZAP-70 and Syk. Further support for a distinct binding selectivity of the Cbl PTB domain is provided by parallel binding reactions, which failed to reveal an interaction of GST-Shc-PTB (25) with ZAP-70 from anti-CD3-stimulated Jurkat cell lysates (Fig. 4A). In contrast, GST-Shc-PTB showed a markedly stronger binding to activated EGF receptor than GST-Cbl-N in lysates from an EGF-stimulated mammary epithelial cell-line (Fig. 4B).

Finally, in order to assess if Cbl-N/ZAP-70 interaction could occur in vivo, we carried out transient transfections of a Jurkat derivative (JMC-T) with HA-tagged Cbl-N or vector alone (mock transfection) (Fig. 4C). Anti-Tyr(P) immunoblotting of anti-HA IPs revealed an activation dependent co-immunoprecipitation of ZAP-70 in HA-Cbl-N- but not in mock-transfected anti-HA IPs revealed an activation dependent co-immunoprecipitation of ZAP-70 in HA-Cbl-N- but not in mock-transfected cells (compare lane 2 with lane 8). Interestingly, the only other phosphoproteins that co-immunoprecipitated with HA-Cbl-N were phospho-\(\zeta\) (20 kDa) and an approximately 40-kDa phosphoprotein of undefined identity, suggesting that ZAP-70 is an even stronger selectivity for binding to ZAP-70/\(\zeta\) complexes may exist. Furthermore, Cbl/ZAP-70 interaction in vivo may be regulated by additional factors such as the level of tyrosine phosphorylation. For example, the stoichiometry of Cbl/ZAP-70 association in Jurkat cells (data not shown) was low compared to that previously observed in a murine T cell hybridoma over-expressing a constitutively active Lck (14).

The presence of a PTB domain within the transforming N-terminal region of Cbl is likely to be significant for the function of this molecule. The likelihood of this possibility is enhanced by our findings that Cbl's PTB function requires an evolutionarily conserved region whose point mutation leads to loss of function in the C. elegans Cbl homologue, SLI-1. It is possible that the PTB domain recruits Cbl, and the proteins that associate with Cbl's proline-rich region (such as Grb2) and Tyr(P) sites (such as Crk and PI-3 kinase), to tyrosine kinases, analogous to the role of the PTB domain in IRS-1. Genetic analysis of SLI-1 suggest it to be a negative regulator of LET-23 (EGF receptor) (18) and the PTB domain of Cbl may also participate in such regulatory functions through selective binding to Tyr(P) sites, by preventing phosphorylation of adjacent Tyr(P) sites, protecting the Tyr(P) sites from phosphatases, or by other direct effects. Further studies will be needed to assess what if any regulatory role Cbl's PTB domain may exert on ZAP-70.

The fact that the N-terminal region of Cbl harbors a PTB domain also has implications for the mechanisms of onco gene-sis by v-Cbl. Since full-length Cbl polypeptide, even when over-expressed, is non-transforming (8), Cbl's N-terminal domain is likely to be regulated via inter- or intramolecular interactions involving the C-terminal region of Cbl. Removal of this inhibition by truncation, as in v-Cbl, or by mutations, as seen in naturally occurring (17-amino acid deletion) 70Z3-Cbl or experimentally created transforming mutations (17), may result in constitutive engagement of critical growth-promoting signaling molecules by Cbl's PTB domain resulting in heightened proliferative signals and consequent progression to oncogenesis. In this context, it is noteworthy that the G306E mutation abrogates the transforming activity of Cbl-N in rodent fibroblasts.\(^3\)

In summary, our studies identify a novel PTB domain in the transforming region of Cbl, which selects ZAP-70 tyrosine kinase for binding in T cells. The function of this domain is abrogated by a point mutation identified as a loss of function mutation in genetic screens for LET-23 (EGF receptor) regulators in C. elegans (18), indicating a strong evolutionary conservation of this domain. Future experiments to determine the

\(^a\) M. L. Lupher, Jr. and H. Band, unpublished data.

\(^3\) W. Y. Langdon, unpublished data.
minimal structural requirements of this novel PTB domain, its specificity, and the nature of its interacting proteins should help substantially in elucidating the role of this domain in Cbl's physiological function and mechanisms of its oncogenic activation.

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REFERENCES

1. Weiss, A., and Littman, D. (1994) Cell 76, 263–274
2. Defranco, A. L. (1995) Curr. Opin. Cell Biol. 7, 163–175
3. Reedquist, K., Fukazawa, T., Druker, B., Panchamoorthy, G., Shoelson, S., and Band, H. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 4135–4139
4. Panchamoorthy, G., Fukazawa, T., Stolz, L., Payne, G., Reedquist, K., Shoelson, S., Songyang, Z., Cantley, L., Walsh, C., and Band, H. (1994) Mol. Cell. Biol. 14, 6372–6385
5. Fukazawa, T., Reedquist, K., Trub, T., Seltsif, S., Panchamoorthy, G., Druker, B., Cantley, L., Shoelson, S., and Band, H. (1995) J. Biol. Chem. 270, 19141–19150
6. Donovan, J., Wange, R., Langdon, W., and Samelson, L. (1994) J. Biol. Chem. 269, 22921–22929
7. Pawson, T. (1995)
8. Blake, T., Shapiro, M., Morse, H., III, and Langdon, W. (1991) Mol. Cell. Biol. 11, 4515–4523
9. Meisner, H., Conway, B., Hartley, D., and Czech, M. (1995) Mol. Cell. Biol. 15, 3571–3578
10. Panchamoorthy, G., Fukazawa, T., Miyake, S., Soltoff, S., Reedquist, K., Druker, B., Shoelson, S., Cantley, L., and Band, H. (1996) J. Biol. Chem. 271, 3187–3194
11. Rivera-Lezcano, O., Sameshima, J., Marcilla, A., and Robbins, K. (1994) J. Biol. Chem. 269, 17363–17366
12. Reedquist, K. A., Fukazawa, T., Panchamoorthy, G., Langdon, W. Y., Shoelson, S. E., Druker, B. J., and Band, H. (1996) J. Biol. Chem. 271, 8435–8442
13. Marcilla, A., Rivera-Lezcano, O. M., Agarwal, A., and Robbins, K. C. (1995) J. Biol. Chem. 270, 9115–9120
14. Fournel, M., Davidson, D., Weil, R., and Veillette, A. (1996) J. Exp. Med. 183, 263–269
15. Langdon, W., Hartley, H., Klinken, S., Russettii, S., and Morse, H., III (1989) Proc. Natl. Acad. Sci. U. S. A. 86, 1168–1172
16. Blake, T., Heath, K., and Langdon, W. (1993) EMBO J. 12, 2017–2026
17. Andoniou, C. E., Thien, C. B. F., and Langdon, W. Y. (1994) EMBO J. 13, 4515–4523
18. Yoon, C. H., Lee, J., Jongeward, G. D., and Sternberg, P. W. (1995) Science 269, 1102–1105
19. Spits, H., Keizer, G., Borst, J., Terhorst, C., Hekman, A., and de Vries, J. E. (1984) Hybridoma 2, 423–427
20. Gan, G., Hauser, S. H., Liu, X.-L., Wazer, D. E., Mads-Jones, H., and Band, V. (1996) Cancer Res. 56, 3129–3133
21. Fukazawa, T., Miyake, S., Band, V., and Band, H. (1996) J. Biol. Chem. 271, 14554–14559
22. Druker, B., Mamont, T., and Roberts, T. (1988) N. Engl. J. Med. 321, 1383–1391
23. Wilson, I. A., Niman, H. L., Houghten, R. A., Cherensen, A. E., Connolly, M. L., and Lerner, R. A. (1984) Cell 37, 776–777
24. Tanaka, S., Hattori, S., Kurata, T., Nagashima, R., Fukui, Y., Nakamura, S., and Matsuda, M. (1993) Mol. Cell. Biol. 13, 4409–4415
25. Wolf, G., Trub, T., Ottinger, E., Groninga, L., Lynch, A., White, M., Miyazaki, M., Lee, J., and Shoelson, S. E. (1995) J. Biol. Chem. 270, 27407–27410
26. Bukowski, J. F., Morita, T., Fukazawa, T., Miyake, S., Band, V., and Band, H. (1996) J. Immunol. 154, 998–1006
27. Sieh, M., Batzer, A., Schlessinger, J., and Weiss, A. (1994) Mol. Cell. Biol. 14, 4435–4442
28. Chan, A., Iwashima, M., Turck, C., and Weiss, A. (1992) Cell 71, 649–662
29. Galisteo, M. L., Dikir, I., Batzer, A. G., Langdon, W. Y., and Schlessinger, J. (1995) J. Biol. Chem. 270, 20242–20245
30. Wange, R. L., Malek, S. N., Desiderio, S., and Samelson, L. E. (1993) J. Biol. Chem. 268, 15797–15801
31. Kavannagh, W. M., and Williams, L. T. (1994) Science 266, 1862–1865
32. Blakie, I., Immanuel, D., Wu, J., Li, N., Yajnik, V., and Margolis, B. (1994) J. Biol. Chem. 269, 32031–32034
33. van der Geer, P., Wiley, S., Lai, V. K.-M., Olivier, J. P., Gish, G. D., Stephenson, R., Kaplan, D., Shoelson, S. E., and Pawson, T. (1995) Curr. Biol. 5, 404–412
34. Zhou, M.-M., Ravichandran, K. S., Olejnizek, E. T., Petros, A. M., Meadows, R. F., Harlan, J. E., Wade, W. S., Burakoff, S. J., and Fesik, S. W. (1995) Nature 373, 7784–7788
35. Eck, M., Dhe-Paganon, S., Trub, T., Nolte, R. T., and Shoelson, S. E. (1995) J. Biol. Chem. 270, 17363–17366
36. Watts, J. D., Affolter, M., Krebs, D. L., Wange, R. L., Samelson, L. E., and Aebersold, R. (1994) J. Biol. Chem. 269, 29520–29529
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