Commentary

The focal adhesion kinase

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The focal adhesion kinase, FAK or pp125^{FAK}, is a 125 kDa protein tyrosine kinase (PTK), whose name is derived from its subcellular localization (Schaller *et al*. 1992). Although originally identified as a putative substrate for pp60$^{v\text{-}src}$ (Kanner *et al*. 1990), an oncogenic PTK, FAK has gained its notoriety as an element of a signaling pathway regulated by cell surface receptors called integrins (Schaller & Parsons 1993, 1994). Integrins are heterodimeric, transmembrane proteins that can simultaneously bind to proteins of the extracellular matrix (ECM), e.g. fibronectin, and to components of the actin cytoskeleton, e.g. talin and α-actinin (Burridge *et al*. 1988, Turner & Burridge 1991). In addition to their role in cell adhesion to ECM and in anchoring the cytoskeleton, the integrins can transduce extracellular cues into cytoplasmic signals (Damsky & Werb 1992, Hynes 1992, Schwartz 1992, Juliano & Haskill 1993), which include the tyrosine phosphorylation and enzymatic activation of FAK (Burridge *et al*. 1992, Guan & Shalloway 1992, Hanks *et al*. 1992, Kornberg *et al*. 1992, Lipfert *et al*. 1992).

The integrins may play a fundamental role in a number of biological processes including adhesion to extracellular matrix, intercellular adhesion, the maintenance of cell morphology, cell migration and the regulation of cell growth and differentiation (Hynes 1992). Through regulation of these basic cellular processes the integrins contribute to the normal development and homeostasis of multicellular organisms, e.g. in establishing tissue organization, blood clotting and in lymphocyte adhesion. Although their function in endocrine cells has not been extensively studied, the integrins play critical roles in the development and normal function of other epithelial tissues. For example, integrin-dependent adhesion to ECM proteins suppresses the expression of a differentiation specific marker in keratinocytes (Adams & Watt 1989). Conversely, the synthesis of milk proteins in mammary epithelial cells is dependent upon integrins binding to their extracellular ligands (Streuli *et al*. 1991). Thus integrins play an important role in regulating differentiation and/or gene expression in these systems. Given these precedents, it is likely that integrin/ECM interactions also profoundly affect some aspect of endocrine cell behavior.

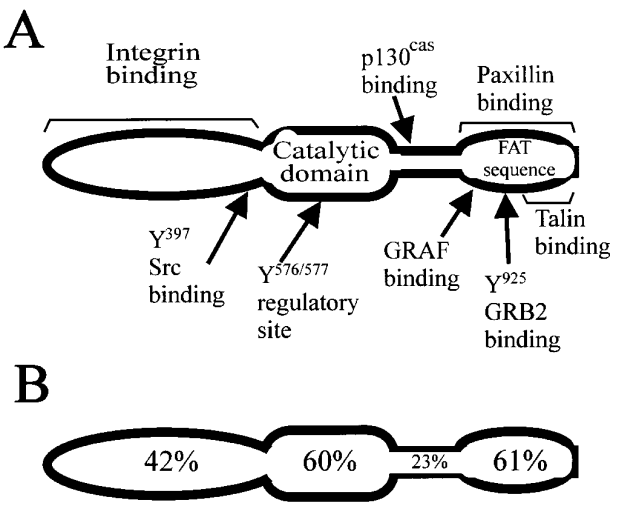

Figure 1 (A) Schematic diagram of FAK. The central catalytic domain and flanking domains are illustrated. Sites of phosphorylation and binding sites for cytoskeletal and signaling proteins are illustrated. (B) Schematic diagram of PYK2/CAKβ. The central catalytic domain and flanking domains are illustrated. The percentage of residues within each domain that are identical to FAK are indicated.

The FAK family of PTKs

FAK is a highly conserved protein, exhibiting ~90% amino acid identity between the *Xenopus*, avian, murine and human homologues (Hanks *et al*. 1992, Schaller *et al*. 1992, Andre & Becker-Andre 1993, Choi *et al*. 1993, Whitney *et al*. 1993, Hens & DeSimone 1995). FAK contains a central catalytic domain flanked by NH_2- and C-terminal noncatalytic domains (see Fig. 1A). Although the function of the NH_2-terminus of FAK remains to be firmly established, the C-terminal domain is comprised of multiple binding sites for cytoskeletal and signaling proteins and probably functions to facilitate the assembly of multiprotein complexes (see below). The C-terminal 150 residues of FAK contain the focal adhesion targeting (FAT) sequence which is responsible for directing and/or anchoring FAK to cellular focal adhesions (Hildebrand *et al*. 1993).

FAK is now the prototypical member of a small family of PTKs comprised of two members, FAK and PYK2/

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Table 1 Conservation of SH2 and SH3 binding sites between FAK and PYK2/CAKβ

	Sequence in FAK	Sequence in PYK2/CAKβ	Function in FAK
Site in FAK			
Tyrosine 397	*Y*AEI	*Y*AEI	Binding to SH2 of Src-like PTKs
Tyrosine 576/577	DST*YY*KAS	DED*YY*KAS	Regulatory?
Tyrosine 925	*Y*ENV	*Y*LNV	GRB2 SH2 binding
Proline 712/715	EA*P*PK*P*SR	EP*P*PK*P*SR	$p130^{cas}$ SH3 binding
Proline 876	APPKK*P*PRP	GPPQK*P*PRL	GRAF SH3 binding

CAKβ (Lev *et al*. 1995, Sasaki *et al*. 1995). FAK and PYK2/CAKβ exhibit 45% amino acid identity (60% in the catalytic domain) and like FAK, PYK2/CAKβ contains a central catalytic domain flanked by large NH_2- and C-terminal noncatalytic domains (see Fig. 1B). Despite the similarities in amino acid sequence between these two PTKs, PYK2/CAKβ does not localize to cellular focal adhesions and its tyrosine phosphorylation is not regulated by adhesion to ECM proteins. PYK2/CAKβ is localized to sites of cell–cell contact (Sasaki *et al*. 1995) and appears to be regulated by changes in cytoplasmic Ca^{2+} (Lev *et al*. 1995). PYK2/CAKβ can induce the tyrosine phosphorylation of the Kv1·2 potassium channel which results in suppression of the passage of current (Lev *et al*. 1995). Despite their different subcellular localization, and presumably function, a number of binding sites for SH2 and SH3 domain-containing FAK binding proteins are conserved in PYK2/CAKβ (Table 1). Thus the same signaling molecules may be recruited into the signaling pathways regulated by FAK and PYK2/CAKβ.

Functions of FAK

FAK regulates cell spreading and migration Perhaps the most pressing issue in FAK signaling is the identification of the biological response controlled by FAK. FAK is clearly essential for embryonic development since the homozygous FAK knockout is an embryonic lethal (Ilic *et al*. 1995). FAK has been proposed to function in the assembly of cellular focal adhesions and cell spreading on ECM proteins since inhibitors of PTKs inhibit both events (Burridge *et al*. 1992). Overexpression of the FAT sequence of FAK in chicken embryo cells perturbs normal FAK function since the phosphotyrosine content of endogenous FAK is reduced (A Richardson and J T Parsons, personal communication). Expression of this dominant negative variant of FAK impairs cell spreading (A Richardson and J T Parsons, personal communication) and fibroblasts derived from $FAK^{-/-}$ embryos exhibit impaired spreading (Ilic *et al*. 1995). FAK may also function in cell migration since motogenic stimuli, e.g. hepatocyte growth factor (scatter factor), trigger the phosphorylation of FAK (Matsumoto *et al*. 1994). Platelet-derived growth factor (PDGF) also stimulates FAK tyrosine phosphorylation with a dose response that correlates with PDGF-induced chemotaxis rather than PDGF-induced DNA synthesis (Rankin & Rozengurt 1994, Abedi *et al*. 1995). Tyrosine kinase inhibitors block the migration of human umbilical vein endothelial cells (HUVEC) in wound healing, implicating some PTK in endothelial cell migration (Romer *et al*. 1994). This kinase is likely to be FAK since the introduction of a dominant negative mutant of FAK, i.e. the C-terminal domain, also inhibits the migration of HUVECs (A P Gilmore & L H Romer, personal communication). Finally FAK-deficient fibroblasts show retarded motility (Ilic *et al*. 1995). These results implicate FAK as a regulatory protein in the basic cellular processes of cell spreading and migration.

FAK: a role in human disease? FAK may play a role in the pathology of human disease. It was originally isolated as a candidate substrate for $pp60^{src}$ and subsequently shown to be a $pp60^{src}$-binding protein (Kanner *et al*. 1990, Cobb *et al*. 1994). FAK is thus a candidate for a mediator of some of the effects of *src* transformation in cells in tissue culture. Enzymatically activated $pp60^{src}$ has recently been found in some human tumors suggesting that the analysis of the $pp60^{src}$ model may be directly applicable to human cancer (Bolen *et al*. 1987, Cartwright *et al*. 1990, Takekura *et al*. 1990, Fanning *et al*. 1992, Ottenhoff-Kalff *et al*. 1992, Talamonti *et al*. 1993, Cartwright *et al*. 1994). Changes in cell surface expression of integrins can modify the tumorigenic and metastatic properties of cells (Albelda 1993, Juliano & Varner 1993), which could conceivably be mediated by altered signaling through FAK. Finally FAK expression levels are elevated in some tumors (Weiner *et al*. 1993, Owens *et al*. 1995). Although these early results are provocative, a true assessment of the value of FAK perturbations as diagnostic or prognostic indicators await more extensive analyses. For these reasons, the investigation of FAK as a potential modulator of some aspects of cancer continues. Indeed as a regulator of basic cellular responses, e.g. migration, FAK may also contribute to the development of other human diseases, e.g. vascular diseases involving the hyperproliferation and migration of vascular smooth muscle cells.

Table 2 Multiple stimuli, which trigger different types of cell surface receptor, can induce the tyrosine phosphorylation of FAK

	Stimulus	Reference
Receptor type		
Integrin	Antibody crosslinking	Kornberg *et al.* (1992)
	Engagement with ligand	Kornberg *et al.* (1992); Guan & Shalloway (1992); Lipfert *et al.* (1992); Hanks *et al.* (1992); Burridge *et al.* (1992)
Receptor protein tyrosine kinases	Platelet-derived growth factor	Rankin & Rozengurt (1994); Abedi *et al.* (1995)
	Hepatocyte growth factor	Matsumoto *et al.* (1994)
	Macrophage colony stimulating factor (M-CSF)	Karbanda *et al.* (1995)
G protein linked receptors	Bombesin	Zachary *et al.* (1992)
	Endothelin	Zachary *et al.* (1992)
	Bradykinin	Leeb-Lundberg *et al.* (1994)
	Lysophosphatidic acid	Seufferlein & Rozengurt (1994)
	Vasopressin	Zachary *et al.* (1992)
	Angiotensin II	Polte *et al.* (1994); Turner *et al.* (1995)
PTK linked receptors	FcεRI	Hamawy *et al.* (1993)
Other	Hyaluronic acid	Hall *et al.* (1994)

Mechanism of action of FAK

Tyrosine phosphorylation of FAK FAK was first shown to be linked to integrin signaling when it was identified as a major substrate for tyrosine phosphorylation, concomitantly becoming enzymatically activated, following antibody crosslinking of cell surface integrins or upon integrin-dependent cell adhesion (Burridge *et al*. 1992, Guan & Shalloway 1992, Hanks *et al*. 1992, Kornberg *et al*. 1992, Lipfert *et al*. 1992). Subsequently, many other stimuli have been shown to induce the tyrosine phosphorylation of FAK including extracellular ligands that stimulate G-protein linked receptors, e.g. bombesin (Zachary *et al*. 1992, Sinnett-Smith *et al*. 1993), ligands that activate receptor protein tyrosine kinases, e.g. platelet-derived growth factor (Rankin & Rozengurt 1994), and other ligands whose mode of signaling is presently obscure, e.g. hyaluronic acid (Hall *et al*. 1994). Thus multiple stimuli that signal through diverse pathways converge to induce the tyrosine phosphorylation of a common substrate, FAK (see Table 2). The integrity of the actin cytoskeleton is crucial for signaling to FAK since cytochalasin D treatment abrogates the tyrosine phosphorylation of FAK in response to many of these stimuli (Lipfert *et al*. 1992, Sinnett-Smith *et al*. 1993, Rankin & Rozengurt 1994, Seufferlein & Rozengurt 1994). It has been suggested that Rho, a Ras-like GTP binding protein that regulates the formation of actin stress fibers and focal adhesions (Ridley & Hall 1992), may be involved in the activation of FAK. Tyrosine phosphorylation of FAK in response to a number of different stimuli can be abolished by the *Clostridium botulinum* exoenzyme, C3 ADP-ribosyltransferase (Kumagai *et al*. 1993, Rankin *et al*. 1994), which ADP-ribosylates Rho and destroys its capacity to transmit signals (Aktories *et al*. 1989, Sekine *et al*. 1989, Paterson *et al*. 1990). Furthermore, treatment of permeabilized cells with GTPγS, which stimulates the activity of GTP binding proteins, induces the tyrosine phosphorylation of FAK and this response is eliminated if the cells are pretreated with C3 toxin (Seckl *et al*. 1995). The GTPγS-induced tyrosine phosphorylation of FAK can also be blocked with a synthetic peptide identical in sequence to the effector domain of Rho, which should bind to downstream signaling elements and uncouple Rho from its downstream effectors (Seckl *et al*. 1995).

Tyrosine phosphorylation of PTKs can fulfill two distinct roles that are important for the enzyme's function: (i) regulation of enzymatic activity and (ii) the creation of high affinity binding sites for other signaling molecules. FAK can autophosphorylate, i.e. phosphorylate itself either intra- or intermolecularly, at tyrosine residue 397 (Y^{397}) and can be phosphorylated at a number of other residues, Y^{407}, Y^{576}, Y^{577} and Y^{925}, presumably by other PTKs (see Table 1) (Schaller *et al*. 1994, Schlaepfer *et al*. 1994, Calalb *et al*. 1995). It is intriguing that FAK can be phosphorylated by other PTKs since some of the stimuli that

Table 3 FAK binding proteins and substrates

Protein	FAK binding	Binding site on FAK	FAK substrate	Consequence of tyrosine phosphorylation
Src kinases	Yes	Tyrosine 397	No	—
GRB2	Yes	Tyrosine 925	No	—
Integrin	Yes	NH_2-terminus	No	—
$p130^{cas}$	Yes	Prolines 712 & 715	Yes	Create binding sites for SH2 adaptor proteins
HEF1	Yes	?	?	?
GRAF	Yes	Proline 878	?	?
Paxillin	Yes	FAT sequence	Yes	Create binding sites for SH2 adaptor proteins
Tensin	No	—	Yes	?
Talin	Yes	FAT sequence	No	—
PI3K	Yes	Prolines 712/715??	Yes	?

induce tyrosine phosphorylation of FAK are known to activate members of the Src-family of PTKs, e.g. PDGF (Ralston & Bishop 1985, Gould & Hunter 1988). Removal of phosphorylation site Y^{397} or Y^{576} and Y^{577} slightly reduces the enzymatic activity of FAK measured in an *in vitro* PTK assay suggesting that phosphorylation of these residues may play a small role in the regulation of FAK's enzymatic activity (Schaller *et al*. 1994, Calalb *et al*. 1995). Elimination of all three sites has a more pronounced effect upon kinase activity (Calalb *et al*. 1995). Perhaps more importantly, tyrosine phosphorylation of FAK regulates complex formation with signaling proteins that contain SH2 domains. SH2 domains are motifs that mediate protein–protein interactions by specifically binding to tyrosine phosphorylated residues in the context of specific amino acid sequences (Cohen *et al*. 1995, Pawson 1995). Tyrosine phosphorylation at Y^{397} of FAK creates a high affinity binding site for the SH2 domain of $pp60^{src}$ (Schaller *et al*. 1994), whereas tyrosine phosphorylation at Y^{925} creates a GRB2 SH2 domain binding site (Schlaepfer *et al*. 1994) (see Table 3). The association of FAK with GRB2 implicates $p21^{ras}$ as a downstream component of FAK signaling since GRB2, a small adaptor protein, regulates the activation of $p21^{ras}$ through an associated guanine nucleotide exchange factor (Cohen *et al*. 1995, Pawson 1995). Complex formation between FAK and $pp60^{src}$ or GRB2 may serve to recruit these signaling molecules to the vicinity of activated FAK resulting in generation of signals in specific cellular locales. Binding of $pp60^{src}$ to FAK may also serve to activate $pp60^{src}$. Current models of $pp60^{src}$ regulation envision repression of enzymatic activity by a physical interaction between the tyrosine phosphorylated negative regulatory domain of $pp60^{src}$ and its own SH2 domain (Cooper & Howell 1993). Complex formation with FAK might displace the negative regulatory domain from the SH2 domain snapping $pp60^{src}$ into its active configuration (Schaller *et al*. 1994).

More FAK binding proteins FAK can bind through sequences that partially overlap the FAT sequence to two focal adhesion-associated proteins, talin and paxillin (Turner & Miller 1994, Chen *et al*. 1995, Hildebrand *et al*. 1995) (see Table 3). Talin also binds to the cytoplasmic domain of β_1 integrins and to another cytoskeletal protein, vinculin, and through these interactions is believed to be instrumental in the anchorage of the actin cytoskeleton to integrins (Burridge *et al*. 1988, Turner & Burridge 1991). Paxillin is also a vinculin-binding protein (Turner *et al*. 1990) and the binding site for both vinculin and FAK is located in the NH_2-terminal half of the molecule (Turner & Miller 1994). Upon tyrosine phosphorylation, paxillin can complex with a number of SH2-containing signaling molecules (Birge *et al*. 1993, Sabe *et al*. 1994, Bergman *et al*. 1995). Despite the fact that the FAT sequence of FAK overlaps the binding sites for paxillin and talin, mutational analysis of FAK has revealed that binding to neither protein alone is responsible for tethering FAK in focal adhesions (Chen *et al*. 1995, Hildebrand *et al*. 1995). It is therefore possible that this region of FAK binds to yet another protein responsible for targeting FAK to focal adhesions.

The C-terminal domain of FAK is relatively proline rich and includes binding sites for two SH3 domain-containing proteins. SH3 domains mediate protein–protein interactions by binding to specific proline-rich sequences (Cohen *et al*. 1995, Pawson 1995). The sequence around proline 712 (P^{712}) and P^{715} of FAK serves as a binding site for the SH3 domain of $p130^{cas}$ (Polte & Hanks 1995, A H Bouton, personal communication) and the sequence around P^{878} binds to the SH3 domain of a novel GTPase activating protein (GAP) called GRAF (J D Hildebrand and J T Parsons, personal communication) (see Table 3). $p130^{cas}$ has an NH_2-terminal SH3 domain and a large tyrosine-rich region containing multiple consensus SH2 binding sites (Sakai *et al*. 1994). Like paxillin, $p130^{cas}$ localizes to focal adhesions (Petch

et al. 1995) and upon tyrosine phosphorylation binds to a number of signaling molecules (Sakai *et al*. 1994). A $p130^{cas}$-related protein, HEF1, was isolated as a human cDNA which induced pseudohyphal growth when expressed in yeast (S Law and E Golemis, personal communication). Like $p130^{cas}$, HEF1 can bind to FAK through its NH_2-terminal SH3 domain. Association with FAK may facilitate the tyrosine phosphorylation of $p130^{cas}$ or tether $p130^{cas}$ and its associated proteins in a specific cellular location. The Rho-GAP-like protein, GRAF, shares homology with the catalytic domain of GAPs for the Rho family of GTP binding proteins, and has been shown to catalyze the hydrolysis of GTP bound to Cdc42 and Rac to GDP *in vitro* (J D Hildebrand and J T Parsons, personal communication). GRAF may serve as an effector protein for GTP binding proteins in the vicinity of FAK or may function as a negative regulatory protein that terminates signal transduction by these proteins.

FAK also associates with phosphatidylinositol 3-kinase (PI3K). Following cell adhesion, this interaction correlates with the tyrosine phosphorylation of FAK and may be mediated in part by the SH2 domain of the p85 subunit of PI3K (Chen & Guan 1994*a*). Conversely, following PDGF stimulation, complex formation between FAK and PI3K does not correlate with FAK phosphorylation (Chen & Guan 1994*b*). Furthermore, the SH3 domain of p85 can bind directly to FAK *in vitro* and a synthetic peptide mimicking residues 706–711 of FAK can bind to the p85 SH3 domain, stimulating PI3K activity twofold (Guinebault *et al*. 1995). In thrombin-stimulated platelets the translocation of PI3K to the cytoskeleton correlates with its association with FAK (Guinebault *et al*. 1995). Thus this interaction may serve to target PI3K to a discrete region of the cell and regulate its activity.

FAK may also be an integrin-binding protein since the NH_2-terminal domain of FAK can associate with synthetic peptides mimicking the cytoplasmic domain of the β_1 integrin subunit (Schaller *et al*. 1995). This interaction plays no role in the association of FAK with focal adhesions. This observed interaction suggests the intriguing hypothesis that FAK may be regulated through binding to the integrin, a hypothesis that remains to be tested.

Substrates of FAK The tyrosine phosphorylation of paxillin and $p130^{cas}$ is probably regulated by $pp125^{FAK}$ since these proteins colocalize in cellular focal adhesions, paxillin and $p130^{cas}$ physically associate with $pp125^{FAK}$ and all three proteins become coordinately phosphorylated on tyrosine in response to multiple stimuli (Burridge *et al*. 1992, Guan & Shalloway 1992, Kornberg *et al*. 1992, Lipfert *et al*. 1992, Zachary *et al*. 1992, 1993, Rankin & Rozengurt 1994, Seufferlein & Rozengurt 1994, Nojima *et al*. 1995, Petch *et al*. 1995) (see Table 3). Experimentally, the tyrosine phosphorylation of paxillin can be induced in a $pp125^{FAK}$-dependent manner (Schaller & Parsons 1995). The induction of paxillin phosphorylation depends upon the integrity of the $pp60^{src}$ binding site within $pp125^{FAK}$, suggesting that FAK might regulate paxillin phosphorylation by directing the activity of $pp60^{src}$ toward this substrate (Schaller & Parsons 1995). Paxillin is a substrate for tyrosine phosphorylation by both $pp125^{FAK}$ and $pp60^{src}$ *in vitro* and becomes phosphorylated at tyrosine residues 31 and 118 both *in vitro* and *in vivo* (Bellis *et al*. 1995, Schaller & Parsons 1995). Tyrosine phosphorylation of paxillin creates binding sites for the SH2 domain containing proteins Crk and Csk (Birge *et al*. 1993, Sabe *et al*. 1994). Crk, like GRB2, is an adaptor protein that serves to dock other signaling molecules, e.g. the $p21^{ras}$ guanine nucleotide exchange factor Sos (Matsuda *et al*. 1994), to tyrosine phosphorylated proteins, e.g. paxillin. Csk is a PTK that can phosphorylate a negative regulatory site within $pp60^{src}$ and repress its enzymatic activity (Nada *et al*. 1991). Tyrosine phosphorylation of $p130^{cas}$ also creates binding sites for SH2 domain-containing signaling molecules including Crk and $pp60^{src}$ (Sakai *et al*. 1994). Thus by regulating the phosphotyrosine content of paxillin and $p130^{cas}$, FAK could regulate the assembly of signaling complexes at discrete sites within the cell.

Tensin is an SH2 domain-containing, actin binding, focal adhesion-associated, cytoskeletal protein (Davis *et al*. 1991, Lo *et al*. 1994). The observations that tensin colocalizes with $pp125^{FAK}$ and becomes tyrosine phosphorylated upon cell adhesion suggests that tensin is a FAK substrate (Bockholt & Burridge 1993). Like paxillin, the tyrosine phosphorylation of tensin can be induced experimentally in a FAK-dependent manner (M D Schaller, unpublished observations), although the consequences of tyrosine phosphorylation of tensin are unknown. PI3K is also a candidate substrate for FAK since the two molecules physically associate and the 85 kDa subunit of PI3K becomes tyrosine phosphorylated in response to cell adhesion (Chen & Guan 1994*a*).

The evidence described above identifies these proteins as candidate substrates of FAK. However, a number of these proteins exhibit tyrosine phosphorylation in FAK-deficient fibroblasts (Ilic *et al*. 1995). This observation may indicate the existence of multiple mechanisms of phosphorylation of these substrates, only one of which is FAK dependent.

Future prospects

The intense scrutiny under which FAK has fallen has led to the rapid identification of its associated proteins and potential substrates. Emerging evidence has implicated FAK as a regulator of cell morphology and migration. Numerous laboratories are striving to elucidate the biochemical pathways that (i) regulate FAK activity and (ii) are utilized by FAK to regulate these biological functions. The successful completion of these studies will provide valuable insight into the mechanisms of regulation of cellular processes such as migration. Once the key elements within this signaling pathway(s) are identified

and the way in which these proteins physically and functionally interact are discovered, rational approaches to specifically disrupt certain of these interactions and abrogate part of the downstream signal will be devised. These tools will be applied to explore FAK regulated signaling further and may serve as the prototypes in the design of novel strategies to control cellular behavior in the treatment of human disease.

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