Tyrosine Phosphorylation of Cbl upon Epidermal Growth Factor (EGF) Stimulation and Its Association with EGF Receptor and Downstream Signaling Proteins*

(Received for publication, July 13, 1995, and in revised form, March 1, 1996)

Toru Fukazawa§, Sachiko Miyake§, Vimla Bandi, and Hamid Band‡**

From the Lymphocyte Biology Section, Division of Rheumatology and Immunology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts 02115 and the Department of Radiation Oncology, New England Medical Center and Department of Biochemistry, Tufts University School of Medicine, Boston, Massachusetts 02111

Tyrosine phosphorylation provides a key switch to regulate cellular activity in response to extracellular stimuli. Many growth factor receptors, such as the epidermal growth factor receptor (EGFR), possess intrinsic tyrosine kinase domains, and their ligand-induced autophosphorylation creates docking sites for Src homology 2 (SH2) domains of cytoplasmic signaling proteins. Some signaling proteins, such as the phospholipase Cγ1, are directly phosphorylated by the receptor tyrosine kinases (RTKs) which results in the activation of their enzymatic activity. Other SH2-containing proteins serve as adaptors. For example, the growth factor receptor-binding protein 2 (Grb2) recruits guanine nucleotide exchanger son-of-sevenless protein to activated EGFR in proximity with the membrane-associated Ras. Finally, the cytoplasmic tyrosine kinases, such as the Src family members Src and Fyn, are also recruited in this manner, presumably to phosphorylate downstream effectors (1–6). Therefore, identification of additional cellular proteins that serve as substrates for RTKs is likely to enhance our understanding of how growth factors induce mitogenesis.

The protein product of the c-cbl proto-oncogene, p120cbl (Cbl), has recently emerged as a prominent substrate of tyrosine phosphorylation downstream of the immune cell surface receptors that signal through noncovalently associated cytoplasmic tyrosine kinases. We and others have shown that Cbl, the protein product of the c-cbl proto-oncogene, is an early target of tyrosine phosphorylation upon stimulation through the immune cell surface receptors, which signal through noncovalently associated cytoplasmic tyrosine kinases. Using human mammary epithelial cells that express a natural epidermal growth factor (EGF) receptor and require EGF as an essential growth factor, we demonstrate here that Cbl is a prominent target of tyrosine phosphorylation upon stimulation through the EGF receptor tyrosine kinase. Phosphorylation of Cbl was EGF dose-dependent, rapid (detectable as early as 5 s and maximal by 2 min), and relatively sustained (detectable even after 1 h). Co-immunoprecipitation studies demonstrated that Cbl became associated with the EGF receptor in an EGF-dependent manner. Cbl was basally associated with the adaptor protein growth factor receptor-binding protein 2 (Grb2), and this interaction was further enhanced by EGF stimulation; however, the interaction was entirely mediated via the Grb2 Src homology 3 (SH3) domains, suggesting that binding of Grb2 SH2 domain to EGF receptor provides one mechanism of Cbl’s association with the EGF receptor. EGF stimulation also induced the association of Cbl with Src homology and collagen (Shc) protein, p85 subunit of the phosphatidylinositol 3-kinase and Crk proteins, in particular with the CrkL isoform. Interactions of Cbl with the EGF receptor and multiple downstream signaling proteins suggest a role for this proto-oncogene product in mitogenic signaling through growth factor receptor kinases.

**To whom correspondence should be addressed: Lymphocyte Biology Section, Dept. of Rheumatology and Immunology, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115. Tel.: 617-432-1557; Fax: 617-432-2799; E-mail: band@mbcr.harvard.edu.
peptide portion (Fig. 1A, lower panel). A 175–180-kDa polypeptide was observed in anti-Tyr(P) blot of anti-Cbl immunoprecipitates, and kinetics of its phosphorylation was similar to that of Cbl. As shown in Fig. 4, this polypeptide represents the EGFR.

Concurrent anti-Tyr(P) immunoblotting of the whole cell lysates revealed that the 175–180-kDa EGFR polypeptide was heavily tyrosine-phosphorylated upon EGF stimulation (Fig. 1B). Aside from the EGFR, the 120-kDa polypeptide was one of the most prominent phosphotyrosyl proteins induced by EGF. The kinetics of phosphorylation of the 120- and 175-kDa bands in whole cell lysates was similar to that noted in anti-Cbl immunoprecipitates (compare Fig. 1, A with B). Thus, EGF stimulation of 16E6-P cells induces a prominent, rapid, and sustained tyrosine phosphorylation of Cbl.

To further characterize the EGF-induced Cbl tyrosine phosphorylation, we carried out anti-Cbl immunoprecipitations from 16E6-P cells stimulated with different concentrations of EGF. Anti-Tyr(P) immunoblotting revealed a dose-related increase in Cbl tyrosine phosphorylation with 1–100 ng/ml EGF (Fig. 2); a small increase was detected with 0.1 ng/ml EGF upon longer exposure of the blot (not shown). For comparison, a dose-related increase in EGF phosphorylation was also noted with 0.1–100 ng/ml EGF, with associated proteins being detectable primarily at higher (1–100 ng/ml) EGF concentrations. Relatively equal loading of immunoprecipitates in various lanes was revealed by anti-Cbl or anti-EGFR immunoblotting.

To rule out the possibility that Cbl phosphorylation in 16E6-P cells was related to their papilloma virus oncogene-induced immortalization, we also examined the 76N normal MECs from which the 16E6-P cell line was derived. A clear EGF-dependent tyrosine phosphorylation of Cbl and its associ-
Cbl-EGF Receptor Interaction

Fig. 1. EGF induces rapid and sustained tyrosine phosphorylation of Cbl in EGF-dependent human mammary epithelial cell line 16E6-P. A, cells were EGF-deprived for 3 days by growth in EGF-free medium. Cells were then left unstimulated (−) or were stimulated with 100 ng/ml EGF for the indicated time points (s, seconds; m, minutes) followed by lysis in Triton X-100 lysis buffer. Anti-Cbl immunoprecipitations, each from lysate of one 100-mm diameter plate, were resolved by SDS-9% PAGE, transferred to PVDF membrane, and immunoblotted with anti-Tyr(P) antibody (upper panel). Membrane was then reacted with protein A-horseradish peroxidase conjugate, and ECL detection was used to visualize the immunoprecipitated species. The filter was stripped and re-blotted with anti-Cbl antibody to show equal Cbl immunoprecipitation (lower panel). Cbl and associated Tyr(P) protein, p175 (EGFR; see Fig. 4), are indicated on the left. B, 1/20th of the cell lysates used in Fig. 1 A were directly analyzed by anti-Tyr(P) immunoblotting. p120 (Cbl) and p175 (EGFR) are indicated on the left. Reprobing of this filter with anti-Cbl (not shown) demonstrated equal loading.

Communoprecipitation of a 175-kDa phosphotyrosyl protein, comigrating with the EGFR, in anti-Cbl immunoprecipitates (Figs. 1A, 2 and 3) suggested that these proteins associate upon EGF stimulation. To characterize this association further, we carried out reciprocal immunoblotting of their immunoprecipitates. Anti-Tyr(P) immunoblotting of the anti-EGFR immunoprecipitates revealed a prominent EGF-dependent tyrosine phosphorylation of the major 175–180-kDa EGFR polypeptide as well as several associated polypeptides migrating at 120, 75, 66, 52, and 48 kDa (Fig. 4, lanes 3 and 4). Based on comigration and immunoblotting, the 66-, 52-, and 48-kDa polypeptides correspond to Shc proteins (Fig. 4, compare lanes 7–10 with lanes 3 and 4). The EGF-associated 120-kDa phosphotyrosyl polypeptide comigrated with directly immunoprecipitated Cbl (Fig. 4, compare lanes 4 and 6) and was immunoblotted by anti-Cbl antibody (see anti-Cbl blot). The major Cbl-associated phosphotyrosyl polypeptide at 175–180 kDa precisely comigrated with directly immunoprecipitated EGFR. Longer exposures of anti-EGFR immunoblot (not shown) revealed that the Cbl-associated 175-kDa polypeptide was reactive with anti-EGFR antibody. Cbl-EGFR association was also observed by performing anti-tag immunoprecipitations from a MEC transfectant expressing an influenza hemagglutinin-tagged Cbl (data not shown). Altogether, the analyses presented above clearly demonstrate that Cbl is a substrate of tyrosine phosphorylation upon EGF stimulation of human mammary epithelial cells and forms a protein complex with the EGFR in an EGF-dependent manner. These results confirm and extend similar results in other cell types that were published while our manuscript was in preparation and review (29–33).
Cbl-EGF Receptor Interaction

Previous studies have demonstrated that EGF-dependent association of cytoplasmic signaling proteins with the EGF receptor is mediated by binding of their SH2 domains to phosphorylated peptide motifs on the autophosphorylated receptor (1–6). Cbl lacks an SH2 domain, suggesting that its interaction with the EGF receptor may be mediated either through SH2 domain-containing adaptor proteins or a novel SH2-independent mechanism. Grb2 and Nck represented two likely candidates to serve as adaptor roles, since they are known to bind to proline-rich sequences within Cbl through their SH3 domains (7–10, 12, 15–17, 19) and to tyrosine-phosphorylated EGFR via their SH2 domain (1–6, 34). To assess this possibility, an immunoprecipitation–immunoblotting strategy was employed.

As expected, Grb2 showed a prominent EGF-dependent association with tyrosine-phosphorylated EGFR and Shc proteins (Fig. 4, lanes 7 and 8 versus lanes 3 and 4 or 9 and 10). In addition, a prominent 120-kDa phosphotyrosyl polypeptide which comigrated with Cbl (Fig. 4, compare lanes 6 and 8) was coimmunoprecipitated with Grb2. Direct anti-Cbl immunoblotting revealed this polypeptide to be Cbl (Fig. 4, anti-Cbl blot, lane 8). Reciprocal coimmunoprecipitation of Grb2 with Cbl was also observed (Fig. 4, anti-Grb2 blot, lane 6). Grb2-Cbl association was observed both in unstimulated and EGF-stimulated cells. However, in contrast to T cells, where similar levels of Grb2 associated with Cbl before and after activation (9), Cbl-Grb2 interaction in 16E6-P cells was modestly increased by EGF treatment (Fig. 4, anti-Cbl blot, lanes 7 and 8; anti-Grb2 blot, lanes 5 and 6).

To elucidate the nature of Grb2-Cbl interaction in EGF-stimulated MECs, in vitro binding analyses were performed using GST fusion proteins of Grb2 carrying mutations in SH2 or SH3 domains. Lysates of unstimulated or EGF-stimulated 16E6-P cells were incubated with bead-immobilized GST fusion proteins, and bound polypeptides were detected by anti-Cbl and anti-Tyr(P) immunoblotting (Fig. 5). Similar amounts of Cbl associated with the wild-type GST Grb2 fusion protein regardless of whether the lysates were derived from unstimulated or EGF-stimulated cells (Fig. 5, lanes 7 and 8), as was the case using GST Fyn-SH3 (lanes 3 and 4). Importantly, Cbl binding capacity was fully retained in GST-Grb2 fusion protein with a mutation in the SH2 domain (Fig. 5, lanes 9 and 10). Conversely, GST-Grb2 with mutations in both SH3 domains failed to bind to Cbl (Fig. 5, lanes 11 and 12); GST fusion protein of the isolated Grb2 SH2 domain also failed to bind to Cbl (lanes 5 and 6). Anti-Tyr(P) reprobing of the blot demonstrated that Cbl was tyrosine-phosphorylated upon EGF stimulation and associated with the EGFR (Fig. 5, lower panel, lanes 13 and 14). Furthermore, GST-Grb2 with a mutated SH2 (lanes 9 and 10) showed a dramatically reduced binding to the EGFR, whereas Grb2-SH2 (lanes 5 and 6) and Grb2 fusion protein with SH3 domain mutations (lanes 11 and 12) were fully active. These data demonstrate that EGF stimulation does not induce a Grb2 SH2 domain-binding site on Cbl, indicating that the Cbl-Grb2 interaction in MECs is exclusively Grb2 SH3 domain-mediated, similar to our findings in T and B cells (9, 12).

Grb2 can also associate with the EGFR indirectly, via Grb2 SH2 binding to tyrosine-phosphorylated Shc; Shc binds to the EGFR via its SH2 domain (1–6). Consistent with this scheme, EGF-dependent Grb2-Shc and EGFR-Shc associations were prominent in 16E6-P cells (Fig. 4, lanes 3 and 4 and 7 and 10). Importantly, a small amount of Cbl coimmunoprecipitated with Shc (lane 10, anti-Tyr(P) and anti-Cbl blots); a small amount of Shc was also observed in anti-Cbl immunoprecipitates upon

![Figure 4](https://example.com/figure4.png)

**Figure 4.** In vivo association of Cbl with the EGFR, Grb2, Shc, and Crk proteins and the p85 subunit of PI 3-kinase in 16E6-P mammary epithelial cells. Immunoprecipitations were carried out with indicated antibodies (I.P. antibody) from lysates of unstimulated cells (–) or cells stimulated for 10 min with 100 ng/ml EGF (+). Proteins were resolved by SDS-PAGE, transferred to PVDF membrane, immunoblotted with anti-Tyr(P) antibody followed by protein A–horseradish peroxidase conjugate, and detected by ECL (upper panel). The membrane was then cut into different size regions, stripped, and serially probed as appropriate with antibodies shown on right. Locations of identified polypeptides are shown on left. Anti-Crk blotting showed equal amounts of Crk II (shown) as well as Crk I (not shown) in lanes 11 and 12. Ig, Ig heavy chain.

![Figure 5](https://example.com/figure5.png)

**Figure 5.** Binding of Cbl to GST fusion proteins of Grb2 is exclusively mediated through Grb2 SH3 domains. Cbl lysates from one-half of a 100-mm diameter plate of unstimulated cells (–) or cells stimulated with 100 ng/ml EGF for 10 min (+) were incubated for 1 h with GST fusion proteins noncovalently immobilized on glutathione–Sepharose beads (5 μl of packed beads; 10 μg of fusion protein; total volume, 1 ml), and bound proteins were solubilized in sample buffer. Binding reactions or whole cell lysate (from 1/20th of a plate) were resolved by SDS-PAGE and subjected to anti-Cbl immunoblotting (upper panel) using protein A–horseradish peroxidase conjugate and ECL detection. w.t., wild-type Grb2, 3-2-3 refers to NH2-terminal SH3 and SH2 and COOH-terminal SH3 domains of Grb2. Asterisks denote mutated domains. Mutated residues were: NH2-terminal SH3, P49L; SH2, R86K; COOH-terminal SH3, P206L. The filter was stripped and immunoblotted with anti-Tyr(P) antibody (lower panel). Cbl and EGFR are indicated on left. α Cbl p.I. (lanes 13 and 14), immunoprecipitation from the same amount of cell lysate as used for binding reactions.
longer exposure of anti-Shc immunoblot (not shown). Consistent with Grb2-mediated Shc-Cbl interaction, Shc-Cbl complex was much less abundant compared with either the Shc-Grb2 or Grb2-Cbl complexes (Fig. 4), and a GST-Shc SH2 fusion protein did not bind to Cbl in either unstimulated or the EGF-stimulated cells (data not shown).

Since Nck is known to bind to activated EGF through its SH2 domain (34) and to Cbl via its SH3 domains (17), Nck represented another potential adaptor that could mediate Cbl-EGFR association. However, anti-Nck immunoprecipitates did not reveal a detectable association with Cbl although Nck associated with the EGFR in activated 16E6-P cells (data not shown). In addition, we did not observe a complex between Cbl and Fyn, another protein that associates with Cbl via its SH3 domain in T and B cells (7, 12), although a small fraction of the EGFR co-immunoprecipitated with anti-Fyn antibodies (data not shown). Altogether, the above results are consistent with a major role for Grb2 in mediating Cbl-EGFR association.

While this paper was under review, other reports on the potential mechanisms of Cbl-EGFR association have appeared. Meisner and Czech (31) showed that in human embryonic cell line 293 Cbl is constitutively associated with Grb2, and EGF stimulation induces a strong association between Cbl and the EGFR. In addition, these workers showed that both the Grb2 and Cbl were released from the EGFR by a proline-rich peptide specific for Grb2 SH3 domains. Independently, Galisteo et al. (30) also observed Grb2 and Shc in anti-Cbl immunoprecipitates of EGF-stimulated murine fibroblasts overexpressing the human EGFR. Thus, these studies, like ours, support the role of Grb2 proteins in Cbl-EGFR association. However, Galisteo et al. (30) also demonstrated a direct in vitro binding between the NH2-terminal half of Cbl expressed as a GST fusion protein and the tyrosine-phosphorylated EGFR cytoplasmic tail. Notably, Bowtell and Langdon (32) expressed the NH2-terminal portion of Cbl, devoid of its proline-rich regions, in murine fibroblasts and showed that it co-immunoprecipitated with the EGFR in unstimulated cells with a modest increase of this association upon EGF stimulation. Interestingly, this association was considerably lower compared with that observed with either the wild-type Cbl or mutants that retained the proline-rich region. Altogether, it appears likely that both the direct and adaptor-dependent interactions contribute to Cbl-EGFR association, although additional studies will be needed to clarify their relative importance particularly in the context of different cell types where the relative levels of Cbl, EGFR, and Grb2 proteins may be quite different. Independently, genetic studies in Caenorhabditis elegans have identified a structurally conserved Cbl homolog, sli-1, as a negative regulator of the EGFR, let-23, which controls vulval development through a signaling pathway involving Grb2 and Ras homologs (35).

Recent analyses in T and B cells have demonstrated an activation-dependent, primarily SH2-mediated, complex of the p85 subunit of PI 3-kinase with Cbl (9, 12, 15). Furthermore, a substantial fraction of the PI 3-kinase activity was associated with Cbl upon antigen receptor stimulation (9, 12, 15). Since PI 3-kinase is known to be recruited into EGF signaling (36), we examined if Cbl-PI 3-kinase p85 complexes are induced by EGFR stimulation of 16E6-P cells. As seen in Fig. 4 (anti-p85 blot, lanes 5 and 6; anti-Tyr(P) and anti-Cbl blots, lanes 15 and 16), a prominent EGF-dependent association of Cbl and PI 3-kinase p85 was observed in 16E6-P cells. Notably, a smaller but significant EGF-dependent coimmunoprecipitation of PI 3-kinase p85 with the EGFR (lanes 3 and 4), Grb2 (lanes 7 and 8), and Shc (lanes 9 and 10) was also observed. In view of the lack of a consensus p85 SH2 domain binding motif on the EGFR (36), association of the PI 3-kinase p85 subunit with tyrosine-phosphorylated Cbl may provide one mechanism to recruit this enzyme to the EGFR. A similar role for Cbl has been suggested by Soltoff and Cantley (33), based on their studies on PC12 and other cells.

Our recent analyses have revealed that Cbl is a major Crk- and CrkL-associated tyrosine-phosphorylated polypeptide in activated T cells (13). Since Crk proteins are widely expressed, and Crk SH2 domain can interact with the EGFR (37, 38), we examined the possible association of Cbl with Crk proteins. Anti-CrkL, and to lesser extent anti-Crk antibody (which recognizes CrkI and II) (13), co-immunoprecipitated a small amount of EGFR in EGF-stimulated 16E6-P cells (Fig. 4, lanes 11–14). In addition, a small but reproducible tyrosine phosphorylation of CrkL (Fig. 4, lane 14) and CrkI (seen upon longer exposure, not shown) was observed upon EGFR stimulation. Notably, these analyses showed that Cbl was the major coimmunoprecipitating tyrosyl phosphoprotein in anti-Crk (Fig. 4, lanes 11 and 12) and in particular in anti-CrkL (lanes 13 and 14) immunoprecipitates. Anti-CrkL immunoblotting revealed that a small amount of CrkL was co-immunoprecipitated by anti-Cbl (Fig. 4, lane 6). Thus, in addition to their direct association, Crk proteins may also be recruited to EGFR signaling indirectly through their association with tyrosine-phosphorylated Cbl. We have shown previously that Cbl association with the Crk proteins is SH2 domain-mediated, which allows a ternary complex to be formed between tyrosine-phosphorylated Cbl and C3G, a guanine nucleotide exchange factor for the small GTP-binding protein Rap 1A that is constitutively associated with the SH3 domains of Crk proteins (13, 39). Thus, Cbl-Crk interaction could provide an alternate mechanism to recruit this novel signaling pathway to the EGFR.

In conclusion, we show that Cbl is a major substrate for the EGFR, associates with this receptor upon EGF stimulation, and forms complexes with several signaling proteins that play key roles in EGFR-mediated cell growth. Identification of Cbl as a proto-oncoprotein as a downstream element in signaling through both the hematopoietic and nonhematopoietic cell receptors suggests an important role for this protein. The present system, in which EGFR mediates an essential growth signal, should complement other cell systems to more precisely define the biological function(s) of Cbl.

Acknowledgments—We thank Dr. Brian Druker for a generous gift of 4G10 antibody; Drs. Steve Soltoff, Lou Cantley, and Wallace Langdon for discussion; and David Bonita and Kris Reedquist for reading the manuscript.

REFERENCES
1. Schlessinger, J., and Ullrich, A. (1992) Neuron 9, 383–391
2. Fanti, W. J., Jahnson, D. E., and Williams, L. T. (1993) Annu. Rev. Biochem. 62, 453–481
3. Schlessinger, J. (1994) Curr. Opin. Genet. Dev. 4, 25–30
4. van der Geer, P., Hunter, T., and Lindberg, R. A. (1994) Annu. Rev. Cell Biol. 10, 251–337
5. Downward, J. (1994) FEBS Lett. 338, 113–117
6. Pawson, T. (1995) Nature 373, 573–580
7. Reedquist, K. A., Fukazawa, T., Druker, B., Panchamoorthy, G., Shoelson, S. E., and Band, H. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 4335–4339
8. Donovan, J. A., Wane, R. L., Langdon, W. Y., and Samelston, L. E. (1994) J. Biol. Chem. 269, 22921–22924
9. Fukazawa, T., Reedquist, K. A., Trub, T., Soltoff, S., Panchamoorthy, G., Druker, B., Cantley, L., Shoelson, S. E., and Band, H. (1995) J. Biol. Chem. 270, 19141–19150
10. Oda, H., Sasaki, K., Iwamatsu, A., Harazono, Y., Tanaka, T., Miltani, K., Yazaki, Y., and Hirai, H. (1995) J. Biol. Chem. 270, 10880–10885
11. Marcella, A., Rivero-Lezcano, O. M., Agarwal, A., and Robbins, K. C. (1995) J. Biol. Chem. 270, 9115–9120
12. Panchamoorthy, G., Fujitawa, M., Miyake, S., Soltoff, S., Reedquist, K., Druker, B., Chantley, L., Shoelson, S. E., and Band, H. (1996) J. Biol. Chem. 271, 3187–3194
13. Reedquist, K., Fukazawa, T., Panchamoorthy, G., Langdon, W. Y., Shoelson, S. E., Druker, B., and Band, H. (1996) J. Biol. Chem. 271, 8435–8442
14. Blake, T. J., Shapiro, M., Morse, H. C., and Langdon, W. Y. (1991) Oncogene 6, 653–657
15. Meisner, H., Conway, B. R., Hartley, D., and Czech, M. P. (1995) Mol. Cell. Biol. 15, 3571–3578
16. Fukazawa, T., Reedquist, K. A., Panchamoorthy, G., Soltoff, S., Trub, T.,
    Druker, B., Cantley, L., Shoelson, S. E., and Band, H. (1995). J. Biol. Chem. 270,
    20177–20182
17. Rivero-Lezcano, O. M., Sameshima, J. H., Marcella, A., and Robbins, K. C.
    (1994). J. Biol. Chem. 269, 1383–1391
18. Druker, B., Mamon, T., and Roberts, T. (1989). N. Engl. J. Med. 321, 1383–1391
19. Panchamoorthy, G., Fukazawa, T., Stolz, L., Payne, G., Reedquist, K.,
    Shoelson, S., Zhou, S., Cantley, L., Walsh, C., and Band, H. (1994). Mol. Cell. Biol. 14,
    6372–6385
20. Suen, K. L., Bustelo, X. R., Pawson, T., and Barbacid, M. (1993). Mol. Cell. Biol. 13,
    5500–5512
21. Band, V., and Sager, R. (1989). Proc. Natl. Acad. Sci. U. S. A. 86, 1249–1253
22. Band, V., Delmolino, L., Kulesa, V., and Sager, R. (1991). J. Virol. 65, 6671–6676
23. Band, V., Zajchowski, D., Kulesa, V., and Sager, R. (1990). Proc. Natl. Acad. Sci. U. S. A. 87,
    463–467
24. Band, V., Dalal, S., Delmolino, L., and Androphy, E. J. (1993). EMBO J. 12,
    1847–1852
25. Blake, T. J., Heath, K. G., and Langdon, W. Y. (1993). EMBO J. 12, 2017–2026
26. Andoniou, C. E., Thien, C. B. F., and Langdon, W. Y. (1994). EMBO J. 13,
    4515–4523
27. Langdon, W. Y., Hyland, C. D., Grumont, R. J., and Morse, H. C. (1989)
    J. Virol. 63, 5420–5424
28. Band, V., Zajchowski, D., Swisshelm, K., Trask, D., Kulesa, V., Cohen, C.,
    Connolly, J., and Sager, R. (1990). Cancer Res. 50, 7351–7357
29. Tanaka, S., Neff, L., Baron, R., and Levy, J. B. (1995). J. Biol. Chem. 270,
    14347–14351
30. Galisteo, M. L., Dikic, I., Batzer, A. G., Langdon, W. Y., and Schlessinger, J.
    (1995). J. Biol. Chem. 270, 20242–20245
31. Meisner, H., and Czech, M. P. (1995). J. Biol. Chem. 270, 25332–25335
32. Bowtell, D. D., and Langdon, W. Y. (1995). Oncogene 11, 1561–1567
33. Soltoff, S. P., and Cantley, L. C. (1996). J. Biol. Chem. 271, 563–567
34. Li, W., Hu, P., Skolnik, E. Y., Ullrich, A., and Schlessinger, J. (1992). Mol. Cell. Biol. 12,
    5824–5833
35. Yoon, C. H., Lee, J., Jongeward, G. D., and Sternberg, P. W. (1995). Science 269,
    1102–1105
36. Carraway, K. L., III, and Cantley, L. C. (1994). Cell 78, 5–8
37. Moran, M. F., Koch, C. A., Anderson, D., Ellis, C., England, L., Martin, G. S.,
    and Pawson, T. (1990). Proc. Natl. Acad. Sci. U. S. A. 87, 8622–8626
38. Birge, R. B., Fajardo, J. E., Mayer, B. J., and Hanafusa, H. (1992). J. Biol. Chem. 267,
    10588–10595
39. Gotoh, T., Hatani, S., Nakamura, S., Kitayama, H., Noda, M., Takai, Y.,
    Kaibuchi, K., Matsui, H., Hatase, O., Takahashi, H., Kurata, T., and
    Matsuda, M. (1995). Mol. Cell. Biol. 15, 6746–6753
Tyrosine Phosphorylation of Cbl upon Epidermal Growth Factor (EGF) Stimulation and Its Association with EGF Receptor and Downstream Signaling Proteins
Toru Fukazawa, Sachiko Miyake, Vimla Band and Hamid Band

J. Biol. Chem. 1996, 271:14554-14559.
doi: 10.1074/jbc.271.24.14554

Access the most updated version of this article at http://www.jbc.org/content/271/24/14554

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 39 references, 26 of which can be accessed free at http://www.jbc.org/content/271/24/14554.full.html#ref-list-1