The Dimerization Property of Glutathione S-Transferase Partially Reactivates Bcr-Abl Lacking the Oligomerization Domain

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Bcr-Abl oncoproteins are responsible for the pathogenesis of human leukemias with a reciprocal chromosome translocation t(9;22). The amino-terminal Bcr sequence has a potential to form a homotetramer (tetramer domain), and destructions of the tetramer domain cause a complete loss of biological activities in Bcr-Abl. Here we show that Bcr-Abl in which the tetramer domain is replaced with glutathione S-transferase (GST) with a dimerizing ability (GST/Bcr-Abl(Δ1-160)) can no longer induce an interleukin-3 (IL-3) independence in Ba/F3 cells or transform mouse bone marrow cells but still retains by 30–40% the ability to transform Rat1 cells. Compared with the wild type Bcr-Abl, autophosphorylation of GST/Bcr-Abl(Δ1-160) was 50% reduced in Rat1 cells and undetectable in Ba/F3 cells. In Rat1 cells expressing GST/Bcr-Abl(Δ1-160), phosphotyrosine contents of p62 and Shc were 70% decreased.

The reciprocal chromosome translocation t(9;22)(q34;q11) induces two types of human leukemias with two different forms of Bcr-Abl oncoproteins, chronic myelocytic leukemia with P210 Bcr-Abl and acute lymphocytic leukemia with P185 Bcr-Abl. P185 Bcr-Abl has a higher tyrosine kinase activity and transforming potential than P210 Bcr-Abl as judged by Rat1 fibroblast transformation assay. Both of these can also transform mouse hematopoietic cells in high density bone marrow cultures and abrogate dependency of hematopoietic cells on cytokines including interleukin-3 (IL-3), IL-7, and so forth (3, 4).

The initial step for activation of Abl tyrosine kinase in Bcr-Abl appears to be an oligomerization of the protein. Both the intact Bcr and P210 Bcr-Abl proteins expressed in baculovirus can be purified as large molecules of homotetramer size. When the Bcr sequence encoded by its first exon is tagged with GST (glutathione S-transferase) at the amino terminus (GST-Bcr 1st exon) and is coexpressed with P185 Bcr-Abl in baculovirus, they form a hetero-oligomer complex through the Bcr first exon sequence (7). The amino-terminal 60 amino acids of Bcr have recently been shown to have an α-helical coiled-coil structure with an ability to form a homotetramer (8). Bcr-Abls with mutations to destroy this structure have reduced auto-phosphorylations and are biologically inactive (8, 9). This activation mechanism reminds us of receptor tyrosine kinases in which binding of ligands induces dimerization or oligomerization of receptors with autophosphorylations and recruitments of signal transduction molecules (10, 11). A recent discovery of Tel-platelet-derived growth factor receptor, a chimeric oncoprotein found in chronic myelocytic leukemia with the reciprocal chromosome translocation t(5;12)(p33;p13), shows that the tyrosine kinase domain of the receptor can be activated by the fusion to an Ets-related transcription factor Tel with a dimerizing potential (12). These facts raise a question of whether the Bcr sequence-mediated oligomerization has any biological significances or, simply, any types of oligomerizations are sufficient for activation of Abl. To address this issue, P185 Bcr-Abl was tagged with GST at the amino terminus in the presence or absence of the tetramer domain. Crystal structure analyses have shown that GST has an ability to form a homodimer (13, 14). Transformation of Rat1 cells as well as of mouse bone marrow cells and IL-3 independence in Ba/F3 cells were tested for those mutated Bcr-Abls.

EXPERIMENTAL PROCEDURES

Cell Culture—The Rat1 fibroblast cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum, the WEHI-3B cells in RPMI with 10% fetal calf serum, and the IL-3-dependent mouse Ba/F3 cells in RPMI with 10% fetal calf serum and 15% WEHI-3B conditioned medium (CM). A large stock of the WEHI-3B CM was obtained when cells were growing exponentially and was used for all of the experiments. This CM could support the growth of Ba/F3 cells even at the concentration of 1.0%.

Molecular Construction—The unique EcoRI site in the original pSRuMSVtkneo vector (9) and the AattI site (1224) of the pGEX-3X vector (15) were converted to Xbal by blunting with Klenow followed by Xbal linker additions (pSRuMSVtkneoEcoRI to Xbal). The HindIII/Xbal fragment containing the GST cDNA and stop codons downstream was cloned into Smal and Xbal sites of pGEM4 (Promega) whose original Asp-718 site was converted to Xbal using the HindIII/Xbal fragment. The SallI/EcoRI site was truncated to create the pGEX-3X-Aattl site (1224). The EcoRI/Xbal fragment containing the original EcoRI site was destroyed by blunting and religation (pGEM4-GST-Aps-718 to Xbal-EcoRI(−)). P185 bcr-ecol (EcoRI/EcoRI fragment) and P185 bcr-Δ1-160 (BamHI/EcoRI fragment) with or without premature stop codons created by Xbal linker insertion mutagenesis at the PvuII site were cloned into pGEM4-GST-Aps-718 to Xbal-EcoRI(−). The Xbal fragments containing Bcr-Abls fused in-frame with GST were cloned into pSRuMSVtkneoEcoRI(Δ1-160) to Xbal. The 5′-terminal bcr EcoRI/PstI fragment (17) (the PstI site was blunted by T4 DNA polymerase) was cloned into EcoRI/Smal sites of pGEX-3X for expression in Escherichia coli.

Expression in E. coli and Cross-linking Study—Bacterial expression and purification of GST fusion proteins were performed as described (15). The glutaraldehyde cross-linking reactions were carried out for 2 h at 25 °C in 50 mM triethanolamine, pH 8.0, 100 mM sodium chloride, 0.01% glutaraldehyde (8). The reactions were stopped by adding sample buffer containing 2% SDS, 100 mM Tris-HCl, pH 6.8. Cross-linked proteins were visualized by staining gels with silver nitrate.

Retroviral Expression—Procedures for obtaining retroviral stocks and for infections were previously described by Muller et al. (9). The titers of viruses were examined by infecting Rat1 cells followed by

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1. The abbreviations used are: IL, interleukin; GST, glutathione S-transferase; CM, conditioned medium.
counting G418-resistant colonies after 2 weeks. For retroviral expression in Ba/F3 cells, cells were infected at $1 \times 10^6$ cells/ml with 8 $\mu$g/ml of Polybrene for 4 h in the presence of 10% WEHI-3B CM. Approximately 48 h after infection G418 was added to the culture medium at 2 mg/ml. To test the ability of cells to survive in the absence of IL-3, cells were grown in the absence of WEHI-3B CM and G418 10 days after starting G418 selection. Transformation assays of mouse hematopoietic cells were performed as described (2).

Western Blot Analysis, Immunoprecipitation, and In Vitro Kinase Assay—Western blot analysis and immunoprecipitation of proteins were performed as described previously (4). Glutathione-Sepharose 4B was used to precipitate GST-tagged proteins expressed in COS cells. The in vitro phosphorylation reaction was performed as described (18) in the presence of 10 mM MnCl$_2$ and 1 mM cold ATP for 20 min. Tyrosine phosphorylations were detected by Western blot analyses using an anti-phosphotyrosine antibody (PY20) (ICN).

For communoprecipitation experiments, SDS was omitted for protein extractions. The anti-Abl antibody pSR was described previously (4). A polyclonal antibody raised against the GST protein fused to the Gnr-2 SH2 domain was a gift from Dr. T. Takekawa at the Institute of Medical Science, University of Tokyo (19). The anti-Shc antibody was purchased from UBI.

Gel Filtration Chromatography—High speed supernatants were obtained by Dounce homogenization and centrifugation as described previously (5, 6) and were directly applied onto a Sephacryl S-300 column (5). The column was calibrated with high molecular weight standards (Pharmacia Biotech, Inc.).

**RESULTS**

Expression of GST-tagged cDNA in COS Cells—In order to test if cDNA tagged with GST at the amino terminus can be expressed in mammalian cells, we cloned P185 bcr-abl into pSRaMSVtkneo-GST and transfected the construct in COS cells. Glutathione beads precipitated P185 tagged with GST as shown in Fig. 1, A and C. Although the sequences around the translation initiation codon differ between bcr and GST, the efficiencies of protein production in COS cells were equivalent.

Abilities of GST and GST-tagged Proteins to Oligomerize in Vitro—Crystal structure analyses have shown that GST is a dimeric molecule (13, 14). In order to confirm that the GST protein expressed in E. coli has an ability to oligomerize in vitro, we performed a glutaraldehyde cross-linking study with purified GST and Bcr amino-terminal fragment-(1–60) fused with GST (GST-Bcr-(1–60)). Utilizing the same experimental procedure, the E. coli-expressed Bcr amino-terminal fragment-(1–71) was shown to form a tetramer (8). When the GST protein was used, cross-linked bands were exclusively of dimer after 2 h of incubation with glutaraldehyde (Fig. 1B). The GST-Bcr-(1–60) on the other hand, predominantly formed a cross-linked protein of a size of dimer, but bands of trimer and tetramer sizes were also observed (Fig. 1A, A and C, B). We think that those oligomerized proteins are stable because they were still observed even after 2 h. These data suggest that GST-tagged Bcr-Abys may exist within cells as dimers in the absence of the Bcr tetramer domain but also as trimers or tetramers in smaller amounts if the Bcr tetramer domain is present.

Ability of GST-tagged Bcr-Abl to Oligomerize in Vivo—GST- P185, GST-P185-(Δ1–160), P185, and P210 were retrovirally expressed in two biological systems. One is Rat1 fibroblast cells and the other is IL-3-dependent mouse Ba/F3 cells. Cells were infected and selected by G418 for 10 days. Total cell lysates were subjected to an anti-Abl Western blot analysis as shown in Fig. 2. In order to test if Bcr-Abl forms a large complex of a homotetramer size over 670 kDa in Rat1 cells as in the case of Bcr-Abl expressed in baculovirus system (5), we performed a gel filtration assay as described previously (5, 6). Unexpectedly, P185 Bcr-Abl migrates as a high molecular mass complex between 670 and 230 kDa while GST-P185-(Δ1–160) was around 230 kDa (Fig. 3A). Because the size of GST-P185-(Δ1–160) complex in the peak fraction is even below that of a homodimer, we attempted communoprecipitation assays to examine whether GST could mediate oligomerization of GST- P185-(Δ1–160). Premature stop codons were created in the carboxy-terminal Abl sequence of GST-P185-(Δ1–160), which results in an approximately 50-kDa smaller protein that cannot be recognized by an anti-Abl antibody orpEX-5 (16). GST- P185-(Δ1–160) and GST-P185-(Δ1–160)(+ stops) were cotransfected into COS cells. The vector containing P185 bcr-abl (P185, lanes 2 and 5), or GST-P185 bcr-abl (GST-P185, lanes 3 and 6). Three days after transfection total protein lysates (lanes 1–3) and glutathione 48-Sepharose beads after incubation with the lysates were run on a SDS-PAGE and were subjected to anti-Abl Western blot analyses.

Tyrosine-phosphorylated Proteins in Cells Expressing GST-tagged Bcr-Abls—Tyrosine phosphorylations of Ras-GAP (GTPase activating protein)-associated protein p62 and of Shc are good indicators of Bcr-Abl-mediated transformations (9, 20). Phosphotyrosine contents of the two proteins relative to protein amounts of Bcr-Abl or its mutants were quantitated. In Rat1 cells, compared with the wild type P185, there were 50 and 70% reductions in the relative phosphotyrosine contents of p62 in GST-P185 and GST-P185-(Δ1–160), respectively (Fig. 2). In Ba/F3 cells, the reductions were by 75 and 75%, respectively. The phosphotyrosine-containing bands which migrate faster than and next to p62 are the Shc proteins of 52 kDa because anti-Shc immunoprecipitates run in parallel with total protein lysates in the same gel showed exactly comigrating bands with phosphotyrosines (Fig. 4, C and D). There were almost no reductions in the relative phosphotyrosine contents of the Shc proteins in GST-P185 and GST-P185-(Δ1–160) (Fig. 2). An

![Fig. 1](http://www.jbc.org)
However, the respectivity, less than that of the wild type P185 (Fig. 2 and D1–160) relative to the protein amounts were 50 and 75%.

Dependence in Ba/F3 Cells—GST-P185 was equivalent to that of P185 or P210 as shown in Fig. 5.

Grb-2 Associates with GST-tagged Bcr-Abl in Rat1 Cells but Can Neither Transform Mouse Bone Marrow Cells Nor Abolish IL-3 Dependence in Ba/F3 Cells—The morphology of Rat1 cells infected with GST-P185 retroviruses showed similar transformed changes to those of the wild type P185. The changes were weak in GST-P185 (Δ1–160) (Fig. 6A). When cells were subjected to agar colony assays to quantitate the transforming ability, GST-P185 was as transforming as P185 (Fig. 6B). GST-P185 (Δ1–160) was 30–40% as transforming as P185 (Fig. 6B). Therefore, the addition of GST with an oligomerizing potential can restore but not completely the transforming potential to Bcr-Abl with the amino-terminal truncation.

Surprisingly, those GST-tagged Bcr-Abls when expressed in IL-3-dependent Ba/F3 cells could not abrogate the IL-3 dependence. When Ba/F3 cells were infected with GST-tagged Bcr-Abl retroviruses, selected by G418 for 10–14 days, total proteins were run on a SDS-PAGE and were subjected to either anti-phosphotyrosine (upper panel) or anti-Ab (lower panel) Western blot analyses. Bands of p62 and Shc proteins were indicated.

Autophosphorylation levels of GST-P185 and GST-P185-(Δ1–160) relative to the protein amounts were 50 and 75%, respectively, less than that of the wild type P185 (Figs. 2 and 5). However, the in vitro autophosphorylation activity of GST-P185 was equivalent to that of P185 or P210 as shown in Fig. 5, 8 and D. We suppose that this is because an enrichment of proteins in immunoprecipitates causes artificial aggregations which mimic a higher level of oligomerization of the proteins.

Fig. 2. Expressions of GST-tagged Bcr-Abls in two biological systems. The Rat1 cells (lanes 1–4) and the Ba/F3 cells (lanes 5–8) were infected with retroviruses expressing GST (lanes 1 and 5), GST-P185 (lanes 2 and 6), GST-P185-(Δ1–160) (lanes 3 and 7), or P185 (lanes 4 and 8). After selection by G418 for 10–14 days, total proteins were run on a SDS-PAGE and were subjected to either anti-phosphotyrosine (upper panel) or anti-Ab (lower panel) Western blot analyses. Bands of p62 and Shc proteins were indicated.

Fig. 3. Oligomerization of Bcr-Abl in vivo. A, total cell lysates of Rat1 cells expressing either P185 (1) or GST-P185-(Δ1–160) (2) were directly applied onto Sephacyr S-300 gel filtration chromatography as described before (5). The column was calibrated by blue dextran ( Void volume), Thyroglobulin (670 kDa), Ferritin (440 kDa), and Catalase (230 kDa). Starting lysates (St) and each fraction (Fr.) were subjected to anti-Ab Western blot analyses. B, COS cells were transfected with GST-P185-(Δ1–160) (lane 1), GST-P185-(Δ1–160)(+ stops) (lane 2), or a combination of these. Total cell lysates were immunoprecipitated with anti-phos-F5 which cannot recognize the truncated form GST-P185-(Δ1–160)(+ stops) and were subjected to an anti-GST Western blot analysis. An arrow indicates the GST-P185-(Δ1–160)(+ stops) protein.

Fig. 4. Phosphorylation of the Shc proteins. A and B, anti-Shc immunoprecipitates of Rat1 cells expressing GST (lane 1), GST-P185 Bcr-Abl (lane 2), GST-P185 Bcr-Abl-(Δ1–160) (lane 3), or P185 Bcr-Abl (lane 4) were probed with the same anti-Shc antibody (A) or with anti-phosphotyrosine antibody (PY20) (B). The Shc protein of 52-kDa species is indicated in B. C and D, total protein lysates from Ba/F3 cells expressing P185 Bcr-Abl (lane 1), anti-Shc immunoprecipitates of the same P185 expressing Ba/F3 cells (approximately 0.1 μg of IgG bound to protein A-Sepharose beads), 0.2 μg (lane 3) or 2.0 μg (lane 4) of the same rabbit anti-Shc antibody alone were probed with mouse PY20 (C) or anti-Shc antibody (D). For the second antibody, horseradish peroxidase-conjugated anti-mouse (C) or anti-rabbit (D) antibody was used. Anti-mouse secondary antibody can hardly recognize 2.0 μg of the rabbit anti-Shc antibody (C, lane 4).

Because the GST-tagged Bcr-Abl proteins were less autophosphorylated in vivo, we examined the status of Grb-2 binding to

reduces the transforming ability of Bcr-Abl in Rat1 cells (21).
those GST-tagged Bcr-Abls. In Rat1 cells anti-Abl immunoprecipitates of GST-tagged Bcr-Abls contained Grb-2 proteins but the amount of bound Grb-2 proteins was 50% less in GST-P185-(Δ1-160) (Fig. 7, left panel). This is consistent with the relatively decreased transforming potential of this protein as judged by Rat1 agar assay (Fig. 6). Intriguingly, however, the GST-tagged Bcr-Abls expressed in Ba/F3 cells had no detectable Grb-2 recruitments (Fig. 7, right panel).

**DISCUSSION**

Although GST has a potential to mediate oligomerization both in vitro and in vivo, it cannot fully complement the deletion of the Bcr tetramer domain. We suppose that at least four explanations could be made. First, the deleted Bcr sequence 1-160 has other unknown functions which cannot be restored by GST.

Second, the Bcr tetramer domain has a higher oligomerizing
activity than GST. Results of in vitro cross-linking studies as well as of gel filtration chromatography support this idea. Interestingly, GST-P185 cannot induce growth factor independence but still retains its ability to transform Rat1 cells as efficiently as the wild type P185. We assume that GST has negative functional effects on the amino-terminal Bcr sequences. For example, the dimerizing ability of GST may dominate over the tetramerizing ability of the Bcr sequence when both of these are cis-linked.

Third, there may exist as yet unknown autophosphorylation sites that are biologically important. The reduced transforming potential of GST-P185-(A1-160) in Rat1 cells could be due to less efficient recruitment of Grb-2 proteins with this mutant. Because the junctional point between GST and Bcr (amino acid 160 of Bcr) is so close to the Grb-2 binding site Tyr-177, the change of the surrounding sequence might affect the efficiency of autophosphorylation at this particular site and Grb-2 binding in this mutant. The inability of GST-tagged Bcr-Abls to induce IL-3 independence in Ba/F3 cells cannot be explained by the poor autophosphorylations at the Grb-2 binding site. A Bcr-Abl with a mutation at Grb-2 binding site can still induce growth factor independence (20). Therefore the loss of Grb-2 recruitment with GST-tagged Bcr-Abls may simply be due to less autophosphorylation activity of those molecules in Ba/F3 cells. The ability of the Bcr sequence 161–413 with serine/threonine phosphorylations to bind to the Abl SH2 domain is essential for activation in Bcr-Abl (22). Tyrosine residues in this region can be phosphorylated by other tyrosine kinases like v-Fps (23). Therefore if Bcr-Abl has additional autophosphorylations in these sites in this region, they may not only enhance the binding to the Abl SH2 domain but also be involved in certain signalings.

Fourth, GST-tagged Bcr-Abls may not be able to phosphorylate certain substrates efficiently. We could observe 70% reductions of tyrosine phosphorylation of both p62 and Shc in Rat1 cells. This indicates that certain substrate molecules, although they may not necessarily be direct substrates of Bcr-Abl, are sensitive to reduced enzymatic activities of Bcr-Abl for being phosphorylated. The biological role of p62 is still unknown, but its abilities to associate with Ras-GAP and to bind to nucleic acids (24) suggest that it may play a role for connecting signals between cytoplasm and nucleus. Recently it has been shown that IL-3 activates JAK2 and the SH2 domain-containing Stat 5 homologs (25). The Stat family proteins are tyrosine-phosphorylated on ligand binding, self-associate through phosphotyrosine-SH2 domain interactions, and transduce signals by entering the nucleus. GST-tagged Bcr-Abls may have less efficient phosphorylation of the Stat family of proteins in Ba/F3 cells. Another candidate of Bcr-Abl substrate would be the Crkl protein which is constitutively tyrosine-phosphorylated in Philadelphia chromosome-positive human leukemias (26, 27). The Crkl protein binds to the Sos protein that is a GDP/GTP exchanger (activator) for Ras (26). The cellular Bcr protein is also a target of activated tyrosine kinases like Fps and Bcr-Abl (23, 28). Tyrosine-phosphorylated Bcr can bind to the Grb-2-Sos complex through tyrosine residues homologous to Tyr-177 in Bcr-Abl (23). Alterations of tyrosine phosphorylations in quantity and/or in quality of those molecules (p62, Shc, Crkl, Bcr, and possibly Stat) may make a difference in the biological activities of Bcr-Abl.

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