Src Homology 2 Protein Tyrosine Phosphatase (SHPTP2)/ Src Homology 2 Phosphatase 2 (SHP2) Tyrosine Phosphatase Is a Positive Regulator of the Interleukin 5 Receptor Signal Transduction Pathways Leading to the Prolongation of Eosinophil Survival

By Konrad Pazdrak, Tetsuya Adachi, and Rafeul Alam

*From the University of Texas Medical Branch, Department of Internal Medicine, Allergy and Immunology Division, Galveston, TX 77555-0762

Summary
Interleukin-5 (IL-5) regulates the growth and function of eosinophils. It induces rapid tyrosine phosphorylation of Lyn and Jak2 tyrosine kinases. The role of tyrosine phosphatases in IL-5 signal transduction has not been investigated. In this study, we provide first evidence that SH2 protein tyrosine phosphatase 2 (SHPTP2) phosphotyrosine phosphatase plays a key role in prevention of eosinophil death by IL-5. We found that IL-5 produced a rapid activation and tyrosine phosphorylation of SHPTP2 within 1 min. The tyrosine phosphorylated SHPTP2 was complexed with the adapter protein Grb2 in IL-5-stimulated eosinophils. Furthermore, SHPTP2 appeared to physically associate with β common (βc) chain of the IL-5 receptor (IL-5βcR). The association of SHPTP2 with IL-5βcR was reconstituted using a synthetic phosphotyrosine-containing peptide, bc605–624, encompassing tyrosine (Y)612. The binding to the phosphotyrosine-containing peptide increased the phosphatase activity of SHPTP2, whereas the same peptide with the phosphorylated Y612→F mutation did not activate SHPTP2. Only SHPTP2 antisense oligonucleotides, but not sense SHPTP2, could inhibit tyrosine phosphorylation of microtubule-associated protein kinase, and reverse the eosinophil survival advantage provided by IL-5. Therefore, we conclude that the physical association of SHPTP2 with the phosphorylated βc receptor and Grb2 and its early activation are required for the coupling of the receptor to the Ras signaling pathway and for prevention of eosinophil death by IL-5.

Eosinophils play an integral role in the pathogenesis of allergic and parasitic disorders (1). IL-5 is a cytokine that primarily promotes the differentiation of eosinophils from the stem cells and stimulates the survival and function of mature eosinophils (2). This diverse effect of IL-5 on eosinophils has been proposed as the key mechanism for the development of blood and tissue eosinophilia in the course of allergic inflammation.

IL-5R is a member of the hematopoietic receptor superfamily and is composed of a ligand-specific α subunit and shared with IL-3 and GM-CSF β common (βc) subunit (3). Although neither of the receptor subunits contain a kinase-like catalytic domain, IL-5 does induce a rapid and reversible tyrosine phosphorylation of various cellular proteins (4). Recent findings indicate that for IL-5R type, the binding of the ligand results in the activation of cytoplasmic tyrosine kinases of the Jak/Tyk and Src type families (5, 6). Indeed, we have shown that the stimulation of eosinophils with IL-5 results in phosphorylation and activation of the receptor-bound Lyn and Jak2 kinases. The consequence of activation of these tyrosine kinases is the propagation of signal through the ras-raf-1-MEK-MAP (MAP, microtubule-associated protein, MEK, MAP or Erk kinase) kinase pathway and the Jak-STAT pathway. These observations clearly support a major role of protein tyrosine phosphorylation in IL-5-mediated signaling.

Little is known about the function of protein tyrosine phosphatases (PTPs)1 in the signaling process initiated by the receptors of the cytokine receptor superfamily. The PTP Src homology (SH)PTP2, recently designated Src homology 2 phosphatase 2 (SHP2) and also called PTP1D or Syp, is one member of a small family of Src homology 2 (SH2) domain-containing PTPs, which also includes Corkscrew (Csw) and PTP-1C (also called SH-PTP1 or HCP) (7, 8). SHPTP2 contains two SH2 domains and a single catalytic domain. This phosphatase is ubiquitously expressed and found to be tyrosine phosphorylated and activated in response

1Abbreviations used in this paper: βc, β common; ITIM, immunoreceptor tyrosine-based inhibitory motif; MAP, microtubule-associated protein; ODN, oligodeoxynucleotide; PDGF, platelet-derived growth factor; PTP, protein tyrosine phosphatase; SH, Src homology.
Materials and Methods

Reagents. Percoll was purchased from Pharmacia, Inc. (Piscataway, N.J.). The mAb against antiphosphotyrosine (clone 4G10) was obtained from Upstate Biotechnology Inc. (Lake Placid, NY). Rabbits polyclonal anti-SHPTP2, anti-Grb2, anti-Erk 2, and monoclonal anti-IL-5Rα antibodies were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Enhanced chemiluminescence detection system was purchased from Amersham Corp. (Arlington Heights, IL).

Eosinophil Purification. Peripheral blood for eosinophil purification was obtained from subjects with mild to moderate eosinophilia (6–12%). Eosinophils were isolated by sedimentation with a gauge needle, and detergent insoluble materials were removed by centrifugation, washed rapidly with PBS, and lysed in a buffer containing 0.25% sodium deoxycholate, 1 mM PMSF, 1 mM NaCl, 60 mM KCl, 0.1 mM PM SF, 1 μM pepstatin, 5 μg/ml apro tinin, 1 μg/ml leupeptin (15, 18). Phosphatase activity was assayed by resuspending the final pellet in a total volume of 80 μl of reaction buffer (phosphatase buffer, pH 5.5, containing 1 mg/ml bovine serum albumin, 5 mM EDTA, 10 mM dithiothreitol). The reaction was initiated by the addition of para-nitrophenyl phosphate (10 nM, final concentration) for 30 min at 30°C. The reaction was stopped by the addition of 0.9 ml of 1 N NaOH, and the absorbance of the samples was measured at 410 nm.

Peptide Binding Assay. A biotinylated and tyrosine phosphorylated peptide corresponding to the amino acid residues 605–624 of IL-5R (Biotin-PPGSLF phosphorylated tyrosine [pY]2LC-PAGQQVQLV-NH2) was synthesized by the Quality Controlled Biochemicals Inc. (Hopkinton, MA). Two control peptides were also synthesized. N-cholesterol was replaced with F. SHPTP2 is likely to bind β3 through its SH2 domain. Since SH2 domain binds to pY only but not to Y residues, we used a second control peptide derived from β3, 450-465 which contained two nonphosphorylated Y residues biotin-Y G Y R L L R K W K E K P N P. All peptides had a COOH-terminal amide. The peptides were purified by HPLC to >95% purity and evaluated by mass spectrometry for correct molecular weight. The tyrophosphilated peptides were reconstituted in distilled water and then diluted in 100 mM Hepes, pH 7.4. For peptide binding assay we used lysates from promyelocytic human cell line HL-60, which expresses SHPTP2 (CCL 240; American Type Culture Collection, Rockville, MD). These nondifferentiated leukemic cells were maintained in R PMI 1640 with 10% FCS. SHPTP2 immunoprecipitated from HL-60 has no detectable phosphotyrosine and its basal phosphatase activity is comparable to that obtained from nondonitiated eosinophils. HL-60 cell lysates were prepared as described above and precleared with avdin-conjugated agarose beads (Sigma Chemical Co., St. Louis, MO) for 1 h. Aliquots of cell lysates (equivalent to 107 cells) were then incubated with biotinylated peptides (50 μM) for 2–4 h, and subsequently with avdin-conjugated agarose beads (50 μl) for 2 h at 4°C. After the last incubation, the beads were washed five times with the lysis buffer. The beads were suspended in 50 μl of 2 times concentrated electrophoresis buffer, boiled for 4 min, and subjected to electrophoresis and Western blotting with anti-SHPTP2 Ab.

In another set of experiments, HL-60 cell lysates (equivalent of 2 x 106 cells) were incubated with appropriate peptides (100 μM) for 2 h at 4°C, and then immunoprecipitated with anti-SHPTP2 and subjected for phosphatase activity assay as described above.

Gel Electrophoresis and Immunoblotting. SDS-polyacrylamide gels were prepared according to the Laemmli protocol and used for immunoblotting. The concentration of polyacrylamide was either...
7 or 12%, depending on the molecular weight range of the proteins studied. Gels were blotted onto Hybond membranes for Western blotting using the enhanced chemiluminescence system (Amersham Corp.). Blots were incubated in blocking buffer containing 5% BSA in TBST buffer (20 mM Tris base, 137 mM NaCl, made to pH 7.6, and 0.05% Tween 20) for 1 h followed by incubation with the primary Ab (0.1 μg/ml) for 1 h. After washing five times in TBST buffer, blots were incubated for 30 min with a horseradish peroxidase conjugated secondary antibody (0.1 μg/ml) directed against the primary Ab. The blots were developed with the enhanced chemiluminescence substrate according to manufacturer’s protocol. In some experiments, blots were reprobed with another Ab after stripping in a buffer of 62.5 mM Tris-HCl (pH 6.7), 100 mM 2-mercaptoethanol, and 2% SDS at 50°C for 30 min.

Expression of SHPTP2. The bottom thick bands are due to the rabbit IgH in the immunoprecipitate with an anti–Erk-2 antibody followed by Western blotting with antiphosphotyrosine antibody.

Results

A division of SHPTP2. It has been reported that the tyrosine phosphorylation of SHPTP2 is associated with increased phosphatase activity (19). Therefore, we first tested whether IL-5 induced tyrosine phosphorylation of SHPTP2. In this analysis, eosinophils were stimulated with IL-5 for various time periods and then lysed and immunoprecipitated with a polyclonal anti-SHPTP2 antibody. Western blotting with an antiphosphotyrosine antibody revealed phosphorylation of SHPTP2 as early as 1 min, reaching the highest level 5 min after the stimulation (Fig. 1). This suggests a relatively early involvement of SHPTP2 in the IL-5 signaling pathway. Reprobing the membrane with the anti-SHPTP2 antibody confirmed the presence of equal amounts of the immunoprecipitated protein.

Next, we assessed whether IL-5 stimulated the enzymatic activity of SHPTP2. SHPTP2 was immunoprecipitated from control or IL-5-treated eosinophils, and the phosphatase activity was measured. The results are shown in Fig. 2. The kinetics of phosphatase activity was similar to the pattern of tyrosine phosphorylation, reaching the peak in 5 min. A significant activity was detectable as late as 30 min after stimulation. A two- to threefold increase in phosphatase activity was consistently observed in three independent experiments.

Physical Association with Grb2. Once phosphorylated on tyrosine, SHPTP2 conforms to the consensus binding site, pYXXN, for the SH2 domain of Grb2 adapter protein (20). Since the binding of Grb2 to SHPTP2 might explain Ras activation after IL-5 stimulation, we asked whether SHPTP2 could bind Grb2 in stimulated eosinophils. To analyze the interaction between SHPTP2 and Grb2, first we performed immunoprecipitation of Grb2 from IL-5-stimulated and control cells followed by immunoblotting with antiphosphotyrosine and anti-SHPTP2 antibodies.

As shown in Fig. 3A, we detected a band of a 70-kD tyrosine phosphorylated protein in the immunoprecipitate of Grb2 from IL-5-stimulated cells. Reprobing the same membrane with the anti-SHPTP2 antibody confirmed the presence of SHPTP2 in immunoprecipitate of Grb2 (Fig. 3B).
A firmed the identity of the phosphatase. (B) SHPTP2 from IL-5–stimulated eosinophils. Immunoblotting with anti-phosphotyrosine antibody revealed the presence of Grb2 immunoprecipitated with anti-Grb2 antibody and anti-SHPTP2 antibody. Western blotting with anti-Grb2 antibody confirmed the identity of the phosphatase. (B) Eosinophil lysates were immunoprecipitated with anti-Grb2 antibody and anti-SHPTP2 antibody. Western blotting with anti-Grb2 antibody revealed the presence of Grb2 in its own immunoprecipitates as well as in immunoprecipitates of SHPTP2 from IL-5–stimulated eosinophils.

A). In a next set of experiments, we looked for the presence of Grb2 in the immunoprecipitates of SHPTP2. As shown in Fig. 3 B, Grb2 was detectable in the in SHPTP2 immunoprecipitates and predictably in the anti-Grb2 immunoprecipitate of IL-5–stimulated eosinophils. These experiments suggest a physical association of SHPTP2 and Grb2 that occurs in an IL-5–dependent manner.

Physical association with IL-5βR. The next set of coimmunoprecipitation experiments was carried out to investigate the physical association of SHPTP2 with IL-5βR. For this purpose, eosinophil lysates were immunoprecipitated with anti-SHPTP2 antibody and immunoblotted with anti-receptor IL-5βR antibody. We found the presence of IL-5βR in immunoprecipitate of SHPTP2 obtained from IL-5–stimulated cells (Fig. 4 A). In the next set of experiments we looked for the presence of SHPTP2 in immunoprecipitates of IL-5βR. Western blotting with anti-SHPTP2 antibody revealed the presence of the phosphatase in immunoprecipitate of IL-5βR (Fig. 4 B). The association between SHPTP2 and receptor appears to be present only in stimulated eosinophils.

The binding of SHPTP2 with IL-5βR only in stimulated cells suggests that the physical association occurs through the SH2 domains of SHPTP2. The SH2 domain of SHPTP2 is predicted to bind to a consensus sequence of SXXY and F YXXL (21, 22). The βc subunit of IL-5R has seven tyrosine residues in cytosolic region and one of the tyrosine residues at position 612 conforms best to the tyrosine binding motif of protein tyrosine phosphatases. We synthesized a tyrosine phosphorylated (pY612) peptide encompassing the residues 605–624 of IL-5βR. Two peptides were used as controls. The first control peptide had the same sequence except the replacement of pY612 with F. Since SH2 domain binds to phosphorylated Y and not to nonphosphorylated Y residues, we used a second control peptide, βc450–465 that contained two nonphosphorylated Y residues. All peptides were biotinylated. For peptide binding experiments, we used lysates from HL-60 cells instead of eosinophils. HL-60 cells constitutively express SHPTP2 and served as a readily available source of the phosphatase. The peptides were incubated with HL-60 cell lysates and the precipitated proteins were blotted with anti-SHPTP2 antibody. As shown in Fig. 5, only the phosphotyrosine-containing peptide bound SHPTP2. This experiment shows that the phosphorylated β receptor can directly bind to SHPTP2 phosphatase.

To examine the potential effect of the IL-5βR binding to SHPTP2, we asked whether addition of the phosphopeptide, βc 605–624, affected SHPTP2 activity. SHPTP2 activity was assayed in the absence or presence of the phosphopeptide. The mutated peptide was used as the control. The addition of the phosphopeptide βc 605–624 strongly inhibited SHPTP2 activity.
stimulated SHPTP2 activity by more than fivefold (Fig. 6) suggesting that binding of the phosphatase alone is responsible for its activation. The mutated βc 605–624 peptide did not activate the phosphatase.

Survival of Eosinophils Treated with SHPTP2 Antisense ODNs. Since eosinophils are terminally differentiated cells with life spans of 4–6 days, the use of antisense oligodeoxynucleotides is the most practical method to specifically alter expression of SHPTP2. Eosinophils were incubated with ODNs without FCS to protect stability of ODNs. As demonstrated in Fig. 7, eosinophils exposed to 7.5 μM antisense ODN for 6 h expressed little or no detectable SHPTP2, whereas sense or nonsense ODNs did not alter SHPTP2 level. Antisense ODNs used in our assay did not alter expression of a closely related phosphatase, SHPTP1 (data not shown). The viability of eosinophils assessed at this time (immediately before stimulation with IL-5) always exceeded 90% and was not different from control samples, indicating that at concentration of 7.5 μM the ODNs were not toxic to the cells. After 2 h of stimulation, eosinophils were resuspended in medium without IL-5, ODNs, and FCS. We excluded FCS from this stage of experiment, since in a previous study by Inhorn et al., serum appeared to alleviate the requirement for the Ras pathway for GM-CSF-dependent viability and proliferation in mutant cells with β receptor lacking the 626–676 amino acid residues (23). Viability of the cells cultured without serum was always higher than 55% as assessed 24 h after stimulation with IL-5. In contrast to IL-5-stimulated cells, there was usually <40% viable control (not treated with IL-5) eosinophils at the same time. However, as shown in Fig. 8, SHPTP2 antisense oligonucleotides blocked the ability of IL-5 to prevent eosinophil death (35.0 ± 6.8 versus 66.2 ± 8.0 versus 60.2 ± 5.4% for antisense, sense, and nonsense ODN-treated cells, respectively, P < 0.05) indicating critical role of SHPTP2 phosphatase in IL-5-induced survival of eosinophils.

Next we addressed the question of requirements of SHPTP2 phosphatase in IL-5-induced phosphorylation of MAP/Erk2 kinase. As shown in Fig. 9, there was significant reduction in MAP kinase tyrosine phosphorylation in eosinophils that were treated with the antisense ODNs. Since MAP kinase is considered a downstream molecule of the Ras signaling pathway, these results suggest that SHPTP2 plays a positive role in IL-5-induced activation of the Ras-MAP kinase pathway.

**Discussion**

Previously, we have demonstrated that IL-5 stimulates the phosphorylation and activation of the receptor-bound tyrosine kinases in eosinophils. In this report, we show that the IL-5 stimulation results in the phosphorylation and activation of the protein tyrosine phosphatase, SHPTP2. Others have reported the tyrosine phosphorylation of SHPTP2 in IL-3 and GM-CSF–stimulated murine myeloid cell lines (12). Our data extend these findings by showing that SHPTP2 binds to the β chain of the IL-5R in human eosinophils. In additional studies, we have demonstrated that the tyrosine phosphorylated βc 605–624 peptide encompassing pY612 binds and activates SHPTP2. There was no binding of SHPTP2 to the same peptide when phosphotyrosine (pY612) was replaced with phenylalanine. This is the first
In our study, we found that βc coprecipitates with SHPTP2, suggesting that physical association of these molecules occurs in IL-5–stimulated eosinophils. The direct association of SHPTP2 and βc seems reasonable since the synthetic 20-mer peptide, β605–624 containing a phosphorylated tyrosine (Y612), was able to bind SHPTP2. However, the exact binding site for SHPTP2 on βc receptor remains to be clarified. There are four tyrosine residues (Y612, Y621, Y806, and Y869) located COOH-terminal to amino acid 589 on βc receptor surrounded by amino acid residues partially matching a consensus sequence of Y(I/V)Xaa(V/I/L/P) that favors the binding of the NH2-terminal SH2 domain of SHPTP2 (21). We speculate that Y612 and/or Y750 are likely binding sites for SHPTP2, since the sequence surrounding Y612 and Y750 human IL-5βcR conform to the so-called immunoreceptor tyrosine-based inhibitory motif (ITIM) sequence motif of IT(S)XX(pY)XXL (22). Synthetic phosphopeptides representing the ITIM sequence have been shown to bind tyrosine phosphatases SHPTP1 and SHPTP2 and, what is of much interest, this binding results in dramatic increase in their phosphatase activity (26). Indeed, we have shown that addition of a phosphotyrosine peptide comprising the region around pY612 stimulates SHPTP2 activity four- to sixfold, whereas the nonphosphorylated peptide has no stimulatory effect. The phosphorylated βc, 612–624 reported here is the first native peptide derived from βc that potently stimulates SHPTP2 phosphatase activity.

The current model of the IL-5/IL-3/GM-CSF signaling pathway predicts that the stimulation of the receptor by the ligand causes the activation of the receptor bound tyrosine kinases. The activated tyrosine kinases then phosphorylate βc receptor. Tyrosine kinases bound to box 1 (W453-P465) are likely to be responsible for this event, since deletion of this motif results in loss of tyrosine phosphorylation of βc (25). Indeed, in mutant cells lacking Jak2 kinase, there was no phosphorylation of βc in response to GM-CSF. Moreover, these cells failed to phosphorylate SHPTP2 (27). We believe that one of the phosphorylated tyrosines on βc creates the binding site for the SH2 domain of SHPTP2. It is possible that SHPTP2 binds to more than one phosphorylated tyrosine residue, and which one is critical for SHPTP2 activation remains to be determined. The occupancy of the SH2 domain results in an increase in phosphatase activity, presumably due to the induction of conformational changes in SHPTP2 (28). The role of increased phosphatase activity of SHPTP2, as well as its target molecule remains unclear. One possible target for activated SHPTP2 phosphatase is βc. Upon βc binding, activated SHPTP2 might attenuate the βc signal by dephosphorylating the receptor, receptor-associated proteins, or itself. However, the observation that SHPTP2 remains associated with the phosphorylated IL-5βcR might argue against this model. We did not observe dephosphorylation of βc, SHPTP2, Jak2, and Lyn immunoprecipitated from IL-5–stimulated cells at the time of maximal activation of SHPTP2 (data not shown). An alternative possibility is that SHPTP2 acts as a positive signal transducer by dephosphorylating inhibi-
tory phosphotyrosine residues. Although we did not observe inhibition of Lyn and Jak2 phosphorylation in eosinophils lacking SHPTP2 phosphatase, we cannot exclude other tyrosine kinases as a target of the phosphatase. Feng et al. showed that SHPTP2 becomes constitutively tyrosine phosphorylated in v-Src-transformed cells (29). The authors suggested that SHPTP2 might dephosphorylate c-src on Tyr527, whose phosphorylation blocks tyrosine kinase activity. IL-5 has been shown to activate several tyrosine kinases including members of Src kinases family Lyn and Fyn and tyrosine kinase Syk (5, 30, 31). Moreover, SHPTP2 and βc have been shown to coprecipitate with PI-3 kinase (12). Whether SHPTP2 is involved in regulation of any of these kinases in response to IL-5 remains to be determined.

SHPTP2 is phosphorylated on tyrosine residues after IL-5 stimulation. However, the biological significance of this event as well as its relation to phosphatase activity is not yet clear. Our data predict that the binding to the receptor alone stimulates its catalytic activity. This result is consistent with a model in which IL-5 activates tyrosine kinases and tyrosine kinases phosphorylate several tyrosines within βc. SHPTP2 then binds, via its SH2, to one or two phosphorylated tyrosines, which leads to a conformational change in SHPTP2 and an increase of phosphatase activity. Once bound to the receptor, SHPTP2 becomes a target for receptor-associated tyrosine kinases, perhaps Jak2 or Lyn kinases. It has been postulated that tyrosine phosphorylation of SHPTP2 modulates its interaction with other SH2-containing signaling proteins such as Grb2. Grb2 tends to bind to YXXN motif which is present on SHPTP2 (e.g., Y542 and Y580). The binding of SHPTP2 to Grb2 is inhibited by phosphopeptide containing this motif (32). In our study, SHPTP2 and Grb2 were coimmunoprecipitated by anti-SHPTP2 and anti-Grb2 antibody, respectively. At this time we do not know whether Grb2 also binds to βc receptor. Grb2 is known to bind to nucleotide-exchange protein Sos, which activates Ras. Thus, tyrosine phosphorylation of SHPTP2 may result in recruitment of the Grb2-Sos complex to the membrane, where the substrate for Sos, Ras, is located (13).

Recently, it has been demonstrated that SHPTP2 functions as a positive growth regulator. Microinjection of anti-SHPTP2 antibody results in decreased insulin-mediated mitogenesis (16). Mutant inactive forms of SHPTP2 strongly inhibited the mitogenic signals induced by PDGF, α-thrombin (15), and IFN-α and -β (33). Further, negative mutations of SHPTP2 led to inhibition of prolactin-induced lactogenic signaling (11). Using antisense oligodeoxynucleotides against SHPTP2, we demonstrated a positive role of phosphatase in IL-5-induced activation of eosinophils. Regardless of the target molecule for SHPTP2, this phosphatase appears to act upstream of Ras-Raf-MAP kinase pathway activated in response to IL-5. Further, an activation of SHPTP2 phosphatase and Ras-Raf-MAP kinase pathway seems to be required for the delay of the death in eosinophils. In a recent paper, Yousefi et al. showed the requirement of Lyn and Syk tyrosine kinases for the prevention of apoptosis by IL-5 and GM-CSF in eosinophils (31). Our identification of SHPTP2 provides a further definition of intracellular signaling pathways activated by IL-5 by showing the requirement of the tyrosine phosphatase for eosinophil survival.

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Address correspondence to Dr. Rafeul Alam, The University of Texas Medical Branch, Department of Internal Medicine, Rm. 0672, Galveston, TX 77555-0762. Phone: 409-772-3411; FAX: 409-772-5841; E-mail: ralam@impo1.utmb.edu

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