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Identification of B cell adaptor for PI3-kinase (BCAP) as an Abl interactor 1-regulated substrate of Abl kinases

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Abstract In previous work we showed that Abl interactor 1 (Abi-1), by linking enzyme and substrate, promotes the phosphorylation of Mammalian Enabled (Mena) by c-Abl. To determine whether this mechanism extends to other c-Abl substrates, we used the yeast two-hybrid system to search for proteins that interact with Abi-1. By screening a human leukocyte cDNA library, we identified BCAP (B-cell adaptor for phosphoinositide 3-kinase) as another Abi-1-interacting protein. Binding experiments revealed that the SH3 domain of Abi-1 and the C-terminal polyproline structure of BCAP are involved in interactions between the two. In cultured cells, Abi-1 promoted phosphorylation of BCAP not only by c-Abl but also by v-Abl. The phosphorylation sites of BCAP by c-Abl were mapped to five tyrosine residues in the C-terminal region that are well conserved in mammals. These results show that Abi-1 promotes Abl-mediated BCAP phosphorylation and suggest that Abi-1 in general coordinates kinase-substrate interactions.

Keywords: c-Abl; v-Abl; Adaptor; Abi-1; B cell adaptor for PI3-kinase; Phosphorylation; *trans*-acting regulation

1. Introduction

Regulation of tyrosine kinases has been shown to be important for diverse cellular functions such as growth and differentiation. *c-abl*, which was identified as the protooncogene of the Abelson leukemia virus oncogene *v-abl*, encodes a tyrosine kinase, c-Abl [1,2]. Although the activity of c-Abl is tightly regulated, v-Abl kinase possesses an increased and unregulated activity [3,4]. Thus, elucidation of the mechanism of regulation of Abl kinase activity is critical to understanding not only the c-Abl signal transduction pathway, but also the mechanism underlying v-Abl-induced leukemia. While recent findings have shown that the kinase activity of c-Abl is autoregulated by its intramolecular folding [5–7], the mechanism of how the activity of c-Abl kinase is regulated by protein–protein interactions is poorly understood.

Our group has suggested that *trans*-acting adaptor molecules, such as c-Crk and Abl interactor 1 (Abi-1), are important for the regulation of c-Abl kinase [8,9]. Abi-1 was first identified as a c-Abl-binding protein that suppresses *v-abl* transforming activity [10]. We showed that Abi-1 interacts with Mammalian Enabled (Mena) and promotes its phosphorylation by c-Abl [9]. Our results suggest that Abi-1 presents Mena as a better substrate for c-Abl by acting as an adaptor protein.

To examine whether this scenario for Abi-1 is applicable to other c-Abl substrates, we sought to identify Abi-1 interacting proteins using yeast two-hybrid screening. B cell adaptor for phosphoinositide 3-kinase (BCAP) was found to be an Abi-1-binding protein. As observed for Mena, Abi-1 promoted the phosphorylation of BCAP by c-Abl in cultured cells.

2. Materials and methods

2.1. Plasmids

pcDNA3 c-Abl was a gift from David Baltimore. pFLAG-CMV2 Abi-1 was constructed as described previously [9]. The coding sequence of *v-abl* [1] was subcloned into the *Bam*HI site of pcDNA3, resulting in pcDNA3 v-Abl.

Mammalian expression plasmid pEBG (a gift from Bruce Mayer) was used to express proteins fused with a glutathione-*S*-transferase (GST) tag. Full-length human BCAP cDNA was amplified by polymerase chain reaction (PCR), using Marathon-Ready human bone marrow cDNA (Clontech) as a template, the forward primer 5′-cgcggatccaccatggcagcctcaggggtgcc-3′, and the reverse primer 5′-cgcggatcctcagcgtcctctgggtggaac-3′. The PCR product was digested with *Bam*HI and inserted into the *Bam*HI site of pEBG, resulting in pEBG BCAP. A fragment encoding amino acids (aa) 461–805 of human BCAP was subcloned into the *Bam*HI and *Not*I sites of pEBG, resulting in pEBG BCAP (461–805). Deletion mutants of BCAP were produced by PCR and verified by DNA sequencing.

To generate BCAP mutants in which the tyrosine residues of BCAP were replaced with phenylalanines, oligonucleotide-directed mutagenesis was carried out with a Quickchange Site-Directed Mutagenesis kit (Stratagene) according to the manufacturer's instructions, using pEBG BCAP (461–805) as the template. The mutations were verified by sequencing. Plasmids bearing pEBG BCAP (461–805) mutations were digested with *Van*91I and *Not*I, and the resulting fragments were inserted into the *Van*91I and *Not*I sites of pEBG BCAP to create pEBG BCAP Y513, Y553, Y570, Y594, Y694, and CT5F.

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Abbreviations: BCAP, B cell adaptor for PI3-kinase; GST, glutathione-*S*-transferase; PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction

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2.2. Antibodies

The following antibodies were used: anti-Abl (8E9; Pharmingen), anti-FLAG (M2; Sigma), anti-GST (Santa Cruz Biotechnology), and anti-phosphotyrosine (4G10; Upstate Biotechnology, Inc.).

2.3. Two-hybrid screen and analysis

The full-length cDNA of human Abi-1 [9] was subcloned into yeast expression vector pGBKT7. The pGBKT7 Abi-1 was transformed into yeast strain Y190, and two-hybrid screening was then carried out according to the manufacturer's protocol using a GAL4 DNA activation domain fusion library in pGAD10 (MATCHMAKER human leukocyte cDNA library; Clontech). Positive clones were isolated and sequenced.

To examine protein–protein interactions, cDNA fragments encoding aa 461–805 of BCAP were inserted into pGBKT7, and full-length Abi-1 and its deletion mutants (SH3 or polyproline deletion) into pGAD424. Yeast strain Y190 was transformed with the constructed pGBKT7 and pGAD424 vectors. Filter assays for β-galactosidase activity were performed according to the manufacturer's protocol (Clontech).

2.4. Transfection and GST pull-down assay

293T cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and antibiotics.

Fugene6 reagent (Boehringer–Mannheim) was used for transfection of plasmids into 293T cells. Forty-eight hours after transfection, the cells were lysed in lysis buffer (1% Triton X-100, 10 mM Tris–HCl, pH 7.6, 50 mM NaCl, 30 mM sodium pyrophosphate, 50 mM sodium fluoride, 20 mM β-glycerophosphate, 1 mM EDTA, 1 mM EGTA, 1 mM sodium vanadate, 20 μg/ml aprotinin, and 1 mM phenylmethylsulfonyl fluoride). The lysates were centrifuged in a microcentrifuge for 15 min at 15000 rpm to remove insoluble materials. After protein content was determined using BCA protein assay reagent (Pierce), aliquots of lysates containing 500 μg protein were mixed with glutathione–Sepharose 4B beads (Amersham Pharmacia Biotech) for 2 h at 4 °C with gentle rotation. The beads were washed four times with lysis buffer, suspended in SDS–polyacrylamide gel electrophoresis (PAGE) sample buffer, and boiled for 10 min. Proteins pulled down with the beads were analyzed by 8% SDS–PAGE.

3. Results

3.1. BCAP is an Abi-1-binding protein

Our previous study suggested that Abi-1 promotes c-Abl-mediated phosphorylation of Mena, by interacting with both c-Abl and the substrate [9]. To test the generality of this mechanism, we looked for c-Abl substrates, other than Mena, that bind to Abi-1. Yeast two-hybrid screening of a human leukocyte cDNA library was performed using Abi-1 as bait. We anticipated that screening of a leukocyte cDNA library would allow us to find new Abi-1-binding proteins that are important for the Abl-signaling pathway, because Abelson leukemia virus preferentially transforms pre-B cells [11] and *c-abl* knockout (−/−) mice exhibit lymphoid abnormalities [12,13]. Among several clones obtained, one was found to encode a C-terminal fragment aa 461–805 of BCAP. BCAP was identified as a molecule binding to phosphoinositide 3-kinase (PI3-K) [14], and has been implicated in B cell development and humoral immune responses [15,16].

We further analyzed the interaction between BCAP and Abi-1 using the yeast two-hybrid system. Abi-1 contains an SH3 domain and a polyproline structure near the C terminus (Fig. 1(a)). As shown in Fig. 1(b), Abi-1 (ΔPP) lacking aa 335–362 interacted with BCAP (461–805), whereas Abi-1 (ΔSH3) lacking aa 392–475 did not. These results suggest that the SH3 domain, but not the polyproline structure, of Abi-1 is critical for the interaction with BCAP.

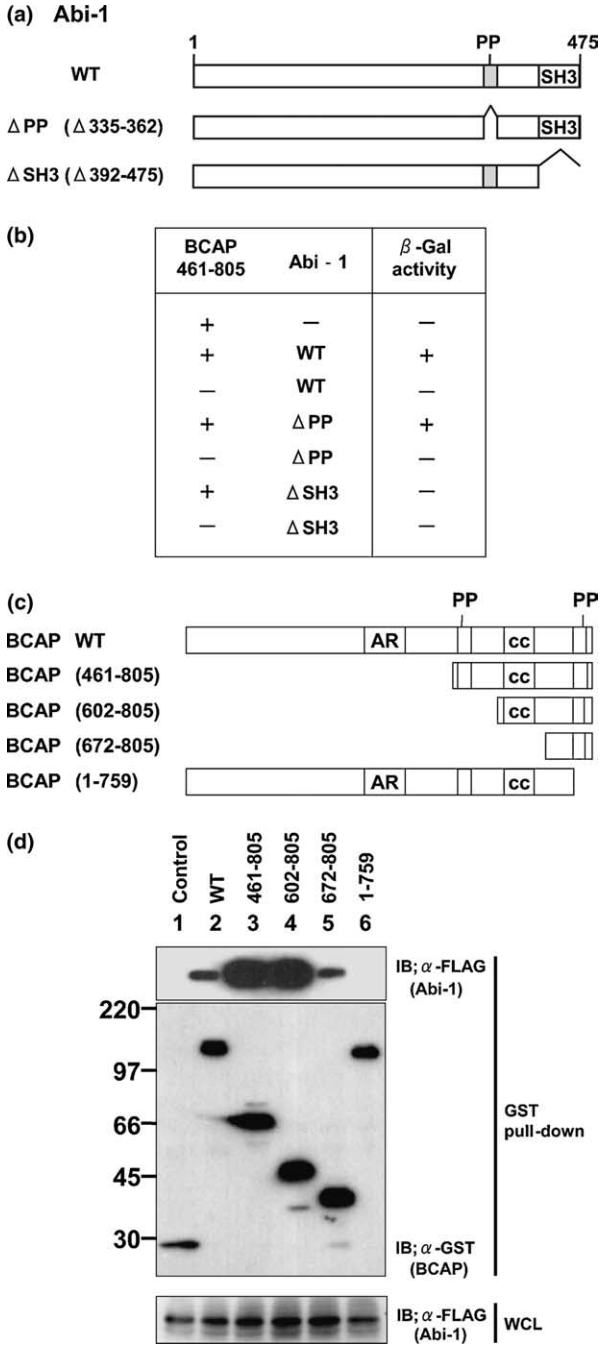

Fig. 1. Analysis of the interaction between BCAP and Abi-1. (a) Deletion mutants of Abi-1 are shown schematically. PP, polyproline structure. (b) BCAP (461–805) was cloned into a GAL4 DNA-binding domain vector, and Abi-1 or one of its deletion mutants was cloned into a GAL4 activation domain vector. Reporter yeast cells were transformed with the two kinds of vectors. β-Galactosidase activity was monitored on a filter; colonies either turned blue (+) or remained white (−). (c) Schematic representation of BCAP and its deletion mutants. AR, ankyrin repeat; PP, Polyproline structure; CC, coiled-coil region. (d) Pull-down assay. GST (lane 1), GST–BCAP (wild type) (lane 2), GST–BCAP (461–805) (lane 3), GST–BCAP (602–805) (lane 4), GST–BCAP (672–805) (lane 5), or GST–BCAP (1–759) (lane 6) was co-expressed with FLAG-Abi-1 in 293T cells. Lysates of the transfected cells were incubated with glutathione beads, and bound proteins were detected by immunoblotting with anti-FLAG and anti-GST antibodies (GST pull-down). For estimation of the amounts of expressed proteins, each cell lysate was separated and immunoblotted with anti-FLAG antibody (WCL).

3.2. Binding of BCAP to Abi-1 in mammalian cells

The interaction between BCAP and Abi-1 was confirmed using a mammalian cell system. Full-length BCAP cDNA was amplified by PCR, and an expression plasmid for GST-tagged BCAP was constructed, as described in Section 2. GST or GST–BCAP was co-expressed with FLAG-tagged Abi-1 in 293T cells, and then pulled down with glutathione beads. As shown in Fig. 1(d), FLAG-Abi-1 co-precipitated with GST–BCAP (lane 2), but not with GST (lane 1), indicating that exogenously expressed BCAP and Abi-1 interact with each other in 293T cells.

We next investigated the Abi-1-binding region of BCAP. Deletion mutants used in this study are schematically shown in Fig. 1(c). Each was expressed as a GST-fusion protein in 293T cells with FLAG-Abi-1, and pull-down assays were performed (Fig. 1(d)). As expected, FLAG-Abi-1 co-precipitated with GST–BCAP (461–805) (lane 3), which contains the region corresponding to the sequence encoded by the positive clone in yeast two-hybrid screening. This fragment contains two polyproline structure and one coiled-coil region (Fig. 1(c)). The fact that the amount of FLAG-Abi-1 co-precipitating with GST–BCAP (461–805) was larger than that with GST–BCAP suggests that the N-terminal region may negatively regulate the interaction between Abi-1 and BCAP. Deletion of the first polyproline structure had no effect on the interaction (Fig. 1(d); compare lane 4 with lane 3). Notably, FLAG-Abi-1 was pulled down with GST–BCAP (672–805), which possesses only the C-terminal polyproline structure, albeit less efficiently than with the mutant containing both the coiled-coil region and the C-terminal polyproline structure (GST–BCAP (602–805)). These results indicate that the C-terminal polyproline structure is important for binding to Abi-1. Indeed, FLAG-Abi-1 was not pulled down with GST–BCAP (1–759), a mutant lacking only the C-terminal polyproline structure (Fig. 1(d), lane 6). The C-terminal polyproline structure of BCAP is therefore critical for the interaction with Abi-1, and the coiled-coil region of BCAP may contribute somewhat to the interaction.

3.3. Abi-1 promotes c-Abl-mediated phosphorylation of BCAP

Next, we examined whether or not Abi-1 affects the phosphorylation of BCAP by c-Abl (Fig. 2). 293T cells were cotransfected with the expression plasmids for c-Abl, FLAG-Abi-1, and GST–BCAP. GST–BCAP was pulled down from the cell lysates and its phosphorylation state was investigated by Western blotting with anti-phosphotyrosine antibody. The degree of phosphorylation of GST–BCAP was low when GST–BCAP was co-expressed with c-Abl alone (Fig. 2, lane 3), but a marked increase was observed when GST–BCAP was co-expressed with both FLAG-Abi-1 and c-Abl (lane 4). Reprobing of the filter used to detect the phosphorylation state of GST–BCAP with anti-GST antibody showed that comparable levels of GST–BCAP existed in all samples. These results demonstrate that Abi-1 promotes c-Abl-mediated phosphorylation of BCAP.

3.4. Tyosines 513, 553, 570, 594, and 694 are the phosphorylation sites of BCAP

BCAP (461–805) contains five tyrosine residues (aa 513, 553, 570, 594, and 694), which are conserved in other species including chicken, mouse and rat. To examine if these tyrosines are phosphorylated by c-Abl kinase, we made BCAP mutants in which either four (Y513, Y553, Y570, Y594, and Y694) or all (CT5F) of these tyrosines were replaced by phenylalanines (Fig. 3(a)). Plasmids encoding c-Abl, FLAG-tagged Abi-1, and the GST–BCAP mutants were cotransfected into 293T cells. The GST–BCAP mutants were pulled down and their phosphorylation status was assessed by Western blotting with anti-phosphotyrosine antibody.

As shown in Fig. 3(b), wild-type BCAP and mutants retaining one tyrosine residue were phosphorylated to varying degrees, whereas the CT5F mutant was not phosphorylated (lane 7). These results indicate that all five tyrosine residues in the C-terminal region of BCAP are phosphorylated by c-Abl kinase.

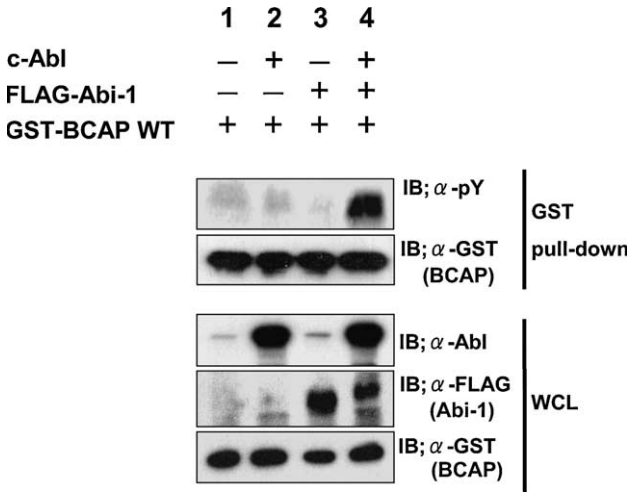

Fig. 2. Analysis of BCAP phosphorylation by c-Abl kinase. 293T cells were transfected with the expression plasmids indicated at the top. GST–BCAP was pulled down as described in the legend of Fig. 1. The precipitated proteins were analyzed by immunoblotting with anti-phosphotyrosine and anti-GST antibodies. For estimation of the amounts of expressed proteins, each cell lysate was separated and immunoblotted with anti-Abl, anti-FLAG, and anti-GST antibodies (WCL).

3.5. Phosphorylation of BCAP by v-Abl

Oncogenic forms of Abl, namely v-Abl and Bcr-Abl, possess increased and unregulated kinase activities [3,17]. We next examined the effect of Abi-1 on v-Abl-mediated phosphorylation of BCAP. 293T cells were cotransfected with the expression plasmids for v-Abl, FLAG-Abi-1 and either GST–BCAP or GST–BCAP CT5F. GST–BCAP and CT5F were pulled down and their phosphorylation status was investigated. As shown in Fig. 4, although v-Abl phosphorylated GST–BCAP in the absence of Abi-1, the levels of GST–BCAP phosphorylation were higher in its presence. Phosphorylation of GST–BCAP CT5F was barely detectable, regardless of whether or not Abi-1 was present. Abi-1 thus promotes phosphorylation of BCAP by v-Abl as well as by c-Abl.

4. Discussion

We showed previously that Abi-1 promotes c-Abl-mediated phosphorylation of Mena, via interactions with both c-Abl and Mena [9]. In the present study, we searched for other c-Abl substrates whose phosphorylation is promoted by Abi-1. BCAP was identified as an Abi-1-binding protein, and Abi-1

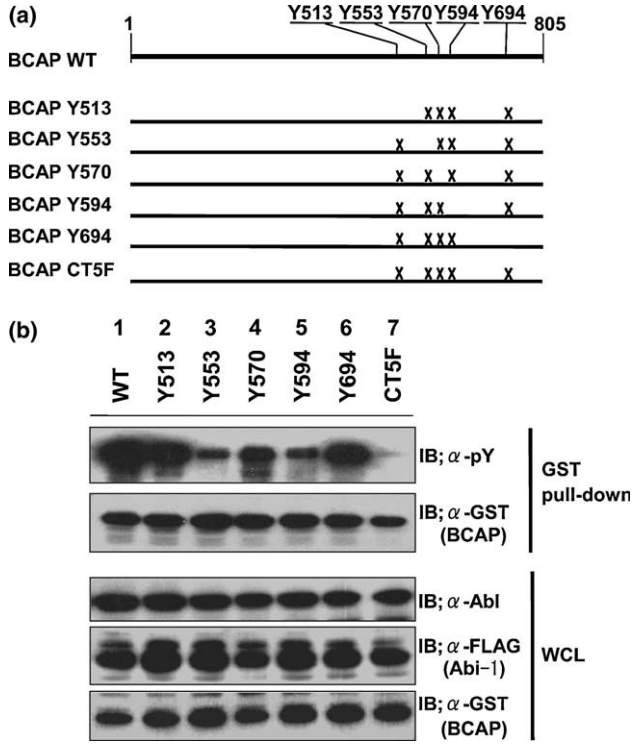

Fig. 3. Phosphorylation sites of BCAP. (a) Schematic representation of the mutants of BCAP. X denotes the positions of mutated tyrosine residues. (b) 293T cells were cotransfected with the expression plasmids for c-Abl, FLAG-Abi-1, and either GST–BCAP (wild type) or one of its mutants (Y513, Y553, Y570, Y594, Y2694, or CT5F), as indicated at the top. GST–BCAP or its mutants were pulled down from the cell lysates as described in the legend to Fig. 1, and then the precipitated proteins were then analyzed by immunoblotting with anti-phosphotyrosine and anti-GST antibodies (GST pull-down). Each cell lysate was subjected to immunoblotting with anti-Abl, anti-GST, and anti-FLAG antibodies (WCL).

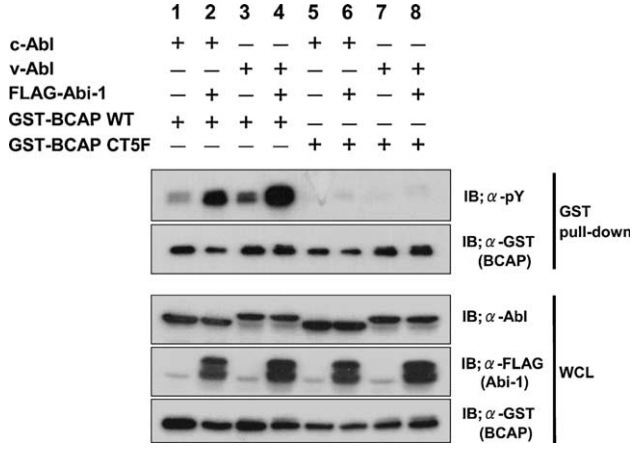

Fig. 4. Analysis of BCAP phosphorylation by v-Abl kinase. (a) 293T cells were transfected with the expression plasmids indicated at the top. GST–BCAP or the GST–BCAP CT5F mutant was pulled down from the cell lysates, and the precipitated proteins were analyzed by immunoblotting with anti-phosphotyrosine and anti-GST antibodies (GST pull-down). Each cell lysate was subjected to immunoblotting with anti-Abl, anti-FLAG, and anti-GST antibodies (WCL).

facilitated phosphorylation of BCAP by c-Abl. These results taken together suggest that Abi-1 is a general coordinator of kinase–substrate interactions.

The interaction between Abi-1 and BCAP occurred both in yeast (two-hybrid analysis) and in mammalian cells (GST pull-down experiments). The results showed that the SH3 domain, but not the polyproline structure, of Abi-1 is critical for the interaction with BCAP. Conversely, the polyproline structure, rather than the SH3 domain is critical for the interaction with Mena. Therefore, the binding surfaces of Abi-1 for these two substrates must be different. The SH3 domain of Abi-1 has also been reported to interact with c-Abl [10], and Fan et al. [18] showed recently that Abi-1 forms oligomers for its function. Oligomerization of Abi-1 might generate multiple binding sites and permit complex interactions; for example, different Abi-1 molecules within an oligomer could bind to c-Abl kinase and substrate.

The molecular mechanism by which Abi-1 activates c-Abl is not known. Recently, Woodring et al. [19] showed that Crk adaptor protein overcomes the actin-mediated inhibition of c-Abl. Although the precise mechanism of adaptor-regulated activation of c-Abl remains unclear, kinase activation and the adaptor–substrate interaction both seem to be important. As shown in Fig. 4, Abi-1 also promotes v-Abl-mediated phosphorylation of BCAP. Abi-1 may be necessary for both c-Abl and v-Abl to recognize BCAP as a substrate. Alternatively, Abi-1 may positively regulate BCAP as a substrate for Abl kinases. Interactions between Abi-1 and BCAP may result in structural changes to BCAP, leading in turn to effective phosphorylation by Abl kinases.

Analysis of *bcap*(−/−) mice showed that BCAP plays an important role in B cell development and function [16]. *c-abl*(−/−) mice exhibit abnormalities in B cell progenitor cells [12,13]. Abelson leukemia virus, possessing the *v-abl* oncogene, transforms pre-B cells [11,12]. These observations suggest a functional link between BCAP and c-Abl in B cells. Previous studies revealed that the tyrosine residues in the N-terminal region of BCAP are phosphorylated by both Syk and Btk kinases [14]. Mutational analysis also suggested that other tyrosine residues of BCAP were phosphorylated in B cells that were stimulated by the receptors [14,20]. It is possible that the C-terminal tyrosine residues of BCAP are phosphorylated in B cells by c-Abl that has been activated by stimuli such as CD19 [21] or integrin [22]. In this way, BCAP and Abl kinases may coordinate to regulate B cell development.

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