The Kinase-null EphB6 Receptor Undergoes Transphosphorylation in a Complex with EphB1*

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Unique for the Eph family of receptor tyrosine kinases, the EphB6 receptor is catalytically inactive due to the alteration of several critical residues in its kinase domain. This has cast doubt upon its ability to participate in cytoplasmic signaling events. We show here that despite its lack of kinase activity, EphB6 undergoes inducible tyrosine phosphorylation upon stimulation with the Eph-B receptor subfamily ligand ephrin-B1. We also demonstrate, for the first time, evidence of cross-talk between Eph receptors. Overexpression of a catalytically active member of the Eph-B subfamily, EphB1, resulted in increased EphB6 phosphorylation. EphB1-induced EphB6 phosphorylation was ligand-dependent and required the functional catalytic activity of EphB1. EphB1 not only transphosphorylated EphB6, but together they also formed a stable hetero-complex. In addition, we identify the proto-oncogene c-Chl as an EphB6-binding protein. Although EphB6-Cbl association appeared to be constitutive, Cbl required a functional phosphotyrosine binding domain in order to bind the receptor, whereas its RING finger motif ubiquitin-transfer domain was not necessary. Our findings demonstrate that EphB6 is an actively signaling receptor that undergoes transphosphorylation upon ligand binding and that can initiate specific cytoplasmic signaling events.

The regulation of development and cell proliferation in higher organisms involves signaling through receptor tyrosine kinases (RTK). Ligand binding to the extracellular domain of RTKs induces receptor dimerization or oligomerization and stimulates their intrinsic tyrosine kinase activity (1–5). As a consequence, RTKs undergo autophosphorylation, causing further changes in receptor configuration and providing specific docking sites for cytoplasmic signaling proteins containing Src homology 2 (SH2) or phosphotyrosine binding (PTB)1 domains (6–8).

RTKs can be divided into families on the basis of their structural organization (9). Eph receptors form the largest known family, with 14 known members (10–12). Edfs bind a group of ligands known as ephrins (Eph family receptor interacting), nine of which are currently known. All the ephrins are membrane-anchored, either by glycosylphosphatidylinositol (ephrinA1-A6) or a transmembrane domain (ephrinB1-B3) (12, 13). Two classes of Eph receptors are recognized, EphA or EphB, according to the class of ephrin bound (14–18). It is a characteristic of Eph-ephrin interaction that specificity is degenerate within a group (11). Both the Eph receptors and their ligands must be membrane-bound in order to be active (19–21).

Ephs and ephrins are typically most highly expressed in neuronal and endothelial cells (11), and currently most descriptions of their function concern the development of the nervous system, angiogenesis, and embryogenesis (22–30). Stimulation of Eph receptor signaling upon cell-cell contact results in the activation of integrins and a rearrangement of the actin cytoskeleton. Eph receptors use these events to generate adhesive or repulsive signals, and in the neural system, they can guide the movement of axonal growth cones, cell migration, and synapse formation (22, 25, 31–37).

EphB6 is the most recently identified member of the Eph family and has a typical Eph subfamily structure (38, 39). Closer analysis reveals, however, that while the major EphB receptor autophosphorylation sites (Tyr-638 and Tyr-644) are conserved, there are several critical alterations to the kinase domain. These differences include the substitution of a crucial lysine residue in the ATP binding site, resulting in a receptor that does not demonstrate detectable kinase activity (38, 39). This lack of catalytic activity has cast doubt upon the ability of EphB6 to undergo tyrosine phosphorylation upon ligand stimulation and to initiate cytoplasmic signaling cascades. However, to draw an analogy with ErbB-3, a well-characterized catalytically inactive member of the EGF receptor family (40), EphB6 may be transactivated by catalytically active Eph receptors and thus transduce intracellular signals.

In this study, we demonstrate that the kinase-inactive EphB6 receptor undergoes tyrosine phosphorylation upon stimulation with membrane-bound ephrin-B1. EphB6 forms a hetero-receptor complex with co-expressed EphB1 receptor and undergoes transphosphorylation by the catalytically active EphB1 in a ligand-dependent manner. We also demonstrate that the EphB6 receptor associates with the c-Chl oncogene. Cbl participates in the signaling pathways of many receptors, functioning as a regulator of receptor activity and binding a variety of signal-transducing molecules (41–51). Cbl induces ubiquitination of the EGF, PDGF, and CSF receptors (49, 50, 52, 53), an ability derived from its RING finger domain (54). Cbl binding to EphB6 was found to be constitutive, and oncogenic 70-Z Cbl, containing a deleted RING finger motif, bound EphB6 essentially like wild type Cbl. In contrast, binding was lost upon the introduction of a Cbl G306E “loss of function” mutation. This mutation ablates the function of the Cbl PTB

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§ The abbreviations used are: PTB, phosphotyrosine binding; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; EGFR, EGF receptor; CSF, colony-stimulating factor.
domain, a domain that is also crucial for interaction with other receptor tyrosine kinases (55).

EXPERIMENTAL PROCEDURES

Antibodies and Recombinant Proteins—Monoclonal anti-phosphotyrosine was obtained from Upstate Biotechnology, Inc. (Lake Placid, NY). Antibodies to EphB6, Myc, Cbl, and EphB1 were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Soluble dimerized ephrin-B1 and soluble EphB6 receptors were purchased from R&D Systems (Minneapolis, MN). Anti-T7 was purchased from Novagen.

Subcloning—cDNAs for Cbl, EphB1, EphB6, ephrin-A1, and ephrin-B1 were cloned from normal human thymocyte RNA by reverse transcriptase PCR into the expression vector pcDNA3 (Invitrogen) and sequenced. Mutants of Cbl (G306E and deletion homologous to murine 70Z) and EphB1 (truncation of 102 C-terminal amino acids) were created using PCR to introduce the required base changes using cloned cDNAs as the template. The following sense oligomers and perfect match antisense oligomers were utilized for site-directed mutagenesis.

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\begin{align*}
\text{sense oligomer} & : & \text{gaccatatcaagtttgctgctgaaaatgac} \\
\text{antisense oligomer} & : & \text{-gatcatcttatctagggtgttgac}
\end{align*}
\]

The deletion of the B1 receptor was created with the following antisense oligomer: 5'-gatctcttagtctttagtgagtct. The deletion of the B1 receptor was created by mutating lysine 651 to glutamine (K651Q). The resulting cDNAs were cloned and sequenced to confirm the mutations. Myc-tagged versions of EphB6 and of the truncated EphB1 receptor were generated by insertion of a Myc tag, and all constructs were verified by sequencing. Expression of wild type proteins and mutants was examined by Western blotting in COS-7 cells and Western blotting with appropriate antibodies. By in vitro kinase assay, both the wild type and truncated forms of EphB1 were active kinases (data not shown).

Transfection of Cell Lines—COS-7, HEK 293, and NIH 3T3 cells were routinely transiently transfected using the lipid reagent LipofectAMINE (Invitrogen). The DNA/lipid mixtures were applied to the cells for 5 h in the absence of serum before the addition of complete medium. Cells were allowed 72 h to express the transfected proteins before harvest.

Stimulation of EphB6-transfected Cells with Membrane-bound and Soluble Ligand—To assay for stimulation with membrane-bound forms of the ephrin ligands, receptor-expressing cells were resuspended using 2.5 mM EDTA, and after washing, they were overlaid on a confluent monolayer of control or ligand-expressing cells. After incubation at 37 °C for 1 h, all the cells were solubilized in 1% Triton X-100 buffer. Soluble ephrin-B1-Fc fusion protein dimer was purchased from R&D Systems. The dimeric ephrin-B1 fusion protein was precomplexed with Fab', goat anti-human Fc (Pierce) to form oligomers. Fab', goat anti-human Fc was used as a control (no stimulation) where necessary. Although murine ephrin-B1 was utilized, this effectively induced human EphB6 phosphorylation.

Immunoprecipitation and Western Blotting—Cells were quickly resuspended in ice-cold lysis buffer consisting of 50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM ethylene glycol-bis (β-aminothyl)ether)N, EDTA, 10 μg/ml leupeptin, 10 μg/ml aprotinin, 1 mM phenylmethylsulfonyl fluoride, 1 mM sodium orthovanadate, and 50 mM NaF. After solubilization on ice for 15 min, debris was removed by centrifugation at 12,000 × g for 10 min at 4 °C. Antibodies and 20 μl of 50% protein G-Sepharose were added to cleared lysates and incubated at 4 °C with constant shaking for 12–16 h. Immunoprecipitates were collected by a brief centrifugation and washed three to four times in lysis buffer (without phenylmethylsulfonyl fluoride) before the addition of SDS sample buffer. Samples were separated on SDS-polyacrylamide gels and transferred to nitrocellulose membranes (Amerham Biosciences, Inc.). Membranes were blocked overnight at 4 °C with 7% blotting grade non-fat milk (Bio-Rad, Richmond, CA) in PBS (phosphate-buffered saline). Immunoblotting antibodies were added at optimal dilutions in PBS-T (PBS with 0.1% Tween 20) and incubated at 4 °C overnight. After extensive washing with PBS-T, bound antibodies were detected using horseradish peroxidase-conjugated donkey anti-rabbit or sheep anti-mouse antibodies and ECL reagents (Amerham Biosciences, Inc.).

RESULTS

Ephrin-B1 Stimulation Induces Tyrosine Phosphorylation of the EphB6 Receptor—EphB receptors are activated by membrane-bound ephrin-B ligands, demonstrating highly degenerate specificity with ephrin-B1 and ephrin-B2 activating most EphB receptors. To determine whether the catalytically inactive EphB6 receptor could be tyrosine-phosphorylated in response to ephrin-B ligand stimulation, we transiently expressed Myc-tagged human EphB6 in COS-7 cells and exposed the cells to EphB1. To provide cell surface-expressed ligands, we transfected COS-7 cells with pcDNA3 expression vector containing either ephrin-A1 or ephrin-B1 cDNA. Ligand expression was verified by immunoblotting (Fig. 1A, bottom panel). Western blot analysis did not detect endogenous ephrin-B1 expression in COS-7 cells or several other adherent cell lines (NIH 3T3; HEK 293; —, not shown).

EphB6-expressing cells were overlaid on cells transfected with ephrin-B1, ephrin-A1, or empty vector and co-incubated for 1 h at 37 °C. The EphB6 receptor was then precipitated with anti-Myc and immunoblotted with anti-phosphotyrosine antibody. Stimulation of EphB6 with ephrin-B1-expressing cells resulted in a marked increase in EphB6 tyrosine phosphorylation, whereas co-incubation with ephrin-A1-expressing or control cells had no effect (Fig. 1A, top panel). The increase in EphB6 tyrosine phosphorylation upon co-incubation with ephrin-B1 expressing cells was also observed in EphB6-transfected NIH 3T3 fibroblasts and HEK 293 human embryonic kidney cells, demonstrating that the effect was not cell-specific (Fig. 1B).

EphB6 tyrosine phosphorylation was detectable within 20 min of stimulation and increased thereafter (Fig. 2A). The time required to observe EphB6 phosphorylation was relatively...
FIG. 2. Time and ligand concentration dependence of EphB6 phosphorylation. EphB6-M-expressing COS-7 cells were co-incubated with ephrin-B1-transfected COS-7 cells for the indicated time periods (A). EphB6-M receptor phosphorylation and expression were determined as described in the legend for Fig. 1. PY, anti-phosphotyrosine; IP, immunoprecipitates; WB, Western blot. Ligand concentration-dependent EphB6 phosphorylation is shown (B). EphB6-M-expressing COS-7 cells were co-incubated for 1 h with COS-7 cells transfected with 5 μg of pcDNA3 (●) or varying amounts of ephrin-B1-pcDNA3 (B1) as indicated. The correlation between increasing amounts of ephrin-B1 cDNA and protein expression was confirmed by Western blot of the transfected cell lysates.

In contrast to soluble monomers of ephrins, which inhibit Eph receptor signaling, dimerized or oligomerized forms can stimulate receptor autophosphorylation and signaling (19, 20). Soluble dimerized ephrin-B1 was also found to induce EphB6 phosphorylation (Fig. 3). Although dimerized soluble murine ephrin-B1 was utilized for this experiment, this induced EphB6 phosphorylation as effectively as the membrane-expressed human ephrin-B used in Fig. 1. The induction of EphB6 phosphorylation by soluble dimerized ephrin-B1 could be completely blocked by the addition to the medium of a soluble form of the EphB6 receptor extracellular domain (5 μg/ml) (Fig. 3), strongly suggesting the existence of a direct interaction between ephrin-B1 and EphB6 receptors.

EphB6 Associates with and Is Transphosphorylated by Active EphB1 Receptor—Because EphB6 is catalytically inactive, the tyrosine phosphorylation observed upon ephrin-B1 stimulation must reflect the activity of an endogenous tyrosine kinase. To pose an analogy with the catalytically inactive ErbB-3 receptor of the EGFR family, EphB6 may be transphosphorylated by catalytically active members of the Eph family. To investigate this possibility, we co-expressed EphB6 with the human EphB1 receptor in COS-7 cells. COS-7 cells demonstrated a very low level of endogenous EphB1 (not shown). However, when overexpressed, EphB1 was found to become constitutively activated, as observed previously with the EphB3 receptor (58, 59). When co-expressed with EphB1, EphB6 did indeed appear to undergo significant tyrosine phosphorylation, transphosphorylating in a manner analogous to the EGFR family receptor ErbB-3 (Fig. 4A). Only catalytically active EphB1 induced EphB6 phosphorylation as no effect was observed upon EphB6 co-expression with a kinase-null K651Q EphB1 mutant (Fig. 4B, B1-KD). In NIH 3T3 fibroblasts, where the basal activity of EphB1 was determined to be lower than in 293 or COS-7 cells, EphB6 transphosphorylation by EphB1 occurred in a ligand-independent manner (Fig. 4C).

The ability of EphB1 to induce EphB6 phosphorylation suggested that the two receptors might be complexed when co-expressed. Indeed, EphB6 and EphB1 could be co-immunoprecipitated from co-transfected COS-7 cells (Fig. 4D), suggesting the existence of a direct interaction between the receptors and the formation of a relatively stable complex. Furthermore, this suggested that the catalytically active EphB1 receptor might directly phosphorylate EphB6.

The co-precipitation of EphB1 and EphB6, combined with their similar electrophoretic mobility, raised the possibility that the apparent phosphorylation of EphB6 observed upon EphB1 co-expression could be due to co-precipitation of phosphorylated EphB1. To unambiguously distinguish between the receptors, we constructed a Myc-tagged truncated EphB1 receptor lacking 102 C-terminal residues but with its kinase domain intact (B1-Tr). The truncated receptor was constitutively tyrosine-phosphorylated, similar to the wild type EphB1 but now clearly smaller than EphB6. Similar to overexpression of the wild type EphB1 receptor, overexpression of the truncated EphB1 also increased EphB6 phosphorylation in a ligand-independent manner (Fig. 5, A and B).

In sum, these findings demonstrated that EphB6 could form hetero-receptor complexes with an active Eph receptor and undergo transphosphorylation by the associated receptor. They also suggest that ephrin-B1-induced EphB6 phosphorylation in the absence of co-transfected EphB1 may similarly result from transphosphorylation by endogenous active Eph receptors.

c-Cbl Binds EphB6 in a PTK-dependent Manner—Cbl participates in the signaling pathways of many receptors, functioning as a regulator of receptor activity through the initiation of receptor ubiquitination and indubitably hiding a variety of signal-transducing molecules (41–51). The ability of Cbl to
interact with a variety of tyrosine kinase receptors led us to examine whether Eph receptors might also bind Cbl.

We co-expressed the EphB6 and EphB1 receptors in COS-7 cells with human c-Chi and examined their potential to associate. Although we did not detect any association between Cbl and the catalytically active EphB1 receptor, Cbl strongly co-precipitated with EphB6 (Fig. 6A). This association appeared to be constitutive because stimulation with ephrin-B1-expressing cells altered neither the level of EphB6-Chi association nor the tyrosine phosphorylation of Cbl (not shown). Although COS-7 cells express endogenous Cbl, association with EphB6 could only be consistently detected upon overexpression of both Cbl and the receptor, similarly to other receptor tyrosine kinases.

To further characterize the interaction, we examined the binding of two well characterized mutants of Cbl to the EphB6 receptor. The first, G306E (Cbl*), was initially identified as a mutation in the Caenorhabditis elegans Cbl orthologue sli-1 (60), which causes loss of Cbl binding to the ErbB1 and PDGF receptors (55, 61). The G306E mutation disrupts the function of the PTB domain of Cbl, through which it binds phosphorylated tyrosine residues. The second naturally occurring mutant, 70-Z Cbl (Cbl**), was first isolated as an oncogene from a murine B
EphB6 Associates with and is Phosphorylated by EphB1

FIG. 6. EphB6 binds c-Cbl in a PTB-dependent manner. COS-7 cells were transiently transfected with Cbl and EphB6-M (B6-M) or Cbl and EphB1 as indicated (A). After 72 h, Cbl was precipitated, and association with EphB6-M and EphB1 was examined by blotting with anti-Myc and anti-EphB1, respectively. IP, immunoprecipitates; WB, Western blot. COS-7 cells were transiently transfected with wild type Cbl, G306E Cbl (Ch^*), or the oncogenic 70-Z Cbl mutant (Ch^+), either alone or in combination with EphB6-M as indicated (B). After 72 h, EphB6-M association with Cbl was examined by immunoblotting Cbl immunoprecipitates with anti-Myc. Expression of each form of Cbl and EphB6 was confirmed by Western blotting of cell lysates.

In co-immunoprecipitation assays, the 70-Z mutation had little effect upon Cbl binding to the EphB6 receptor, whereas the G306E point mutation completely abolished association (Fig. 6B). Thus, although Cbl-EphB6 association appeared to be constitutive, it would seem to be dependent upon the Cbl PTB domain and therefore probably dependent upon tyrosine phosphorylation of either the EphB6 receptor or an adapter molecule.

DISCUSSION

Although the general structure of EphB6 is typical of the EphB receptors, its kinase domain contains numerous alterations to critical catalytic residues, and neither murine nor human EphB6 exhibits kinase activity (38, 39). We have demonstrated that despite these structural abnormalities, the human EphB6 receptor responds to ephrin-B1 stimulation by undergoing tyrosine phosphorylation. In addition, we show that this EphB6 tyrosine phosphorylation can be provided by a catalytically active Eph receptor, in particular by EphB1. While EphB1 receptor transphosphorylation of EphB6 was observed in co-transfected cells, EphB6 may potentially interact with multiple members of the EphB subfamily in vivo.

The ability to co-immunoprecipitate EphB1 and EphB6 suggested that transphosphorylation occurred as the result of the formation of an Eph receptor hetero-oligomeric complex on the plasma membrane. Indeed, lacking catalytic activity, EphB6 is unlikely to operate as an independent receptor but rather as part of such a hetero-oligomeric signaling complex with active EphB receptors in vivo. Until now, ErbB-3 of the EGFR family has been the only example of a transphosphorylated kinase-inactive receptor (40); however, our findings suggest that this may be a common mechanism for signaling through catalytically inactive receptor tyrosine kinases. The ErbB-3 receptor acts to modulate the intensity and duration of signaling by its active partner (40, 50), and transphosphorylation results in the recruitment of Shc and phosphatidylinositol 3-kinase specifically to the ErbB-3 receptor chain (63, 64). In a similar fashion, the catalytically inactive EphB6 receptor may recruit specific cytoplasmic signaling molecules and thus modulate cell responses induced by ephrin-B1 stimulation. In addition to initiating specific signaling pathways upon transphosphorylation, the catalytically inactive ErbB3 receptor is known to regulate the behavior of other EGFR family members. Similarly, as all EphB receptors are essentially activated by the same ligands, it is highly likely that they are all involved in functional cross-talk with EphB6, inducing EphB6 signaling through transphosphorylation and possibly undergoing modulation in return.

EphB6, similar to the ErbB1 and PDGF receptors, was found to physically associate with Cbl. The G315E mutation of the C. elegans Cbl orthologue Sli-1 prevents interaction with the nematode ErbB protein (let-23) (60), and the analogous Cbl mutation disrupts binding to PDGF and ErbB-1 receptors (55, 61). This mutation also abolished Cbl association with EphB6. The G306E mutation disrupts the Cbl PTB domain, suggesting that EphB6 phosphorylation may be important for Cbl binding; however, we did not detect ligand-induced binding of Cbl to EphB6 despite increased receptor tyrosine phosphorylation. In summary, we have demonstrated that despite its lack of regulation, EphB6 may simply recruit Cbl to the cell membrane and into Eph receptor complexes rather than modifying its function through phosphorylation. The absence of inducible Cbl phosphorylation also suggests that it is not a substrate of the catalytically active EphB6 partner. Cbl is known to interact with regulators of cytoskeletal rearrangement, and recruitment of Cbl to sites of cell-cell contact by Eph receptors could therefore be important for the regulation of cell-cell interaction.

Although EGF stimulation of the ErbB-1 receptor induces tyrosine phosphorylation of Cbl (56), we did not detect increased Cbl phosphorylation upon ephrin-B1 stimulation of EphB6 (not shown). This lack of Cbl phosphorylation presumably reflects the absence of EphB6 catalytic activity, suggesting that EphB6 may simply recruit Cbl to the cell membrane and into Eph receptor complexes rather than modifying its function through phosphorylation. The absence of inducible Cbl phosphorylation also suggests that it is not a substrate of the catalytically active EphB6 partner. Cbl is known to interact with regulators of cytoskeletal rearrangement, and recruitment of Cbl to sites of cell-cell contact by Eph receptors could therefore be important for the regulation of cell-cell interaction.

The ability of Cbl to bind EphB6 also raises the possibility that EphB6 expression may be regulated by Cbl-mediated modification. It is now clear that Cbl is responsible for the physical down-regulation of many receptors through the induction of receptor ubiquitination (49–51). The addition of ubiquitin to the lysine residues of a protein targets it for degradation, either in cytoplasmic proteasomes or in the lysosomal compartment (57). Cbl binding induces ubiquitination of the EGFR, PDGF, and CSF receptors (49, 50, 52, 53), an ability derived from its RING finger domain (54). As all receptors binding to Cbl undergo ubiquitination, it is likely that EphB6 is similarly regulated.

In summary, we have demonstrated that despite its lack of...
kinase activity, EphB6 is an actively signaling receptor that undergoes ligand-inducible transphosphorylation and initiates specific cytoplasmic signaling events. Furthermore, we have also shown, for the first time, evidence of cross-talk between members of the Eph receptor family, demonstrating the innate complexity of the Eph receptor signaling system and the potential sophistication in responses to a single ephrin.

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