Histol Histopathol (1999) 14: 1001-1009

http://www.ehu.es/histol-histopathol

Histology and Histopathology

Invited Review

Integrin-mediated signal transduction pathways

L.A. Cary, D.C. Han and J.-L. Guan

Department of Molecular Medicine, Cornell University, Ithaca, USA

Summary. Integrins serve as adhesion receptors for extracellular matrix proteins and also transduce biochemical signals into the cell. They regulate a variety of cellular functions, including spreading, migration, proliferation and apoptosis. Many signaling pathways downstream of integrins have been identified and characterized and are discussed here. In particular, integrins regulate many protein tyrosine kinases and phosphatases, such as FAK and Src, to coordinate many of the cell processes mentioned above. The regulation of MAP kinases by integrins is important for cell growth or other functions, and the putative roles of Ras and FAK in these pathways are discussed. Phosphatidylinositol lipids and their modifying enzymes, particularly PI 3-kinase, are strongly implicated as mediators of integrin-regulated cytoskeletal changes and cell migration. Similarly, actin cytoskeleton regulation by the Rho family of GTPases is coordinated with integrin signaling to regulate cell spreading and migration, although the exact relationship between these pathways is not clear. Finally, intracellular pH and calcium fluxes by integrins are suggested to affect a variety of cellular proteins and functions.

Key words: Extracellular Matrix (ECM), Focal Adhesion Kinase (FAK), Mitogen-Activated Protein (MAP) Kinase, Phosphatidylinositol 3-kinase (PI 3-kinase)

Introduction

Extracellular matrix (ECM) proteins such as fibronectin, vitronectin, laminin and collagen form a complex network to which cells attach and respond. These cell-ECM interactions are important for a variety of biological processes. ECM proteins are recognized by cell surface receptors, one family of which is the integrins (reviewed in Hynes, 1992). At present at least 16 distinct integrin α subunits and 8 ß subunits have been identified which can combine to form at least 20 different receptors. The combination of a particular α and ß polypeptide confers the specificity of the receptor for the ECM ligand; for example, the $\alpha_5\beta_1$ integrin is a well characterized fibronectin receptor. Integrins not only serve as adhesion molecules, but can also transduce biochemical signals into the cell to regulate a variety of cellular functions, including cell proliferation, apoptosis and migration (reviewed in Ruoslahti and Reed, 1994; Lauffenburger and Horwitz, 1996; Assoian, 1997; Bottazzi and Assoian, 1997). The purpose of this review is to describe these signaling pathways as a step towards understanding the mechanisms of integrin regulation of cellular functions.

Offprint requests to: Dr. Jun-Lin Guan, Department of Molecular Medicine, Cornell University, Ithaca, NY 14853, USA. Fax: (607) 253-3708. e-mail: jg19@cornell.edu

Discussion

Protein tyrosine kinases and phosphatases

Integrin activation results in increased tyrosine phosphorylation of several different cellular proteins (Guan et al., 1991; Kornberg et al., 1991; Burridge et al., 1992), and many of the kinases involved in these pathways have been identified. Perhaps the most extensively studied of these is focal adhesion kinase (FAK), a non-receptor protein tyrosine kinase which is localized to focal adhesions (Hanks et al., 1992; Schaller et al., 1992). FAK demonstrates both increased kinase activity (Guan and Shalloway, 1992; Lipfert et al., 1992) and tyrosine phosphorylation (Guan et al., 1991; Kornberg et al., 1991, 1992; Burridge et al., 1992; Hanks et al., 1992; Lipfert et al., 1992) in response to integrin activation, which is dependent on an intact integrin ß cytoplasmic tail (Guan et al., 1991). The major site of FAK autophosphorylation *in vivo* and *in vitro* has been mapped to Y397 (Chan et al., 1994; Schaller et al., 1994; Eide et al., 1995), which serves as a binding site for the SH2 domains of Src family members (Schaller et al., 1994; Eide et al., 1995) and phosphatidylinositol 3-kinase (PI 3-kinase) (Chen et al., 1996a). FAK has been demonstrated to play a role in several integrin-mediated cellular events, including cell migration (Ilic et al., 1995; Cary et al., 1996; Gilmore and Romer, 1996), cell proliferation (Gilmore and Romer, 1996; Zhao et al., 1998), and cell death or anoikis (Frisch et al., 1996; Hungerford et al., 1996; Xu et al., 1996). FAK-regulated

cell migration is dependent on Y397 (Cary et al., 1996), which allows for both Src-mediated phosphorylation of FAK-associated p130^{Cas} (Cary et al., 1998) and an independent PI 3-kinase-mediated pathway (Reiske et al., 1998). FAK-regulated cell proliferation (Zhao et al., 1998) and anoikis (Frisch et al., 1996) also require Y397, suggesting roles for Src and/or PI 3-kinase in these events as well. Furthermore, FAK-regulated anoikis may involve caspase-mediated cleavage of FAK to generate a FRNK-like polypeptide (Crouch et al., 1996; Wen et al., 1997; Gervais et al., 1998; Levkau et al., 1998). In addition, FAK is suggested to play a role in integrin-mediated cell spreading from studies with the C-terminal FAK-related non-kinase (FRNK) (Richardson and Parsons, 1996; Richardson et al., 1997). Therefore FAK is clearly an important regulator of several integrin-initiated signal transduction pathways.

Another tyrosine kinase regulated by integrins is Src (reviewed in Thomas and Brugge, 1997), which demonstrates increased kinase activity in fibroblasts plated on fibronectin (Kaplan et al., 1995; Schlaepfer et al., 1998). The Src family members Hck and Fgr are also important in $ß_2$ integrin-mediated signaling in neutrophils (Berton et al., 1994; Lowell et al., 1996). Src clearly functions intimately with FAK in many integrin signaling pathways, as mentioned above, and it may play additional roles in integrin signaling as well. While c-Src is normally localized with endosomal membranes in fibroblasts (Kaplan et al., 1992), under some conditions various Src constructs are localized to focal adhesions or similar structures (Howell and Cooper, 1994; Kaplan et al., 1994, 1995; Fincham et al., 1996; Fincham and Frame, 1998), as is the negative-regulatory Src kinase Csk (Howell and Cooper, 1994; Bergman et al., 1995). Interestingly, Src$^{-/-}$ cells demonstrate decreased spreading on fibronectin (Kaplan et al., 1995) while Csk overexpression results in decreased cell adhesion (Bergman et al., 1995), suggesting that Src plays a role in these integrin-mediated events.

A third tyrosine kinase with a role in integrin signaling is c-Abl, which contains a protein tyrosine kinase domain, SH2 and SH3 domains, and actin and DNA-binding domains (reviewed in Wang, 1993). Transformation of cells in culture by the chimeric oncogene Bcr/Abl results in anchorage-independent but serum-dependent cell growth (Renshaw et al., 1995). Further evidence that Abl is involved in integrin signaling is the demonstration that Bcr/Abl regulates proteins with known or suggested functions in integrin signaling, including p130^{Cas} and CasL, paxillin, Crk, PI 3-kinase, and tensin (Salgia et al., 1995, 1996; de Jong et al., 1997; Skorski et al., 1997). In addition, c-Abl activity is decreased in detached cells and increased upon fibronectin replating, and a fraction of activated c-Abl is transported to the nucleus where it may act on specific genes (Lewis et al., 1996). The functional role of c-Abl in integrin signal transduction is not currently known.

The protein tyrosine kinase Syk is regulated by integrins in various leukocytes. Integrin $ß_1$ activation in neutrophils results in increased tyrosine phosphorylation of Syk and a correlative increase in interleukin-1ß expression through an NF-KB-dependent mechanism (Lin et al., 1994, 1995). Increased activity and phosphorylation of Syk has been demonstrated upon integrin activation in a variety of cell types (Clark et al., 1994; Keely and Parise, 1996; Gao et al., 1997; Yan et al., 1997). The function of Syk in response to integrins is not clear, but it is suggested to regulate gene expression based on the correlation of these events.

Protein tyrosine kinases clearly play an important role in integrin signaling, and dephosphorylation of their substrates by specific phosphatases (reviewed in Denu et al., 1996; Tonks and Neel, 1996) is also an important factor in these pathways. Several specific phosphatases involved in integrin function have been identified. Both association of the phosphatase SHP-2 with its substrate SHPS-1 as well as tyrosine phosphorylation of SHPS-1 are regulated by cell adhesion to ECM (Fujioka et al., 1996), effects which are dependent on FAK and Src regulation (Tsuda et al., 1998). Regulation of these proteins by SHP-2 is believed to affect integrin-dependent MAP kinase activation (Tsuda et al., 1998) as well as focal adhesion formation and cell migration (Yu et al., 1998). The phosphatase PTEN regulates FAK phosphorylation, focal adhesion formation, cell spreading and migration, effects which are suggested to contribute to its functions as a tumor suppressor gene (Tamura et al., 1998). In addition, several phosphatases interact with the integrin-regulated signaling molecules p130^{Cas} (Garton et al., 1996; Liu et al., 1996; Black and Bliska, 1997) and paxillin (Shen et al., 1998). In particular, PTP1B association with and dephosphorylation of p130^{Cas} is believed to regulate mitogen-activated protein (MAP) kinases, cell spreading and migration by integrins (Liu et al., 1998). Thus the tyrosine phosphorylation as well as dephosphorylation of many proteins are important mechanisms of integrin signaling.

Mitogen-activated protein kinases

Regulation of several protein serine/threonine kinases by integrins has been well documented. Best characterized of these pathways involve the MAP kinases, particularly the Erk (extracellular signal-regulated kinase) subfamily. Activation of integrins, either by plating cells on ECM proteins or by receptor cross-linking using anti-$ß_1$ antibodies, results in activation of Erks in a number of cell types (Chen et al., 1994; Morino et al., 1995; Zhu and Assoian, 1995). In addition to Erks, activation of the JNK (Jun N-terminal kinase) subfamily of MAP kinases also occurs by fibronectin (Miyamoto et al., 1995).

Based on the well established role of Ras in regulating MAP kinases by mitogenic stimuli, an important question is whether integrins also regulate MAP kinases through Ras. At present the answer to this

question is not clear. The involvement of Ras is supported by the early observations of its activation by integrins (Kapron-Bras et al., 1993; Clark and Hynes, 1996; Zheng et al., 1996). Integrin-mediated Erk activation is blocked by a dominant-negative Ras construct in several cell types (Clark and Hynes, 1996; Schlaepfer and Hunter, 1997; Wei et al., 1998). However, in another system, fibronectin does not activate Ras, nor does a dominant-negative Ras inhibit fibronectin-stimulated Erk activation (Chen et al., 1996b). Thus while the role for the Raf kinase is well-supported (Lin et al., 1997b), the role of Ras is not clear. A recent study may provide an explanation for these results, as it demonstrates a time-dependent response of Ras, such that Ras is required only for an initial phase of Raf and Erk activation by integrins but not for a sustained response (Howe and Juliano, 1998).

FAK has been suggested to play a role in MAP kinase activation by integrins, but like that of Ras, the role of FAK in this pathway is controversial. It was first suggested that FAK may mediate MAP kinase activation by its association with Grb2 at FAK Y925 (Schlaepfer et al., 1994), a hypothesis supported by the demonstration that transient FAK expression in HEK 293 cells enhances fibronectin-stimulated Erk activation (Schlaepfer and Hunter, 1997; Schlaepfer et al., 1998). However, several studies have demonstrated a dissociation of FAK tyrosine phosphorylation and MAP kinase activation (Seufferlein et al., 1996; Lin et al., 1997a); and furthermore, FAK overexpression in a chinese hamster ovary (CHO) cell system does not result in the activation of MAP kinases (Cary et al., 1998). The explanation for these conflicting results is not clear. They may reflect cell-specific signaling pathways. It is also possible that complete FAK phosphorylation is not necessary for its promotion of Erk activity, therefore a dissociation of these events does not indicate a functional dissociation of these proteins. Clearly, future work is needed to resolve these discrepancies.

In systems where a clear role for FAK in fibronectin-stimulated Erk activation has been demonstrated, this pathway has been extensively studied. It was originally suggested that Src binding to Y397 of FAK allows for Src phosphorylation of FAK Y925, Grb2 binding, and subsequent activation of Erks (Schlaepfer et al., 1994; Schlaepfer and Hunter, 1996). However, while Y925 is only partially required for Erk activation by FAK, Y397 is completely necessary (Schlaepfer and Hunter, 1997; Schlaepfer et al., 1998). Three different pathways have therefore been suggested to mediate Erk activation by the FAK/Src complex: a major pathway involving tyrosine phosphorylation of Shc and its association with Grb2 (Schlaepfer et al., 1998), a minor pathway involving FAK/Grb2 association, and another minor pathway involving phosphorylation of FAK-associated $p130^{Cas}$ (Schlaepfer et al., 1997). Further supporting the importance of Shc in integrin regulation of MAP kinases, a dominant-negative Shc construct inhibits integrin-mediated Erk activation, although this is likely to occur through a FAK/Src-independent pathway (Wary et al., 1996). Thus there are believed to be several pathways downstream of integrins in the regulation of MAP kinases.

The functional role of integrin-stimulated Erk activation may be several-fold. Primarily, it is believed to act synergistically with mitogenic signaling pathways to regulate cell growth (Lin et al., 1997b; Eliceiri et al., 1998; Short et al., 1998). In G_0-synchronized NIH 3T3 cells, for example, PDGF is responsible for a rapid and transient MAP kinase activation, while fibronectin mediates a slower, sustained response, and both stimuli are required for maximal DNA synthesis (Zhu and Assoian, 1995). In addition, Erk activation has been suggested to regulate integrin-dependent cell spreading and migration (Klemke et al., 1997; Reszka et al., 1997). Finally, while R-Ras affects integrin affinity to increase cell adhesion on fibronectin (Zhang et al., 1996), H-Ras suppresses integrin functions, an effect which correlates with Erk activation (Hughes et al., 1997). These results suggest that Erks may act in a feedback mechanism downstream of Ras to regulate integrin receptors. Clearly the MAP kinases are important mediators of integrin signaling, and an understanding of the mechanisms as well as the outcome of their involvement in these pathways is central to an understanding of integrin signaling.

Phosphatidylinositides

Phosphatidylinositol lipids have been identified as second messengers in a variety of signal transduction pathways. In addition to serving as a substrate for phospholipase Cγ, $PI(4,5)P_2$ has also been shown to regulate actin cytoskeleton dynamics by directly binding to a number of cytoskeletal proteins. These include profilin (Lassing and Lindberg, 1985), gelsolin (Janmey et al., 1987), capping protein (Schafer et al., 1996), α-actinin (Fukami et al., 1992), vinculin (Gilmore and Burridge, 1996), and ezrin/radixin/moesin proteins (Hirao et al., 1996). These effects of $PI(4,5)P_2$ are believed to increase F-actin polymerization, bundling, and linking to the plasma membrane. Indeed, reduction in the amount of $PI(4,5)P_2$ by expression of a specific phosphatidylinositol phosphatase decreases actin stress fibers and bundling (Sakisaka et al., 1997).

Like other signaling pathways, integrins have also been shown to regulate various phosphatidylinositol-modifying enzymes. Integrin stimulation of mouse fibroblasts by plating on fibronectin results in increased levels of $PI(4,5)P_2$ (McNamee et al., 1993), which is possibly a result of Rho-mediated activation of PI(4)P 5-kinase (Chong et al., 1994; Ren et al., 1996). This suggests an attractive model in which integrin-mediated generation of $PI(4,5)P_2$ affects actin cytoskeleton by the mechanisms described above. Activation of integrin $\alpha_{IIb}\beta_3$ in platelets results in increased levels of $PI(3,4)P_2$, which may be produced by either the inositol 5-phosphatase SHIP (Giuriato et al., 1997), PI(3)P 4-

kinase (Banfic et al., 1998), and/or PI 3-kinase (Guinebault et al., 1995). This effect coincides with translocation of PI 3-kinase to the actin cytoskeleton (Guinebault et al., 1995). In addition, platelet spreading on fibrinogen is dependent on PI 3-kinase (Heraud et al., 1998). PI 3-kinase involvement in integrin signaling has been shown in other cell types as well. Cell migration on collagen is mediated by PI 3-kinase, which is predicted to act downstream of Rac and/or Cdc42 (Keely et al., 1997). Carcinoma cell invasion by the $\alpha_6\beta_4$ integrin is dependent on its activation of PI 3-kinase (Shaw et al., 1997). Finally, an adhesion-dependent association of PI 3-kinase with FAK has been shown (Chen and Guan, 1994) which is mediated by direct binding of PI 3-kinase to FAK Y397 (Chen et al., 1996a) and which regulates CHO cell migration on fibronectin (Reiske et al., 1998). Integrins therefore regulate phosphatidylinositides through various modifying enzymes, resulting in effects on actin cytoskeleton dynamics, cell spreading and cell migration.

Rho family GTPases

Regulation of the actin cytoskeleton and subsequent cellular functions by the Rho family of Ras-related low molecular weight GTPases has been well characterized (reviewed in Hall, 1994; Tapon and Hall, 1997). Cdc42 controls the formation of filopodial extensions, Rac controls lamellipodia and membrane ruffling through regulation of cortical actin, and Rho controls actin stress fibers and formation of focal adhesions. These events are all important aspects of cell adhesion, spreading and motility and are also events mediated by integrins, but the relationship between integrin signaling and Rho family members is still not clear.

Many studies have suggested that Rho lies upstream of integrin signaling pathways and possibly integrins themselves. Cell transformation by the Rho exchange factors Dbl or Lbc induces anchorage-independent cell growth (Schwartz et al., 1996). Fibronectin matrix assembly, an integrin-dependent event, is also regulated by Rho (Zhang et al., 1994) and likely occurs through its effects on the actin cytoskeleton (Zhang et al., 1997). More specifically, some studies have shown that focal adhesion formation is dependent on Rho and Rac (Hotchin and Hall, 1995) and that complete formation of actin stress fibers by Rho is dependent on integrins (Machesky and Hall, 1997), suggesting that integrin signaling does not occur without first being activated from within the cell by these GTPases. Further supporting this hypothesis are several studies demonstrating that Rho lies upstream of FAK. Treatment of cells with lysophosphatidic acid (LPA) to activate Rho results in increased FAK kinase activity (Rodriguez-Fernandez and Rozengurt, 1998) as well as tyrosine phosphorylation (Barry and Critchley, 1994; Ridley and Hall, 1994; Seufferlein and Rozengurt, 1994), and this effect is inhibited by specific ADP-ribosylation and inhibition of Rho (Kumagai et al., 1993). Furthermore, the formation of stress fibers by activated Rho requires a tyrosine kinase (Ridley and Hall, 1994), and since FAK phosphorylation is increased by activated Rho (Flinn and Ridley, 1996) it is proposed to be one such kinase.

On the other hand, some studies have suggested that integrins are upstream of these GTPases (Bourdoulous et al., 1998). Integrin activation by either fibronectin or anti-β_1 antibodies activates PAK, a downstream effector of Rac and Cdc42 (Price et al., 1998). In addition, integrin aggregation induces the colocalization of p190-B, a protein with GAP activity for Rho, Rac and Cdc42 (Burbelo et al., 1995), and also induces its tyrosine phosphorylation (Nakahara et al., 1998). A resolution to these seemingly conflicting conclusions may be that this pathway is not linear but rather is cyclical. Cell contractility is required for the formation of stress fibers and focal adhesions by Rho (Chrzanowska-Wodnicka and Burridge, 1996). Recently, Clark et al. (1998) demonstrated that early focal adhesion formation and regulation of FAK/Src in cells on ECM is mediated independently of Rho proteins, but that subsequently Rho GTPases regulate the complete formation of focal adhesion and stress fibers. These results suggest that integrins may initiate focal adhesion formation and signal transduction pathways. Upon activation of Rho proteins, perhaps in an integrin-dependent manner, stress fibers are formed and contracted, which in turn ultimately affects integrins and integrin signaling. Thus integrins may be both dependent and independent of Rho family GTPases; clearly further studies are needed to reconcile these seemingly conflicting observations.

Intracellular ion fluxes

Regulation of intracellular pH by integrins was first suggested by Schwartz et al. (1989), who demonstrated that the degree of cell spreading correlated with intracellular pH levels. This is an effect of the $\alpha_5\beta_1$ integrin, independent of cell shape, and regulated by the Na/H antiporter (Schwartz et al., 1991). Similarly, plating endothelial cells on increasing concentrations of fibronectin results in increased intracellular pH, which is controlled by the Na/H antiporter (Ingber et al., 1990). As with other integrin-mediated events, regulation of intracellular pH occurs synergistically with growth factors in some cell types (Ingber et al., 1990; Schwartz and Lechene, 1992). Furthermore, integrin-dependent regulation of intracellular pH can occur by the Rho GTPase, and is believed to be necessary for Rho-mediated effects on the actin cytoskeleton, focal adhesions, cell adhesion and cell spreading (Tominaga and Barber, 1998).

Integrins also regulate cytosolic calcium levels. Activation of integrins in various cell types results in increased cytosolic Ca^{2+} (Pardi et al., 1989; Ng-Sikorski et al., 1991; Leavesley et al., 1993; Schwartz, 1993). These calcium transits are believed to be mediated by both influx of extracellular calcium as well as release of intracellular calcium stores (Schwartz, 1993; Sjaastad et

al., 1996). These calcium fluxes may activate a positive feedback loop to activate integrins (Sjaastad et al., 1994), and they may also be important for efficient cell migration (Marks et al., 1991; Hendey and Maxfield, 1993; Leavesley et al., 1993). Based on its distribution within a migrating cell (lowest at the leading edge and highest at the cell rear) (Hahn et al., 1992), calcium is believed to regulate proteins responsible for release of the cell rear. Indeed, the calcium-dependent protease calpain is required for efficient migration mediated by either β_1 or β_3 integrins (Huttenlocher et al., 1997), which may be due to its cleavage of such focal adhesion proteins as talin and Src (Schoenwaelder et al., 1997). In addition, inhibition of calcineurin, a Ca^{2+}-calmodulin-dependent protein phosphatase, inhibits neutrophil migration on vitronectin, apparently as a result of inefficient release of the cell rear (Hendey et al., 1992).

Acknowledgments. Research in the authors' laboratory is supported by NIH grants R01GM48050 and R01GM52890. Jun-Lin Guan is an Established Investigator of the American Heart Association. We thank Molly Ingersoll for critical reading of the manuscript.

References

Assoian R.K. (1997). Anchorage-dependent cell cycle progression. J. Cell Biol. 136, 1-4.

Banfic H., Tang X-W., Batty I.H., Downes C.P., Chen C.-S. and Rittenhouse S.E. (1998). A novel integrin-activated pathway forms PKB/Akt-stimulatory phosphatidylinositol 3,4-bisphosphate via phosphatidylinositol 3-phosphate in platelets. J. Biol. Chem. 273, 13-16.

Barry S.T. and Critchley D.R. (1994). The RhoA-dependent assembly of focal adhesions in Swiss 3T3 cells is associated with increased tyrosine phosphorylation and the recruitment of both pp125^{FAK} and protein kinase C-δ to focal adhesions. J. Cell Sci. 107, 2033-2045.

Bergman M., Joukov V., Virtanen I. and Alitalo K. (1995). Over-expressed Csk tyrosine kinase is localized in focal adhesions, causes reorganization of αvβ5 integrin, and interferes with HeLa cell spreading. Mol. Cell. Biol. 15, 711-722.

Berton G., Fumagalli L., Laudanna C. and Sorio C. (1994). β2 interin-dependent protein tyrosine phosphorylation and activation of the FGR protein tyrosine kinase in human neutrophils. J. Cell Biol. 126, 1111-1121.

Black D.S. and Bliska J.B. (1997). Identification of p130^{Cas} as a substrate of Yersinia YopH (Yop51), a bacterial protein tyrosine phosphatase that translocates into mammalian cells and targets focal adhesions. EMBO J. 16, 2730-2744.

Bottazzi M.E. and Assoian R.K. (1997). The extracellular matrix and mitogenic growth factors control G1 phase cyclins and cyclin-dependent kinase inhibitors. Trends Cell Biol. 7, 348-352.

Bourdoulous S., Orned G., MacKenna D.A., Pasqualini R. and Ruoslahti E. (1998). Fibronectin matrix regulates activation of RHO and CDC42 GTPases and cell cycle progression. J. Cell Biol. 143, 267-276.

Burbelo P.D., Miyamoto S., Utani A., Brill S., Yamada K.M., Hall A. and Yamada Y. (1995). p190-B, a new member of the Rho GAP family, and Rho are induced to cluster after integrin cross-linking. J. Biol. Chem. 270, 30919-30926.

Burridge K., Turner C.E. and Romer L.H. (1992). Tyrosine phosphorylation of paxillin and pp125^{FAK} accompanies cell adhesion to extracellular matrix: a role in cytoskeletal assembly. J. Cell Biol. 119, 893-903.

Cary L.A., Chang J.F. and Guan J.-L. (1996). Stimulation of cell migration by overexpression of focal adhesion kinase and its assocation with Src and Fyn. J. Cell Sci. 109, 1787-1794.

Cary L.A., Han D.C., Polte T.R., Hanks S.K. and Guan J.-L. (1998). Identification of p130^{Cas} as a mediator of focal adhesion kinase-promoted cell migration. J. Cell Biol. 140, 211-221.

Chan P.-Y., Kanner S.B., Whitney G. and Aruffo A. (1994). A transmembrane-anchored chimeric focal adhesion kinase is constitutively activated and phosphorylated at tyrosine residues identical to pp125^{FAK}. J. Biol. Chem. 269, 20567-20574.

Chen H.-C. and Guan J.-L. (1994). Association of focal adhesion kinase with its potential substrate phosphatidylinositol 3-kinase. Proc. Natl. Acad. Sci. USA 91, 10148-10152.

Chen Q., Kinch M.S., Lin T.H., Burridge K. and Juliano R.L. (1994). Integrin-mediated cell adhesion activates mitogen-activated protein kinases. J. Biol. Chem. 269, 26602-26605.

Chen H.-C., Appeddu P.A., Isoda H. and Guan J.-L. (1996a). Phosphorylation of tyrosine 397 in focal adhesion kinase is required for binding phosphatidylinositol 3-kinase. J. Biol. Chem. 271, 26329-26334.

Chen Q., Lin T.H., Der C.J. and Juliano R.L. (1996b). Integrin-mediated activation of mitogen-activated protein (MAP) or extracellular signal-related kinase kinase (MEK) and kinase is independent of Ras. J. Biol. Chem. 271, 18122-18127.

Chong L.D., Traynor-Kaplan A., Bokoch G.M. and Schwartz M.A. (1994). The small GTP-binding protein Rho regulates a phosphatidylinositol 4-phosphate 5-kinase in mammalian cells. Cell 79, 507-513.

Chrzanowska-Wodnicka M. and Burridge K. (1996). Rho-stimulated contractility drives the formation of stress fibers and focal adhesions. J. Cell Biol. 133, 1403-1415.

Clark E.A., Shattil S.J., Ginsberg M.H., Bolen J. and Brugge J.S. (1994). Regulation of the protein tyrosine kinase pp72syk by platelet agonists and the integrin αIIbβ3. J. Biol. Chem. 269, 28859-28864.

Clark E.A. and Hynes R.O. (1996). Ras activation is necessary for integrin-mediated activation of extracellular signal-regulated kinase 2 and cytosolic phopholipase A2 but not for cytoskeletal organization. J. Biol. Chem. 271, 14814-14818.

Clark E.A., King W.G., Brugge J.S., Symons M. and Hynes R.O. (1998). Integrin-mediated signals regulated by members of the rho family of GTPases. J. Cell Biol. 142, 573-586.

Crouch D.H., Fincham V.J. and Frame M.C. (1996). Targeted proteolysis of the focal adhesion kinase pp125^{FAK} during c-Myc-induced apoptosis is suppressed by integrin signalling. Oncogene 12, 2689-2696.

de Jong R., van Wijk A., Haataja L., Heisterkamp N. and Groffen J. (1997). BCR/ABL-induced leukemogenesis causes phosphorylation of Hef1 and its association with Crk1. J. Biol. Chem. 272, 32649-32655.

Denu J.M., Stuckey J.A., Saper M.A. and Dixon J.E. (1996). Form and function in protein dephosphorylation. Cell 87, 361-364.

Eide B.L., Turck C.W. and Escobedo J.A. (1995). Identification of Tyr-397 as the primary site of tyrosine phosphorylation and pp60^{src} association in the focal adhesion kinase, pp125^{FAK}. Mol. Cell. Biol.

15, 2819-2827.

Eliceiri B.P., Klemke R., Stromblad S. and Cheresh D.A. (1998). Integrin αvβ3 requirement for sustained mitogen-activated protein kinase activity during angiogenesis. J. Cell Biol. 140, 1255-1263.

Fincham V.J., Unlu M., Brunton V.G., Pitts J.D., Wyke J.A. and Frame M.C. (1996). Translocation of Src kinase to the cell periphery is mediated by the actin cytoskeleton under the control of the Rho family of small G proteins. J. Cell Biol. 135, 1551-1564.

Fincham V.J. and Frame M.C. (1998). The catalytic activity of Src is dispensable for translocation to focal adhesions but controls the turnover of these structures during cell motility. EMBO J. 17, 81-92.

Flinn H.M. and Ridley A.J. (1996). Rho stimulates tyrosine phosphorylation of focal adhesion kinase, p130 and paxillin. J. Cell Sci. 109, 1133-1141.

Frisch S.M., Vuori K., Ruoslahti E. and Chan-Hui P.Y. (1996). Control of adhesion-dependent cell survival by focal adhesion kinase. J. Cell Biol. 134, 793-799.

Fujioka Y., Matozaki T., Noguchi T., Iwamatsu A., Yamao T., Takahashi N., Tsuda M., Takada T. and Kasuga M. (1996). A novel membrane glycoprotein, SHPS-1, that binds the SH2-domain-containing protein tyrosine phosphatase SHP-2 in response to mitogens and cell adhesion. Mol. Cell Biol. 16, 6887-6899.

Fukami K., Furuhashi K., Inagaki M., Endo T., Hatano S. and Takenawa T. (1992). Requirement of phosphatidylinositol 4,5-bisphosphate for α-actinin function. Nature 359, 150-152.

Gao J., Zoller K.E., Ginsberg M.H., Brugge J.S. and Shattil S.J. (1997). Regulation of the pp72syk protein tyrosine kinase by platelet integrin αIIbβ3. EMBO J. 16, 6414-6425.

Garton A.J., Flint A.J. and Tonks N.K. (1996). Identification of $p130^{Cas}$ as a substrate for the cytosolic protein tyrosine phosphatase PTP-PEST. Mol. Cell. Biol. 16, 6408-6418.

Gervais F.G., Thornberry N.A., Ruffolo S.C., Nicholson D.W. and Roy S. (1998). Caspases cleave focal adhesion kinase during apoptosis to generate a FRNK-like polypeptide. J. Biol. Chem. 273, 17102-17108.

Gilmore A.P. and Burridge K. (1996). Regulation of vinculin binding to talin and actin by phosphatidylinositol-4-5-bisphosphate. Nature 381, 531-535.

Gilmore A.P. and Romer L.H. (1996). Inhibition of focal adhesion kinase (FAK) signaling in focal adhesions decreases cell motility and proliferation. Mol. Biol. Cell 7, 1209-1224.

Giuriato S., Payrastre B., Drayer A.L., Plantavid M., Woscholski R., Parker P., Erneux C. and Chap H. (1997). Tyrosine phosphorylation and relocation of SHIP are integrin-mediated in thrombin-stimulated human blood platelets. J. Biol. Chem. 272, 26857-26863.

Guan J.-L. and Shalloway D. (1992). Regulation of focal adhesion-associated protein tyrosine kinase by both cellular adhesion and oncogenic transformation. Nature 358, 690-692.

Guan J.-L., Trevithick J.E. and Hynes R.O. (1991). Fibronectin/integrin interaction induces tyrosine phosphorylation of a 120-kDa protein. Cell Regul. 2, 951-964.

Guinebault C., Payrastre B., Racaud-Sultan C., Mazarguil H., Breton M., Mauco G., Plantavid M. and Chap H. (1995). Integrin-dependent translocation of phosphoinositide 3-kinase to the cytoskeleton of thrombin-activated platelets involves specific interactions of p85a with actin filaments and focal adhesion kinase. J. Cell Biol. 129, 831-842.

Hahn K., DeBiasio R. and Taylor D.L. (1992). Patterns of elevated free calcium and calmodulin activation in living cells. Nature 359, 736-738.

Hall A. (1994). Small GTP-binding proteins and the regulation of the actin cytoskeleton. Annu. Rev. Cell Biol. 10, 31-54.

Hanks S.K., Calalb M.B., Harper M.C. and Patel S.K. (1992). Focal adhesion protein tyrosine kinase phosphorylated in response to cell spreading on fibronectin. Proc. Natl. Acad. Sci. USA 89, 8487-8491.

Hendey B., Klee C.B. and Maxfield F.R. (1992). Inhibition of neutrophil chemokinesis on vitronectin by inhibitors of calcineurin. Science 258, 296-299.

Hendey B. and Maxfield F.R. (1993). Regulation of neutrophil motility and adhesion by intracellular calcium transients. Blood Cells 19, 143-164.

Heraud J.-M., Racaud-Sultan C., Gironcel D., Albiges-Rizo C., Giacomini T., Roques S., Martel V., Breton-Douillon M., Perret B. and Chap H. (1998). Lipid products of phophoinositide 3-kinase and phosphatidylinositol 4',5'-bisphosphate are both required for ADP-dependent cell spreading. J. Biol. Chem. 273, 17817-17823.

Hirao M., Sato N., Kondo T., Yonemura S., Monden M., Sasaki T., Takai Y., Tsukita S. and Tsukita S. (1996). Regulation mechanism of ERM (ezrin/radixin/moesin) protein/plasma membrane association: possible involvement of phosphatidylinositol turnover and Rho-dependent signaling pathway. J. Cell Biol. 135, 37-51.

Hotchin N.A. and Hall A. (1995). The assembly of integrin adhesion complexes requires both extracellular matrix and intracellular rho/rac GTPases. J. Cell Biol. 131, 1857-1865.

Howe A.K and Juliano R.L. (1998). Distinct mechanisms mediate the initial and sustained phases of integrin-mediated activation of the Raf/MEK/Mitogen-activated protein kinase cascade. J. Biol. Chem. 273, 27268-27274.

Howell B.W. and Cooper J.A. (1994). Csk suppression of Src involves movement of Csk to sites of Src activity. Mol. Cell. Biol. 14, 5402-5411.

Hughes P.E., Renshaw M.W., Pfaff M., Forsyth J., Keivens V.M., Schwartz M.A. and Ginsberg M.H. (1997). Suppression of integrin-activation: a novel function of a Ras/Raf-initiated MAP kinase pathway. Cell 88, 521-530.

Hungerford J.E., Compton M.T., Matter M.L., Hoffstrom B.G. and Otey C.A. (1996). Inhibition of $pp125^{FAK}$ in cultured fibroblasts results in apoptosis. J. Cell Biol. 135, 1383-1390.

Huttenlocher A., Palecek S.P., Lu Q., Zhang W., Mellgren R.L., Lauffenburger D.A., Ginsberg M.H. and Horwitz A.F. (1997). Regulation of cell migration by the calcium-dependent protease calpain. J. Biol. Chem. 272, 32719-32722.

Hynes R.O. (1992). Integrins: versatility, modulation and signaling in cell adhesion. Cell 69, 11-25.

Ilic D., Furuta Y., Kanazawa S., Takeda N., Sobue K., Nakatsuji N., Nomura S., Fujimoto J., Okada M., Yamamoto T. and Aizawa S. (1995). Reduced cell motility and enhanced focal contact formation in cells from FAK-deficient mice. Nature 377, 539-544.

Ingber D.E., Prusty D., Frangioni J.V., Cragoe E.J., Lechene C. and Schwartz M.A. (1990). Control of intracellular pH and growth by fibronectin in capillary endothelial cells. J. Cell Biol. 110, 1803-1811.

Janmey P.A., Iida K., Yin H.L. and Stossel T.P. (1987). Polyphosphoinositide micelles and polyphosphoinositide-containing vesicles dissociate endogenous gelsolin-actin complexes and promote actin assembly from the fast-growing end of actin filaments blocked by gelsolin. J Biol. Chem. 262, 12228-12236.

Kaplan K.B., Swedlow J.R., Varmus H.E. and Morgan D.O. (1992). Association of $p60_{c\text{-}src}$ with endosomal membranes in mammalian

fibroblasts. J. Cell Biol. 118, 321-333.

Kaplan K.B., Bibbins K.B., Swedlow J.R., Arnaud M., Morgan D.O. and Varmus H.E. (1994). Association of the amino-terminal half of c-Src with focal adhesions alters their properties and is regulation by phosphorylation of tyrosine 527. EMBO J. 13, 4745-4756.

Kaplan K.B., Swedlow J.R., Morgan D.O. and Varmus H.E. (1995). c-Src enhances the spreading of src$^{-/-}$ fibroblasts on fibronectin by a kinase-independent mechanism. Genes Dev. 9, 1505-1517.

Kapron-Bras C., Fitz-Gibbon L., Jeevaratnam P., Wilkins J. and Dedhar S. (1993). Stimulation of tyrosine phosphorylation and accumulation of GTP-bound p21ras upon antibody-mediated $\alpha 2\beta 1$ integrin activation in T-lymphoblastic cells. J. Biol. Chem. 268, 20701-20704.

Keely P.J. and Parise L.V. (1996). The $\alpha 2\beta 1$ integrin is a necessary co-receptor for collagen-induced activation of Syk and the subsequent phosphorylation of phospholipase $C\gamma 2$ in platelets. J. Biol. Chem. 271, 26668-26676.

Keely P.J., Westwick J.K., Whitehead I.P., Der C.J. and Parise L.V. (1997). Cdc42 and Rac1 induce integrin-mediated cell motility and invasiveness through PI(3)K. Nature 390, 632-636.

Klemke R.L., Cai S., Giannini A.L., Gallagher P.J., Lanerolle P. and Cheresh D.A. (1997). Regulation of cell motility by mitogen-activated protein kinase. J. Cell. Biol. 137, 481-492.

Kornberg L., Earp S.E., Turner C.E., Procktop C. and Juliano R.L. (1991). Signal transduction by integrins: increased protein tyrosine phosphorylation caused by clustering of ß1 integrins. Proc. Natl. Acad. Sci. USA 88, 8392-8396.

Kornberg L., Earp H.S., Parsons J.T., Schaller M. and Juliano R.L. (1992). Cell adhesion or integrin clustering increases phosphorylation of a focal adhesion-associated tyrosine kinase. J. Biol. Chem. 267, 23439-23442.

Kumagai N., Morii N., Fujisawa K., Nemoto Y. and Narumiya S. (1993). ADP-ribosylation of rho p21 inhibits lysophosphatidic acid-induced protein tyrosine phosphorylation and phosphatidylinositol 3-kinase activation in cultured Swiss 3T3 cells. J. Biol. Chem. 268, 24535-24538.

Lassing I. and Lindberg U. (1985). Specific interaction between phosphatidylinositol 4,5-bisphosphate and profilactin. Nature 314, 472-474.

Lauffenburger D.A. and Horwitz A.F. (1996). Cell migration: a physically integrated molecular process. Cell 84, 359-369.

Leavesley D.I., Schwartz M.A., Rosenfeld M. and Cheresh D.A. (1993). Integrin ß1- and ß3-mediated endothelial cell migration is triggered through distinct signaling mechanisms. J. Cell Biol. 121, 163-170.

Levkau B., Herren B., Koyama H., Ross R. and Raines E.W. (1998). Caspase-mediated cleavage of focal adhesion kinase pp125^{FAK} and disassembly of focal adhesions in human endothelial cell apoptosis. J. Exp. Med. 187, 579-586.

Lewis J.M., Baskaran R., Taagepera S., Schwartz M.A. and Wang J.Y.J. (1996). Integrin regulation of c-Abl tyrosine kinase activity and cytoplasmic-nuclear transport. Proc. Natl. Acad. Sci. USA 93, 15174-15179.

Lin T.H., Yurochko A., Kornberg L., Morris J., Walker J.J., Haskill S. and Juliano R.L. (1994). The role of protein tyrosine phosphorylation in integrin-mediated gene induction in monocytes. J. Cell Biol. 126, 1585-1593.

Lin T.H., Rosales C., Mondal K., Bolen J.B., Haskill S. and Juliano R.L. (1995). Integrin-mediated tyrosine phosphorylation and cytokine message induction in monocytic cells. J. Biol. Chem. 270, 16189-16197.

Lin T.H., Aplin A.E., Shen Y., Chen Q., Schaller M., Romer L., Aukhil I. and Juliano R.L. (1997a). Integrin-mediated activation of MAP kinase is independent of FAK: evidence for dual integrin signaling pathways in fibroblasts. J. Cell Biol. 136, 1385-1395.

Lin T.H., Chen Q., Howe A. and Juliano R.L. (1997b). Cell anchorage permits efficient signal transduction between Ras and its downstream kinases. J. Biol. Chem. 272, 8849-8852.

Lipfert L., Haimovich B., Schaller M.D., Cobb B.S., Parsons J.T. and Brugge J.S. (1992). Integrin-dependent phosphorylation and activation of the protein tyrosine kinase pp125^{FAK} in platelets. J. Cell Biol. 119, 905-912.

Liu F., Hill D.E. and Chernoff J. (1996). Direct binding of the proline-rich region of protein tyrosine phosphatase 1B to the src homology 3 domain of p130^{Cas}. J. Biol. Chem. 271, 31290-31295.

Liu F., Sells M.A. and Chernoff J. (1998). Protein tyrosine phosphatase 1B negatively regulates integrin signaling. Curr. Biol. 8, 173-176.

Lowell C.A., Fumagalli L. and Berton G. (1996). Deficiency of Src family kinases p59/61hck and p58c-fgr results in defective adhesion-dependent neutrophil functions. J. Cell Biol. 133, 895-910.

Machesky L.M. and Hall A. (1997). Role of actin polymerization and adhesion to extracellular matrix in Rac- and Rho-induced cytoskeletal reorganization. J. Cell Biol. 138, 913-926.

Marks P.W., Hendey B. and Maxfield F.R. (1991). Attachment to fibronectin or vitronectin makes human neutrophil migration sensitive to alterations in cytosolic free calcium concentration. J. Cell Biol. 112, 149-158.

McNamee H.P., Ingber D.E. and Schwartz M.A. (1993). Adhesion to fibronectin stimulates inositol lipid synthesis and enhances PDGF-induced inositol lipid breakdown. J. Cell Biol. 121, 673-678.

Miyamoto S., Teramoto H., Coso O.A., Gutkind J.S., Burbelo P.D., Akiyama S.K. and Yamada K.M. (1995). Integrin function: molecular hierarchies of cytoskeletal and signaling molecules. J. Cell Biol. 131, 791-805.

Morino N., Mimura T., Hamasaki K., Tobe K., Ueki K., Kikuchi K., Takehara K., Kadowaki T., Yazaki Y. and Nojima Y. (1995). Matrix/integrin interaction activates the mitogen-activated protein kinase, p44erk-1 and p42erk-2. J. Biol. Chem. 270, 269-273.

Nakahara H., Mueller S.C., Nomizu M., Yamada Y., Yeh Y. and Chen W.-T. (1998). Activation of ß1 integrin signaling stimulates tyrosine phosphorylation of p190^{RhoGAP} and membrane-protrusive activities at invadopodia. J. Biol. Chem. 273, 9-12.

Ng-Sikorski J., Andersson R., Patarroyo M. and Andersson T. (1991). Calcium signaling capacity of the CD11b/CD18 integrin on human neutrophils. Exp. Cell Res. 195, 504-508.

Pardi R., Bender J.R., Dettori C., Giannazza E. and Engleman E.G. (1989). Heterogeneous distribution and transmembrane signaling properties of lymphocyte function-associated antigen (LFA-1) in human lymphocyte subsets. J. Immunol. 143, 3157-3166.

Price L.S., Leng J., Schwartz M.A. and Bokoch G.M. (1998). Activation of Rac and Cdc42 by integrins mediates cell spreading. Mol. Biol. Cell 9, 1863-1871.

Reiske H.R., Kao S.-C., Cary L.A., Guan J.-L., Lai J.-F. and Chen H.-C. (1998). Requirement of phosphatidylinositol 3-kinase in focal adhesion kinase-promoted cell migration. (Submitted).

Ren X.-D., Bokoch G.M., Traynor-Kaplan A., Jenkins G.H., Anderson R.A. and Schwartz M.A. (1996). Physical association of the small GTPase Rho with a 68-kDa phosphatidylinositol 4-phosphate 5-kinase in Swiss 3T3 cells. Mol. Biol. Cell 7, 435-442.

Renshaw M.W., McWhirter J.R. and Wang J.Y. (1995). The human

leukemia oncogene bcr-abl abrogates the anchorage requirement but not the growth factor requirement for proliferation. Mol. Cell. Biol. 15, 1286-1293.

Reszka A.A., Bulinski J.C., Krebs E.G. and Fischer E.H. (1997). Mitogen-activated protein kinase/extracellular signal-regulated kinase 2 regulates cytoskeletal organization and chemotaxis via catalytic and microtubule-specific interactions. Mol. Biol. Cell 8, 1219-1232.

Richardson A. and Parsons J.T. (1996). A mechanism for regulation of the adhesion-associated protein tyrosine kinase pp125^{FAK}. Nature 380, 538-540.

Richardson A., Malik R.K., Hildebrand J.D. and Parsons J.T. (1997). Inhibition of cell spreading by expression of C-terminal domain of focal adhesion kinase (FAK) is rescued by coexpression of Src or catalytically inactive FAK: a role for paxillin tyrosine phosphorylation. Mol. Cell. Biol. 17, 6906-6914.

Ridley A.J. and Hall A. (1994). Signal transduction pathways regulating Rho-mediated stress fibre formation: requirement for a tyrosine kinase. EMBO J. 13, 2600-2610.

Rodriguez-Fernandez J.L. and Rozengurt E. (1998). Bombesin, vasopressin, lysophosphatidic acid, and sphingosylphosphorylcholine induce focal adhesion kinase activation in intact Swiss 3T3 cells. J. Biol. Chem. 273, 19321-19328.

Ruoslahti E. and Reed J.C. (1994). Anchorage dependence, integrins, and apoptosis. Cell 77, 477-478.

Sakisaka T., Itoh T., Miura K. and Takenawa T. (1997). Phosphatidylinositol 4,5-bisphosphate phosphatase regulates the rearrangement of actin filaments. Mol. Cell. Biol. 17, 3841-3849.

Salgia R., Uemura N., Okuda K., Li J.L., Pisick E., Sattler M., de Jong R., Druker B., Heisterkamp N. and Chen L.B. (1995). CRKL links p210BCR/ABL with paxillin in chronic myelogenous leukemia cells. J. Biol. Chem. 270, 29145-29150.

Salgia R., Pisick E., Sattler M., Li J.-L., Uemura N., Wong W.-K., Burky S.A., Hirai H., Chen L.B. and Griffin J.D. (1996). p130^{Cas} forms a signaling complex with the adapter protein CRKL in hematopoietic cells transformed by the BCR/ABL oncogene. J. Biol. Chem. 271, 25198-25203.

Schafer D.A., Jennings P.B. and Cooper J.A. (1996). Dynamics of capping protein and actin assembly in vitro: uncapping barbed ends by polyphosphoinositides. J. Cell Biol. 135, 169-179.

Schaller M.D., Borgman C.A., Cobb B.S., Reynolds A.B. and Parsons J.T. (1992). pp125^{FAK}, a structurally distinctive protein tyrosine kinase associated with focal adhesions. Proc. Natl. Acad. Sci. USA 89, 5192-5196.

Schaller M.D., Hildebrand J.D., Shannon J.D., Fox J.X., Vines R.R. and Parsons J.T. (1994). Autophosphorylation of the focal adhesion kinase, pp125^{FAK}, directs SH2-dependent binding of pp60$_{src}$. Mol. Cell. Biol. 14, 1680-1688.

Schlaepfer D.D., Hanks S.K., Hunter T. and van der Geer P. (1994). Integrin-mediated signal transduction linked to ras pathway by Grb2 binding to focal adhesion kinase. Nature 372, 786-791.

Schlaepfer D.D. and Hunter T. (1996). Evidence for *in vivo* phosphorylation of the Grb2 SH2-domain binding site on focal adhesion kinase by Src-family protein-tyrosine kinases. Mol. Cell. Biol. 16, 5623-5633.

Schlaepfer D.D. and Hunter T. (1997). Focal adhesion kinase overexpression enhances Ras-dependent integrin signaling to ERK2/mitogen-activated protein kinase through interaction with and activation of c-Src. J. Biol. Chem. 272, 13189-13195.

Schlaepfer D.D., Broome M.A. and Hunter T. (1997). Fibronectin-stimulated signaling from a focal adhesion kinase-c-Src complex: involvement of the Grb2, p130^{Cas}, and Nck adaptor proteins. Mol. Cell. Biol. 17, 1702-1713.

Schlaepfer D.D., Jones K.C. and Hunter T. (1998). Multiple Grb2-mediated integrin-stimulated signaling pathways to ERK2/mitogen-activated protein kinase: summation of both c-Src- and focal adhesion kinase-initiated tyrosine phosphorylation events. Mol. Cell. Biol. 18, 2571-2585.

Schoenwaelder S.M., Yuan Y., Cooray P., Salem H.H. and Jackson S.P. (1997). Calpain cleavage of focal adhesion proteins regulates the cytoskeletal attachment of integrin αIIbβ3 (platelet glycoprotein IIb/IIIa) and the cellular retraction of fibrin clots. J. Biol. Chem. 272, 1694-1702.

Schwartz M.A. (1993). Spreading of human endothelial cells on fibronectin or vitronectin triggers elevation of intracellular free calcium. J. Cell Biol. 120, 1003-1010.

Schwartz M.A., Both G. and Lechene C. (1989). Effect of cell spreading on cytoplasmic pH in normal and transformed fibroblasts. Proc. Natl. Acad. Sci. USA 86, 4525-4529.

Schwartz M.A., Lechene C. and Ingber D.E. (1991). Insoluble fibronectin activates the Na/H antiporter by clustering and immobilizing integrin α5β1, independent of cell shapte. Proc. Natl. Acad. Sci. USA 88, 7849-7853.

Schwartz M.A. and Lechene C. (1992). Adhesion is required for protein kinase C-dependent activation of the Na^+/H^+ antiporter by platelet-derived growth factor. Proc. Natl. Acad. Sci. USA 89, 6138-6141.

Schwartz M.A., Toksoz D. and Khosravi-Far R. (1996). Transformation by Rho exchange factor oncogenes is mediated by activation of an integrin-dependent pathway. EMBO J. 15, 6525-6530.

Seufferlein T. and Rozengurt E. (1994). Lysophosphatidic acid stimulates tyrosine phosphorylation of focal adhesion kinase, paxillin, and p130. J. Biol. Chem. 269, 9345-9351.

Seufferlein T., Withers D.J., Mann D. and Rozengurt E. (1996). Dissociation of mitogen-activated protein kinase activation from p125 focal adhesion kinase tyrosine phosphorylation in Swiss 3T3 cells stimulated by bombesin, lysophosphatidic acid, and platelet-derived growth factor. Mol. Biol. Cell 7, 1865-1875.

Shaw L.M., Rabinovitz I., Wang H.H., Toker A. and Mercurio A.M. (1997). Activation of phosphoinositide 3-OH kinase by the α6β4 integrin promotes carcinoma invasion. Cell 91, 949-960.

Shen Y., Schneider G., Cloutier J.-F., Veillette A. and Schaller M.D. (1998). Direct association of protein-tyrosine phosphatase PTP-PEST with paxillin. J. Biol. Chem. 273, 6474-6481.

Short S.M., Talbott G.A. and Juliano R.L. (1998). Integrin-mediated signaling events in human endothelial cells. Mol. Biol. Cell 9, 1969-1980.

Sjaastad M.D., Angres B., Lewis R.S. and Nelson W.J. (1994). Feedback regulation of cell-substratum adhesion by integrin-mediated intracellular Ca^{2+} signaling. Proc. Natl. Acad. Sci. USA 91, 8214-8218.

Sjaastad M.D., Lewis R.S. and Nelson W.J. (1996). Mechanisms of integrin-mediated calcium signaling in MDCK cells: regulation of adhesion by IP_3- and store-independent calcium influx. Mol. Biol. Cell 7, 1025-1041.

Skorski T., Bellacosa A., Nieborowska-Skorska M., Majewski M., Martinez R., Choi J.K., Trotta R., Wlodarski P., Perrotti D., Chan T.O., Wasik M.A., Tsichlis P.N. and Calabretta B. (1997). Transformation of hematopoietic cells by BCR/ABL requires activation of a

PI-3k/Akt-dependent pathway. EMBO J. 16, 6151-6161.

Tamura M., Gu J., Matsumoto K., Aota S.-I., Parsons R. and Yamada K.M. (1998). Inhibition of cell migration, spreading and focal adhesions by tumor suppressor PTEN. Science 280, 1614-1617.

Tapon N. and Hall A. (1997). Rho, Rac and Cdc42 GTPases regulate the organization of the actin cytoskeleton. Curr. Opin. Cell Biol. 9, 86-92.

Thomas S.M. and Brugge J.S. (1997). Cellular functions regulated by Src family kinases. Annu. Rev. Cell Dev. Biol. 13, 513-609.

Tominaga T. and Barber D.L. (1998). Na-H exchange acts downstream of RhoA to regulate integrin-induced cell adhesion and spreading. Mol. Biol. Cell 9, 2287-2303.

Tonks N.K. and Neel B.G. (1996). From form to function: signaling by protein tyrosine phosphatases. Cell 87, 361-364.

Tsuda M., Matozaki T., Fukunaga K., Fujioka Y., Imamoto A., Noguchi T., Takada T., Yamao T., Takeda H., Ochi F., Yamamoto T. and Kasuga M. (1998). Integrin-mediated tyrosine phosphorylation of SHPS-1 and its association with SHP-2. J. Biol. Chem. 273, 13223-13229.

Wang J.Y. (1993). Abl tyrosine kinase in signal transduction and cell-cycle regulation. Curr. Opin. Genet. Dev. 3, 35-43.

Wary K.K., Mainiero F., Isakoff S.J., Marcantonio E.E. and Giancotti F.G. (1996). The adaptor protein Shc couples a class of integrins to the control of cell cycle progression. Cell 87, 733-743.

Wei J., Shaw L.M. and Mercurio A.M. (1998). Regulation of mitogen-activated protein kinase activation by the cytoplasmic domain of the α6 integrin subunit. J. Biol. Chem. 273, 5903-5907.

Wen L.-P., Fahrni J.A., Troie S., Guan J.-L., Orth K. and Rosen G.D. (1997). Cleavage of focal adhesion kinase by caspases during apoptosis. J. Biol. Chem. 272, 26056-26061.

Xu L.-H., Owens L.V., Sturge G.C., Yang X., Liu E.T., Craven R.J. and Cance W.G. (1996). Attenuation of the expression of the focal adhesion kinase induces apoptosis in tumor cells. Cell Growth Diff. 7, 413-418.

Yan S.R., Huang M. and Berton G. (1997). Signaling by adhesion in human neutrophils: activation of the p72syk tyrosine kinase and formation of protein complexes containing p72syk and Src family kinases in neutrophils spreading over fibrinogen. J. Immunol. 158, 1902-1910.

Yu D.-H., Qu C.-K., Henegariu O., Lu X. and Feng G.-S. (1998). Protein-tyrosine phosphatase Shp-2 regulates cell spreading, migration, and focal adhesion. J. Biol. Chem. 273, 21125-21131.

Zhang Q., Checovich W.J., Peters D.M., Albrecht R.M. and Mosher D.F. (1994). Modulation of cell surface fibronectin assembly sites by lysophosphatidic acid. J. Cell Biol. 127, 1447-1459.

Zhang Z., Vuori K., Wang H.-G., Reed J.C. and Ruoslahti E. (1996). Integrin activation by R-Ras. Cell 85, 61-69.

Zhang Q., Magnusson M.K. and Mosher D.F. (1997). Lysophosphatidic acid and microtubule-destabilizing agents stimulate fibronectin matrix assembly through Rho-dependent actin stress fiber formation and cell contraction. Mol. Biol. Cell 8, 1415-1425.

Zhao J.-H., Reiske H. and Guan J.-L. (1998). Regulation of the cell cycle by focal adhesion kinase. J. Cell Biol. (In press).

Zheng L., Sjolander A., Eckerdal J. and Andersson T. (1996). Antibody-induced engagement of ß2 integrins on adherent human neutrophils triggers activation of p21ras through tyrosine phosphorylation of the protooncogene *Vav*. Proc. Natl. Acad. Sci. USA 93, 8431-8436.

Zhu X. and Assoian R.K. (1995). Integrin-dependent activation of MAP kinase: a link to shape-dependent cell proliferation. Mol. Biol. Cell 6, 273-282.

Accepted February 5, 1999