Specific Association of Tyrosine-phosphorylated c-Cbl with Fyn Tyrosine Kinase in T Cells*

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Fyn is a Src family protein-tyrosine kinase functionally associated with the T-cell antigen receptor (TcR)/CD3 receptor complex. We have demonstrated earlier that the TcR/CD3-induced activation of Fyn results in tyrosine phosphorylation of several Fyn-associated proteins, including a protein of 116 kDa. In this report, we identify the Fyn-associated 116-kDa phosphoprotein (p116) as c-Cbl. The identity of p116 has been demonstrated by its specific reactivity with anti-Cbl and similarity of phosphopeptides generated by V8 proteolysis of phospho-Cbl and p116. We demonstrate here that the association of Fyn and c-Cbl is direct and does not require the presence of other proteins. We also demonstrate that Fyn is the Src family kinase that preferentially interacts with c-Cbl in T cells. The fraction of c-Cbl capable of coprecipitating with Fyn is increased by TcR/CD3 ligation. This increase is likely due to the involvement of Fyn SH2 in the interactions between Fyn and tyrosine-phosphorylated c-Cbl.

Fyn is a Src family protein-tyrosine kinase expressed in T lymphocytes and functionally associated with the TcR/CD3 receptor complex (reviewed in Refs. 1–3). Fyn appears to play a role in the activation of T cells through the TcR/CD3, based on its physical association with the TcR/CD3 (4–6) and its enzymatic activation and tyrosine phosphorylation following ligation of the TcR/CD3 (7, 8). Physiological responses of T cells to TcR/CD3 stimulation are dramatically affected by targeted disruption of the fyn gene (9, 10) or overexpression of its wild-type and dominant-negative forms (11), confirming that Fyn is critically important in TcR-mediated T-cell activation. Lck is another Src-related kinase involved in TcR signaling. Although Lck appears not to be directly associated with the TcR/CD3, the CD4-Lck complex (12) seems to interact with the TcR/CD3, making Lck a crucial element of the T-cell activation pathway (13, 14). Fyn and Lck appear to trigger the activation of Zap, a Syk family kinase capable of binding to the cytoplasmic sequences of the TcR/CD3 (15–19).

Activation of Fyn following TcR/CD3 cross-linking results in tyrosine phosphorylation of several proteins associated with Fyn (7, 8). The major Fyn-associated phosphoprotein of 116 kDa (p116) becomes phosphorylated on tyrosine in vitro, as well as in vivo, following TcR/CD3 ligation (20, 21). The interaction of Fyn with p116 and the other major Fyn-associated protein, p82, appear to be specific for this Src-related kinase (21, 22) and mediated primarily by the SH2 domain of Fyn, although p82 can also bind to Fyn SH3 (21). Another important difference between the two Fyn-associated proteins is that the tyrosine phosphorylation of p116 is entirely TcR/CD3 ligation dependent, whereas the tyrosine phosphorylation of p82 is little affected by TcR/CD3 ligation (21). These results suggest that p116 may represent a specific physiological substrate of Fyn.

In this report, we identify the Fyn-associated p116 as c-Cbl. c-Cbl is a product of the corresponding proto-oncogene exhibiting several distinct features of a transcription factor (23–25) but whose physiological functions remain to be determined. c-Cbl protein becomes phosphorylated on tyrosine following TcR/CD3 ligation (26) and is capable of binding to Fyn, Grb2, and the p85 subunit of phosphatidylinositol 3′-kinase (26–30). It has not been shown yet whether the 116-kDa protein phosphorylated in vitro in Fyn immune complexes is related to c-Cbl. The specificity and the molecular basis of c-Cbl/Fyn interactions also remain to be elucidated. Here we report that the Fyn-associated p116 protein is recognized by anti-Cbl antibodies and that this recognition is completely and specifically blocked by the c-Cbl antigenic peptide. We also report that the association between Fyn and c-Cbl does not require participation of other proteins and, therefore, is direct. Furthermore, we show in this study that Fyn SH2 is involved in the interactions between Fyn and c-Cbl following the TcR/CD3-induced tyrosine phosphorylation of c-Cbl. Finally, we demonstrate that in T cells, c-Cbl preferentially interacts with Fyn, whereas association between Lck and c-Cbl appears to be insignificant, regardless of whether c-Cbl is phosphorylated.

EXPERIMENTAL PROCEDURES

Antibodies and Peptides—Antisera to glutathione S-transferase (GST) and Src family kinases were described earlier (21). The affinity-purified polyclonal antibody against c-Cbl (C-15), the corresponding antigenic peptide, and PY20 anti-Tyr(P) monoclonal antibody were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). OKT3 anti-CD3 monoclonal antibody has been purified from ascites fluid using protein A-Sepharose. Anti-Cas antisera was kindly provided by Dr. H. Hirai, University of Tokyo. Myeloma proteins used as isotype-matched antibody controls were purchased from Sigma. Rabbit IgG against mouse IgG and goat F(ab′)2 fragments against mouse IgG were purchased from Cappel (Durham, NC). Irrelevant Sc.A7 peptide (31) was a kind gift of Dr. D. Mosser, Temple University, Philadelphia.

Fusion Proteins—GST fusion proteins containing full-length Src family kinases and their fragments were described earlier (21). The Grb2 open reading frame was cloned from a mouse A20/24 B-cell cDNA library (Stratagene, La Jolla, CA) into pBluescript SKII + vector (Stratagene) using a polymerase chain reaction-based strategy with published Grb2 sequences (32). The full-length Grb2 (amino acids 1–217), N-terminal SH3 (amino acids 5–54), SH2 (amino acids 59–158), and
C-terminal SH3 (amino acids 163–208) domains, as well as the fragments containing SH2 with either N-terminal or C-terminal SH3, were amplified from pBluescript/Grb2 plasmid by DNA amplification reaction and cloned into pGEX-2T vector (Pharmacia Biotech Inc.). The GST-Grb2 fusion proteins were expressed in *Escherichia coli* and purified using glutathione-Sepharose columns (Pharmacia).

**Cells**—CEM.3-71 is a CD3⁺ clone of the human T-cell line CEM. These cells and the way they were cultured and activated were described earlier (21).

**Metabolic Labeling**—Cells were labeled in methionine-free/cysteine-free or phosphate-free RPMI 1640 supplemented with 10% dialyzed fetal bovine serum (Life Technologies, Inc.) at a density of approximately 10⁷ cells/ml in the presence of 0.1 mCi/ml Tran35S-label (ICN, Costa Mesa, CA) or 1 mCi/ml [32P]orthophosphate (DuPont NEN) for 3 h.

**In vitro** transcription/translation was carried out using the Promega TNT-coupled reticulocyte lysate system and Tran35S-label reagent. Human c-Cbl cDNA in pGEM4Z vector was kindly provided by Dr. W. Langdon, The University of Western Australia, Nedlands.

**Immunoprecipitation, Immune Complex Kinase Assay, and Immunoblotting**—Cells were lysed, proteins were immunoprecipitated with appropriate antibodies, and immune complex kinase assay and immunoblotting were performed as described earlier (12, 21, 33). Where indicated, immune complexes were dissociated with SDS, and proteins were reprecipitated with the corresponding antibodies or GST-fusion proteins, followed by anti-GST (21). GST-fusion proteins were added to dissociated immune complexes in the molar amount equivalent to 1 µg of GST/1 mg of total protein initially used for immunoprecipitation.

**Coprecipitation with GST-Fusion Proteins**—GST or GST-fusion proteins were added at 1 µg of GST or equimolar amounts of GST-fusion proteins/1 mg of total T-cell lysate protein or 3 µl of reticulocyte transcription/translation reaction mixture containing 60 ng of c-Cbl pGEM4Z vector. GST-containing proteins were precipitated using either glutathione-Sepharose, according to the manufacturer’s recommendation, or anti-GST antiserum (5 µl/1 mg of GST) as described above.

**Phosphopeptide Mapping**—Phosphoprotein bands were excised from a gel and cleaved with V8 protease from *Staphylococcus aureus* (Pierce) as described earlier (34).

### RESULTS

**Identification of the Fyn-associated 116-kDa Protein as c-Cbl**—We sought to determine the identity of the p116 protein, which we have previously established as associating with and undergoing phosphorylation by Fyn. Among various candidate proteins, our attention has been drawn to c-Cbl, one of the newly identified substrates of tyrosine kinases in T cells (26).

To determine whether p116 is c-Cbl, we immunoprecipitated Fyn from T-cell lysates, performed *in vitro* kinase assays with these immunoprecipitates, and attempted to re-precipitate p116 using several antibodies including an affinity-purified antibody against c-Cbl. The p116 protein was detected in immunoprecipitates with anti-Cbl, whereas no immunoprecipitation of p116 was observed with either nonimmune control serum or antiserum against Cas, the 130-kDa substrate of Src (35, 36) (Fig. 1A, left panel, and B). To confirm the specificity of immunoprecipitation of p116 with anti-Cbl, we used the C-terminal c-Cbl peptide C-15, to which the anti-Cbl antibody was raised, to block this immunoprecipitation. The reactivity of p116 with anti-Cbl was completely blocked by low concentrations of C-15, whereas an irrelevant peptide had no effect, even at a much higher concentration (Fig. 2).

Immunoprecipitation of c-Cbl, followed by an immune complex kinase assay, demonstrated that c-Cbl and several other...
proteins, including a 60-kDa protein, become phosphorylated on tyrosine in c-Cbl immunoprecipitates (Fig. 1A, right panel). This indicates that a protein-tyrosine kinase is present in c-Cbl immune complexes. Considerable fractions of the 116-kDa and the p60-kDa phosphoproteins initially immunoprecipitated with anti-Cbl were re-immunoprecipitated with anti-Fyn but not with control immunoglobulins (Fig. 1A, right panel) or anti-Lck (data not shown). This result argues that Fyn is present in c-Cbl immune complexes and is capable, to a certain extent, of reassociating with c-Cbl following dissociation of their complex.

We also compared phosphopeptides generated by V8 proteolysis of the 116-kDa proteins phosphorylated in Fyn and c-Cbl immune complexes and found out that these peptides were essentially identical (Fig. 3). This result further indicates that the Fyn-associated p116 is c-Cbl. Furthermore, the pattern of phosphopeptides generated by V8 cleavage of the c-Cbl-associated 60-kDa phosphoprotein is essentially identical to the pattern of phosphopeptides generated by V8 cleavage of Fyn (data not shown), arguing that these two proteins are identical.

To provide further evidence of association between Fyn and c-Cbl, we labeled CEM.3-71 cells with 35S-labeled amino acids and compared the pattern of anti-Cbl-immunoprecipitated 35S-labeled proteins to the proteins phosphorylated in vitro in Fyn immune complexes from the same cells. Two major 35S-labeled proteins specifically immunoprecipitated with anti-Cbl appeared to comigrate with phosphoproteins of Fyn immune complexes corresponding to Fyn and the Fyn-associated p116 (Fig. 4). No band comigrating with p60(C) was found specifically associated with c-Cbl in these experiments. Furthermore, we metabolically labeled CEM.3-71 cells with [32P]orthophosphate, activated them by CD3 cross-linking or left unstimulated, and immunoprecipitated c-Cbl and Fyn from these cells. The first immunoprecipitation was followed by re-immunoprecipitation with antibodies to c-Cbl, Fyn, or Tyr(P). These experiments have demonstrated that Fyn is associated with a 116-kDa phosphoprotein comigrating with a 116-kDa protein double-immunoprecipitated with anti-Cbl (Fig. 5). Both of these 116-kDa protein bands are phosphorylated on tyrosine, as evidenced by their reactivity with anti-Tyr(P) antibody (Fig.
5). Taken together, these results indicate that the Fyn-associated 116-kDa protein, characterized by us previously (21), represents a tyrosine-phosphorylated form of c-Cbl.

**Stoichiometry of the Interactions between c-Cbl and Fyn in T Cells**—The results of immunoprecipitation of c-Cbl and Fyn from metabolically labeled CEM.3-71 cells demonstrate that the percentage of c-Cbl associated with Fyn is very low. The intensity of the 116-kDa phosphoprotein band re-precipitated with anti-Cbl from Fyn immune complexes, which corresponds to the Fyn-associated fraction of phospho-Cbl, accounts for approximately 1% of the total amount of phospho-Cbl (Fig. 5A, lane 3 versus lane 7; Fig. 5B, lane 8 versus lane 9). An equivalent experiment with 35S-labeled cells provided similar results (data not shown). This indicates a low abundance of the complex between Fyn and c-Cbl in T cells and is consistent with the failure of immunoblotting to detect the presence of c-Cbl in Fyn immunoprecipitates and vice versa (data not shown).

**Interactions of c-Cbl with the Adaptor Protein Grb2**—c-Cbl is
Specific Association of Cbl with Fyn Involves Fyn SH2 Domain

The results reported in this study indicate that the previously described Fyn-associated 116-kDa protein (p116) is a tyrosine-phosphorylated form of c-Cbl. We initially demon-
strated association of Fyn and p116\textsubscript{cbl} using the immune complex kinase assay of Fyn immunoprecipitates (7, 21) (Fig. 1). In addition, we showed coimmunoprecipitation of Fyn and c-Cbl from the lysates of T cells labeled with [\textsuperscript{35}S]methionine/cysteine or [\textsuperscript{32}P]orthophosphate in vivo (Figs. 4 and 5). We also demonstrated that recombinant full-length Fyn binds to c-Cbl (Figs. 6–8). The interaction between Fyn and c-Cbl appears to be direct, based on their coprecipitation in the absence of additional proteins (Figs. 7 and 8).

Taken together with the data published earlier, our results suggest that several domains of Fyn are involved in the interaction with c-Cbl. It has been demonstrated previously that c-Cbl is capable of interacting with SH3 domains of Fyn and other Src-related kinases (26, 29, 39–41). Although we observed no binding of c-Cbl to isolated SH3 domains, apparently due to the high stringency of our experimental system (see Figs. 6–8), the binding of unphosphorylated c-Cbl to Fyn (Figs. 7 and 8) is consistent with the involvement of Fyn SH3 domains. It appears that the c-Cbl/Fyn complex exists in unstimulated T cells, where it is likely stabilized by SH3-mediated interactions (Fig. 4). However, the tyrosine phosphorylation of c-Cbl increases its ability to bind to Fyn (Fig. 7). This increase is apparently caused by the interaction between Tyr(P) residue(s) of c-Cbl and Fyn SH2 domain and is observed once c-Cbl becomes tyrosine phosphorylated following TcR/CD3 ligation (Figs. 7 and 8). Hence, the TcR/CD3-induced tyrosine phosphorylation of c-Cbl is likely to promote formation of the complex between Fyn and c-Cbl in T cells. Although the TcR/CD3-dependent tyrosine phosphorylation of c-Cbl does not necessarily increase the total amount of Fyn/c-Cbl complex, it may effectively change the type of association between c-Cbl and Fyn from primarily SH3-dependent in unstimulated T cells to primarily SH2-dependent in stimulated T cells. This alteration may render the Fyn SH3 domain and c-Cbl proline-rich regions available for interactions with other proteins in activated T cells.

Interestingly, the fraction of c-Cbl found in association with Fyn in CEM.3-71 cells is relatively minor (Fig. 5 and data not shown). This finding likely reflects the fact that Fyn expression in T cells is substantially lower than that of c-Cbl (7, 28) (data not shown). Furthermore, the affinity of c-Cbl/Fyn interactions may not be sufficiently high to cause quantitative binding,
because the fraction of Fyn-associated c-Cbl does not exceed 20%, even in the presence of an excess of recombinant Fyn (Fig. 7 and data not shown). In addition, we should note that coimmunoprecipitation of c-Cbl with Fyn from T-cell lysates may not exactly reflect the extent of their association in vivo, where intracellular conditions and/or compartmentalization may favor this association.

The involvement of a SH2 domain in the interaction between Fyn and c-Cbl raises the question of specificity of their association, because numerous proteins contain SH2 domains. However, we have demonstrated previously that in spite of the ability of several Src family SH2 domains to bind to p116, tyrosine-phosphorylated p116 is found only in Fyn, but not in Lck or Yes, immune complexes from T-cell lysates (21). The present study clearly demonstrates that both unphosphorylated and tyrosine-phosphorylated forms of c-Cbl exhibit preferential binding to Fyn, as compared to Lck (Figs. 1, 4, and 6–8 and data not shown), indicating that Fyn is a specific Src family kinase that interacts with c-Cbl in T cells. This specificity, taken together with the ability of Fyn to phosphorylate c-Cbl in immune complexes in vitro, strongly argues that Fyn is capable of phosphorylating c-Cbl in T cells. However, the possibility that other protein kinases are involved in phosphorylation of c-Cbl in vivo cannot be ruled out at the moment.

It is evident that the adaptor protein Grb2 binds to c-Cbl in the cells analyzed (Figs. 6–8). It is important that Grb2 and Fyn differ with regard to the mechanism of their association with c-Cbl. Although the Fyn SH2 domain appears to be critical for c-Cbl/Fyn interaction in activated CEM.3.71 cells, binding of Grb2 SH2 to c-Cbl has not been observed, regardless of whether c-Cbl is phosphorylated (Figs. 6–8). Furthermore, Tyr(P) does not affect binding of Grb2 to c-Cbl (data not shown), consistent with the idea that this binding is not mediated by SH2-Tyr(P) interactions. These results are in agreement with the earlier reports indicating that c-Cbl primarily interacts with Grb2 SH3 domains (26, 28–30, 37). In accordance with this mechanism, the ability of c-Cbl to form a complex with Grb2 is not affected by TcR/CD3 ligation (Fig. 7).

The physiological role of c-Cbl/Fyn interactions is still unclear and remains to be elucidated. The oncogenic potential of certain truncations and deletion mutants of c-Cbl (23–25) is required to characterize the mechanism and the physiological functions of c-Cbl/Fyn interactions, as well as the involvement of other proteins in these interactions.

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