Focal adhesion kinase: the first ten years

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Summary

The protein tyrosine kinase focal adhesion kinase (FAK) plays a prominent role in integrin signaling. FAK activation, demonstrated by an increase in phosphorylation of Tyr397 as well as other sites in the protein, is best understood in the context of the engagement of integrins at the cell surface. Activation of FAK results in recruitment of a number of SH2-domain- and SH3-domain-containing proteins, which mediate signaling to several downstream pathways. FAK-dependent activation of these pathways has been implicated in a diverse array of cellular processes, including cell migration, growth factor signaling, cell cycle progression and cell survival.

Key words: Kinase, Focal Adhesion, Migration, Cytoskeleton

Introduction

Over ten years has elapsed since the initial identification of focal adhesion kinase (FAK) (Hanks et al., 1992; Schaller et al., 1992) and publication of the first data implicating it in integrin signaling (Guan et al., 1991; Kornberg et al., 1992). In the interim, much progress has been made regarding integrin signaling and the role of protein tyrosine kinases, and FAK in particular, in this pathway (Miranti and Brugge, 2002; Schwartz and Ginsberg, 2002). However, despite these advances, understanding how integrin signals contribute to the regulation of the complex dynamics of cell motility, progression through the cell cycle, cell survival and numerous disease processes continues to be a significant challenge (Webb et al., 2002). Here I seek to summarize the current state of knowledge about FAK and integrate relevant observations into known processes of cell adhesion, migration and growth regulation.

The structure of FAK – clues to function

FAK and PYK2, also referred to as cell adhesion kinase (CAK)-β, related adhesion focal tyrosine kinase (RAFTK) or calcium-dependent protein tyrosine kinase (CADTK) (Avraham et al., 1995; Lev et al., 1995; Sasaki et al., 1995; Yu et al., 1996), are the sole members of the FAK family of non-receptor protein tyrosine kinases. FAK is expressed in most tissues and cell types and is evolutionarily conserved in mammalian species as well as lower eukaryotic organisms, including *Drosophila* and zebrafish (Fox et al., 1999; Hanks et al., 1992; Henry et al., 2001; Palmer et al., 1999; Schaller et al., 1992) (Fig. 1). The expression pattern of PYK2, which shares significant sequence similarity with FAK, appears to be more restricted than that of FAK; Pyk2 is expressed at high levels in the brain and lower levels in the liver, kidney, spleen, lung and cells of hematopoietic origin (Avraham et al., 1995; Lev et al., 1995; Sasaki et al., 1995).

FAK comprises a central catalytic domain flanked by large N- and C-terminal non-catalytic domains (Fig. 1). The N-terminal domain exhibits sequence similarity to a family of proteins containing so-called FERM (erythrocyte band four.1-ezrin-radixin-moesin) domains (Girault et al., 1999; Sun et al., 2002). In general, members of this family link transmembrane glycoproteins to the actin cytoskeleton. In the case of FAK, the role of the FERM domain is unclear. In vitro, the N-terminal domain of FAK binds to sequences in the cytoplasmic domain of β-integrin subunits (Schaller et al., 1995), although a demonstration of a direct interaction between FAK and integrin receptors in vivo is still lacking. Interestingly, recent evidence indicates that the FERM domain of the adhesion protein talin binds to β3 integrin tails and regulates integrin activation (Calderwood et al., 1999). The N-terminal domain also mediates interaction with activated forms of the epidermal growth factor (EGF) receptor, although it is not clear whether these interactions are direct (Sieg et al., 2000). Recently, studies on Etk/BMX, a member of the Btk family of tyrosine kinases, have shown that the activation of Etk by extracellular matrix proteins is regulated by FAK and requires an interaction between the PH domain of Etk and the FERM domain of FAK (Chen, 1994). Additional evidence supports a role for the FERM domain in regulating catalytic activity and subcellular localization (Dunty and Schaller, 2002; Stewart et al., 2002). Thus, the N-terminal FERM domain may direct FAK to sites of integrin or growth factor receptor clustering as well as regulating its interactions with other potential activating proteins.

The C-terminal region of FAK is rich in protein-protein interaction sites. An ~100 residue sequence designated 'FAT' for focal adhesion targeting (Fig. 1) directs FAK to newly formed and existing adhesion complexes (Martin et al., 2002). Sequences within this domain are both necessary and sufficient to target FAK to adhesion complexes (Hildebrand et al., 1993), and the integrity of this region is essential for FAK signaling (Sieg et al., 1999; Thomas et al., 1999) (Fig. 1). Both X-ray crystallography and NMR analysis of the FAT domain reveal a four-helix bundle that resembles structures present in other adhesion proteins, including vinculin, Cas and α-catenin (Arold et al., 2002; Hayashi et al., 2002; Liu, G. et al., 2002). The FAT domain is also the binding site for the focal adhesion protein paxillin. This interaction requires the structural integrity of the helical bundle and is mediated by two

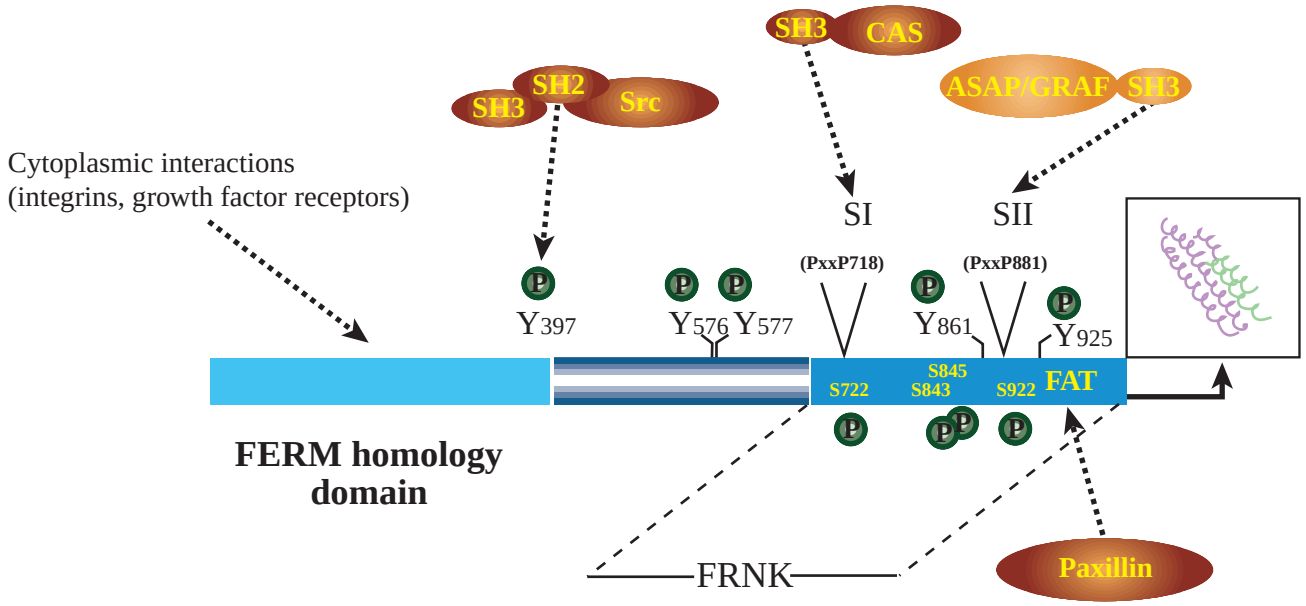

Fig. 1. Organization of the domains of focal adhesion kinase. The N-terminal domain shares similarity with members of the FERM homology domain family of proteins and directs interactions with integrins and growth factor receptors. The central domain is the catalytic domain. The C-terminal domain contains sites for multiple protein-protein interactions. Site I (SI) is an interaction site for the SH3 domain of Cas; site II (SII) is the site of interaction with the SH3 domains of GRAF and ASAP. Y397 is the major site of autophosphorylation and a site of interaction with the SH2 domain of Src. FAT denotes the region required for focal adhesion targeting. The inset illustrates the four helical bundle that makes up the FAT domain. Paxillin interacts within sequences with the FAT domain; these sequences are denoted in yellow in the FAT structure. Additional sites of tyrosine and serine phosphorylation are indicated.

hydrophobic ‘patches’ on opposite faces of the bundle. These ‘patches’ are proposed to bind to two ‘LD’ motifs on paxillin (Arold et al., 2002; Hayashi et al., 2002; Liu, G. et al., 2002). Because paxillin binds directly to the cytoplasmic domains of integrin receptors (Liu et al., 1999; Schaller et al., 1995), as well as to the focal adhesion protein vinculin, paxillin may function as the ‘docking partner’ for FAK in adhesion complexes. Interestingly, certain FAK variants that fail to bind paxillin in vitro are still targeted to adhesions in vivo (Hildebrand et al., 1995). Thus the mechanism for FAK recruitment to adhesion structures may require more than simple paxillin binding.

The C-terminal, non-catalytic domains of both FAK and PYK2, termed FRNK (FAK-related-non-kinase) and PRNK (PYK2 related non-kinase), respectively, are expressed independently in certain cells and may function as negative regulators of kinase activity (Schaller et al., 1993; Taylor et al., 2001; Xiong and Parsons, 1997). In the case of FRNK, expression is controlled by transcriptional elements residing between the 3′-most exon of the kinase domain and the first exon of the C-terminal domain (Nolan et al., 1999). FRNK expression is elevated in vascular smooth muscle cells and appears to be upregulated in response to vascular injury (Taylor et al., 2001). In most cells, forced overexpression of FRNK inhibits cell spreading, cell migration and growth-factor-mediated signals to MAP kinase (Hauck et al., 2001; Richardson et al., 1997; Taylor et al., 2001).

The kinase domain of FAK shares sequence similarity with other receptor and non-receptor protein tyrosine kinases. Interestingly the crystal structure of the FAK kinase domain reveals the presence of a disulphide bond in the N-terminal lobe of the kinase. This is an unusual feature for kinases and suggests a possible role in kinase function (Nowakowski et al., 2002). Clustering of integrins results in rapid phosphorylation of FAK at Tyr397, as well as at several additional sites within the kinase and C-terminal domains (Calalb et al., 1995). Recent evidence indicates that transient dimerization of FAK molecules leads to intermolecular phosphorylation of Tyr397 (Toutant et al., 2002). Phosphorylation at Tyr397 correlates with increased catalytic activity of FAK (Calalb et al., 1995; Lipfert et al., 1992) and appears to be important for tyrosine phosphorylation of focal-adhesion-associated proteins (Cobb et al., 1994; Schaller et al., 1999; Schaller et al., 1994) (Fig. 2) as well as phosphorylation at Tyr576 and Tyr577, two highly conserved residues positioned within the ‘catalytic loop’ of the kinase domain (Owen et al., 1999). Phosphorylation of these tyrosine residues is important for the maximal adhesion-induced activation of FAK and signaling to downstream effectors (Calalb et al., 1995; Owen et al., 1999).

FAK as a ‘switch’ for multiple signaling outputs

Phosphorylation of FAK in response to integrin engagement leads to the formation of phosphotyrosine docking sites for several classes of signaling molecule and may be important for the conformation-induced binding of proteins to other structural motifs within the N- and C-terminal non-catalytic regions. The phosphorylation on Tyr397 creates a high-affinity binding site for the SH2 domain of Src family kinases and leads to the recruitment and activation of Src through the formation of a bipartite kinase complex (Schaller et al., 1994; Xing et al., 1994). Tyr397-dependent activation of FAK and the recruitment of Src have been implicated in the efficient tyrosine phosphorylation of additional sites on FAK (Owen et

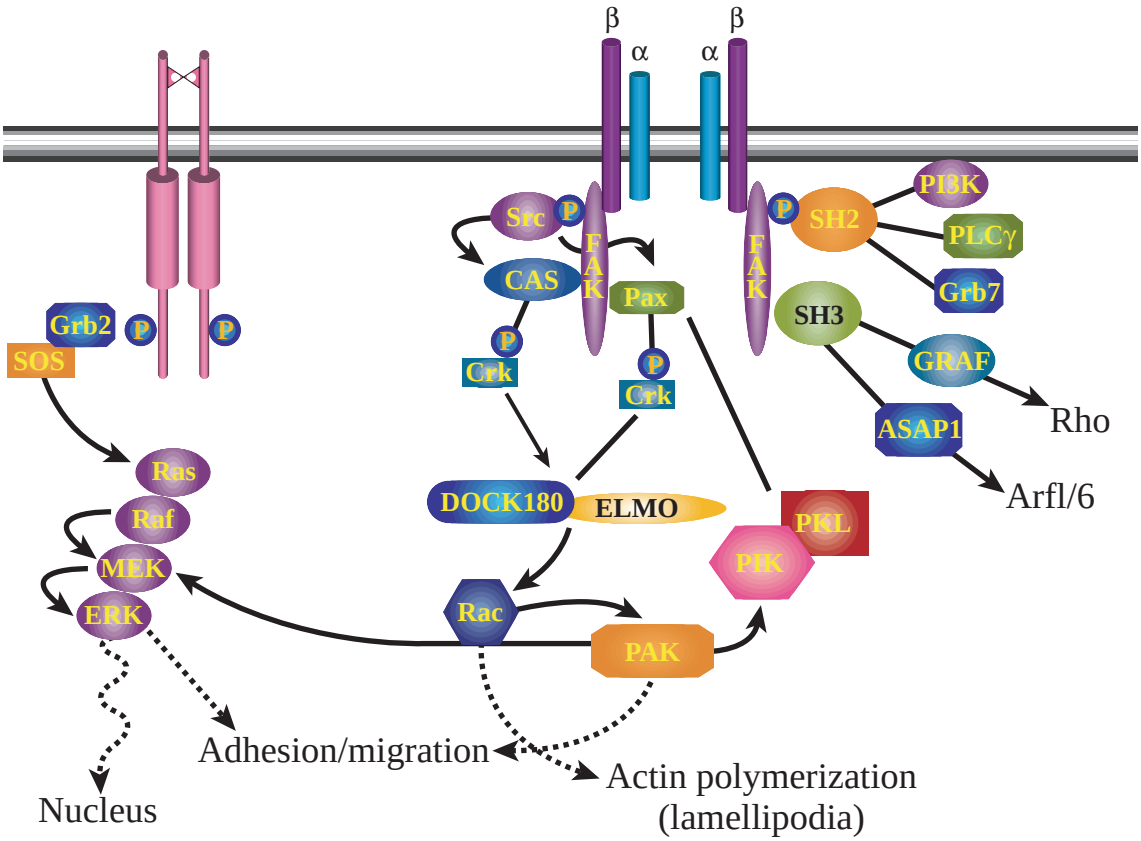

Fig. 2. Proposed interactions among the proteins involved in integrin signaling. As indicated in the text, integrins signal through FAK to signaling pathways that regulate small GTPases of the Rho and Arf families. Signals through FAK to Rac and Pak play a role in modulating cell adhesion and migration, actin polymerization and MAP kinse signaling.

al., 1999) as well as the FAK-binding proteins Cas and paxillin (Schaller et al., 1999). Phosphorylation of Tyr397 also appears to be important for the recruitment of other SH2-containing proteins, including the 85 kDa subunit of phosphoinositide 3-kinase (PI 3-kinase), phospholipase C (PLC)-γ and the adapter protein Grb7 (Akagi et al., 2002; Chen et al., 1996; Chen and Guan, 1994; Han and Guan, 1999). The phosphorylation of Tyr397, as well as Tyr925, creates a binding site for the Grb2-SOS complex (Chen et al., 1994; Schlaepfer et al., 1994; Schlaepfer and Hunter, 1996). Finally, Tyr861 becomes highly phosphorylated in several different cell settings (Slack et al., 2001). Recent data indicate that phosphorylation of Tyr861 might enhance the phosphorylation of Tyr397 (Leu and Maa, 2002).

FAK contains four sites of serine phosphorylation within the C-terminal domain (Ser722, Ser843 and Ser846, and Ser910). The role of serine phosphorylation in the regulation of FAK function is poorly understood; however, the proximity of several of these phosphorylated serine residues to sites of protein-protein interaction is provocative (Ma et al., 2001) and suggests a role for serine phosphorylation in modulating binding/stability of downstream signaling proteins.

The C-terminal domain harbors multiple protein-protein interactions sites. In addition to the paxillin-binding site in the FAT domains, two additional sites contain proline-rich recognition sites for SH3-domain-containing proteins (site I and site II, Fig. 1). Site I provides the major binding motif recognized by the SH3 domain of Cas, a multi-functional adapter protein (Harte et al., 1996; O'Neill et al., 2000; Polte and Hanks, 1995). Upon integrin clustering, Cas is localized to adhesion complexes and is phosphorylated on tyrosine (Harte et al., 1996; O'Neill et al., 2000; Petch et al., 1995; Polte and Hanks, 1995). FAK mutants that lack the binding site for Cas exhibit compromised signaling to downstream effectors (see below). The site II motif binds the SH3 domains of two regulators of small GTPases: GRAF, a GAP (GTPase-activating protein) for Rho; and ASAP1, a GAP for Arf 1 and Arf 6 (Liu et al., 2002b; Randazzo et al., 2000; Taylor et al., 1998; Taylor et al., 1999). Interestingly, neither GRAF nor ASAP appears to be efficiently tyrosine phosphorylated in either the bound or unbound state (Liu, Y., 2002; Taylor et al., 1998). In addition, whereas the expression of GRAF is cell type specific, interactions between FAK and ASAP appear to be common to many cell types (Liu, Y., 2002). Thus the binding of ASAP and/or GRAF to FAK appears important to link adhesion complex signaling with the concerted regulation of small GTP-binding proteins in the Rho and Arf families, proteins that clearly play an important function in cytoskeletal reorganization.

The interaction of FAK with multiple binding partners raises several interesting questions. When and how do different effectors bind FAK? And what contributions do individual SH2- and SH3-containing binding partners make to the signaling pathways downstream of activated FAK? One

interesting possibility is that the spatial and temporal activation of FAK in different cellular compartments (e.g. phosphorylation of Tyr397 or other sites in adhesion complexes, focal adhesions or growth factor complexes) provides a 'switch' allowing FAK to signal to multiple different downstream pathways, depending on the structural context of FAK activation. Such selective activation of FAK could result in different physiological outcomes.

The role of FAK in cell adhesion and migration

Considerable evidence implicates FAK in the regulation of cell migration. Most notably, FAK-deficient cells spread more slowly on extracellular matrix proteins, exhibit an increased number of prominent focal adhesions and migrate poorly in response to chemotactic and haptotactic signals (Ilic et al., 1995; Owen et al., 1999; Sieg et al., 2000; Sieg et al., 1999). Overexpression of FRNK also inhibits the rate of cell spreading, chemotactic and haptotactic migration (Richardson et al., 1997; Sieg et al., 1999; Taylor et al., 2001), presumably by sequestering key regulatory proteins required for efficient FAK signaling. Finally, overexpression of FAK in Chinese hamster ovary (CHO) cells enhances cell migration (Cary et al., 1996). The reconstitution of FAK-deficient cells with wild-type FAK restores cell migration, whereas reintroduction of FAK mutants lacking kinase activity, or the ability to bind Src family kinases (Y397 mutation) or Cas (Site I mutation), fails to restore cell migration. Interestingly, direct binding of paxillin is not required to reconstitute FAK-directed cell migration (Sieg et al., 1999). FAK-deficient cells also exhibit decreased directional persistence: whereas FAK-expressing cells respond to exerted forces by reorienting their movement and forming prominent focal adhesions, FAK-deficient cells fail to exhibit such responses (Wang et al., 2001). Recent experiments indicate that FAK-deficient cells respond to an inhibitor of Rho-associated kinase by resuming fibroblast morphology and exhibiting increased cell motility (Chen et al., 2002), suggesting the possibility that the lack of adhesion complex turnover in FAK-deficient cells may reflect altered regulation of Rho-regulated contractility.

Turnover of adhesions also requires the functional interactions between several FAK-interacting proteins (Webb et al., 2002). For example, cells lacking paxillin expression, Cas expression or Src family kinase expression all exhibit defects in adhesion turnover (Klinghoffer et al., 1999), (Webb and Horwitz, personal communication). These observations argue that FAK is a critical component of a pathway leading to signals that either positively or negatively modulate the assembly and breakdown of adhesions at the leading and/or trailing edges of migrating cells (Webb et al., 2002).

Downstream signals – multiple paths to small GTPases

Understanding the signaling pathways involving FAK-binding partners provides insights into how FAK contributes to regulation of cell migration, growth and survival. Cas appears to function as an important 'mediator' for migration signals by binding to the SH2/SH3 adapter protein Crk (Vuori et al., 1996). Cell migration is stimulated by overexpression of Cas or Crk and is dependent upon Cas tyrosine phosphorylation and formation of Cas-Crk complexes (Cary et al., 1998; Klemke et al., 1998). Dominant-negative forms of Cas or Crk also block migration. Dominant-negative Rac but not dominant-negative Ras blocks the increased migration in response to Cas/Crk expression, which suggests that Rac is an important downstream effector of the FAK-Cas-Crk complex. Increasing evidence points to DOCK180 and related family members as direct activators of Rac (Brugnera et al., 2002; Gu et al., 2001; Meller et al., 2002). *DOCK180* is the human counterpart of the *Drosophila melanogaster* and *Caenorhabditis elegans* genes *mbc* and *ced-5*, respectively, which are genes implicated in the regulation of phagocytosis and cell migration events (Erickson et al., 1997; Wu and Horvitz, 1998). Spreading of cells on fibronectin leads to an increase in Cas-Crk complex formation and a concomitant increase in formation of Crk-DOCK180 complexes. Furthermore, coexpression of DOCK180 along with Cas and Crk promotes membrane ruffling and accumulation of DOCK180-Cas-Crk complexes at focal adhesions (Kiyokawa et al., 1998). Although DOCK180 shows no sequence similarity to guanine nucleotide exchange factors (GEFs), recent evidence shows that DOCK180, when bound to its binding partner ELMO, stimulates the GTP loading of Rac (Brugnera et al., 2002). The Cas-Crk recruitment of DOCK 180-ELMO may provide a mechanism for the localized activation of Rac in the context of newly formed adhesions at the leading edge of cells. FAK therefore would provide one (but not necessarily the only) pathway to the recruitment and activation of Cas-Crk-DOCK-ELMO, stimulating the localized activation of Rac and its effectors, some of which might be required for actin assembly, protrusive activity or modulation of adhesion complex stability.

Paxillin is proposed to play a role in targeting effectors of activated Rac rather than stimulating Rac activation (Brown et al., 2002; Manser et al., 1997). The N-terminal region of paxillin contains five copies of a leucine-rich repeat termed the LD motif, which comprise the binding sites for FAK and vinculin (Turner, 2000b). LD4 also binds a complex of proteins containing PAK (p21-activated kinase), PIX (PAK-interacting exchange factor) and a multidomain ARF-GAP protein, PKL (paxillin-kinase linker) (Bagrodia et al., 1999; Bagrodia and Cerione, 1999; Turner et al., 1999). As its name implies, PKL recruits PIX to adhesion structures by binding to paxillin. Perturbation of this process by overexpression of the paxillin LD4 domain significantly reduces migration of cells into a wound (Turner et al., 1999). In contrast, expression of a paxillin variant lacking the LD4 motif results in persistent Rac activation, increased membrane protrusiveness, lamellipodia formation and a decrease in directional motility (Brown et al., 2002). Thus appropriate localization of the paxillin-PKL-PIX complex appears important for organization and turnover of adhesion complexes.

Members of the PIX/COOL family of proteins were originally identified as regulators of PAK because of their ability to bind and activate it (Manser et al., 1998; Turner, 2000a). Recent evidence points to a role for the paxillin-PKL interaction in the recruitment of activated PAK-PIX complexes to adhesions. Data support a model by which Cdc42/Rac activation of PAK stimulates the binding of PAK to PIX, which in turn induces binding of PAK-PIX to PKL-paxillin (Brown et al., 2002; Turner, 2000a). As a consequence, activated PAK is targeted to newly formed (Rac-induced) adhesions, which

promotes PAK phosphorylation of proteins controlling adhesion complex assembly and disassembly (e.g. MLC, MLCK and LIM kinase) (Kumar and Vadlamudi, 2002).

Adhesion-induced phosphorylation of paxillin on Tyr31 and Tyr118 stimulates Crk binding to paxillin and formation of paxillin-Crk complexes (Turner, 2000b). It is unclear whether paxillin-Crk signals to the DOCK180-ELMO complex. However, tyrosine phosphorylation of paxillin has been implicated in the binding of two other protein tyrosine kinases: Csk, a negative regulator of Src family kinases, and Abl. The role of these kinases in downstream signaling by paxillin is unclear (Turner, 2000a).

Cooperative signals with growth factors

Integrins provide cooperative signals to promote efficient and robust growth factor stimulation of the MAP kinase pathway. Although adhesion of cells to ECM proteins in the absence of growth factors stimulates MAP kinase activity (Moro et al., 1998; Schlaepfer et al., 1994; Wary et al., 1998), blocking the integrin signal by placing cells in suspension significantly inhibits the ability of growth factors to activate the Raf, MEK-Erk cascade efficiently (Aplin and Juliano, 1999; Aplin et al., 2001; Assoian and Schwartz, 2001; Howe et al., 2002; Schwartz and Assoian, 2001). The block in signaling appears to be at the level of Raf/MEK, since growth factor receptor activation and signaling to Ras are uncompromised. The cooperative signals from integrins require FAK, since expression of constitutively activated FAK rescues the suspension-induced block in MAP kinase activation (Renshaw et al., 1999; Renshaw et al., 1997). In addition, evidence also points to a role for Rac and PAK in cooperative signaling. In cells in suspension, Rac fails to activate its downstream effector PAK. Cell adhesion stimulates the translocation of Rac to the membrane and subsequent activation of PAK (del Pozo et al., 2000). Recent evidence implicates adhesion-induced (Rac-dependent) PAK activation in promoting the stable association of components of the MAP kinase pathway (Eblen et al., 2002). PAK phosphorylation of MEK leads to stimulation of the stable association of MEK1 and MAP kinase, whereas cells in suspension exhibit reduced PAK activation and reduced levels of MEK-ERK complexes. Phosphorylation of PAK at a unique site (Ser298) appears necessary for cell-adhesion-induced activation of MEK1. In addition, the rapid and efficient activation of PAK and phosphorylation of MEK1 on Ser298, induced by adhesion of cells to fibronectin, requires FAK and Src (J. Slack-Davis, A. Catling, S. Eblen, M. Weber and J.T.P., unpublished). Thus, these observations point to MEK1 as a point of convergence for cooperative signals through growth factor and integrin receptors. Localized and coordinated activation of growth factor receptors and integrins undoubtedly plays an important role in adhesion complex remodeling as well as providing signals controlling cell growth and progression through the cell cycle (Assoian and Schwartz, 2001; Mettouchi et al., 2001; Zhao et al., 1998).

FAK and cancer

Cancer cells exhibit profound changes in cytoskeletal organization, adhesion, motility, growth regulation and survival. Not surprisingly, analysis of human tumor samples and cell lines derived from tumors reveals elevated expression of FAK (Owens et al., 1995). In such cells, increased FAK expression has been correlated with increased cancer cell motility, invasiveness and proliferation (Owens et al., 1995; Slack et al., 2001; Wang et al., 2000). Inhibition of FAK function, either by antisense oligonucleotide or siRNA treatment or by overexpression of FRNK, leads to a reduction in protease secretion and inhibition of cell migration, invasion and proliferation (Hauck et al., 2002; Hauck et al., 2001; Slack et al., 2001). In some cancer cells, inhibition of FAK by overexpression of FRNK or in combination with inhibition of growth factor receptor signaling leads to the induction of apoptosis (Golubovskaya et al., 2002). Although it remains unclear how FAK contributes to the regulation of growth factor and integrin signals in cancer cells, the documented role of FAK in adhesion turnover and cooperative signaling through growth factors certainly contributes to increased motility, invasiveness, growth and survival of cancer cells.

Prospects for the next ten years

Remarkable progress in the past ten years has delineated the complex web of signaling pathways involving integrins and growth factor receptors. It is clear that FAK plays an important role in relaying signals generated by an increasingly large repertoire of cellular adhesion molecules and other cell surface proteins. The challenge for the next ten years will be to dissect the role of FAK and other tyrosine kinases in regulating these complex signaling networks. We must, for example, understand the spatial and temporal nature of integrin and growth factor signals, the molecular mechanism(s) of adhesion turnover, how FAK is linked/connected to the cytoplasmic domains of clustered integrins, the molecular and biochemical composition of adhesion complexes and their dynamic regulation. The experimental plate is overflowing with questions, and answers await new and innovative approaches to analyze signals in space and time.

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