Physical and Functional Association of the cbl Protooncogene Product with an Src-Family Protein Tyrosine Kinase, p53/56\textsuperscript{bn}, in the B Cell Antigen Receptor-mediated Signaling

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Summary
To identify novel signal transducers involved in signaling mediated by the Src-family protein tyrosine kinases (PTKs), we used a yeast two-hybrid system with a probe corresponding to the regulatory region of p56\textsuperscript{bn}, a member of Src-family PTKs. One of the isolated clones contained the COOH-terminal 470 amino acid residues of p120\textsuperscript{c-bt}, the product of the cellular homologue of the v-cbl retroviral oncogene. p120\textsuperscript{c-bt} is a cytoplasmic protein with nuclear protein-like motifs. Here we show in vivo association of p120\textsuperscript{c-bt} with p53/56\textsuperscript{bn}. After stimulation of the B cell antigen receptor (BCR), p120\textsuperscript{c-bt} was rapidly tyrosine phosphorylated. Studies with lyn- or syk-negative chicken B cells demonstrated that p53/56\textsuperscript{bn}, but not p72\textsuperscript{src}, was crucial for tyrosine phosphorylation of p120\textsuperscript{c-bt} upon stimulation of the BCR. We also show the importance of p59\textsuperscript{fr} in tyrosine phosphorylation of p120\textsuperscript{c-bt} in the T-cell receptor-mediated signaling, using fyn-overexpressing T cell hybridomas and splenic T cells from fyn-deficient mice. These results suggest that p120\textsuperscript{c-bt} is an important substrate of Src-family PTKs in the intracellular signaling mediated by the antigen receptors.

The Src-family protein tyrosine kinases (PTKs) are intracytoplasmic PTKs that are generally localized on the inner part of the plasma membrane via myristylation. Accumulating evidence shows that these PTKs transduce signals from specific cell surface receptors, including the B cell antigen receptor (BCR) (1–5). Stimulation of the BCR initiates a series of intracellular signaling events, such as protein tyrosine phosphorylation, phosphatidylinositol turnover, Ras activation, and Ca\textsuperscript{2+} mobilization (5). Since Src-family PTKs are associated both physically and functionally with the BCR, they have been thought to be critically important in triggering the BCR-mediated signaling. In B cell activation, several significant PTK substrates have been identified, including components of the BCR complex, phospholipase C-\gamma (PLC-\gamma), phosphatidylinositol-3 (PI-3) kinase, Ras GTPase-activating protein (GAP), GAP-associated protein p62, Vav, HS1, and Shc (2, 5–7). Many of these PTK substrates have been reported to be physically associated with Src-family PTKs in various cell types (2, 6, 8). Thus, it is proper to search for Src-family PTK-interacting proteins to identify and discern the molecules that are involved in B cell activation.

The viral oncogene v-cbl was originally discovered as the transforming gene of the murine Cas NS-1 retrovirus, which induces pre-B lymphomas and myelogenous leukemias (9). The transforming gene product p100\textsuperscript{v-cbl} is a Gag-fused protein containing the NH\textsubscript{2}-terminal 355-amino acid sequence of the c-cbl gene product (9, 10). Although the function of p120\textsuperscript{c-bt} has not yet been uncovered, it possesses the following protein motifs (10): (a) a YY-1 transcription factor-like basic region; (b) a nuclear localization signal; (c) a RING finger; (d) two regions rich in acidic amino acids; (e) a stretch of 208 amino acids rich in Pro, Ser, and Thr; and (f) a putative leucine zipper. Expression of c-cbl is high in thymus and testis (11). It is also expressed in spleen at the lower level. p120\textsuperscript{c-bt} is a cytoplasmic protein, whereas p100\textsuperscript{v-cbl} localizes both in cytoplasm and nucleus (12). Recent evidence shows that p120\textsuperscript{c-bt} becomes tyrosine phosphorylated upon TCR stimulation (13). In addition, the SH3 domain of various signaling molecules is shown to bind to p120\textsuperscript{c-bt} in vitro (14).

One of the Src-family PTKs, p53/56\textsuperscript{bn}, participates in the intracellular signaling mediated by the BCR, as well as the FcERI and FcYRI (1–5). In this study, we searched for novel p56\textsuperscript{bn}-associated molecules to characterize further the signaling pathway of p53/56\textsuperscript{bn}. Using a yeast two-
hybrid system with the regulatory region of p56^tr" as a probe, we identified the chl protooncogene product as a p53/p56^tr"-interacting molecule. Here we report that the Src-family PTKs p53/p56^tr" and p59^tr" are crucially important in tyrosine phosphorylation of p120^-" upon stimulation of the lymphocyte antigen receptors.

Materials and Methods

**Yeast Two-Hybrid Screening.** The sequence encoding the NH2-terminal 235 amino acids of p56^tr" (15) was cloned in-frame into pAS2. The resultant plasmid, designated as pAS2-Lyn(1-235), expresses the regulatory region of p56^tr" fused to the GAL4 DNA-binding domain, as was confirmed by Western blotting. A random-primed adult rat cDNA library was synthesized using the Time Saver cDNA Synthesis Kit (Pharmacia, Uppsala, Sweden) and cloned into pGAD424 (Clontech Laboratories Inc., Palo Alto, CA). For yeast two-hybrid screening, the bait plasmid pAS2-Lyn(1-235) was cotransdvided with the library plasmids into yeast strain Y190 by a lithium acetate method. Random-primed adult rat cDNA library was synthesized using the Time Saver cDNA Synthesis Kit (Pharmacia, Uppsala, Sweden) and cloned into pGAD424 (Clontech Laboratories Inc., Palo Alto, CA). For yeast two-hybrid screening, the bait plasmid pAS2-Lyn(1-235) was cotransdvided with the library plasmids into yeast strain Y190 by a lithium acetate method. Transformants (2 x 10^6 cells) were plated on dropout media lacking Trp, Leu, and His and containing 40 mM of 3-amino-1,2,4-triazole and analyzed as described previously (16). DNA sequences were determined using the "BdBest Sequencing Kit (Takara Shuzo Corp., Shiga, Japan).

**Cell Culture.** WEHI-231, DT40, and HBC21.7.31 (HBC) cells were maintained as described previously (2, 17, 18). lyn-negative and syk-negative DT40 cells were established by gene targeting (17). HBC21.7.31 is a class II-restricted murine helper T cell hybridoma. Establishment of fyn-overexpressing HBC21.7.31 cells, named N17 cells, was reported previously (18). Splenic T cells were prepared from wild-type and fyn-deficient mice (19) by using nylon wool columns (20).

**Antibodies.** Polyclonal rabbit Abs against p120^-" (C-15), p55^cbl (K-23), and p56/59^hck (N-30) were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA). Mouse mAbs against p59^cbl (301), p53/56^tr" (Lyn-8), and p72^src (101) were from Wako Pure Chemical Industries (Osaka, Japan). Mouse anti-p56^hck mAb was from Y. Koga (Tokai University, Kanagawa, Japan) (21). PY20, an antiphosphotyrosine mAb, was from ICN (Irvine, CA). For cross-linking of the lymphocyte antigen receptors, the following Abs were used: hamster anti-mouse CD3e, 145-2C11 (gift of T. Katagiri, Kitasato University, Tokyo, Japan); rabbit anti-hamster IgG (Cappel Laboratories, West Chester, PA); goat anti-mouse IgM (Sigma Chemical Co., St. Louis, MO); and goat anti-chicken IgM (Bethyl Laboratories Inc., Montgomery, TX).

**Immunoprecipitation and Kinase Assay.** Rat spleens were homogenized in 1% digitonin buffer (1). The lysates were incubated with anti-p120^-" at 4°C for 1 h, and the immune complexes were precipitated with protein A-Sepharose (Pharmacia). The immunoprecipitates were washed five times with 1% digitonin buffer, three times with kinase buffer (20 mM Hepes-NaOH, 10 mM MgCl2, 10 mM MnCl2, pH 7.4) and then subjected to the kinase reaction in the presence of [γ-32P]ATP (Amersham Corp., Arlington Heights, IL) at 25°C for 30 min. The reaction complexes were dissociated with solubilizing buffer (1). The supernatants were reimmunoprecipitated with the second Abs as shown in Fig. 1. The immunoprecipitates were separated by 8.5% SDS-PAGE, and phosphorylated proteins were visualized by autoradiography.

**Cell Stimulation.** Stimulation of B cells with anti-IgM was performed basically as described (2). In the case of HBC cells and mouse splenic T cells, the cells were incubated with the hamster anti-mouse CD3e. After being washed twice, they were stimulated by rabbit anti–hamster IgG (18).

**Immunoprecipitation and Western Blotting.** The cells were lysed with 1 ml of ice-cold TNE buffer and then subjected to immunoprecipitation as described (2). The immunoprecipitates or the whole-cell lysates were separated by 7.5% SDS-PAGE, transferred to polyvinylidene difluoride membrane (Bio-Rad Laboratories, Richmond, CA), and then blocked as described (6). The filter was probed with an appropriate first Ab, followed by either horseradish peroxidase–conjugated Ab (Amersham Corp.) or alkaline phosphatase–coupled Ab (Promega Corp., Madison, WI) to rabbit IgG or to mouse IgG. The signals were detected either with Renaissance (DuPont, Boston, MA) or with the Protoblot NBT and BCIP color development system (Promega Corp.). For reprobing, the filters were stripped and then reblocked according to the manufacturer's protocol (Amersham Corp.).

Results and Discussion

**Identification of p120^-" as a Novel p53/p56^tr"--associated Protein.** For identification of proteins that associate with p53/p56^tr" , we used a yeast two-hybrid system. A probe corresponding to the unique, SH3, and SH2 regions of p56^tr" was fused to the GAL4 DNA binding domain. As a prey, a random-primed adult rat cDNA library was generated using pGAD424, a vector that produces cDNA-encoded proteins fused to the GAL4 transcriptional activation domain. By screening 2 x 10^6 yeast transformants, we isolated five

**Figure 1.** Physical association of p120^-" with p53/p56^tr". The 1% digitonin lysates of rat spleens were immunoprecipitated with anti-p120^-" Ab, and the immunoprecipitates were subjected to kinase reaction in the presence of [γ-32P]ATP. The reaction products were dissociated with solubilizing buffer, and then the extracts were reimmunoprecipitated with the second Abs (RelP). The reimmunoprecipitates were separated by 8.5% SDS-PAGE. B shows a longer exposure of A. Positions and sizes (kD) of standard protein markers are indicated.
Critical Role of p53/56tr in Rapid Tyrosine Phosphorylation of p120\(^{\text{c-cbl}}\) upon BCR Stimulation.

Previous studies have shown that p53/56\(^{\text{tr}}\) is activated by stimulation of the BCR (2). To examine the possibility that p120\(^{\text{c-cbl}}\) was a substrate of p53/56\(^{\text{tr}}\) in the BCR-mediated signaling, we evaluated tyrosine phosphorylation of p120\(^{\text{c-cbl}}\) after activation through the BCR. p120\(^{\text{c-cbl}}\) was rapidly tyrosine phosphorylated, being maximally phosphorylated within 30 s upon BCR stimulation on WEHI-231 cells (Fig. 2, top). The amount of p120\(^{\text{c-cbl}}\) did not change over the assay period (Fig. 2, middle). Since p120\(^{\text{c-cbl}}\) was tyrosine phosphorylated upon TCR stimulation (13), p120\(^{\text{c-cbl}}\) was suggested to be a common target of PTKs participating in the antigen receptor-mediated signaling in both B cells and T cells.

Tyrosine phosphorylation of signaling molecules can promote their association with Src-family PTKs, which is at least partially mediated by the SH2 domain of Src-family PTKs (6, 8). Since tyrosine-phosphorylated p120\(^{\text{c-cbl}}\) binds to a variety of SH2 domains in vitro (13), the association between p120\(^{\text{c-cbl}}\) and Src-family PTKs could increase upon BCR stimulation. The amount of p120\(^{\text{c-cbl}}\) in p53/56\(^{\text{tr}}\) immunoprecipitates, however, did not change upon stimulation of the BCR on WEHI-231 cells (Fig. 3). Thus, tyrosine phosphorylation of p120\(^{\text{c-cbl}}\) might recruit other SH2-containing proteins to p120\(^{\text{c-cbl}}\). It is also possible that tyrosine-phosphorylated p120\(^{\text{c-cbl}}\) may signal in an SH2-independent manner.

Stimulation of the BCR activates three classes of nonreceptor PTKs, namely, PTKs of the Src-family (p53/56\(^{\text{tr}}\) and
Figure 4. Tyrosine phosphorylation of p120$^{c-cbl}$ in wild-type, lyn-negative, and syk-negative DT40 cells upon stimulation of the BCR. Wild-type (A), lyn-negative (B), and syk-negative (C) DT40 cells ($8 \times 10^6$) were stimulated with 10 μg of anti-chicken IgM for the indicated time. (Top) Anti-p120$^{c-cbl}$ immunoprecipitates from $8 \times 10^6$ cells were tested for phosphotyrosine. (Middle) The same filters used in the top panel were reprobed with anti-p120$^{c-cbl}$. (Bottom) Whole-cell lysates from $2 \times 10^5$ cells were tested for phosphotyrosine. Positions and sizes (kD) of standard protein markers are indicated.

Figure 5. Importance of p59$^{fyn}$ in tyrosine phosphorylation of p120$^{c-cbl}$ in the TCR-mediated signaling. (A) Parental and fyn-overexpressing HBC cells ($10^7$) were incubated with (+) or without (−) hamster anti-mouse CD3ε (145-2C11; supernatant of hybridoma, diluted 1:2) on ice for 1 h. After washing, the cells were then stimulated with 1 μg of anti-hamster IgG at 37°C for 1 min. The parental cells are designated as H cells, and fyn-overexpressing cells as N17 cells. (Top) Anti-p120$^{c-cbl}$ immunoprecipitates from $10^7$ cells were tested for phosphotyrosine. An equal amount of p120$^{c-cbl}$ was analyzed (data not shown). (Bottom) Whole-cell lysates from $2 \times 10^5$ cells were tested for the amount of p59$^{fyn}$. (B) Splenic T cells ($2 \times 10^7$) from wild-type and fyn-deficient mice were stimulated as described in A. Anti-p120$^{c-cbl}$ immunoprecipitates from $2 \times 10^7$ cells were tested for phosphotyrosine. An equal amount of p120$^{c-cbl}$ was analyzed (data not shown). Positions and sizes (kD) of standard protein markers are indicated.
similar to that in wild-type cells, although the level was slightly lower (Fig. 4 C). Thus, p53/56\textsuperscript{\textsubscript{fr}} was crucial for tyrosine phosphorylation of p120\textsuperscript{cbl} upon activation through the BCR. In addition, the time course of p120\textsuperscript{cbl} phosphorylation is similar to that of activation of p53/p56\textsuperscript{fr} rather than that of p72\textsuperscript{fr} or p77\textsuperscript{fr} (2, 23), suggesting that p120\textsuperscript{cbl} is a substrate of Src-family PTKs.

A low level of tyrosine phosphorylation of p120\textsuperscript{cbl} was observed in lyn-negative DT40 cells at 3 and 10 min after BCR stimulation (Fig. 4 B). p72\textsuperscript{fr} could be activated in the absence of p53/p56\textsuperscript{fr}, although maximal activation of p72\textsuperscript{fr} required p53/p56\textsuperscript{fr} (24). The level of tyrosine phosphorylation of p120\textsuperscript{cbl} was only slightly less in syk-negative DT40 cells than that in wild-type DT40 cells (Fig. 4 C). Thus, ZAP-70/Syk-family PTKs may contribute to a lesser extent to tyrosine phosphorylation of p120\textsuperscript{cbl}.

Another Src-family PTK, p59\textsuperscript{fr}, plays an important role in TCR-mediated signaling (5). In addition, p120\textsuperscript{cbl} was rapidly tyrosine phosphorylated upon stimulation of the TCR in Jurkat T cells (13; Tezuka, T., and T. Yamamoto, unpublished data). To further confirm the functional interaction of p120\textsuperscript{cbl} with Src-family PTKs, we investigated the involvement of p59\textsuperscript{fr} in tyrosine phosphorylation of p120\textsuperscript{cbl} upon TCR stimulation. The fyn-overexpressing T cell hybridomas, N17 cells, fyn-deficient mice were used. Expression of p59\textsuperscript{fr} was at least five times higher in N17 cells compared with that in parental HBC cells (reference 18 and Fig. 5 A, bottom). Both HBC and N17 cells exhibited increased tyrosine phosphorylation of p120\textsuperscript{cbl} by CD3\textsubscript{\textepsilon} cross-linking (Fig. 5 A, top). Apparently, tyrosine phosphorylation of p120\textsuperscript{cbl} was elevated in fyn-overexpressing cells compared with that in parental cells. To confirm the importance of p59\textsuperscript{fr} in tyrosine phosphorylation of p120\textsuperscript{cbl}, we prepared splenic T cells from wild-type and fyn-deficient mice (19). Tyrosine phosphorylation of p120\textsuperscript{cbl} was significantly increased upon TCR stimulation in splenic T cells from wild-type mice. In contrast, elevation of tyrosine phosphorylation of p120\textsuperscript{cbl} was completely absent in splenic T cells from fyn-deficient mice (Fig. 5 B). Based on these results, we concluded that p59\textsuperscript{fr} played an essential role in tyrosine phosphorylation of p120\textsuperscript{cbl} upon TCR-mediated signaling.

Tyrosine phosphorylation of p120\textsuperscript{cbl} has been correlated with tumorigenicity of p120\textsuperscript{cbl} (12), suggesting that p120\textsuperscript{cbl} is involved in regulation of cell proliferation. However, the mechanism by which p120\textsuperscript{cbl} or the v-cbl oncogene product would induce growth of cells is not established. Role(s) of p120\textsuperscript{cbl} in lymphocyte signaling is not known either. We have shown here that p120\textsuperscript{cbl} was hardly tyrosine phosphorylated upon BCR stimulation in lyn-negative DT40 cells and upon TCR stimulation in mature splenic T cells from fyn-deficient mice. Mature splenic T cells from fyn-deficient mice showed impaired Ca\textsuperscript{2+} flux and depressed IL-2 production in spite of relatively normal proliferation (5). Therefore, p120\textsuperscript{cbl} might be involved in the signaling toward Ca\textsuperscript{2+} flux and IL-2 production. Cross-linking of the BCR on lyn-negative DT40 cells evokes a delayed and slow Ca\textsuperscript{2+} mobilization, despite the normal kinetics of inositol-1,4,5-trisphosphate (IP\textsubscript{3}) production (17). Thus, although IP\textsubscript{3} is the essential mediator for Ca\textsuperscript{2+} mobilization, an additional factor that involves p53/p56\textsuperscript{fr} is thought to be required for the BCR-mediated Ca\textsuperscript{2+} mobilization (17). p53/p56\textsuperscript{fr}-dependent tyrosine phosphorylation of p120\textsuperscript{cbl} suggests that p120\textsuperscript{cbl} is a candidate of such a factor regulated by p53/p56\textsuperscript{fr}.

Upon antigenic stimulation, lymphocytes become activated and undergo either apoptosis or proliferation and differentiation. It is important to establish how p120\textsuperscript{cbl} contributes to these cellular responses.

After we completed this study, p120\textsuperscript{cbl} was shown to be tyrosine phosphorylated by a variety of stimuli that include EGF, CSF-1, Epo, GM-CSF, and FcγRI cross-linking (25–27). In vivo association of p120\textsuperscript{cbl} with Src-family PTKs is observed in HL-60, HER14, P388D1, and SRD cells (26, 27).

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