Tyrosine Phosphorylation of Focal Adhesion Kinase Stimulated by Hepatocyte Growth Factor Leads to Mitogen-activated Protein Kinase Activation

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Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase involved in integrin-mediated signal transduction pathway. In this report, we describe that the treatment of hepatocyte growth factor (HGF) stimulates a significant increase in the tyrosine phosphorylation of FAK in human embryonic kidney 293 cells. This stimulation is independent of cell adhesion or the integrity of the actin cytoskeleton, suggesting potentially different mechanisms by which the HGF receptors and integrins regulate the tyrosine phosphorylation of FAK. Our results also suggest that the activation of Src upon HGF stimulation is likely to be one, if not the only, of the mechanisms responsible for the HGF-induced tyrosine phosphorylation of FAK. Furthermore, we showed that a mutation in the Grb2 binding site Tyr-925 of FAK partially abolishes its increase in HGF-induced phosphorylation. Finally, we demonstrated that HGF stimulates the association of FAK with Grb2 in vitro and in intact cells and provided evidence that FAK might contribute to the activation of mitogen-activated protein kinase through Ras in HGF signaling by functioning as an adapter molecule.

Focal adhesion kinase (FAK)1 is a 125-kDa cytoplasmic tyrosine kinase localized in focal contacts (1, 2) that has been implicated to play an important role in regulating cell migration in response to cell adhesion to extracellular matrix (ECM) proteins (3–5). Recent studies have also suggested that FAK may be involved in mediating the anchorage-dependent cell survival (6–8). Clustering of integrins through binding to ECM proteins leads to activation and tyrosine phosphorylation of FAK (1, 9). Tyrosine residue 397 has been identified as the major site of FAK autophosphorylation (10) and the binding site for the Src homology 2 (SH2) domains of Src family kinases (11, 12) and phosphatidylinositol 3-kinase (13, 14). After binding to FAK, Src family kinases (Src or Fyn) phosphorylate p130cas, leading to the association of p130cas with Crk-C3G complex (15, 16). Furthermore, Src can also phosphorylate FAK on tyrosine residues 925, creating a binding site for the Grb2-Sos complex, but the stoichiometry of this event appears to be low (17, 18). Because C3G and Sos can function as a guanine nucleotide exchange factor for Ras (19, 20), it has been proposed that FAK can link integrin-initiated signals to the Ras/mitogen-activated protein kinase (MAPK) pathway (17, 18, 21). In addition, FAK phosphorylation is also stimulated by many other stimuli, including v-Src transformation (1, 9), aggregation of high affinity IgE receptors (22, 23), and exposure to lysophosphatidic acid (24), mitogenic neupeptides (e.g. bombesin; Ref. 25), and growth factors (e.g. hepatocyte growth factor (HGF); Ref. 26). Thus, FAK may play a role in integrating the cellular responses to multiple extracellular stimuli. However, the mechanism and the functional significance of FAK phosphorylation in these stimuli are poorly understood.

HGF, also known as scatter factor, is a multifunctional growth factor that elicits mitogenic, motogenic, and morphogenic activities in various cell types (27). The diverse biological effects of HGF are transmitted through activation of its transmembrane receptor encoded by the c-met proto-oncogene (28, 29). The Met receptor is a heterodimer composed of a 45-kDa α chain that remains entirely extracellular, and a 145-kDa β chain that traverses the plasma membrane and contains the intracellular tyrosine kinase domain (30–33). Upon HGF binding, the intrinsic tyrosine kinase of the receptor is activated, resulting in autophosphorylation on specific tyrosine residues in the β chain (34, 35). The phosphorylated tyrosine residues can then associate with molecules containing SH2 and phosphotyrosine binding domains that act to transduce extracellular signals to the cell interior (36). In the present study, we have investigated the mechanisms by which HGF stimulates FAK tyrosine phosphorylation and the functional consequence of this event.

**EXPERIMENTAL PROCEDURES**

**Materials**—Recombinant HGF, protein A-Sepharose 4B, glutathione-agarose beads, polylysine, cytochalasin D, myelin basic protein (MBP), poly(Glu-Tyr) (4:1), and rabbit anti-mouse IgG antibody were purchased from Sigma. Fibronection and LipofectAMINE were purchased from Life Technologies, Inc. The anti-FAK monoclonal antibody (clone 77) and anti-phosphotyrosine (anti-PY) monoclonal antibody PY20 were purchased from Transduction Laboratories (Lexington, KY). The rabbit polyclonal anti-c-Met (C-28), anti-Grb2 (C-23), and anti-ERK (C-16) antibodies were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). The anti-Src monoclonal antibody was purchased from Upstate Biotechnology (Lake Placid, NY). The monoclonal anti-Ras (Ab-1) was purchased from Calbiochem (San Diego, CA). Monoclonal antibody (12CA5) against an epitope of the hemagglutinin (HA) protein of the influenza virus (YPYDVPDYA, HA epitope) and a rabbit polyclonal...
anti-FAK serum were kindly provided by Dr. J.-L. Guan (Cornell University, Ithaca, NY) and described previously (37).

**Cell Culture**—Human embryonic kidney 293 cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal calf serum (Life Technologies, Inc.). For HGF stimulation, subconfluent cells were serum starved for 18 h in serum-free DMEM. They were washed once with DMEM, treated with 10 ng/ml HGF for 15 min at 37 °C, and then lysed as described below. In other experiments, serum-starved cells were pretreated with 2.5 μM cytochalasin D as described previously (38) before HGF stimulation.

**Immunoprecipitations, Western Blotting, and In Vitro Kinase Assays**—293 cells were lysed with 1% Nonidet P-40 lysis buffer (1% Nonidet P-40, 20 mM Tris-HCL, pH 8.0, 137 mM NaCl, 10% glycerol, and 1 mM Na3VO4) containing protease inhibitors (1 mM phenylmethylsulfonyl fluoride, 0.2 mM trypsin inhibitor units/ml aprotinin, and 20 μg/ml leupeptin). The lysates were centrifuged for 10 min at 4 °C to remove debris, and the protein concentrations were determined using the Bio-Rad protein assay (Hercules, CA). For immunoprecipitations, aliquots of lysates were incubated with 3 μl of various polyclonal antibodies or 6 μl of monoclonal antibody 12CA5 for 1.5 h at 4 °C. Immunocomplexes were collected on protein A-Sepharose beads. For 12CA5, protein A-Sepharose beads were coupled with rabbit anti-mouse IgG before use. The beads were washed three times with 1% Nonidet P-40 lysis buffer, boiled in a small volume in SDS sample buffer, subjected to SDS-polyacrylamide gel electrophoresis (PAGE), and transferred to nitrocellulose (Schleicher and Schuell). Western blotting was performed with monoclonal anti-β1 integrin (1:1000), anti-FAK (1:1000), or anti-Src (1:1000) using the Amersham Pharmacia Biotech enhanced chemiluminescence system for detection. For MAPK assays, polyclonal anti-ERK was used to immunoprecipitate MAPK from cells. In vitro kinase reactions were carried out in 30 μl of kinase buffer (20 mM Tris-HCl, pH 7.5, 10 mM MgCl2) containing 10 μg of MBP and 10 μCi of (γ-32P)ATP (3000 Ci mmol⁻¹, NEN Life Science Products) for 20 min at 25 °C. Reactions were terminated by the addition of SDS sample buffer, and proteins were resolved by SDS-PAGE.

**Expression Plasmids and Transient Transfection of 293 Cells**—The pKH3 plasmids encoding HA epitope-tagged FAK and its two mutants kd (kinase-defective; Lys-454 mutated to Arg) and Y397F (Tyr-397 to Phe) of FAK were generated using site-directed mutagenesis by overlap extension using the polymerase chain reaction. The desired mutation was confirmed by deoxy DNA sequencing (U. S. Biochemical Corp.). It was then cloned into pKH3 vector for the expression of HA epitope-tagged Y397F mutant. The pEVX plasmids encoding wild-type (WT) C-Src and its kd mutant (Lys-295) were kindly provided by Dr. D. Shalloway (Cornell University, Ithaca, NY). The pZipneoSV plasmid was then cloned into pKH3 vector for the expression of HA epitope-tagged Y925F mutant. The pEVX plasmids encoding a dominant-negative Ras (Asn-17) was obtained from Dr. L. Feig (Tufts University, Boston, MA) and described previously (39).

For transient transfection of 293 cells, one day after plating 5 × 104 cells on 60-mm dishes, the cells were transiently transfected with various concentrations (as indicated in figure legends) of expression plasmids using 10 μl of LipofectAMINE. One or two days after transfection, cells were serum starved for 18 h, treated with 10 ng/ml HGF, and lysed as described above.

**In Vitro Binding Assays**—pGEX-Grb2.SH2 was kindly provided by Dr. T. Pawson (Mt. Sinai Hospital, Toronto, Canada). GST fusion proteins were produced and purified as described previously (14). GST fusion proteins were immobilized on glutathione-agarose beads and then incubated with lysates from serum-starved or HGF-treated 293 cells in 1% Nonidet P-40 lysis buffer for 1 h at 4 °C. The complexes were washed four times with 1% Nonidet P-40 lysis buffer, resolved by SDS-PAGE, and analyzed by Western blotting with monoclonal anti-FAK or 12CA5.

**RESULTS**

The effect of HGF on the tyrosine phosphorylation of FAK was examined in human embryonic kidney 293 cells (Fig. 1A). HGF induced a prominent tyrosine phosphorylation of several cellular proteins with molecular weights between 100 and 145 kDa in 293 cells (lanes 1 and 2). Importantly, HGF induced a significant increase (~10-fold) in the level of FAK tyrosine phosphorylation (lanes 3 and 4). An increase in tyrosine phosphorylation of the 145-kDa β chain of c-Met in response to HGF was also detected (lanes 5 and 6). Control experiments confirmed that an equal amount of FAK or c-Met was present in immunocomplexes from serum-starved or HGF-treated cells (data not shown). The increase in FAK tyrosine phosphorylation upon HGF stimulation was further examined by performing time-course experiments (Fig. 1B). An increase in the level of FAK tyrosine phosphorylation was detectable as early as 3 min after HGF stimulation. This increase reached a plateau by 30 min and gradually declined at 120 min. Using a similar approach, the effect of different concentrations of HGF on FAK tyrosine phosphorylation was analyzed (Fig. 1C). The elevated tyrosine phosphorylation of FAK was readily detected upon HGF stimulation at 1 ng/ml, and the maximal increase of FAK tyrosine phosphorylation was observed at 10 ng/ml of HGF. To determine whether HGF-induced tyrosine phosphorylation of FAK is dependent on cell adhesion to ECM proteins, serum-starved 293 cells were plated onto culture dishes that had been coated with either polylysine or fibronectin. After 30 min of plating, cells were further incubated for 15 min in the presence or absence of 10 ng/ml HGF (Fig. 2A). Consistent with previous reports (9, 36), FAK from cells plated on fibronectin contained more tyrosine phosphorylation than that plated on polylysine in the absence of HGF (lanes 1 and 3). Interestingly,
HGF was capable of stimulating FAK tyrosine phosphorylation in cells plated both on polylysine and fibronectin (lanes 2 and 4), indicating that stimulation of FAK tyrosine phosphorylation by HGF is independent of cell adhesion to fibronectin.

It was shown that stimulation of FAK tyrosine phosphorylation by cell adhesion (40) or other stimuli such as neuromodulins (41) and platelet-derived growth factor (42) requires the integrity of the actin cytoskeleton. To examine whether disruption of the actin cytoskeleton could affect the HGF-induced phosphorylation of FAK, serum-starved 293 cells were preincubated with (+) or without (−) 2.5 μM cytochalasin D (cyt.D) for 1 h at 37 °C. Cells were further incubated with (+) or without (−) 10 ng/ml HGF for 15 min and then lysed. The lysates were used in the assays as described in Fig. 1B.

It is known that Src directly phosphorylates FAK upon cell adhesion to ECM proteins (18, 43) and that Src is activated in response to HGF stimulation (36). Thus, it is possible that the increased tyrosine phosphorylation of FAK upon HGF stimulation is because of the activation of Src. To test this possibility, 293 cells were transiently transfected with increasing amounts of expression vector encoding wild-type c-Src (Src-wt, panel A) or its kinase-defective mutant (Src-kd, panel B), as indicated. One day after transfection, these cells were serum-starved for 18 h and then treated with (+) or without (−) 10 ng/ml HGF. The lysates were prepared, and FAK was immunoprecipitated using polyclonal anti-FAK and analyzed by Western blotting with anti-PY (panels A and B, upper). Aliquots (50 μg) of the lysates were analyzed by Western blotting with monoclonal anti-Src to verify the expression of Src (panels A and B, lower).

These results suggest that activation of Src by HGF may play a positive role in the HGF-induced tyrosine phosphorylation of FAK. To examine whether Src kd mutant could block the HGF-stimulated FAK phosphorylation, 293 cells were transiently transfected with increasing amounts of expression vector encoding c-Src kd mutant (Fig. 3B). The result showed that the effect of HGF on the stimulation of FAK phosphorylation could actually be blocked by a high level expression of c-Src kd mutant (lane 5). Together, these results suggest that the activation of Src upon HGF stimulation is likely to be one, if not the only, of the mechanisms responsible for the HGF-induced tyrosine phosphorylation of FAK.

To determine the potential phosphorylation sites on FAK in response to HGF stimulation, HA epitope-tagged FAK and three mutants including kd, Y397F, and Y925F were transiently expressed in 293 cells. One day after transfection, these cells were serum starved, treated with HGF, and lysed. The ectopically expressed FAK proteins were immunoprecipitated by 12CA5 and then analyzed by Western blotting with anti-PY. As shown in Fig. 4, the tyrosine phosphorylation of kd mutant was elevated to a level similar to the WT FAK in response to HGF stimulation. This result suggests that the HGF-stimulated increase in FAK phosphorylation is not dependent on its own catalytic activity or that the observed tyrosine phosphorylation of ectopically expressed FAK kd mutant is because of a trans-phosphorylation by endogenous FAK. In addition, a mutation in Tyr-397 of FAK only slightly decreased the HGF-stimulated FAK phosphorylation, suggesting that, unlike stimulation by ECM proteins, Tyr-397 of FAK is not a primary phosphorylation site upon HGF stimulation. Interestingly, the tyrosine phosphorylation of Y925F mutant was about 21% lower than that of the WT FAK upon HGF stimulation (110 versus 140%), indicating that Tyr-925 is one of the phosphorylation sites of FAK in response to HGF stimulation.

It is known that Tyr-925 of FAK is the binding site for the SH2 domain of Grb2 (17, 18). To examine if the increased

**FIG. 2.** Effect of cell adhesion and cytochalasin D on HGF-stimulated tyrosine phosphorylation of FAK. A, serum-starved 293 cells were plated onto culture dishes that had been coated with 100 μg/ml polylysine (PLL) or 10 μg/ml fibronectin (FN). After 30 min of plating, cells were stimulated with (+) or without (−) 10 ng/ml HGF for 15 min and then lysed. The lysates were used in the assays as described in Fig. 1B. B, serum-starved 293 cells grown on culture dishes without coating polylysine or fibronectin were preincubated with (+) or without (−) 2.5 μM cytochalasin D (cyt.D) for 1 h at 37 °C. Cells were further incubated with (+) or without (−) 10 ng/ml HGF for 15 min and then lysed. The lysates were used in the assays as described in Fig. 1B.

**FIG. 3.** Role of Src in HGF-stimulated tyrosine phosphorylation of FAK. 293 cells were seeded on culture dishes without coating polylysine or fibronectin for 24 h. Cells were then transiently transfected with different amounts of expression vectors encoding wild-type c-Src (Src-wt, panel A) or its kinase-defective mutant (Src-kd, panel B), as indicated. One day after transfection, these cells were serum-starved for 18 h and then treated with (+) or without (−) 10 ng/ml HGF. The lysates were prepared, and FAK was immunoprecipitated using polyclonal anti-FAK and analyzed by Western blotting with anti-PY (panels A and B, upper). Aliquots (50 μg) of the lysates were analyzed by Western blotting with monoclonal anti-Src to verify the expression of Src (panels A and B, lower).
Fig. 4. Stimulation of tyrosine phosphorylation of HA epitope-tagged FAK and mutants by HGF. 293 cells were transiently transfected with expression vectors (1 μg) encoding the HA epitope-tagged FAK (wt), kinase-defective (kd), Y397F, or Y925F mutant. One day after transfection, these cells were serum starved for 18 h, treated with (+) or without (−) 10 ng/ml HGF, and lysed. The HA epitope-tagged FAK and mutants were immunoprecipitated using 12CA5 and then analyzed by Western blotting with anti-PY. Quantitation of FAK tyrosine phosphorylation was carried out using a densitometer. Values are expressed as percentage (%) relative to WT FAK in the absence of HGF stimulation, which is defined as 100%, and are averages of three independent experiments.

Fig. 5. Stimulation of the association of FAK with Grb2 by HGF. A, immobilized GST or GST-Grb2.SH2 was incubated with serum-starved (−) or HGF-treated (+) 293 cell lysates. After washing, the bound proteins were resolved by SDS-PAGE and analyzed by Western blotting with anti-FAK. B, an equal amount of the lysates from serum-starved (−) or HGF-treated (+) 293 cells was incubated with polyclonal anti-Grb2. The immunocomplexes were washed and analyzed by Western blotting with monoclonal anti-FAK. C, immobilized GST-Grb2.SH2 was incubated with the lysates as prepared in Fig. 4 and the bound proteins were analyzed by Western blotting with 12CA5 (anti-HA).

Fig. 6. Enhancement of HGF-induced MAPK activation by overexpression of FAK. A, 293 cells were transiently transfected with empty vector (1 μg, lanes 1 and 2) or vector encoding WT FAK (1 μg, lanes 3 and 4). In one case (lane 5), 293 cells were cotransfected with expression vectors for WT FAK (1 μg) and RasN17 (10 μg). Two days after transfection, these cells were serum starved for 18 h and then treated with (+, lanes 2, 4, and 5) or without (−, lanes 1 and 3) 10 ng/ml HGF for 15 min. The lysates were prepared and incubated with polyclonal anti-ERK. The activity of ERK was measured by an in vitro kinase assay using myelin basic protein (MBP) as a substrate as described under “Experimental Procedures.” Quantitation was carried out using a phosphoimager. Data are expressed as fold increase compared with control serum-starved cells (lane 1) and are averages of three independent experiments. B, an equal amount of the lysates prepared as above was analyzed by Western blotting with 12CA5 or anti-Ras.

The ability of FAK to recruit Grb2 in response to HGF stimulation raised the possibility that one of its physiological roles is to link HGF-receptor activation to the Ras/MapK signaling pathway. To examine this possibility, 293 cells were transiently transfected with vector alone or vector encoding FAK, and then the activity of the endogenous ERK was measured in immunocomplexes using myelin basic protein as a substrate. As shown in Fig. 6A, HGF induced about 3-fold activation of MAPK in cells transfected with empty vectors (lane 2). Overexpression of WT FAK led to a slight activation (−1.5-fold) of MAPK without HGF stimulation (lane 3). In contrast, overexpression of WT FAK led to a strong MAPK activation (−8.5-fold) upon HGF stimulation (lane 4). This enhancement of MAPK activation was also achieved by overexpression of FAK kd mutant (data not shown). As expected, overexpression of FAK Y925F mutant was unable to induce such a response (data not shown). To examine the role of Ras in this process, the effect of FAK overexpression on MAPK activation in the presence of a dominant-negative mutant of Ras (RasN17) was analyzed. The results showed that expression of RasN17 efficiently blocked FAK-enhanced MAPK activation in response to HGF stimulation (lane 5). Taken together, these results suggest that FAK may function as a link between HGF-receptor activation and the Ras/MapK signaling pathway.

DISCUSSION

Although the mechanism of FAK activation by integrins is unclear, it is likely to involve the aggregation of FAK with
integrins and other cytoskeletal proteins at focal contacts (44, 45). Treatment of cells with cytochalasin D, which selectively disrupts actin cytoskeleton, can block FAK activation and phosphorylation by integrins (40). However, we report here that stimulation of the tyrosine phosphorylation of FAK by HGF is independent of cell adhesion or the integrity of actin cytoskeleton. Similarly, the enhanced tyrosine phosphorylation of FAK by fibroblast growth factor has also been shown to be cell adhesion-independent (46). Together, these results suggest that a mechanism different from that involving integrin signaling is responsible for FAK activation by HGF and that the dependence of FAK activation on cell adhesion and intact actin cytoskeleton may be varied among distinct stimuli.

In integrin-mediated signaling, the catalytic activity of Src is activated by binding to the phosphorylated Tyr-397 of FAK via its SH2 domain, presumably by displacement of the C-terminal regulatory tyrosine residue 527 from the SH2 domain (10, 11). Our results reported here suggest that Src may function as an upstream regulator of FAK tyrosine phosphorylation in HGF signaling. Overexpression of WT c-Src enhances the effect of HGF on the stimulation of FAK tyrosine phosphorylation. In contrast, overexpression of c-Src kd mutant blocks it. This is similar to the previous finding that epidermal growth factor-induced FAK phosphorylation can be completely abolished by the expression of Src kd mutant in NBT-II carcinoma epithelial cells (47). Although our results strongly suggest that Src is likely to be a mediator responsible for HGF-induced FAK phosphorylation, we cannot exclude the possibility that kinase(s) other than Src may directly phosphorylate FAK. For example, after activated by Src, FAK may trans-phosphorylate itself upon HGF stimulation. In fact, the tyrosine phosphorylation of ectopically expressed FAK kd mutant by endogenous FAK has been shown in Chinese hamster ovary cells (5) in which FAK kd mutant behaved like WT FAK to promote cell migration in response to ECM proteins. This trans-phosphorylation mechanism may be responsible also for the increased phosphorylation of FAK kd mutant and its ability to activate MAPK in response to HGF stimulation as described in this report.

The autophosphorylation site Tyr-397 is essential for Src binding and the function of FAK in integrin signaling (44, 45). However, we report here that the loss of Tyr-397 has only a very slight effect on the stimulation of FAK tyrosine phosphorylation by HGF. It is possible that other tyrosine residues may have compensated for the loss of Tyr-397. Alternatively, HGF treatment may induce a subcellular translocation of FAK and/or Src, bring two proteins to a closer position, and finally lead to a direct phosphorylation of FAK by Src. Indeed, in subcellular fractionation experiments, more FAK was recovered in cytosol and membrane fractions from HGF-treated cells than from serum-starved cells (data not shown), implying that a redistribution of FAK from insoluble fractions to soluble fractions may occur upon HGF stimulation. Hamawy et al. (21) reported that aggregation of high affinity IgE receptors increases the tyrosine phosphorylation of kd and Y397F mutants to the same extent as WT FAK in RBL-2H3 mast cells and suggested that Syk/ZAP70 family kinases may be involved in this stimulation. Together, these data raise the possibility that FAK may function as an adapter or linker molecule independent of its own catalytic activity and Tyr-397 in some signaling pathways.

Although it has been proposed that FAK can link integrin-initiated signals to the Ras/MAPK pathway, recent studies have provided evidence that, in normal fibroblasts and endothelial cells, the activation of MAPK by integrin ligation is independent of FAK (49, 50). However, it remains possible that FAK plays such a role upon overexpression in carcinomas (51, 52) or under certain circumstances. In the present study, we show that FAK may function as a link between the activation of HGF receptor and the Ras/MAPK pathway. Overexpression of FAK enhances the activation of MAPK upon HGF stimulation. This enhancement by FAK overexpression can be efficiently blocked by the dominant-negative Ras. Consistent with the role of Grb2/Sos in MAPK activation, the Y925F mutant of FAK fails to enhance HGF-induced MAPK activation. Furthermore, the mutation of Tyr-925 of FAK partially abolishes its increased tyrosine phosphorylation upon HGF stimulation, indicating that HGF can stimulate the phosphorylation of FAK on Tyr-925 and thereby promote the association of FAK with Grb2. Because the mutation of Tyr-925 does not completely abolish the HGF-induced phosphorylation of FAK, it is likely that other tyrosine residues in addition to Tyr-925 are also phosphorylated upon HGF stimulation. However, it is not clear whether these potential phosphorylation sites upon HGF stimulation are the same as those upon cell adhesion.

The role of FAK/Ras/MAPK pathway in HGF-elicited cellular functions is currently unknown. Because the activation of the MAPK pathway is known to lead to transcriptional control of genes important for cell proliferation and differentiation (53, 54), it is likely that FAK may contribute to HGF-stimulated cell proliferation. Recently, MAPK has also been shown to play roles in promoting cell migration and suppressing integrin activation (55, 56). In accord with the role of FAK in promoting cell migration on ECM proteins (5), it is possible that FAK may be involved in HGF-triggered cell migration or morphological changes. Finally, HGF has been shown to protect epithelial cells from apoptosis induced by disruption of cell adhesion to ECM proteins (57), it is possible that FAK may play a role in this process. Experiments to test these possibilities are in progress.

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Involvement of FAK in HGF Signaling

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