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Review

Clinical significance of FAK expression in human neoplasia

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Summary. Focal Adhesion Kinase is a 119-121 kDa nonreceptor protein kinase widely expressed in various tissues and cell types. Several studies showed that FAK plays an important role in integrin signaling. Once activated by integrin and non-integrin stimuli, it binds and activates several other molecules, such as Src, $p130^{Cas}$, Grb2, PI3K and paxillin, thus promoting signaling transduction. In normal cells FAK activity is under constant regulation by mechanisms such as gene amplification, alternative splicing and action of phosphatases. On the contrary, *in vitro* studies showed that in transformed cells unopposed FAK signaling promoted cancer cells' malignant characteristics. FAK was held responsible for cancer cells' uninhibited proliferation, protection from apoptosis, invasion, migration, adhesion and spreading, as well as tumor angiogenesis. Several *in vivo* studies supported the above observations and further correlated FAK expression with various clinicopathological parameters of several types of human malignancies. The purpose of this article is a comprehensive review of the existing data on FAK expression and signaling and their clinical significance in human malignancy.

Key words: FAK, Cancer, Human, Prognosis

Index: AML: acute myeloid leukemia, BCR: B cell receptor, CCK2R: cholecystokinin-2 receptor, Cdk: Cyclin-dependent kinase, Cdki: cyclin-dependent kinase inhibitor, CML: chronic myelogenous leukemia, DAP: death-associated protein, DH: Dbl homology, DISC: death-inducing signaling complex, ECM: Extracellular matrix, EGF: Epidermal Growth Factor, Erk: Extracellular-regulated kinase, FADD: Fas-associated protein with death domain, FAK: Focal Adhesion Kinase, FAs: Focal Adhesions, FAT: Focal Adhesion Targeting, FIP: FAK inhibitory protein, FRNK: FAK-related non-kinase, GnRHa: Gonadotropin releasing hormone analogue, GSK3ß: glucogen synthetase kinase-3 type-ß, HCC: hepatocellular carcinoma, HGF: Hepatocyte Growth Factor, JNK: Janus Kinase, KLF8: Kruppel-like factor-8, LMW-PTP: low molecular weight tyrosine phosphatase, MAP: Mitogen-activated protein, MLC: regulatory light chain of myosin II, MMPs: Metalloproteinases, NSCLC: non-small-cell lung carcinoma, PDGF: Platelet-Derived Growth Factor, PH domain: pleckstrin homology domain, PIN: Prostate Intraepithelial Neoplasia, PI3K: phosphatidylinositol-3-hydroxyl kinase, PIP3: phosphatidylinositol-3,4,5-triphosphate, PKC: Protein Kinase C, PLA2: phospholipase-A2, PLC: Phospholipase C, PCR: Polymerase Chain Reaction, PTP-PEST: p130Cas and paxillin-associated PTP, PTEN: Phosphatase and Tensin homologue deleted on chromosome 10, PTKs: Protein Tyrosine Kinases, RIP: Receptor-Interacting Protein, ROK: Rho-kinase (or Rac or ROCK): Rho-associated coil-coil forming protein kinase, SCC: squamous cell carcinoma, SCLC: small-cell lung carcinoma, SHP2: SH-2 containing tyrosine phosphatase-2, siRNA: silence RNA, STAT3: Signal Transducer and Activator of Transcription-3, STP1: serine/threonine protein phosphatase type-1, SUMO: Small Ubiquitin-related Modifier, TNF: Tumor Necrosis Factor, TRAF: TNF receptor associated factor, UPA: Urokinase Plasminogen Activator, VEGF: Vascular Endothelial Growth Factor.

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Introduction

Focal adhesion kinase (FAK) was first described in 1992 as a member of the protein tyrosine kinases (PTKs) family and particularly of the nonreceptor PTKs subfamily (Hanks et al., 1992; Lipfert et al., 1992;

Zachary et al., 1992). FAK was originally identified as a protein that is highly tyrosine phosphorylated in chicken embryo fibroblasts transformed with the v-srs oncogene (Zachary, 1997). The cDNA of FAK encodes a protein with a predicted molecular weight of 119-121 kDa depending on different species, though on the basis of its migration in gels it is known as p125FAK (Zachary, 1997).

FAK is expressed in a variety of species, including human, rodent, chicken, frog, Drosophila and Xenophus, indicating that it is evolutionarily conserved (Cary and Guan, 1999; Schlaepfer et al., 1999). It has been mapped on mouse chromosome 15 and human chromosome 8 (Zachary, 1997). FAK is widely expressed in various tissues and cell types such as mesenchymal cells, neuronal cells, platelets, lymphocytes and erythrocytes (Schaller and Parsons, 1994; Zachary, 1997), while macrophages and mast cells appear to express little FAK (Schaller and Parsons, 1994).

Many studies showed that FAK plays an important role as an early key modulator in the integrin signaling cascade. Integrins are a family of transmembrane receptors which, apart from linking extacellular matrix (ECM) proteins with actin cytoskeleton and thus regulating cell shape, can initiate signal transduction that affects many cellular functions (Coppolino and Dedhar, 2000). Integrin clustering results in FAK autophosphorylation and the binding of the Src, another kinase that phosphorylates FAK at several domains potentiating its kinase activity. The FAK/Src complex binds and phosphorylates many downstream molecules, transducing signaling by distinct, complex pathways that interact with each other. Signaling through FAK regulates various basic cellular functions, such as cell proliferation and growth, protection from apoptosis, adhesion and spreading, invasive and migration properties. Thus, by modulating cell phenotype, FAK participates in many cellular processes, such as platelet aggregation (Malarkey et al., 1995), endothelial cell migration (Kaczmarek et al., 2005), neuronal signaling (Siciliano et al., 1996), trophoblast development (MacPhee et al., 2001), embryogenesis and morphogenesis (Lu et al., 1995; Sorenson and Sheibani, 1999; Sorenson and Sheibani, 2002). The hypothesis that FAK signaling is uncontroled in transformed cells and thus promotes their malignant phenotypic characteristics has been thoroughly studied. FAK has been held responsible for the malignant cells' uninhibited proliferation, resistance to apoptosis and their ability to survive under anchorage-independent conditions, increasing in this way their invasiveness and migration capability. All these are components of the malignant phenotype, which promote tumor growth, progression and metastasis, as well as the resistance to chemotherapy or radiotherapy. Finally, FAK signaling has been implicated in neoangiogenesis, which is also very important for tumor growth and cancer progression.

The purpose of this review is to analyze the data existing on FAK expression and signaling and their possible clinical significance in human malignancy. Since FAK uncontroled signaling participates in cancer pathophysiology, modulation of its action could be a potential target for future cancer therapeutics.

FAK molecule and its function

Surrounding, structure and related molecules

A feature of FAK is its subcellular localization to specialized submembranous structures called focal adhesions (FAs) (Zachary, 1997). FAs are large integrin-based multiprotein complexes that mediate strong cell-substrate adhesion and transmit information in a bidirectional manner between extracellular molecules and cytoplasm (Cukirman et al., 2001). They consist of integrins, integrin-associated adaptor and signaling proteins, such as FAK, Src, Grb2, $p130^{Cas}$, paxillin, vinculin, tensin, growth factor receptors and their related downstream targets (Cukirman et al., 2001; Hehlgans et al., 2007). Cell adhesion molecules of the integrin family consist of 18 α and ß subunits which form 24 known αß-heterodimers depending on cell type and function (Hehlgans et al., 2007). Integrins are the main receptors for ECM proteins, such as fibronectin, collagen and laminin. Each one has a large extracellular, a short transmembrane and a small intracellular domain. FAK is reported to bind the intracellular regions of ß-integrin subunits (Brunton et al., 2004).

FAK is unique among PTKs in comprising of a central catalytic (kinase) domain flanked by two very large non-catalytic regions consisting of approximately 400 amino acids each (Schaller and Parsons, 1994), the NH_2-terminal region, which has homology with the band 4.1 protein as well as with ezrin, radixin and moesin and thus is called FERM domain (Schlaepfer et al., 2004; Cox et al., 2006) and the COOH-terminal region. Neither exhibit significant homologies with motifs in the non-catalytic regions of other PTKs (Zachary, 1997). Unlike many other PTKs, FAK does not have SH2 or SH3 domains, but it does have SH2 and SH3 domain-interacting phosphotyrosines and proline-rich regions respectively (Cary and Guan, 1999), by which, when activated, it interacts with various proteins (Fig. 1).

The kinase domain at the center of FAK molecule includes the tyrosine 576 and 577 domains, which are phosphorylated by Src and positively regulate FAK kinase activity (Cary and Guan, 1999).

The three most important ligands and downstream effectors of activated FAK are Src, p130Cas and paxillin. Association of FAK with Src family members has been demonstrated *in vivo* and *in vitro*. The outcome of Src binding to FAK is the phosphorylation of several tyrosine residues in FAK and FAK-associated proteins. FAK tyrosine sites that are phosphorylated by Src are tyrosines 407, 576, 577, 861 and 925. The phosphorylation of tyrosines 576 and 577 in the kinase domain of FAK positively regulates FAK catalytic

activity. The roles of tyrosines 407 and 861 phosphorylation are not clear, but are suggested to mediate binding to SH2 domains based on neighboring residues (Cary and Guan, 1999; Schlaepfer et al., 2004). Another study suggested that phosphorylation of tyrosine 861 by Src takes part in the regulation of $\alpha_v\beta_5$-FAK association in the retinal pigment epithelium during the phagocytosis of integrin-bound photoreceptors (Finnemann, 2003). Finally, phosphorylation of tyrosine 925 has been mapped as a binding site for the SH2 domain of the Grb2 adaptor protein, which is believed to partially mediate activation of Extracellular-regulated kinase (Erk) family of Mitogen Activated Protein (MAP) kinases.

An important role has been demonstrated for p130Cas in integrin signaling tranduction pathways (Cary and Guan, 1999). Integrin activation induces tyrosine phosphorylation of p130Cas on varius ECM proteins, as well as in cells activated by anti-integrin antibodies. Although FAK does phosphorylate $p130^{Cas}$ directly, this event allows for Src binding to $p130^{Cas}$ and subsequently the complete phosphorylation of $p130^{Cas}$ at sites in the substrate domain. This model predicts that integrin-mediated phosphorylation of $p130^{Cas}$ by the FAK/Src complex results in its association with Crk (Schlaepfer et al., 1999). Additionally, Brabek et al. showed that increased $p130^{Cas}$ expression leads to elevated phosphorylation of FAK and paxillin and that this ability of $p130^{Cas}$ is dependent on the substrate domain YxxP tyrosine phosphorylation site, suggesting that p130Cas may act both upstream and downstream of FAK to promote invasive behavior (Brabek et al., 2004, 2005).

Paxillin was first identified as a cytoskeletal protein with increased tyrosine phosphorylation in v-Src transformed fibroblasts, which occurs concomitantly with FAK upon integrin activation (Cary and Guan, 1999). Due to its lack of enzymatic activity, paxillin is generally believed to act as a scaffolding protein in FAs by mediated interactions with other signaling and/or cytoskeletal proteins. The role of FAK association with paxillin remains unclear. Significant data exist suggesting that FAK localization to FAs is mediated by binding to paxillin through FAT domain (Zachary, 1997; Cary and Guan, 1999; Schlaepfer et al., 1999), thus, in this model, paxillin is upstream of FAK. The only data which sheds doubt on this model, is that a FAK construct with a C-terminal epitope tag is localized to FAs and does not bind paxillin, but it is possible that this interaction is only distabilized by this epitope tag (Cary and Guan, 1999). However, a number of studies suggest that paxillin may also be a downstream mediator of FAK signaling transduction pathways. It is believed that paxillin phosphorylation occurs in a FAK-dependent manner, as it occurs concomitantly with FAK. Indeed, increased tyrosine phosphorylation of paxillin has been

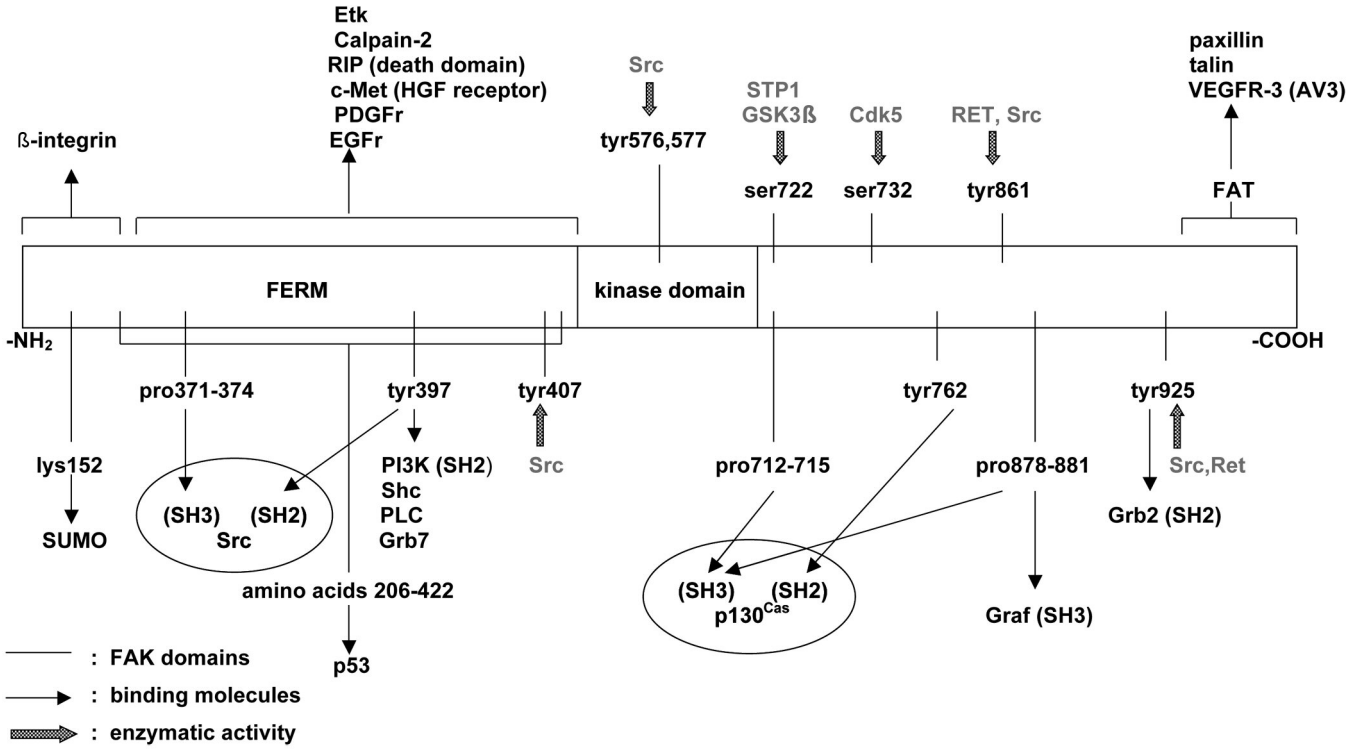

Fig. 1. FAK and interacting molecules

demonstrated in CEF cells overexpressing FAK. However, several lines of evidence suggest that Src rather than FAK is responsible for paxillin phosphorylation. *In vitro* and *in vivo* studies showed that phosphorylation of paxillin at tyrosine 118 by FAK or by Src is necessary for the creation of a binding site for the Crk SH2 domain. Recently, a direct interaction between paxillin and PTP-PEST (p130Cas and paxillin-associated PTP) has been demonstrated. Dephosphorylation of paxillin and/or associated proteins by this phosphatase was suggested as an important regulatory mechanism of paxillin-mediated signaling pathways. Another possible consequence of paxillin phosphorylation is the regulation of the actin cytoskeleton (Guan, 1997), as paxillin phosphorylation was shown to lead to vinculin binding, resulting in the altering of the vinculin's actin-binding site.

Activation

Initially, FAK was shown to be activated by integrins (Schlaepfer et al., 1999). Integrin clustering after binding of their ligament or integrin cytoplasmic domain conformation and alterations may promote the binding of the FERM domain of FAK to the tail of a ß-integrin or another ligand, thus exposing tyrosine 397. These FAK conformational changes can lead to the unmasking of the FAK active site and/or allow the catalytic domain to adapt active conformation. This would permit transphosphorylation of FAK at tyrosine 397 and the subsequent recruitment of Src, resulting in the phosphorylation of tyrosines 576 and 577 in the FAK activation loop and full catalytic FAK activation.

At least four integrin heterodimers can trigger FAK phosphorylation (Schaller and Parsons, 1994). Direct binding of FAK to ß-integrin cytoplasmic tails has been demonstrated in an *in vitro* system (Cary and Guan, 1999), however concerns are raised whether this interaction is sufficient for FAK activation. Indirect association of FAK with the ß-integrin through talin is believed to be the most likely model based on several observations.

Additionally, FAK has been shown or proposed to be activated directly or indirectly by a number of other cellular stimuli, substances, receptors and under various pathological conditions, able to generate signals through either G-protein linked receptors, transmembrane growth factor receptors or through unknown mechanisms (Table 1).

In 1999 a model was proposed by Rodrigues-Fernandez to explain FAK activation by integrin and non-integrin stimuli as a whole (Rodriguez-Fernandez, 1999). According to this model FAK activation depends on integrin adhesion receptor clustering. The receptor clustering can be produced in a variety of ways. Neuropeptides, bioactive lipids and growth factors, through their receptors, as well as neurotoxins, act through Rho GTPase and its downstream targets, serine/threonine protein kinase ROK (Rho-kinase) (or ROCK, Rho-associated coiled-coil forming protein kinase, or Pac) (Imamura et al., 2000), regulatory light chain of myosin II (MLC) and myosin-associated MLC-phosphatase (Kimura et al., 1996; Essler et al., 1998; Rozengurt et al., 2002), resulting in integrin adhesion receptor clustering and thus FAK activation.

FAK signaling in malignant cells

FAK signaling regulates a wide number of cellular activities through various thickened and complex downstream cascades. Essential for the selection of the way the signal transduction will follow is the dynamic balance between FAK phosphorylation and de-phosphorylation.

FAK stimulation occurs transiently in normal cells and FAK activity is under continuous regulation by mechanisms such as gene amplification, alternative splicing, action of phosphatases, like the SH2-containing tyrosine phosphatase 2 (SHP2) (Manes et al., 1999; Vadlamudi et al., 2002; Schlaepfer et al., 2004; Wang et al., 2005), low molecular weight tyrosine phosphatase (LMW-PTP) (Schlaepfer et al., 2004) and phosphatase and tensin homologue deleted on chromosome 10 (PTEN), also called MMAC1 or TEP1 (Davies et al., 1998; Gu et al., 1998; Tamura et al., 1998, 1999a,b,c; Park et al., 2002; Zhang et al., 2004) and other enzymes, glycogen synthetase kinase 3 type ß (GSK3ß) and serine/threonine protein phosphatase type 1 (STP1) (Cox et al., 2006).

With respect to malignant cells, some evidence has been presented rendering FAK an important regulator of the malignant phenotype. FAK was found overexpressed in a variety of malignancies, but FAK expression alone is not sufficient to transform cells (Westhoff et al., 2004). Additionally, in v-Src transformed cells, FAK tyrosine phosphorylation levels were significantly elevated even in cells deprived of integrin-generated adhesion signals (Schlaepfer et al., 1999), while FAK phosphorylation by v-Src occured at sites other than tyrosine 397 and led to FAK degredation and subsequent cell rounding and detachment (Malik and Parsons, 1996). It is believed that altered FAK signaling promotes cancer cells' malignant characteristics, more specifically enables cancer cells' uninhibited proliferation and survival under anchorage-independent conditions, increasing their ability to migrate and metastasize. In the following paragraphs several data will be presented that increased signaling downstream of FAK promoted the malignant phenotype. Interestingly, evidence also exists that inhibition of FAK signaling was responsible for the induction of the malignant phenotypic characteristics (Lu et al., 2001). One explanation for this seemingly contradictory role of FAK is provided by the concept of the dynamic regulation of FAK phosphorylation and dephosphorylation cycles during cell movement (Mitchinson and Cramer, 1996; Lu et al., 2001). The initial dephosphorylation of FAK results in loose attachments of cells, giving them the ability to initiate

motility, while the subsequent reattachment of cells on the ECM restores FAK phosphorylation through integrin activated signaling.

Although FAK signaling cascades are complex and interact with each other, a simple approach can be achieved by categorizing them based on their final outcome.

Proliferation

FAK contributes to uninhibited proliferation of cancer cells mainly though the Erk signaling pathway. It has been shown that FAK phosphorylation at tyrosine 397 leads to the binding of Src and the consequent phopshorylation of the Grb2-binding site at tyrosine 925. Then the FAK/Grb2 complex binds Shc and partially activates Erk2 (P42 MAP kinase) through MEK activation by the Sos/Ras/Raf1 complex (Cary and Guan, 1999; Schlaepfer et al., 1999). Erk2 phosphorylates Ets transcription factors and induces the transcription of cyclin-D1, thus promoting cell proliferation (Cox et al., 2006). Erk2 activation through MEK and Sos/Ras/Raf1 complex can also be induced by Nck. Activated FAK binds $p130^{Cas}$ leading to the activation of Crk and the subsequent activation of Nck (Cary and Guan, 1999; Schlaepfer et al., 1999). Phosphatidylinositol-3-hydroxyl kinase (PI3K) activation by FAK and the subsequent activation of Rap1 and Raf also leads to Erk activation (Sheta et al., 2000). It should be emphasized that one distinguishing feature between integrin receptor- and growth factor receptor-stimulated Erk2 activation events is that the integrin signals are dependent upon the integrity of the actin cytoskeleton, whereas growth factor receptor PTKs can signal to Erk2 in the presence of cytochalasin-D (Schlaepfer et al., 1999). In a study on human

Table 1. Non-integrin stimuli activating FAK.

Neurotransmitters	
Glutamate	Siciliano et al., 1996; Millan et al., 2001
Acetylcholine	Tanaka and Nishizuka, 1994
Anandamide	Derkinderen et al., 1996
Neuromedin-B	Tsuda et al., 1997
Neurotensin	Lee et al., 2001; Magazin et al., 2004
Bombesin	Duncan et al., 1996; Aprikian et al., 1997; Lee et al., 2001; Lacoste et al., 2005
Growth factors and their receptors	
TGF-ß	Wang et al., 2004; Horowitz et al., 2007
Insulin-like growth factor-I	Leventhal et al., 1997; Casamassima et al., 1998; Tai et al., 2003; Qiang et al., 2004
Fibroblast growth factor-2	Korah et al., 2004
Vascular endothelial growth factor	Chevalier et al., 2002
Epidermal growth factor	Brunton et al., 1997; Meierjohann et al., 2006
Hepatocyte growth factor and its receptor c-Met	Pongchairerk et al., 2005; Chen and Chen, 2006
Hepatocyte growth factor/scatter factor	Matsumoto et al., 1994
Proepithelin	Monami et al., 2006
Cytokines	
CD151	Kohno et al., 2002
CD44	Li et al., 2001
IL-15	Budagian et al., 2004
IL-8	Lee et al., 2004
TNFα	Mon et al., 2006
Hormones and their receptors	
Gastrin	Yu et al., 2004; Yu et al., 2006
Gastrin-releasing peptide	Glover et al., 2004
Estrogen receptors	Planas-Silva et al., 2006
Testosterone receptors	Papakonstanti et al., 2003
LH receptors	Mizutani et al., 2006
Conditions	
Pressure	Basson et al., 2000; Thamilselvan and Basson, 2004; Thamilselvan and Basson, 2005
Hypoosmotic stress	Kim et al., 2001
Hydrogen peroxide	Sonoda et al., 1997; Sonoda et al., 1999
Ionizing radiation	Beinke et al., 2003

glioblastoma cells it was shown that FAK overepression *in vivo* promoted Erk activity and increased the transcription of the Kruppel-like factor 8 (KLF8), which directly activated cyclin-D1 transcription and thus promoted cell proliferation (Cox et al., 2006). Furthermore, Graf activation by the FAK/Src complex might lead to cell proliferation, since Graf is believed to be a substrate of MAP kinase, suggesting that it may respond to mitogenic or other stimuli (Cary and Guan, 1999). Additionally, the FAK-induced activation of the Signal Transducer and Activator of Transcription-3 (STAT3) by Etk has also been held responsible for uninhibited cancer cell proliferation (Tsai et al., 2000; Chen et al., 2001). Furthermore, FAK phosphorylation at tyrosine 397 has been shown to preceed hepatoma cell proliferation through the PI3K/Akt/AP1 signaling pathway (Kim et al., 2001), one that has been confirmed by other studies (Reddy et al., 1997; Dong et al., 1999; Almeida et al., 2000). Finally, FAK overexpression was suggested to decrease the expression of the cyclin-dependent kinase inhibitors (CDKI) $p27^{Kip1}$ and $p21^{Waf1}$, by regulating the proteins' turnover, and increase cyclin-D1 and -E expression, leading to uninhibited cell proliferation (Ding et al., 2005; Bryant et al., 2006; Cox et al., 2006).

Invasion

Cancer cells can invade three-dimensional matrices by two distinct mechanisms, the mesenchymal-like and the amoeboid-like invasion. During the mesenchymal-like, FAK-induced Erk activation through $p130^{Cas}$, Grb2 (Cary and Guan, 1999; Schlaepfer et al., 1999) and PI3K (Sheta et al., 2000) has a central role. Erk2 has been held responsible for μ-calpain secretion (Sawhney et al., 2006) and the Janus Kinase (JNK)-induced secretion of the matrix metalloproteinase (MMP)-9, MMP-2 and urokinase plasminogen activator (uPA) leading to enhanced proteolytic activity and consequent cell invasion (Hu et al., 2006; Mitra and Schlaepfer, 2006). PI3K activation has also been shown to induce MMPs secretion through another pathway. The study of Zeng et al. presented data showing that FAK-induced PI3K activation led to PIP3 formation (Zeng et al., 2006), which in turn activated Protein Kinase C (PKC) resulting in MMP-1 secretion and cancer cell invasion (Toker et al., 1994).

On the contrary, evidence was presented that 'mesenchymal to amoeboid' transition was associated with weakened integrin-dependent adhesion, consistently reduced cell surface expression of the alpha-2-beta-1 integrin collagen receptor and impaired downstream signalling, as judged by reduced autophosphorylation of FAK (Carragher et al., 2006). Additionally, distinct from mesenchymal invasion, amoeboid invasion is independent of intracellular calpain-2 proteolytic activity, which is usually needed for turnover of integrin-linked adhesions during two-dimensional planar migration. Moreover, an inhibitor of Rho/ROCK signalling, which specifically impaired amoeboid-like invasion, restored the cell surface expression of alpha-2-beta-1 integrin, downstream FAK autophosphorylation and calpain-2 sensitivity-features of mesenchymal invasion.

Protection from apoptosis

One of the most important effects of FAK in malignant cells is the protection from apoptosis. In several studies FAK has been demonstrated to protect cells from a form of apoptosis known as anoikis, which is induced by cell detachment from the ECM (Hungerford et al., 1996; Cary and Guan, 1999), while De Belle et al. showed that human HT1080 fibrosarcoma cells were able to escape apoptosis after irradiation due to a combination of Erg1-dependent effects (Erg1 is a tumor suppressor-like gene that is found to induce apoptosis in some cells and in others to counteract apoptosis), including high levels of FAK (De Belle et al., 1999).

Recent evidence suggested that FAK prevents apoptosis through a pathway involving phospholipase A2 (PLA2) and PKC, although the exact way is not clear (Cary and Guan, 1999). Another proposed way for this effect of FAK is through p53 downregulation. FAK-induced activation of Erk (Cary and Guan, 1999; Schlaepfer et al., 1999) resulted in JNK activation, which further downregulated p53 and thus protected the cell from anoikis (Almeida et al., 2000; Van Nimwegen et al., 2007). Supporting this are the results of Golubovskaya et al. showing that FAK and p53 were directly associated *in vitro* and *in vivo* (Golubovskaya et al., 2005). More specifically, the N-terminal transactivation domain of p53 and the N-terminal amino acids 206-422 of FAK participated in this interaction. Erk could also be activated by the FAK/PI3K/Rap1/Raf signaling pathway (Sheta et al., 2000), while Raf protected the cell from apoptosis also in a direct way (Hood et al., 2003). Further, Wang et al. presented data showing that FAK activation blocked death associated protein (DAP) kinase-induced upregulation of p53, thus preventing anoikis (Wang et al., 2002). Another pathway involves the activation of c-Myc and STAT3 (Westhoff et al., 2004). The role of STAT3 was also investigated by Tsai et al., who suggested the existence of a signaling pathway upstream of STAT3, essential for v-Src malignant transformation (Tsai et al., 2000). It was shown that v-Src activated Etk, a member of the Btk nonreceptor tyrosine kinase family, through an interaction between the pleckstrin homology (PH) domain of Etk and the FERM domain of FAK (Chen et al., 2001), which in turn activated STAT3.

Finally, a study on the effect of FAK in Tumor Necrosis Factor (TNF)-α-induced apoptosis in embryonic fibroblasts suggested that after TNF-α receptor activation, FAK interacted with Receptor-Interacting Protein (RIP), acting as a bridge linking TRAF2 to RIP, which led to the activation of NFκB, leading to the formation of the protein complex I and cell survival. On the contrary, in the absence of FAK,

RIP interacted with FADD and procaspase-8, leading to the formation of protein complex II, or death-inducing signaling complex (DISC) and cell apoptosis (Takahashi et al., 2007).

Migration

Since cancer cells survive the apoptotic stimuli, they can migrate to distant sites and form metastases. Perhaps the best defined role of FAK in integrin-mediated cellular functions is the promotion of cell migration through its promotion of membrane protrusion and FA turnover (Cary and Guan, 1999; Cox et al., 2006). FAK is believed to regulate cell migration through at least two distinct pathways: one involving the tyrosine phosphorylation of FAK-associated $p130^{Cas}$ by Src, and the consequent Crk/DOCK180/Rac activation and lamellipodia formation (Kiyokawa et al., 1998; Mitra and Schlaepfer al., 2006; Van Nimwegen et al., 2007), and the other involving a pathway initiated by the PI3K kinase binding to FAK and the downstream action of Akt and S6K serine/threonine kinases (Guan, 1997; Cary and Guan, 1999). Rac could also be activated by another pathway involving PI3K (Das et al., 2000; Chang et al., 2007). Upon stimulation of the cell by engagement of mitogenic receptors PI3K is activated, leading to a reduction in the inhibitory PI3K substrate and an increase in activating PI3K products. This change favors the association of PI3K products with the PH domain of Vav. Upon binding of the PI3K product to Vav, the affinity of the PH domain for the Dbl homology (DH) domain is lessend, allowing the tyrosine phosphorylation of Vav by the Lck-related tyrosine kinase, which further lessens the affinity of the PH domain for the DH domain. This permits the binding and the consequent activation of Rac to the DH domain. A third pathway for the activation of Rac is through ßPIX (Chang et al., 2007). FAK associates with and tyrosine phosphorylates ßPIX, which then exhibits increased binding to Rac. This leads to Rac activation and its targeting to FAs, mediated by the specific intramolecular binding interaction between the ßPIX SH3 domain and the proline rich sequence near the COOH-terminus of Rac (Ten Klooster et al., 2006). Calpain-2 secretion and the subsequent FA turnover due to Erk activation, which is a known downstream effector of FAK's interaction with $p130^{Cas}$, Grb2 (Cary and Guan, 1999; Schlaepfer et al., 1999) and PI3K (Sheta et al., 2000), also leads to cancer cell migration (Brunton et al., 2004; Westhoff et al., 2004). Another pathway leading to cell migration is that involving Etk. Etk is activated by its direct binding to FAK (Chen et al., 2001). Then, Etk binds and activates Pak1, which is also a downstream target of Rac, inducing cell migration (Kiosses et al., 1999; Kiosses et al., 2002).

Studies on colon and lung cancer cells suggested that FAK has an important role in adhesion changes associated with the epithelial to mesenchymal transition in cancer cells, with consequent migrative capabilities (Avizienyte and Frame, 2005). In cancer cells, elevated Src activity resulted in the activation of integrins and FAK signaling, which led to the internalization of E-cadherin and the suppression of cell-to-cell adhesion. Additionally, peripherally localized activated Src caused integrins to interact with ECM, leading to the phosphorylation of FAK. Downstream signaling events resulted in the activation of Erk, MLCK and P-MLC, which correlated with disorganization of the cadherin-mediated cell-to-cell contacts and epithelial cell migration. Furthermore, downregulation of paxillin and FAK and peripheral activation of Rac1 led to the same outcome.

Adhesion and spreading

FAK has also been shown to regulate cells' adhesion and spreading, a process which is very important in the last step of the metastasis formation, as well as for the local progression of cancer. Brunton et al. showed that FAK mediates the formation of integrin-dependent adhesions of colon carcinoma cells to ECM proteins (Brunton et al., 2001). It was shown that FAK tyrosine 397 phosphorylation and the subsequent activation of the Erk signaling pathway were essential for the formation of cell adhesions to ECM, as FAK mutants on tyrosine 397 and treatment with Erk inhibitors caused a significant reduction in adhesion formation. FAK activation was a crucial event for the rapid actin stress fiber assembly and focal adhesion formation that promote initial cell adhesion and spreading, events mediated at least in part by calpain activity (Westhoff et al., 2004). Further, FAK-induced activation of the Nck/PAK/PIX/PKL signaling cascade suppressed Rac activity, thus leading to cell adhesion (Brown et al., 2005; Mitra and Schlaepfer, 2006). Finally, cell spreading is favored by the lamellipodia formation due to Rac activation through the various signaling pathways described above. Important for these cellular activities is the regulation of the actin cytoskeleton. Studies suggested that one consequence of paxillin's FAK-induced phosphorylation is it's binding to vinculin. This binding leads to an alteration in the structure of the vinculin molecule revealing the actin-binding site. In this way FAK triggers a pathway for the regulation of the actin cytoskeleton (Guan, 1997). Another pathway leading to the regulation of actin cytoskeleton is through the activation of the Rho and Cdc42 GTPases by Graf, when activated by the FAK/Src complex (Cary and Guan, 1999).

Angiogenesis

Apart from cell proliferation, another important parameter for tumor growth is angiogenesis. The ability of FAK to promote cell migration, proliferation and invasion suggests a potential role for endothelial sprouting and angiogenesis in malignancy. This hypothesis was confirmed by Haskell et al., who found that FAK was expressed in the endothelial cells of high grade astrocytoma specimens, but not in any of the low grade ones or normal brain samples (Haskell et al.,

2003).

A significant reduction in migration and in branched tube formation and tube length was observed when cells were transfected with a dominant interfering form of FAK, FAK-related nonkinase (FRNK). Such data suggested that FAK promoted angiogenesis, at least in part, by promoting endothelial cell migration, and rendered it as a potential target in the angiostatic treatment of malignant astrocytic tumors. Furthermore, FAK contributes to the induction of angiogenesis through several pathways. FAK-induced activation of Erk (Cary and Guan, 1999; Schlaepfer et al., 1999), apart from cell proliferation, also resulted in Vascular Endothelial Growth Factor (VEGF) transcription, with consequent induction of angiogenesis and tumor growth (Mitra and Schlaepfer, 2006). A second pathway involves the activation of PI3K by FAK upon cell-to-cell interaction, which in turn activates the Rap1/Raf/Erk pathway with consequent stimulation of VEGF transcription (Sheta et al., 2000). An important observation is that although Raf could also be activated by Ras, this pathway was independent of Ras activity. Furthermore, in Ras-transformed cells, integrin-induced FAK activation led to the direct interaction with Etk and activated it (Chen et al., 2001). Activated Etk, through its N-terminal PH domain, binded to PAK1, which is also a known downstream target of Rac and activated it. Pak has been shown to be important for angiogenesis (Kiosses et al., 1999; Kiosses et al., 2002). Additionally, Bryant et al. presented evidence that FAK regulated the levels of expression of CDKIs $p27^{Kip1}$ and $p21^{Cip1}$ in human endothelial cells (Bryant et al., 2006). FAK has been shown to reduce CDKIs levels leading to cell proliferation and probably explaining another way by which FAK regulates angiogenesis during tumor progression.

FAK expression in malignancy

Based on the evidence of studies showing that FAK promotes cancer cells' malignant characteristics *in vitro*, various studies were conducted evaluating the significance of FAK expression and its phosphorylation status in human malignancies and its correlation with clinicopathological parameters of the disease. Data regarding FAK expression and its clinical significance in various malignancies are presented in this part of the manuscript (Table 2).

Neurological neoplasia

Astrocytomas represent the most common primary intracranial neoplasms, representing 60% of all primary brain tumors. Gutenberg et al. studied the expression of FAK in 331 human astrocytomas immunohistochemically (Gutenberg et al., 2004). The study included 36 pilocytic astrocytomas (WHO grade I), 39 diffuse (WHO grade II), 55 anaplastic (WHO grade III) and 201 glioblastomas (WHO grade IV), consisting of 184 primary and 17 recurrent cases. Of the 36 pilocytic astrocytomas, 29 expressed no FAK (80.5%), 6 (16.7%) exhibited mild, 1 (2.8%) moderate and none intense FAK immunoreactivity. Of the 39 diffuse astrocytomas, 29 expressed no FAK (74.4%), 7 (17.9%) exhibited mild, 2 (5.1%) moderate and 1 (2.6%) intense FAK immunoreactivity. Of the 55 anaplastic astrocytomas, 34 expressed no FAK (61.8%), 13 (23.6%) exhibited mild, 6 (10.9%) moderate and 2 (3.7%) intense FAK immunoreactivity. Of the 201 glioblastomas, 104 expressed no FAK (51.8%), 26 (12.9%) exhibited mild, 34 (16.9%) moderate and 37 (18.4%) intense FAK immunoreactivity. The study results suggested a correlation between the intensity of FAK immunoreactivity and the rising grade of human astrocytic tumors. This was further supported by other studies showing that FAK expression (Wang et al., 2000; Jones et al., 2001; Hecker et al., 2002) and FAK phosphorylation status (Hecker et al., 2002) were positively correlated with histopathological grade of astrocytic tumors, while normal brain tissue samples exhibit no FAK immunostaining (Wang et al., 2000). Furthermore, FAK expression has been shown to increase during tumor progression, as FAK levels were higher in a recurrent glioblastoma following radiotherapy compared to the initial tumor (Jones et al., 2001).

Cerebral metastases are the most common intracranial tumors. Ludwig et al. investigated the intensity of FAK immunostaining in 130 patients with cerebral metastases and its correlation with Pyk2, VEGFR, NOS isoenzymes' expression, capillary density and tumor histology (Ludwig et al., 2000). They consisted of 41 lung, 18 breast, 13 melanoma, 13 kidney, 6 prostate, 7 intestine metastases and 32 adenocarcinomas of unknown origin. FAK immunoreactivity was observed in 50% of the examined samples. A significant coexpression with Pyk2 was observed, which was expressed in 74% of the samples, as well as with VEGFR and NOS III, which were expressed in 70% and in 39,4% of the specimens, respectively. FAK expression was also statistically significantly correlated with tumor burden and histological grade. Such data suggested a correlation between FAK and Pyk2 expression and the metastatic and invasive tumor characteristics, and that a possible interaction of FAK with VEGFR and NOS III might be important for the infiltrative behavior.

Head and neck neoplasia

One of the first studies evaluating FAK expression in head and neck tumors is the study of Kornberg on 20 oral cancer specimens (Kornberg, 1998). It was shown that invasive carcinomas of the oral cavity presented increased intensity of FAK immunoreactivity compared to the adjacent normal tissue, while preinvasive *in situ* carcinomas contained cell subpopulations which showed enhanced FAK staining compared to neighboring cells. These observations were confirmed by Schneider et al., who showed that 10 normal tissue, 10 chronic mucositis

Table 2. Correlation of FAK expression with basic clinicopathological parameters in various human malignancies.

FAK expression in tumors in vivo	Method	Sample size	Grade	Stage	pT	pN	pM	Proliferation (mitotic index or Ki67)	Survival/ Prognosis
Astrocytic tumors									
Wang et al., 2000	IHC (intensity)	14	+						
Jones et al., 2001	IHC (intensity)	27	+						
Hecker et al., 2002	Western blot (levels of FAK expression) and	10	+						
	Immunoprecipitation (levels of phosphorylated FAK expression)	10	+						
Gutenberg et al., 2004	IHC (intensity)	331	+						
Head and neck carcinomas									
He et al., 2006	IHC (intensity)	80	+	+		+			+
Canel et al., 2006	IHC (intensity)	211	-	-	-	-			-
Thyroid cancer									
Kim et al., 2004	IHC (intensity)	59					-		
Laryngeal carcinoma									
Aronsohn et al., 2003	IHC (intensity)	35	+			-			
Yu et al., 2004	IHC (intensity)	100				+			+
Lung cancer									
Nishimura et al., 1996	Immunoblotting (levels of phosphorylated FAK expression)	44			-*	+*			+*
Imaizumi et al., 1997	Immunoblotting (levels of phosphorylated FAK expression)	41	+*		+*	+*			+*
Wang XY et al., 2005	IHC (expression)	240	+	+		+			
Carelli et al., 2006	Western blot (levels of FAK expression)	16		+					
	RT-PCR (levels of mRNA)	60		+		+			
Esophageal cancer									
Miyazaki et al., 2003; Miyazaki et al., 2005	IHC (intensity+extent)	91	+	+		+	-	-	+
Gastric cancer									
Su et al., 2002	IHC (intensity)	75	+			+			
Colon cancer									
Ayaki et al., 2001	Western blot (levels of FAK expression) and IHC (intensity)	10					+		
Lark et al., 2003	IHC (intensity)	18					-		
	Real time quantitive PCR	17					+		
Theocharis et al., 2003	IHC (intensity)	80	-	-		-		-	-
Yu et al., 2006	IHC (intensity)	45		+		+*			
	Immunoblotting (levels of FAK and phosphorylated FAK expression)	45		+		+*			
Hepatocellular carcinoma									
Su et al., 2002	IHC (intensity)	16	+						+
Itoh et al., 2004	IHC (extent)	64	+						+
Fujii et al., 2004	RT-PCR (levels of mRNA)	60	+						+
Pancreatic cancer									
Furuyama et al., 2006	IHC (intensity+extent)	50	-	-		-			-
Prostate cancer									
Tremblay et al., 1996	Western blot (levels of FAK expression)	25		+					
	RT-PCR (levels of mRNA)	36		+					
Rovin et al., 2002	IHC (intensity)	88		-					
Endometrial cancer									
Livasy et al., 2004	IHC (intensity+extent)	115	+						
Cervical cancer									
Gabriel et al., 2006	IHC (intensity+extent)	162	-			+			+
Ovarian cancer									
Judson et al., 1999	Western blot (levels of FAK expression)	26	-	-					
Sood et al., 2004	IHC (extent)	79	+	+		+	+		
Breast cancer									
Lark et al., 2005	IHC (intensity)	629	+	+		+		+	+
AML									
Recher et al., 2004	Western blot (levels of FAK expression)	60							+

*: phosphorylated FAK expression; RT-PCR: reverse transcription PCR; IHC: immunohistochemistry.

and 9 verrucous carcinoma specimens did not demonstrate increased intensity of FAK immnostaining, while 7 of 9 (78%) *in situ* and all 18 (100%) invasive carcinoma samples did (Schneider et al., 2002). Increased FAK expression in malignant tissues was also noted by other studies. He et al., using the same methodology (immunohistochemistry), found that FAK was highly expressed in 80 oral squamous cell carcinoma (SCC) specimens compared to normal epithelium, presenting membraneous and cytoplasmic heterogenous pattern of staining (He et al., 2006).

On the contrary, the study of Canel et al. presented opposite results (Canel et al., 2006). FAK expression was evaluated in 211 tissue specimens exploring its prognostic significance. The specimens included 147 primary carcinomas, 56 nodal metastasis, 3 benign hyperplastic cases and 5 dysplastic ones. Most tissue sections of the primary carcinomas contained a combination of normal, hyperplastic, dysplastic and invasive lesions giving the possibility to compare FAK expression at the different stages of malignant transformation in epithelial cells. In contrast to the normal musosa, transformed non-invasive cells exhibited FAK staining not restricted to the basal layer, but extended towards the intermediate layer in hyperplastic epithelia and towards all layers in dysplastic ones. In marked contrast to normal epithelium, FAK expression in tumor tissue displayed a homogenous distribution throughout the examined tumor. Ninety one tumors (62%) presented intense staining for FAK and 56 (38%) weak, whereas little or no FAK expression was detected in the adjacent normal epithelium. In the 56 nodal metastatic samples, FAK staining was cytoplasmic and homogenous, like that noted in primary tumor sites. Seventy three percent of the samples presented moderate to strong immunoreactivity for FAK. According to this study, FAK overexpression is an early event in the process of transformation, as FAK upregulation was detected not only in non-invasive transformed epithelia but also in hyperplastic and dysplastic ones. Furthermore, the intensity of FAK expression was also evaluated for possible association with clinicopathological variables. No relationship was observed between FAK expression and pT stage, disease stage, histopathological grade of differentiation and tumor recurrence. Higher FAK expression was associated with the presence of nodal metastasis, but no statistically significant difference in FAK expression was found between primary tumors and nodal metastasis. Although patients with elevated FAK levels presented poorer survival rate, this did not reach statistical significance. Additionally, it has been reported that FAK overexpression occured without alteration in the *fak* gene copy number as was demonstrated by real time Polymerase Chain Reaction (PCR), suggesting that FAK protein was overexpressed due to mechanisms other than structural amplification. On the contrary, in another study in oral SCC FAK overexpression, demonstrated immunohistochemically, was correlated with histopathological grade of differentiation, TNM stage and lymph node positivity, while the multivariate analysis showed that FAK expression could be considered as an independent prognostic factor for this type of cancer (He et al., 2006).

Thyroid neoplasia

FAK expression in thyroid tissue was evaluated using immunohistochemistry (Kim et al., 2004). None of the 20 normal tissue specimens or of the 6 nodular hyperplasias examined expressed FAK. Of the 17 follicular adenomas, 8 (47%) were negative for FAK, 4 (23.5%) exhibited weak, 2 (11.7%) moderate and 3 (17.6%) intense immunoreactivity. Of the 9 follicular carcinomas, 1 (11%) exhibited weak, 4 (44.4%) moderate and 4 (44.4%) intense immunoreactivity. Two cases had lymph node metastasis, with 1 (50%) expressing moderate and 1 (50%) intense FAK staining, and one distant metastasis to the skull with intense FAK staining. In the remaining 6 cases, without metastasis, 2 (33.3%) presented intense, 3 (50%) moderate and 1 (16.6%) weak FAK expression. Of the 17 papillary carcinomas, 3 (17.6%) exhibited weak, 4 (23.5%) moderate and 10 (58.8%) intense immunoreactivity. With respect to lymph node metastasis, of the 17 papillary carcinomas 7 had lymph node metastasis, 1 soft tissue invasion and 9 neither. Of the 7 papillary carcinomas with positive lymph nodes, 5 cases (71.4%) exhibited intense, 1 (14.2%) weak and 1 (14.2%) moderate FAK immunostaining. Of the 9 cases without lymph node metastasis or soft tissue invasion, 4 (44.4%) exhibited intense, 3 (33.3%) moderate and 2 (22.2%) weak FAK expression. All the 8 medullary carcinomas exhibited intense immunoreactivity for FAK. Of the 2 anaplastic carcinomas, 1 (50%) exhibited moderate and the other intense immunoreactivity. According to this study FAK expression was significantly higher in thyroid cancer than in benign tumors, but there were no differences between the various types. Patients' sex, tumor size and presence of metastasis did not present statistically significant correlation with FAK expression (Kim et al., 2004).

On the contrary, Owens et al. using Western blot analysis, reported positive correlation between FAK expression and the invasive potential in thyroid neoplasms (Owens et al., 1996). Multinodular goiters and follicular adenomas exhibited similar levels of FAK to normal tissue. Even carcinomas with limited aggressiveness, such as of papillary type, presented almost normal FAK levels. In contrast, the examined follicular carcinomas, which are recognized for their aggressiveness, showed significant FAK overexpression compared with the normal tissue. Furthermore, the highest level of FAK expression occurred in cases presenting distant metastasis.

Laryngeal neoplasia

In their study, Aronsohn et al. presented immunohistochemical evidence that FAK and its

phosphorylated form were overexpressed in SCC of the larynx (Aronsohn et al., 2003). A correlation between the FAK intensity of staining and tumor differentiation, with more intense FAK immunoreactivity in poorly differentiated tumors was also shown. FAK expression was localized at the cytoplasm and membrane, whereas the phosphorylated FAK localization was predominantly nuclear. This rather surprising finding, as phosphorylated FAK is the active form of FAK and it may be expected in large amounts in the cytoplasm, could be explained by either the presence of proteins that associate with FAK and mask the antigen that reacts with phosphorylated tyrosine 397, or the phosphorylation of FAK in domains other than tyrosine 397 in tumor cells. The study showed no correlation between FAK staining and nodal involvement. Cancers with moderate FAK intensity presented a larger percentage of recurrence before 2 years, whereas those with high FAK intensity after 2 years. These seemingly provocative results could reflect the transient downregulation of FAK signaling needed for the beginning of the sequence of events resulting in the metastasis of malignant cells (Lu et al., 2001). The study results were in conformation with those of another study (Yu et al., 2004), which also detected stronger intensity of FAK staining in 100 carcinomas than in 60 normal tissue specimens. FAK levels were higher in cancer cases presenting lymph node metastasis. The 3- and 5-year survival rates were lower in the FAK overexpressing group compared to FAK non-overexpressing one.

Lung neoplasia

The tyrosine phopshorylation of 100-130 kDa proteins, including FAK, in human lung cancer specimens was evaluated by immunoblotting and correlated with various clinicopathological parameters of the disease (Nishimura et al., 1996). Tyrosine phosphorylation of these proteins was exhibited in 47% of the SCCs and 43% of the adenocarcinomas examined, and found not to associate with age, sex, histological classification, tumor size, or pathological T factor of the TNM classification. However, it did correlate with nodal involvement (N factor) and shorter survival length after operation.

Subsequent studies concentrated on FAK and showed that FAK expression was higher in non-small-cell lung cancer (NSCLC) tissues compared with normal tissue specimens, with no significant differences between SCC and adenocarcinoma histological types (Imaizumi et al., 1997; Carelli et al., 2006). FAK mRNA levels, measured by real time reverse transcription PCR, were also significantly higher in neoplastic samples (Carelli et al., 2006). Additionally, the intensity of FAK immunoreactivity was also greater in reactive lesions, such as squamous metaplastic bronchial epithelium and hyperplastic/reactive pneumocytes surrounding the neoplasia, than in normal tissue, but lower than neoplastic (Carelli et al., 2006). Also opposing are the results concerning FAK phosphorylation status, as Carelli et al. showed by Western blot analysis that all of the evaluated tyrosine residues were phosphorylated in both neoplastic and non-neoplastic specimens with no quantitative differences, suggesting that the upregulation of FAK expression does not correlate with increased activation (Carelli et al., 2006). On the contrary, Imaizumi et al. detected, by immunoblotting, FAK tyrosine phosphorylation in malignant tissue, but not in the normal control sample obtained from the same patient (Imaizumi et al., 1997). Additionally, FAK mRNA levels were significantly correlated with disease stage, tumor size and lymph node metastasis (Carelli et al., 2006). FAK protein expression was significantly correlated with disease stage, as demonstrated by Western blot (Carelli et al., 2006) and immunohistochemical analysis (Wang et al., 2005), tumor differentiation and lymph node metastasis, but not to patients' age and gender (Wang et al., 2005). FAK phosphorylation levels, detected by immunoblotting, were significantly correlated with nodal involvement and disease free survival rate (Imaizumi et al., 1997). According to this study, the risk ratio of FAK phosphorylation had a high value, second only to the risk ratio of pT, suggesting that it could be used as a prognostic factor (Imaizumi et al., 1997).

Esophageal neoplasia

Miyazaki et al. evaluated immunohistochemically FAK expression and its clinical sifnificance in 91 esophageal cancer tissue samples (Miyazaki et al., 2003, 2005). FAK overexpression was defined as when >40% of carcinoma cells were more intensely stained than the normal epithelial ones. FAK was located in the cytoplasm of both normal and malignant cells, particularly in those located in the invasive fronts of the cancer nests, and was overexpressed in 54 of 91 (59.3%) malignant tissue specimens. FAK overexpression was significantly correlated with tumor cells' differentiation, depth of tumor invasion, presence and number of regional lymph node metastases and disease stage. On the other hand, no significant association was noted between FAK expression and patients' age, sex, tumor location and the presence of distant metastasis. FAK-overexpressing cells presented increased proliferating capacity (evidenced by Ki-67 immunostaining) compared to non-overexpressing ones, but without reaching statistical significance. On the other hand, the survival rates of patients with FAK-overexpressing tumors were significantly lower than those of non-overexpressing ones. However, multivariate analysis showed that FAK overexpression was not by itself a prognostic factor in this type of cancer.

Gastric neoplasia

According to an early study FAK was expressed in only half of the 10 gastric carcinomas examined immunohistochemically (Tani et al., 1996). A more recent study employing a larger patients group presented

similar percentage of carcinoma cases expressing FAK immunohistochemically, but further correlated the intensity of FAK expression with gastric carcinogenesis (Su et al., 2002). Of the 51 unaffected margin specimens only 2 (4%) showed moderate FAK immunoreactivity and the rest negative or minimal. Of the 75 cancer specimens 43 (57%) showed moderate or intense FAK immunoreactivity. When FAK expression was compared with histopathological and clinical parameters, 30 of 44 cases (68%) of poorly differentiated cancer cases presented moderate or intense immunoreactivity, while only 13 of 31 (42%) well-diferrentiated cancer ones showed moderate or intense immunoreactivity. Forty of the 59 (68%) deep or full-stratum invasive cancers and only 3 of the 16 (23%) superficial or mucosa invasive cancer samples exhibited moderate or intense immunoreactivity in the primary site. Thirty of 39 (77%) cases with lymph node metastasis and 13 of 36 (36%) cases without lymph node metastasis presented moderate or intense immunoreactivity. The study showed a significant association between levels of FAK expression, poor differentiation, deep invasion and lymph node metastasis in human gastric carcinogenesis (Su et al., 2002).

Colorectal neoplasia

Most studies on FAK expression in colon carcinoma suggest that FAK expression increases with malignant transformation of the colonic epithelium as demonstrated by Northern blot (Weiner et al., 1993), Western blot (Owens et al., 1995; Cance et al., 2000; Yu et al., 2006), immunohistochemical analysis (Theocharis et al., 2003; Yu et al., 2006) and immunoprecipitation (Cance et al., 2000). More specifically, in these studies, FAK expression was found to increase as normal colonic epithelium progresses to dysplastic and finally malignant. Indeed, villous adenomas with a diameter more than 2 cm, which are known to present higher malignant potential, expressed low, but detectable FAK levels, whereas other adenomas did not (Weiner et al., 1993). In all studies, the percentage of colon carcinomas presenting moderate to intense FAK immunoreactivity was significantly higher than normal colonic mucosa specimens (Weiner et al., 1993; Owens et al., 1995; Cance et al., 2000; Theocharis et al., 2003; Yu et al., 2006). In a study of our group on 80 colon cancer specimens the prognostic significance of FAK expression and its correlation with clinicopathological parameters were evaluated (Theocharis et al., 2003). FAK was considered to present overexpression if ≥ 30% of tumor cells were stained. Normal colonic mucosa expressed no FAK, while cancer cells were all positive for FAK expression and, particularly, 32 of 80 (40%) cases presented FAK overexpression. The pattern of FAK staining was primarily cytoplasmic and occasionally membraneous. No statistically significant correlation was established between FAK expression and patients' age, tumor histological grade, location, stage, presence of lymphatic invasion and tumor proliferating capacity (Ki-67 positivity and overexpression). Except for stage, no other parameter, including FAK overexpression, proved to be of prognostic significance, as FAK was not correlated with patients' survival. In the opposite direction were the results of Yu et al., who statistically significantly correlated the extent of FAK protein expression and phosphorylated FAK levels with disease stage (Yu et al., 2006). In the same study, FAK was identified as a downstream effector of gastrin's receptor cholocystokinin-2 receptor (CCK2R) in the gastrin-induced increase of colon cancer cells invasiveness.

On the contrary, in a previously published study, Tani et al. showed by immunohistochemistry that only 2 of 10 (20%) studied colon carcinomas expressed FAK (Tani et al., 1996). One of them showed FAK reactivity in the intercellular junctions, while the other in the interface between malignant cell and tumor stroma.

Opposing are also the study results concerning FAK expression in primary colon cancers compared to their liver metastases. Lark et al. detected robust levels of FAK immunoexpression in both primary cancers and their matched liver metastases, with all samples exhibiting intense FAK staining in at least 30% of the tumor cells (Lark et al., 2003). FAK levels in metastases were similar or greater than in their matched primary tumors in 14 of 18 (78%) samples by intensity and in 15 of 18 (83%) for the percentage of cells positive for FAK. Furthermore, the highest levels were seen in metastases. Although a trend was observed for FAK expression to be greater in liver metastases than in the matched primary tumors, no statistical significance was noted. Additionally, the study showed significantly higher FAK mRNA levels, measured by real time PCR, in colorectal cancer specimens compared to normal colorectal mucosa. Finally, the study of another tumor series presented significantly higher FAK mRNA levels in liver metastases from colorectal cancer compared to unmatched primary tumors. Opposing are the results of Ayaki et al. in 10 cases of colorectal adenocarcinoma and synchronous liver metastasis (Ayaki et al., 2001). By Western blot analysis FAK expression was higher in 8 of 10 (80%) cases in the primary carcinoma tissue than in the adjacent normal mucosa and lower in 8 of 10 (80%) cases in liver metastases than in primary carcinoma. Average FAK expression was significantly higher in colorectal adenocarcinoma than in normal mucosa and significantly lower in liver metastasis than in primary site. The results were confirmed by immunohistochemistry. In this study, tissue with more than 50% of tumor cells stained defined as positive for FAK expression. Two of 10 (20%) normal mucosa, all 10 (100%) primary adenocarcinoma and 8 of 9 (88%) liver metastases were positive for FAK, presenting a diffuse cytoplasmic pattern of staining. In 8 of 10 primary adenocarcinoma cases (80%) FAK expression was remarkably increased compared to normal mucosa, whereas in 7 of 9 (77.78%) liver metastases FAK expression was markedly reduced compared to primary

colon tumors.

Liver neoplasia

In hepatocellular carcinoma (HCC) FAK immnoreactivity was significantly higher in carcinomas compared to normal hepatic tissue, suggesting the role of FAK in liver tissue carcinogenesis (Su et al., 2002; Fujii et al., 2004; Itoh et al., 2004). Along with FAK overexpression, PTEN downregulation was found to correlate significantly with the increased FAK phosphorylation levels in cancer cells, pointing out a possible cause of FAK upregulation (Zhang et al., 2004). One study showed that FAK was absent in hepatitis specimens with or without cirrhosis (Itoh et al., 2004), while another exhibited higher FAK mRNA expression, measured by real time quantitive reverse transcriptase PCR , in cirrhotic tissue than in normal, though it did not reach statistical significance (Fujii et al., 2004). The extent (Itoh et al., 2004) and the intensity (Su et al., 2002) of FAK immunoexpression was found to be significantly lower in the least aggressive carcinoma cell lines (Itoh et al., 2004) and in poorly differentiated, compared to moderate or well differrentiated ones (Su et al., 2002). Furthermore, FAK mRNA expression was higher, although not statistically significant, in infiltrative carcinomas than in in situ ones (Fujii et al., 2004). The results on the relationship between FAK expression and invasiveness are opposing. In one study (Fujii et al., 2004) FAK mRNA expression was not correlated with capsular infiltration and vascular invasion, while in another (Itoh et al., 2004) the extent of FAK expression of the main lesion was correlated significantly with portal venous tree invasion. Opposing were also the results on the relationship between FAK expression and patients' gender, as the first study (Fujii et al., 2004) showed that the two parameters were not correlated and the other that they were (Itoh et al., 2004). Furthermore, FAK mRNA expression was significantly correlated with AFP (Fujii et al., 2004) and albumin (Itoh et al., 2004) serum levels, tumor size (Fujii et al., 2004), but not with tumor multiplicity (Fujii et al., 2004). Finally, FAK was determined as an independent predictor of survival (along with grade, TNM stage and intrahepatic metastasis) (Itoh et al., 2004; Fujii et al., 2004) and of recurrence (along with AFP) (Fujii et al., 2004), in this type of neoplasia.

Pancreatic neoplasia

Furuyama et al. evaluated immunohistochemically the intensity and the extent of FAK expression in 50 pancreatic cancer specimens and its correlation with tumors clinicopathological features (Furuyama et al., 2006). FAK mRNA was also detected in all 7 cell lines derived form human pancreatic adenocarcinoma. FAK protein expression was positive in 24 of 50 (48%) specimens and negative in the rest (52%). FAK staining was heterogenously expressed in the tumor and predominantly in the cytoplasm and on the plasma membrane of cancer cells, while in normal tissue FAK staining was observed intensly in the cytoplasm of ductal cells, faintly in islet cells and not in acinar ones. FAK expression was significantly correlated with tumor size, but not with age, sex, histological grade, lymph node metastasis, International Union Against Cancer (UICC) stage, portal venous system invasion, nerve invasion, arterial invasion, anterior pancreatic serosal invasion, retroperitoneal tissue invasion and survival (Furuyama et al., 2006).

Prostatic neoplasia

Studying FAK expression in prostate tissue specimens initially showed that increased FAK protein and mRNA levels, demonstrated by Western blotting and reverse transcription PCR respectivelly, were correlated with advanced stage of prostate cancer, showing progression and invasiveness (Tremblay et al., 1996). FAK was weakly detected in normal and hyperplastic tissue samples studied, whereas in localized and metastatic tumors stained, FAK expression was 5,5-fold and 12-fold higher than in normal tissue respectively. However, the difference was statistically significant only between normal and metastatic tissue. Similar were the results with respect to FAK mRNA levels, which were detected approximately 20-fold higher in localized, and 164-fold higher in metastatic carcinoma compared to normal tissue. However, as observed for protein levels, the difference was statistically significant only between normal and metastatic tissue. The more recent study of Rovin et al. detected intense FAK staining in normal prostatic basal layer cells, while FAK staining was absent or weak in the secretory prostatic epithelium (Rovin et al., 2002). Fourteen benign prostatic hypertrophy specimens were studied and presented an immunostaining pattern similar to that noted in normal tissues. The preinvasive form of carcinoma, high-grade Prostate Intraepithelial Neoplasia (PIN), was analyzed in 25 specimens and expressed intense uniformly cytoplasmic FAK staining. Fifty-five primary tumors with various Gleason's scores were studied, and 70% showed intense heterogenous FAK staining, 1 tumor expressed no FAK and the remaining weak FAK staining. The level of immunoreactivity in PIN appeared equivalent to that noted in invasive tumors. Additionally, there was no correlation between FAK staining and Gleason's score or tumor stage. Further, 33 metastatic prostate cancer cases, including lymph nodes, bone, liver and brain metastases specimens were examined, and 27 (82%) exhibited intense and homogenous FAK expression, which was different from the heterogenous pattern observed in primary cancer sites. Such results suggested that elevated FAK expression is an early event in prostate cells malignant transformation (Rovin et al., 2002).

Endometrial neoplasia

Livasy et al. evaluated immunohistochemically the

intensity and extent of FAK expression in endometrial neoplasia (Livasy et al., 2004). FAK levels were high in 6 of 38 (16%) normal tissue samples, 8 of 21 (38%) hyperplasias without atypia, 4 of 7 (57%) hyperplasias with atypia, 57 of 100 (57%) endometrioid, 8 of 10 (80%) serous and 4 of 5 (80%) clear cell adenocarcinomas. Consequently, FAK overexpression was seen more commonly in hyperplastic endometrium and in adenocarcinomas than in normal endometrium. FAK upregulation was noted more frequently in p53-overexpressing tumors compared with p53-negative ones (78% to 43%, respectively) and proved to be statistically significant. The rate of FAK overexpression was also increased across grade, with high levels observed in 22 of 46 (48%) FIGO grade 1 tumors, 19 of 31 (61%) grade 2, and 28 of 38 (74%) grade 3, a difference that was also proved statistically significant. These results suggested the role of FAK in endometrial carcinogenesis and associated FAK overexpression with aggresiveness, since it is correlated with the two independent prognostic factors for endometrial carcinoma, p53 and histological grade. This was further supported by the fact that retinoic acid treatment reduced the levels of FAK and paxillin and induced actin reorganization and reversion of human endometrial adenocarcinoma cells to a stationary phenotype (Carter and Bellido, 1999).

Furthermore, the intensity of FAK expression was found to be low in 15 leiomyomas by Western blotting and immunohistochemical analysis, but higher than the matched normal myometrium samples (Chegini et al., 2003). Gonadotropin releasing hormone analogue (GnRHa) therapy decreased FAK levels in both leiomyomas and normal myometrium. FAK was localized in the cytoplasm, whereas phosphorylated FAK was found most frequently in the nuclear region of normal and leimyoma cells. These observations suggested that GnRHa-induced leiomyoma regression is part through modulation of FAK signaling (Chegini and Kornberg, 2003).

Cervical neoplasia

Several studies evaluated FAK expression in cervical malignancies, presenting opposing results. Su et al. studied the intensity of FAK immunoexpression in 20 uterocervical carcinomas and 18 unaffected margins (Su et al., 2002). Of the 18 unaffected margins, none exhibited increased FAK levels. Of the 10 adenocarcinomas 1 (10%) exhibited moderate or intense immunoreactivity, and of the 10 SCCs none. With respect to tumor characteristics, only 1 out of 10 (10%) poorly differentiated tumors exhibited moderate or intense FAK immunoreactivity and none of the moderate or well differentiated tumors. Of the 15 carcinomas with deep or full stratum invasion, only 1 (6.66%) exhibited moderate or intense FAK immunoreactivity, while none of the 5 tumors with mucosa or superficial stratum involvement. Consequently, no association was found between FAK and uterocervical carcinogenesis. In the same direction were the results of Moon et al., showing by Western blot analysis comparable FAK levels among malignant (n=26), normal tissue (n=9) and *in situ* carcinoma (n=5), whereas FAK phosphorylation was slightly increased in invasive carcinomas (Moon et al., 2003). The study concluded that most important for cervical cancer invasion is the tyrosine phosphorylation of FAK, rather than the level of its expression. On the contrary, Oktay et al. using immunohistochemical analysis suggested that FAK has a role in the malignant transformation of normal cervical tissue, but it is not a marker for invasiveness (Oktay et al., 2003). In their study FAK was intensely expressed in invasive carcinomas (n=16) and carcinomas *in situ* (n=14), while dysplasias (CIN I and II) (n=17) and normal epithelium (n=31) exhibited no or faint FAK staining. The difference in FAK staining between invasive and *in situ* carcinomas did not reach statistical significance.

The most recent study is that of Gabriel et al., who evaluated immunohistochemically the intensity and extent of FAK expression in 166 patients with early-stage cervical cancer and its possible correlation with clinicopathological characteristics of the disease (Gabriel et al., 2006). Results for FAK expression were retrieved in 162 cases. FAK was expressed in the tumor cells of all cervical cancer samples, whereas hardly any FAK was detected in the adjacent normal epithelium. Cytoplasmic and occasionally membranous FAK localization was restricted to dysplastic and invasive carcinoma cells. Fifty-five of 162 (34%) tumor samples showed weak FAK expression, 63 (39%) moderate and 44 (27%) intense. There were no statistically significant differences between FAK expression and patients' age, tumor histological subtype, grade, depth of invasion, GOG score, LVSI or size. On the contrary, weak FAK expression was associated with poorer 5- and 10-year survival, pelvic lymph node metastasis and reccurent disease. The multivariate Cox regression analysis revealed FAK expression, as well as pelvic lymph node metastasis, as significant independent predictors for patients' survival.

Ovarian neoplasia

Several studies evaluated FAK expression in ovarian neoplasia. Normal ovarian tissue specimens studied by immunohistochemistry (Gabriel et al., 2004; Sood et al., 2004; Grisaru-Granovsky et al., 2005) and Western blot analysis (Gabriel et al., 2004; Sood et al., 2004) exhibited no or low FAK expression. On the contrary, FAK expression in malignant cells of the ovary was significantly higher than normal cells (Judson et al., 1999; Gabriel et al., 2004; Sood et al., 2004; Grisaru-Granovsky et al., 2005) presenting a predominantly cytoplasmic pattern of staining (Gabriel et al., 2004). Immunofluorescence analysis indicated a direct correlation between the level of phosphorylated FAK and ovarian malignancy (Grisaru-Granovsky et al., 2005). Evaluation of FAK expression by ROC curve showed a FAK level of 40 to be most diagnostic for ovarian carcinoma (Judson et al., 1999). FAK level ≥ 40

was associated with ovarian carcinoma at a sensitivity of 93%, specificity of 100%, positive predictive value of 100% and negative predictive value of 83%. Sensitivity, specificity and predictive value increased to 100% for serous carcinoma, the most common type. On the contrary, other studies revealed no association between FAK overexpression and histological subtypes (Judson et al., 1999; Sood et al., 2004), presence of ascites and ability to achieve optimal cytoreduction (Sood et al., 2004). In one study FAK overexpression, demonstrated immunohistochemically, was found to significantly associate with high stage, high grade, higher likelihood of nodal positivity and presence of distal metastasis (Sood et al., 2004), while in another (Judson et al., 1999), the difference in FAK expression, demonstrated by Western blotting, between grade 2 and grade 3 tumors, and between stages I-II and stages III-IV was not statistically significant.

Breast neoplasia

FAK expression has been thoroughly studied in breast malignancies. In all studies FAK levels were significanctly higher in breast cancer tissue specimens (Weiner et al., 1993; Cance and Liu, 1995; Owens et al., 1995; Ignatoski and Ethier, 1999; Cance et al., 2000; Su et al., 2002; Oktay et al., 2003; Lightfott et al., 2004; Lark et al., 2005; Watermann et al., 2005) and in lymph node metastases (Owens et al., 1995; Su et al., 2002) compared to normal tissue specimens (Owens et al., 1995; Cance and Liu, 1995; Cance et al., 2000; Su et al., 2002; Watermann et al., 2005), fibroadenomas (Weiner et al., 1993), fibrocystic disease samples (Lightfott et al., 2004) or atypical ductal hyperplasia specimens (Oktay et al., 2003; Lightfott et al., 2004). The intensity and extent of FAK expression was also increased in carcinomas *in situ* (Oktay et al., 2003; Lightfott et al., 2004). These results showed that FAK expression is significantly associated with breast carcinogenesis and lymph node positivity (Weiner et al., 1993; Cance and Liu, 1995; Owens et al., 1995; Cance et al., 2000; Su et al., 2002; Oktay et al., 2003; Watermann et al., 2005), rather than cancer invasiveness (Oktay et al., 2003; Lightfott et al., 2004). FAK mRNA levels, measured by reverse transcriptase PCR, were not significantly elevated, suggesting that FAK induction was most likely due to post-transcriptional or post-translational processing, rather than primary transcriptional effects (Watermann et al., 2005). Activated FAK levels, thus phosphorylated at tyrosine 397, were also found to be immuno-histochemically significantly elevated in *in situ* (n=9), and in invasive ductal carcinomas (n=20), compared to normal epithelium (n=8) and fibroadenomas (n=7), further supporting the correlation between FAK and malignant transformation (Madan et al., 2006). On the contrary, no statistical significant difference was demonstrated in phosphorylated FAK expression levels between in situ and infiltrating carcinomas, also supporting that FAK expression has no correlation with invasiveness. The study of Lightfoot et al. documented a difference in FAK immunoexpression between comedo and non-comedo carcinomas, with 78% of comedo carcinomas expressing high intensity and extent of FAK staining compared with the 61% of non-comedo ones. Such a difference approached statistical significance, but needs further investigation (Lightfott et al., 2004).

Lark et al. tried to correlate the intensity and extent of FAK immunostaining in 629 breast cancer specimens with several clinocopathological parameters of the disease (Lark et al., 2005). High FAK expression was highly associated with increased mitotic activity (mitotic index of >10 mitoses/10 consequtive H.P.F.) and high nuclear grade tumors. Tumors with high FAK expression were more likely to be architectural grade 3 tumors. FAK expression was associated with markers of poor prognosis, such as ER and PR negative phenotype and Her2/neu overexpression. The possible association between FAK and Her2/neu was first introduced by an *in vitro* study, suggesting that Her2/neu influences metastasis of breast cancer cells through a pathway involving FAK phosphorylation tyrosine 861 via Src activation (Vadlamudi et al., 2003) and further confirmed by Schmitz et al. in their *in vivo* study, proposing that Her2/neu overexpression might contribute to breast cancer aggressive behavior through a pathway invoving FAK, Src, PI3K and Akt (Schmitz et al., 2005). After multivariable adjustment, the only significant predictor of tumors with high FAK expression was Her2/neu positivity (Lark et al., 2005). Furthermore, patients presenting disease stage 3 or 4 or patients with positive lymph nodes were more likely to present high FAK expression. Finally, although not statistically significant, high FAK expression was common in advanced aged patients.

Hematological malignancy

In a study on murine lymphoma cells, data presented that to some extent FAK tyrosine phosphorylation mediated the CD44-induced spreading of these cells (Li et al., 2001). Further, the negative regulation of FAK, as well as paxillin, by the peptide FNIII14, resulted in the inhibition of murine T lymphoma and human Burkitt's lymphoma cells adhesion, migration and metastasis (Kato et al., 2002). Finally, the redistribution of phosphorylated FAK, along with F-actin, mediated the neurotensin-induced migration of human mycosis fungoides cells (transformed T lymphocytes) (Magazin et al., 2004).

Only a few studies deal with the influence of radiation on FAK expression or phosphorylation and evaluated the role of FAK in resistance of leukemia cells against chemotherapy. The study of Kashara et al. revealed protection of FAK overexpressing human myeloid leukemia cells against radiation-induced apoptosis (Kasahara et al., 2002). DNA fragmentation and caspase-3 and -8 activation were significantly reduced in these cells compared to controls. Mutation analysis showed that tyrosine 397 and 925 residues were essential for the anti-apoptotic function of FAK.

Recher et al. evaluated FAK expression in 60 cases of acute myeloid leukemia (AML) by Western blotting and reverse transcription PCR, and correlated it with clinical features (Recher et al., 2004). FAK was detected in 25 of 60 samples (42%) including immature CD34+ AML samples. On the contrary, no FAK was detected in normal $CD34^+$. FAK phosphorylation status was aslo investigated and was always found phosphorylated in fresh AML cells. Additionally, FAK-expressing and non-expressing cells were compared. Although they exhibited similar adhesion properties, FAK-positive cells displayed significantly higher migration efficiency and decreased sensitivity to daunorubicin. FAK was correlated with high leukocytosis and reduced survival, but no correlation was found between FAK expression and histological subtype, cytogenetics, FLT3 status and immunophenotype.

Furthermore, evidence was presented that FAK plays an important role also in chronic myelogenous leukemia (CML) deterioration (Chang et al., 2003). FAK levels measured by flow cytometry were lower in chronic phase cells than in normal mononucleocytes and in blast crisis cells than in cells of chronic phase. Further, Interferon-α treatment increased FAK content of cells in chronic phase. BCR-abl transformation was critical for CML. B cell receptor (BCR) cross-linking induced FAK phosphorylation and activation and thus modulated the IgM-induced apoptotic signaling (Rascan, 2001). In BCR-abl transfected cells, FAK levels were found to be increased compared to controls, but phosphorylated FAK was decreased (Cheng et al., 2002). These effects were attributed to the BCR-abl-induced actin depolymerization and the lack of cell adherence.

Soft tissue and bone neoplasia

In human soft tissue tumors FAK presence was detected by Northern blot (Weiner et al., 1994) and Western blot (Owens et al., 1995) analysis predominantly in high-grade and metastatic sarcomas of smooth muscle origin, though the levels of its expression were not high. Its relative overexpression in metastatic sarcomas may indicate a role of FAK in tumor invasion and perhaps metastasis. Furthermore, FAK levels in malignant tumors, such as malignant fibrous histiosarcomas (n=1), leiomyosarcomas (n=4), rhabdomyosarcoma (n=2), neurofibrosarcoma (n=2), synovial sarcoma (n=1), osteosarcoma (n=2) and cystosarcoma phyllodes (n=1), were compared with levels in benign ones, such as lipomas (n=3) and leiomyomas (n=1) (Owens et al., 1995). FAK expression in benign neoplasms was not significantly elevated, despite their large size and hypercellularity.

Finally, FAK gene expression was increased in Ewing family sarcomas as detected by Northern blot analysis (Moritake et al., 2003). FAK was 5-20-fold upregulated in 6 Ewing sarcomas, 3 Askin tumors (small round cell tumor from the thoracopulmonary region, member of Ewing sarcoma family tumors) and 1 peripheral nerve sheath tumor when compared to control fibroblasts obtained from bone marrow.

Perspectives

FAK is a 119-121 kDa nonreceptor PTK widely expressed in various tissues and cell types. Many studies showed that FAK plays an important role in integrin signaling. Once activated by integrin and non-integrin stimuli, it binds and activates several other molecules, such as Src, $p130^{Cas}$, Grb2, PI3K and paxillin, thus promoting signaling transduction.

In normal cells FAK activity is under constant regulation by mechanisms such as gene amplification, alternative splicing and action of phosphatases. On the contrary, in vitro studies showed that in transformed cells altered FAK signaling promoted cancer cells' malignant characteristics. FAK was held responsible for cancer cells' uninhibited proliferation, protection from apoptosis, invasion, migration, adhesion and spreading, as well as tumor angiogenesis.

These data suggested a potential correlation of FAK expression with the malignant transformation of human cells, as well as the attitude of human malignancies, which have been thoroughly evaluated in several studies. In spite of the variety of the methods used and whether it was the extent or the intensity of FAK expression or the FAK protein or mRNA levels that were evaluated, most studies aggree that FAK expression plays an important role in human malignancy. FAK expression was correlated in most examined malignancies with histological grade and disease stage, as well as lymph node metastasis. On the contrary, most studies failed to reach a statistically significant correlation between FAK expression and distant metastasis. Tumor's proliferating capacity was correlated with FAK expression in breast cancer, but not in esophageal and colon cancer. Additionally, FAK expression was shown to correlate with survival rate and prognosis (Table 2). All these observations suggest that FAK plays an important role in human carcinogenesis and cancer progression and point out the possibility that FAK expression might be used as an independent prognostic factor in some types of malignancies.

The different results and correlations of FAK expression with the various clinicopathological parameters could be explained by the differences among the studies. Several different techniques were used, such as immunohistochemistry, Western blot analysis, Northern blot analysis, immunoprecipitation and immunoblotting, detecting FAK and phosphorylated FAK protein levels, as well as PCR, detecting FAK mRNA levels. The antibodies used also varied, as well as the criteria for FAK overexpression definition. Some studies were concentrated on the intensity of FAK staining, others on the extent and others considered both the intensity and the extent of FAK immunostaining. Additionally, differences among the several studies were also noted in the definition of FAK overexpression, as variable cuttoff points of the percentage of the stained malignant cells were set. Furthermore, and one of most

importance, some of the referred studies were conducted on a limited number of cases, thus increasing the probability of errors in the statistic processing of the data. The conclusions obtained from studies conducted in large samples are far more reliable.

Finally, the key role of FAK in cancer pathophysiology and progression could be used in cancer therapeutics. Since FAK regulates the progression of malignancy, modulation of FAK signaling could slow down disease progression or even potentiate conventional therapeutic regimens. Several cell lines from various types of human cancer were studied in respect to cancer cells' response to FAK blockage. Evidence was presented that the disruption of FAK signaling by the use of PTEN, FAK mutants, FRNK, FAK inhibitory protein (FIP), FAK silence RNA (siRNA) or FAK antisense oligonucleotides significantly sustained cancer cells' invasion and migration *in vitro*, as well as invasion and metastasis *in vivo*. Additionally, FAK signaling disruption exerted anticancer properties in *in vitro* and *in vivo* animal model studies, whether used alone or in combination with chemotherapy (Duxbury et al., 2003; Melkoumian et al., 2005; Smith et al., 2005; Earley and Plopper., 2006; Halder et al., 2006). Further studying should be done on the possibility that FAK targeting is effective in cancer therapy either as monotherapy or in combination with the established regimens.

References

Almeida E.A., Ilic D., Han Q., Hauck C.R., Jin F., Kawakatsu H., Schlaepfer D.D. and Damsky C.H. (2000). Matrix survival signaling: from fibronectin via focal adhesion kinase to c-Jun NH(2)-terminal kinase. J. Cell Biol. 149, 741-754.

Aprikian A.G., Tremblay L., Han K. and Chevalier S. (1997). Bombesin stimulates the motility of human prostate-carcinoma cells through tyrosine phosphorylation of focal adhesion kinase and of integrin-associated proteins. Int. J. Cancer 72, 498-504.

Aronsohn M.S., Brown H.M., Hauptman G. and Kornberg L.J. (2003). Expression of focal adhesion kinase and phosphorylated focal adhesion kinase in squamous cell carcinoma of the larynx. Laryngoscope 113, 1944-1948.

Avizienyte E. and Frame M.C. (2005). Src and FAK signalling controls adhesion fate and the epithelial-to-mesenchymal transition. Curr. Opin. Cell Biol. 17, 542-547.

Ayaki M., Komatsu K., Mukai M., Murata K., Kameyama M., Ishiguro S., Miyoshi J., Tatsuta M. and Nakamura H. (2001). Reduced expression of focal adhesion kinase in liver metastases compared with matched primary human colorectal adenocarcinomas. Clin. Cancer Res. 7, 3106-3112.

Basson M.D., Yu C.F., Herden-Kirchoff O., Ellemeier M., Sanders M.A., Merrel R.C. and Sumpio B.E. (2000). Effects of increased ambient pressure on colon cancer cell adhesion. J. Cell. Biochem. 78, 47-61.

Beinke C., Van Beuningen D. and Cordes N. (2003). Ionizing radiation modules of the expression and tyrosine phosphorylation of the focal adhesion-associated proteins focal adhesion kinase (FAK) and its substrates p130cas and paxillin in A549 human lung carcinoma cells in vitro. Int. J. Radiat. Biol. 79, 721-731.

Brabek J., Constancio S.S., Shin N.Y., Pozzi A., Weaver A.M. and Hanks S.K. (2004). CAS promotes invasiveness of Src-transformed cells. Oncogene 23, 7406-7415.

Brabek J., Constancio S.S., Siesser P.F., Shin N.Y., Pozzi A. and Hanks S.K. (2005). Crk-associated substrate tyrosine phosphorylation sites are critical for invasion and metastasis of SRC-transformed cells. Mol. Cancer Res. 3, 307-315.

Brown M.C., Cary L.A., Jamieson J.S., Cooper J.A. and Turner C.E. (2005). Src and FAK kinases cooperate to phosphorylate paxillin kinase linker, stimulate its focal adhesion localization and regulate cell spreading and protrusiveness. Mol. Biol. Cell 19, 4316-4328.

Brunton V.G., Finchman V.J., McLean G.W., Winder S.J., Paraskeva C.., Marshall J.F. and Frame M.C. (2001). The protrusive phase and full development of integrin-dependent adhesions in colon epithelial cells require FAK- and ERK-mediated actin spike formation: deregulation in cancer cells. Neoplasia 3, 215-226.

Brunton V.G., MacPherson I.R.J. and Frame M.C. (2004). Cell adhesion receptors, tyrosine kinases and actin modulators: a complex three-way circuitry. Bioch. Biophys. Acta 1692, 121-144.

Brunton V.G., Ozanne B.W., Paraskeva C. and Frame M.C. (1997). A role for epidermal growth factor receptor, c-Src and focal adhesion kinase in an in vitro model for the progression of colon cancer. Oncogene 14, 283-293.

Bryant P., Zheng Q. and Pumiglia K. (2006). Focal adhesion kinase controls cellular levels of p27/Kip1 and p21/Cip1 through Skp2-dependent and -independent mechanisms. Mol. Cell Biol. 26, 4201-4213.

Budagian V., Bulanova E., Orinska Z., Pohl T., Borden E.C., Silverman R. and Bulfone-Paus S. (2004). Reverse signaling through membrane-bound interleukin-15. J. Biol. Chem. 279, 42192-42201.

Cance W.G. and Liu E.T. (1995). Protein kinases in human breast cancer. Breast Cancer Res. Treat. 35, 105-114.

Cance W.G., Harris J.E., Iacocca M.V., Roche E., Yang X.H., Chang J., Simkins S. and Xu L.H. (2000). Immunohistochemical analyses of focal adhesion kinase expression in benign and malignant human breast and colon tissues: correlation with preinvasive and invasive phenotypes. Clin. Cancer Res. 6, 2417-2423.

Canel M., Aecade P., Rodrigo J.P., Cabanillas R., Herrero A., Suarez C. and Chiara M.D. (2006). Overexpression of focal adhesion kinase in head and neck squamous cell carcinoma is independent of fak gene copy number. Clin. Cancer Res. 12, 3272-3279.

Carelli S., Zadra G., Vaira V., Falleni M., Bottiglieri L, Nosotti M., Di Giulio A.M., Gorio A. and Bosari S. (2006). Up-regulation of focal adhesion kinase in non-small cell lung cancer. Lung Cancer 53, 263-271.

Carragher N.O., Walker S.M., Scott Carragher L.A., Harris F., Sawyer T.K., Brunton V.G., Ozanne B.W. and Frame M.C. (2006). Calpain 2 and Src dependence distinguishes mesenchymal and amoeboid modes of tumour cell invasion: a link to integrin function. Oncogene 25, 5726-5740.

Carter C.A. and Bellido T. (1999). Decrease in protein tyrosine phosphorylation is associated with F-actin reorganization by retinoic acid in human endometrial adenocarcinoma (RL95-2) cells. J. Cell. Physiol. 178, 320-332.

Cary L.A. and Guan J.L. (1999). Focal adhesion kinase in integrin-mediated signaling. Front. Biosci. 4, D102-113.

Casamassima A. and Rozengurt E. (1998). Insulin-like growth factor I stimulates tyrosine phosphorylation of p130Cas, focal adhesion kinase and paxillin. Role of phosphatidylinositol 3'-kinase and formation of a p130Cas-Crk complex. J. Biol. Chem. 273, 26149-26156.

Chang F., Lemmon C.A., Park D. amd Romer L.H. (2007). FAK potentiates Rac1 activation and localization to matrix adhesion sites: A role for {beta}PIX. Mol. Biol. Cell. 18, 253-264.

Chang X., Liu X.L., Du Q.F., Li R., Feng R., Chen Q., Liu Q.F. and Zhou S.Y. (2003). Study of adhesion-related molecule beta1-integrin and focal adhesion kinase in chronic myeloid leukemia. Di Yi Jun Yi Da Xue Xue Bao. 23, 1047-1049.

Chegini N. and Kornberg L. (2003). Gonadotropin releasing hormone analogue therapy alters signal transduction pathways involving mitogen-activated protein and focal adhesion kinases in leiomyoma. J. Soc. Gynecol. Investig. 10, 21-26.

Chen R., Kim O., Li M., Xiong X., Guan J.L., Kung H.J., Chen H., Shimizu Y. and Qiu Y. (2001). Regulation of the PH-domain-containing tyrosine kinase Etk by focal adhesion kinase through the FERM domain. Nat. Cell. Biol. 3, 439-444.

Chen S.Y. and Chen H.C. (2006). Direct interaction of focal adhesion kinase (FAK) with Met is required for FAK to promote hepatocyte growth factor-induced cell invasion. Mol. Cell. Biol. 26, 5155-5167.

Cheng K., Kurzrock R., Qiu X., Estrov Z., Ku S., Dulski K.M., Wang J.Y.J. and Talpaz M. (2002). Reduced focal adhesion kinase and paxillin phosphorylation in BCR-ABL-transfected cells. Cancer 95, 440-450.

Chevalier S., Defoy I., Lacoste J., Hamel L., Guy L., Begin L.R. and Aprikian A.G. (2002). Vascular endothelial growth factor and signaling in the prostate: more than angiogenesis. Mol. Cell. Endocrinol. 189, 169-179.

Coppolino M.G. and Dedhar S. (2000). Bi-directional signal transduction by integrin receptors. Int. J. Biochem. Cell. Biol. 32, 171-188.

Cox B.D., Natarajan M., Stettner M.R. and Gladson C.L. (2006). New concepts regarding focal adhesion kinase promotion of cell migration and proliferation. J. Cell. Biochem. 99, 35-52.

Cukirman E., Pankov R., Stevens D.R. and Yamada K.M. (2001). Taking cell-matrix adhesions to the third dimension. Science 294, 1708-1712.

Das B., Shu X., Day G.J., Hant J., Krishna U.M, Falck J.R. and Broek D. (2000). Control of intramolecular interactions between the pleckstrin homology and Dbl homology domains of Vav and Sos1 regulates Rac binding. J. Biol. Chem. 275, 15074-15081.

Davies M.A., Lu Y., Sano T., Fang X., Tang P., LaPushin R., Koul D., Bookstein R., Stokoe D., Yung W.K., Millis G.B. and Steck P.A. (1998). Adenoviral transgene expression of MMAC/PTEN in human glioma cells inhibits Akt activation and induces anoikis. Cancer Res. 58, 5285-5290.

De Belle I., Huang R.P., Fan Y., Liu C., Mercola D. and Adamson E.D. (1999). p53 and Egr-1 additively suppress transformed growth in HT1080 cells but Egr-1 counteracts p53-dependent apoptosis. Oncogene 18, 3633-3642.

Derkinderen P., Toutant M., Burgaya F., Le Bert M., Siciliano J.C., De Franciscis V., Gelman M. and Girault JA. (1996). Regulation of a neuronal form of focal adhesion kinase by anandamide. Science 273, 1719-1722.

Ding Q., Grammer J.R., Nelson M.A., Guan J.L., Stewart J.E. Jr and Gladson C.L. (2005). p27Kip1 and cyclin D1 are necessary for focal adhesion kinase regulation of cell cycle progression in glioblastoma cells propagated in vitro and in vivo in the scid mouse brain. J. Biol. Chem. 280, 6802-6815.

Dong Z., Huang C. and Ma WY. (1999). PI-3 kinase in signal transduction, cell transformation, and as a target for chemoprevention of cancer. Anticancer Res. 19, 3743-3747.

Duncan M.D., Harmon J.W. and Duncan K.L.K. (1996). Actin disruption inhibits bombesin stimulation of focal adhesion kinase (pp125FAK) in prostate carcinoma. J. Surg. Res. 63, 359-363.

Duxbury M.S., Ito H., Benoit E., Zinner M.J., Ashley S.W. and Whang E.E. (2003). RNA interference targeting focal adhesion kinase enhances pancreatic adenocarcinoma gemcitabine chemosensitivity. Biochem. Biophys. Res. Commun. 311, 786-792.

Earley S. and Plopper E. (2006). Disruption of focal adhesion kinase slows transendothelial migration of AU-565 breast cancer cells. Biochem. Biophys. Res. Commun. 350, 405-412.

Essler M., Amano M., Kruse H.J., Kaibuchi K., Weber P.C. and Aepfelbacher M. (1998). Thrombin inactivates myosin light chain phosphatase via Rho and its target Rho kinase in human endothelial cells. J. Biol. Chem. 273, 21867-21874.

Finnemann S.C. (2003). Focal adhesion kinase signaling promotes phagocytosis of integrin-bound photoreceptors. EMBO J. 22, 4143-4154.

Fujii T., Koshikawa K., Nomoto S., Okochi O., Kaneko T., Inoue S., Yatabe Y., Takeda S. and Nakao A. (2004). Focal adhesion kinase is overexpressed in hepatocellular carcinoma and can be served as an independent prognostic factor. J. Hepatol. 41, 104-111.

Furuyama K., Ryuchiro D., Tomohiko M., Toyoda E., Ito D., Kami K., Koizumi M., Kida A., Kawaguchi Y. and Fujimoto K. (2006). Clinical significance of focal adhesion kinase in resectable pancreatic cancer. World J. Surg. 30, 219-226.

Gabriel B., Mildenberger S., Weisser C.W., Metzger E., Gitsch G., Schule R. and Muller J.M. (2004). Focal adhesion kinase interacts with the transcriptional coactivator FHL2 and both are overexpressed in epithelial ovarian cancer. Anticancer Res. 24, 921-927.

Gabriel B., zur Hausen A., Stickeler E., Dietz C., Gitsch G., Fischer D.C., Boulda J., Tempfer C. and Hasenburg A. (2006). Weak expression of focal adhesion kinase (pp125FAK) in patients with cervical cancer is associated with poor disease outcome. Clin. Cancer Res. 12, 2476-2483.

Glover S., Delanet M., Dematte C., Kornberg L., Frasco M., Tran-So-Tay R. and Benya R.V. (2004). Phosphorylation of focal adhesion kinase tyrosine 397 critically mediates gastrin-releasing peptide's morphogenic properties. J. Cell Physiol. 199, 77-88.

Golubovskaya V.M., Finch R. and Cance W.G. (2005) Direct interaction of the N-terminal domain of focal adhesion kinase with the N-terminal transactivation domain of p53. J. Biol. Chem. 280, 25008-25021.

Grisaru-Granovsky S., Salah Z., Maoz M., Pruss D., Beller U. and Bar-Shavit R. (2005). Differential expression of protease activated receptor 1 (Par1) and pY397FAK in benign and malignant human ovarian tissue samples. Int. J. Cancer 113, 372-378.

Gu J., Tamura M. and Yamada K.M. (1998). Tumor suppressor PTEN inhibits integrin- and growth factor-mediated mitogen-activated protein (MAP) kinase signaling pathways. J. Cell Biol. 143, 1375-1383

Guan J.L. (1997). Role of focal adhesion kinase in integrin signaling. Int. J. Biochem. Cell. Biol. 29, 1085-1096.

Gutenberg A., Bruck W., Buchfelder M. and Ludwig H.C. (2004). Expression of tyrosine kinases FAK and Pyk2 in 331 human astrocytomas. Acta. Neuropathol (Berl). 108, 224-230.

Halder J., Kamat A.A., Landen C.N. Jr, Han L.Y., Lutgendorf S.K., Lin Y.G., Merritt W.M., Jennings N.B., Chavez-Reyes A., Coleman R.L., Gershenson D.M., Schmandt R., Cole S.W., Lopez-Berestein G. and Sood A.K. (2006). Focal adhesion kinase targeting using in vivo short interfering RNA delivery in neutral liposomes for ovarian

carcinoma therapy. Clin Cancer Res. 12, 4916-4924.

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

Haskell H., Natarajan M., Hecker T.P., Ding Q., Stewart J. Jr, Grammer J.R. and Gladson C.L. (2003). Focal adhesion kinase is expressed in the angiogenic blood vessels of malignant astrocytic tumors in vivo and promotes capillary tube formation of brain microvascular endothelial cells. Clin. Cancer Res. 9, 2157-2165.

He Z.X., He H.W., Wang D. and Fang M.X. (2006). Expression and clinical significance of focal adhesion kinase in oral squamous cell carcinoma. Sichuan Da Xue Xue Bao Yi Xue Ban 37, 876-878.

Hecker T.P., Grammer J.R., Gillespie G.Y., Stewart J. Jr. and Gladson C.L. (2002). Focal adhesion kinase enhances signaling through the Shc/extracellular signal-regulated kinase pathway in anaplastic astrocytoma tumor biopsy samples. Cancer Res. 62, 2699-2707.

Hehlgans S., Haase M. and Cordes N. (2007). Signalling via integrins: Implications for cell survival and anticancer strategies. Biochim. Biophys. Acta 1775, 163-180.

Hood J.D., Frausto R., Kiosses W.B., Schwartz M.A. and Cheresh D.A. (2003) Differential alphav integrin-mediated Ras-ERK signaling during two pathways of angiogenesis. J. Cell Biol. 162, 933-943.

Horowitz J.C., Rogers D.S., Sharma V., Vittal R., White E.S., Cui Z. and Thannickal V.J. (2007). Combinatorial activation of FAK and AKT by transforming growth factor-beta1 confers an anoikis-resistant phenotype to myofibroblasts. Cell Signal. 19, 761-771.

Hu B., Jarzynka M.J., Guo P., Imanishi Y., Schlaepfer D.D. and Cheng S.Y. (2006). Angiopoietin 2 induces glioma cell invasion by stimulating matrix metalloprotease 2 expression through the alphavbeta1 integrin and focal adhesion kinase signaling pathway. Cancer Res. 66, 775-783.

Hungerford J.E., Compton M.T., Matter M.L., Hoffstrom B.G. and Otey C.A. (1996). Inhibition of pp125FAK in cultured fibroblasts results in apoptosis. J. Cell Biol. 135, 1383-1390.

Ignatoski K.M. and Ethier S.P. (1999). Constitutive activation of pp125fak in newly isolated human breast cancer cell lines. Breast Cancer Res. Treat. 54, 173-182.

Imaizumi M., Nishimura M., Takeuchi S., Murase M. and Hamaguchi M. (1997). Role of tyrosine specific phosphorylation of cellular proteins, especially EGF receptor and p125FAK in human lung cancer cells. Lung Cancer 17, 69-84.

Imamura F., Mukai M., Ayaki M. and Akedo H. (2000). Y-27632, an inhibitor of rho-associated protein kinase, suppresses tumor cell invasion via regulation of focal adhesion and focal adhesion kinase. Jpn. J. Cancer Res. 91, 811-816.

Itoh S., Maeda T., Shimada M., Aishima S.I., Shirabe K., Tanaka S. and Maehara Y. (2004). Role of expression of focal adhesion kinase in progression of hepatocellular carcinoma. Clin. Cancer Res. 10, 2812-2817.

Jones G., Machado J. Jr, Tolnay M. and Merlo A. (2001). PTEN-independent induction of caspase-mediated cell death and reduced invasion by the focal adhesion targeting domain (FAT) in human astrocytic brain tumors which highly express focal adhesion kinase (FAK). Cancer Res. 61, 5688-5691.

Judson P.L., He X., Cance W.G. and Van Le L. (1999). Overexpression of focal adhesion kinase, a protein tyrosine kinase, in ovarian carcinoma. Cancer 86, 1551-1556.

Kaczmarek E., Erb L., Koziak K., Jarzyna R., Wink M.R., Guckelberger O., Blusztajn J.K., Trinkaus-Randall V., Weisman G. and Robson S.C. (2005). Modulation of endothelial cell migration by extracellular nucleotides: involvement of focal adhesion kinase and phosphatidylinositol 3-kinase-mediated pathways. Thromb. Haemost. 93, 735-742.

Kasahara T., Koguchi E., Funakoshi M., Aizu-Yokota E. and Sonada Y. (2002). Antiapoptotic action of focal adhesion kinase (FAK) against ionizing radiation. Antioxid. Redox. Signal. 4, 491-499.

Kato R., Ishikawa T., Kamiya S., Oguma F., Ueki M., Goto S., Nakamura H., Katayama T. and Fukai F. (2002). A new type of antimetastatic peptide derived from fibronectin. Clin. Cancer Res. 8, 2455-2462.

Kim R.D., Darling C.E., Roth T.P., Ricciardi R. and Chari R.S. (2001). Activator protein 1 activation following hypoosmotic stress in HepG2 cells is actin cytoskeleton dependent. J. Surg. Res. 100, 176-182.

Kim S.J., Park J.W., Yoon J.S., Mok J.O., Kim Y.J., Park H.K., Kim C.H., Byun D.W., Lee Y.J., Jin S.Y., Suh K.I.I. and Myung H.Y. (2004). Increased expression of focal adhesion kinase in thyroid cancer: immunohistochemical study. J. Korean Med. Sci. 19, 710-715.

Kimura K., Ito M., Amano M., Chihara K., Fukata Y., Nakafuku M., Yamamori B., Feng J., Nakano T., Okawa K., Iwamatsu K. and Kaibuchi K. (1996). Regulation of myosin phosphatase by Rho and Rho-associated kinase (Rho-kinase). Science 273, 245-248.

Kiosses W.B., Daniels R.H., Otey C., Bokoch G.M. and Schwartz M.A. (1999). A role for p21-activated kinase in endothelial cell migration. J. Cell Biol. 147, 831-844.

Kiosses W.B., Hood J., Yang S., Gerritsen M.E., Cheresh D.A., Alderson N. and Schwartz MA. (2002). A dominant-negative p65 PAK peptide inhibits angiogenesis. Circ. Res. 90, 697-702.

Kiyokawa E., Hashimoto Y., Kobayashi S., Sugimura H., Kurata T. amd Matsudaa M. (1998). Activation of Rac1 by a Crk SH3-binding protein, DOCK180. Genes Dev. 12, 3331-3336.

Kohno M., Hasegawa H., Miyake M., Yamamoto T. and Fujita S. (2002). CD151 enhances cell motility and metastasis of cancer cells in the presence of focal adhesion kinase. Int. J. Cancer 97, 336-343.

Korah R., Choi L., Barrios J. and Wieder R. (2004). Expression of FGF-2 alters focal adhesion dynamics in migration-restricted MDA-MB-231 breast cancer cells. Breast Cancer Res. Treat. 88, 17-28. Erratum in: Breast Cancer Res. Treat. 89, 319-322.

Kornberg L.J. (1998). Focal adhesion kinase expression in oral cancers. Head Neck 20, 634-639.

Lacoste J., Aprikian A.G. and Chevalier S. (2005). Focal adhesion kinase is required for bombesin-induced prostate cancer cell motility. Mol. Cell. Endocrinol. 235, 51-61.

Lark A.L., Livasy C.A., Calvo B., Caskey L., Moore D.T, Yang X.H. and Cance W.G. (2003). Overexpression of focal adhesion kinase in primary colorectal carcinomas and colorectal liver metastases: immunohistochemistry and real-time PCR analyses. Clin. Cancer Res. 9, 215-222.

Lark A.L., Livasy C.A., Dressler L., Moore D.T., Millikan R.C., Geradts J., Iacocca M., Cowan D., Little D., Craven R.J. and Cance W. (2005). High focal adhesion kinase expression in invasive breast carcinomas is associated with an aggressive phenotype. Mod. Pathol. 18, 1289-1294.

Lee L.F., Guan J., Qiu Y. and Kung H.J. (2001). Neuropeptide-induced androgen independence in prostate cancer cells: roles of nonreceptor tyrosine kinases Etk/Bmx, Src, and focal adhesion kinase. Mol. Cell. Biol. 21, 8385-8397.

Lee L.F., Louie M.C., Desai S.J., Yang J., Chen H.W., Evans C.P. and Kung H.J. (2004). Interleukin-8 confers androgen-independent growth and migration of LNCaP: differential effects of tyrosine kinases Src and FAK. Oncogene 23, 2197-2205.

Leventhal P.S., Shelden E.A., Bhumsoo K. and Feldman E.L. (1997). Tyrosine phosphorylation of paxillin and focal adhesion kinase during insulin-like growth factor-I-stimulated lamellipodial advance. J. Biol. Chem. 272, 5214-5218.

Li R., Wong N., Jabali M.D. and Johnson P. (2001). CD44-initiated cell spreading induces Pyk2 phosphorylation, is mediated by Src family kinases, and is negatively regulated by CD45. J. Biol. Chem. 276, 28767-28773.

Lightfott H.M. Jr, Lark A., Livasy C.A., Moore D.T., Cowan D., Dressler L., Craven R.J. and Cance W.G. (2004). Upregulation of focal adhesion kinase (FAK) expression in ductal carcinoma in situ (DCIS) is an early event in breast tumorigenesis. Breast Cancer Res. Treat. 88, 109-116.

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 pp125FAK in platelets. J Cell Biol. 119, 905-912.

Livasy C.A., Moore D., Cance W.G. and Lininger R.A. (2004). Focal adhesion kinase overexpression in endometrial neoplasia. Appl. Immunohistochem. Mol. Morphol. 12, 342-345.

Lu P.J., Lu Q.L., Rughetti A. and Taylor-Papadimitriou J. (1995). Bcl-2 overexpression inhibits cell death and promotes the morphogenesis, but not tumorigenesis of human mammary epithelial cells. J. Cell Biol. 129, 1363-1378. Erratum in: J. Cell Biol. 131, following 1121.

Lu Z., Jiang G., Blume-Jensen P. and Hunter T. (2001). Epidermal growth factor-induced tumor cell invasion and metastasis initiated by dephosphorylation and downregulation of focal adhesion kinase. Mol. Cell Biol. 21, 4016-4031.

Ludwig H.C., Akhavan-Shigari R., Rausch S., Schallock K., Quentin C., Bockermann V. and Kolenda H. (2000). Expression of focal adhesion kinase (p125 FAK) and proline-rich tyrosine kinase 2 (PYK2/CAKb) in cerebral metastases, correlation with VEGF-R-, ecNOS III-labelling and morphometric data. Anticancer Res. 20, 1419-1424.

MacPhee D.J., Mostachfi H., Han R., Lye S.J., Post M. and Caniggia I. (2001). Focal adhesion kinase is a key mediator of human trophoblast development. Lab. Invest. 81, 1469-1483.

Madan R., Smolkin M.B., Cocker R., Fayyad R. amd Oktay M.J. (2006). Focal adhesion proteins as markers of malignant transformation and prognostic indicators in breast carcinoma. Hum. Pathol. 37, 9-15.

Magazin M., Poszepczynska-Guigne E., Bagot M., Boumsell L., Pruvost C., Chalon P., Culouscou J.M., Ferrara P. and Bensussan A. (2004). Sezary syndrome cells unlike normal circulating T lymphocytes fail to migrate following engagement of NT1 receptor. J. Invest. Dermatol. 122, 111-118.

Malarkey K., Belham C.M., Paul A., Graham A., McLees A. and Scott P.H. (1995). The regulation of tyrosine kinase signalling pathways by growth factor and G-protein-coupled receptors. Biochem. J. 309, 361-375.

Malik R.K. and Parsons J.T. (1996). Integrin-mediated signaling in normal and malignant cells: a role of protein tyrosine kinases. Biochim. Biophys. Acta 1287, 73-76.

Manes S., Mira E., Gomez-Mouton C., Zhao Z.J., Lacalle R.A. and Martinez-A C. (1999). Concerted activity of tyrosine phosphatase SHP-2 and focal adhesion kinase in regulation of cell motility. Mol. Cell. Biol. 19, 3125-3135.

Matsumoto K., Matsumoto K., Nakamura T. and Kramer R.H. (1994). Hepatocyte growth factor/scatter factor induces tyrosine phosphorylation of focal adhesion kinase (p125FAK) and promotes migration and invasion by oral squamous cell carcinoma cells. J. Biol. Chem. 269, 31807-31813.

Meierjohann S., Wende E., Kraiss A., Wellbrock C. and Schartl M. (2006). The oncogenic epidermal growth factor receptor variant Xiphophorus melanoma receptor kinase induces motility in melanocytes by modulation of focal adhesions. Cancer Res. 66, 3145-3152.

Melkoumian Z.K., Peng X., Gan B., Wu X. amd Guan J.L. (2005). Mechanism of cell cycle regulation by FIP200 in human breast cancer cells. Cancer Res. 65, 6676-6684.

Millan A., Aguilar P., Mendez J.A., Arias-Montano J.A. (2001). Glutamate activates PP125(FAK) through AMPA/kainate receptors in Bergmann glia. J. Neurosci. Res. 66, 723-729.

Mitchinson T. and Cramer L. (1996). Actin-based cell motility and cell locomotion. Cell 84, 371-379.

Mitra S.K. and Schlaepfer D.D. (2006). Integrin-regulated FAK-Src signaling in normal and cancer cells. Curr. Opin. Cell Biol. 18, 516-523.

Miyazaki T., Kato H., Kimura H., Inose T., Faried A., Sohda M., Nakajima M., Fukai Y., Masuda N., Manda R., Fukuchi M., Tsukada K. and Kuwano H. (2005). Evaluation of tumor malignancy in esophageal squamous cell carcinoma using different characteristic factors. Anticancer Res. 25, 4005-4011.

Miyazaki T., Kato H., Nakajima M., Sohda M., Fukai Y., Masuda N., Manda N., Fukuchi M., Tsukada K., and Kuwano H. (2003). FAK overexpression is correlated with tumour invasiveness and lymph node metastasis in oesophageal squamous cell carcinoma. Br. J. Cancer. 89, 140-145.

Mizutani T., Shiraishi K., Welsh T. and Ascoli M. (2006). Activation of the lutropin/choriogonadotropin receptor in MA-10 cells leads to the tyrosine phosphorylation of the focal adhesion kinase by a pathway that involves Src family kinases. Mol. Endocrinol. 20, 619-630.

Mon N.N., Hasegawa H., Thant A.A., Huang P., Tanimura Y., Senga T. amd Hamaguchi M. (2006). A role for focal adhesion kinase signaling in tumor necrosis factor-alpha-dependent matrix metalloproteinase-9 production in a cholangiocarcinoma cell line, CCKS1. Cancer Res. 66, 6778-84.

Monami G., Gonzalez E.M., Hellman M., Gomella L.G, Baffa R., Iozzo R.V. and Morrione A. (2006). Proepithelin promotes migration and invasion of 5637 bladder cancer cells through the activation of ERK1/2 and the formation of a paxillin/FAK/ERK complex. Cancer Res. 66, 7103-7110.

Moon H.S., Park W.I., Choi E.A., Chung H.W. and Kim S.C. (2003). The expression and tyrosine phosphorylation of E-cadherin/catenin adhesion complex, and focal adhesion kinase in invasive cervical carcinomas. Int. J. Gynecol. Cancer 13, 640-646.

Moritake H., Sugimoto T., Kuroda H., Hidaka F., Takahashi Y., Tsuneyoshi M., Yoshida M.A., Cui Q., Akiyoshi K., Izumi T. and Nunoi H. (2003). Newly established Askin tumor cell line and overexpression of focal adhesion kinase in Ewing sarcoma family of tumors cell lines. Cancer Genet. Cytogenet. 146, 102-109.

Nishimura M., Machida K., Imaizumi M., Abe T., Umeda T., Takeshima E., Watanabe T., Ohnishi Y., Takagi K. and Hamaguchi M. (1996). Tyrosine phosphorylation of 100-130 kDa proteins in lung cancer correlates with poor prognosis. Br. J. Cancer 74, 780-787.

Oktay M.H., Oktay K., Hamele-Bena D., Buyuk A. and Koss L.G. (2003). Focal adhesion kinase as a marker of malignant phenotype in breast and cervical carcinomas. Hum. Pathol. 34, 240-245.

Owens L.V., Xu L.H., Craven R.J., Dent G.A., Weiner T.M., Kornberg L., Liu E.T. and Cance W.G. (1995). Overexpression of the focal adhesion kinase (p125FAK) in invasive human tumors. Cancer Res.

55, 2752-2755.

Owens L.V., Xu L.H., Dent G.A., Yang X.H., Sturge G.C., Craven R.J. and Cance W.G. (1996). Focal adhesion kinase as a marker of invasive potential in differentiated human thyroid cancer. Ann. Surg. Oncol. 3, 100-105.

Papakonstanti E.A., Kampa M., Castanas E. and Stournaras C. (2003). A rapid, nongenomic, signaling pathway regulates the actin reorganization induced by activation of membrane testosterone receptors. Mol. Endocrinol. 17, 870-881.

Park M.J., Kim M.S., Park I.C., Kang H.S., Yoo H., Park S.H., Rhee C.H., Hong S.I. and Lee S.H. (2002). PTEN suppresses hyaluronic acid-induced matrix metalloproteinase-9 expression in U87MG glioblastoma cells through focal adhesion kinase dephosphorylation. Cancer Res. 62, 6318-6322.

Planas-Silva M.D., Bruggeman R.D., Grenko R.T. and Smith J.S. (2006). Role of c-Src and focal adhesion kinase in progression and metastasis of estrogen receptor-positive breast cancer. Biochem. Biophys. Res. Commun. 341, 73-81.

Pongchairerk U., Guan J.L. and Leardkamolkam V. (2005). Focal adhesion kinase and Src phosphorylations in HGF-induced proliferation and invasion of human cholangiocarcinoma cell line, HuCCA-1. World J. Gastroenterol. 11, 5845-5852.

Qiang Y.W., Yao L., Tosato G. and Rudikof S. (2004). Insulin-like growth factor I induces migration and invasion of human multiple myeloma cells. Blood 103, 301-308.

Rascan I.M. (2001). Focal adhesion kinase modulates B cell receptor-transduced apoptosis in WEHI 231 cells. Pflugers Arch. 442, R157-158.

Recher C., Ysebaert L., Beyne-Rauzy O., Mansat-De Mas V., Ruidavets J.B., Cariven P., Demur C., Payrastre B., Laurent G. and Racaud-Sultan C. (2004). Expression of focal adhesion kinase in acute myeloid leukemia is associated with enhanced blast migration, increased cellularity, and poor prognosis. Cancer Res. 64, 3191-3197.

Reddy S.A., Huang J.H. and Liao W.S. (1997). Phosphatidylinositol 3-kinase in interleukin 1 signaling. Physical interaction with the interleukin 1 receptor and requirement in NFkappaB and AP-1 activation. J. Biol. Chem. 272, 29167-29173.

Rodriguez-Fernandez J.L. (1999). Why do so many stimuli induce tyrosine phosphorylation of FAK? Bioessays. 21, 1069-1075.

Rovin J.D., Frierson H.F. Jr, Ledinh W., Parsons J.T. and Adams R.B. (2002). Expression of focal adhesion kinase in normal and pathologic human prostate tissues. Prostate 53, 124-132.

Rozengurt E., Guha S. and Sinnett-Smith J. (2002). Gastrointestinal peptide signalling in health and disease. Eur. J. Surg. Suppl. 587, 23-38.

Sawhney R.S., Cookson M.M., Omar Y., Hauser J. and Brattin M.G. (2006). Integrin alpha2-mediated ERK and calpain activation play a critical role in cell adhesion and motility via focal adhesion kinase signaling: identification of a novel signaling pathway. J. Biol. Chem. 281, 8497-8510.

Schaller M.D. and Parsons J.T. (1994). Focal adhesion kinase and associated proteins. Curr. Opin. Cell Biol. 6, 705-710.

Schlaepfer D.D., Hauck C.R. and Stieg D.J. (1999). Signaling through focal adhesion kinase. Prog. Biophys. Mol. Biol. 71, 435-478.

Schlaepfer D.D., Mitra S.K. and Ilic D. (2004). Control of motile and invasive cell phenotypes by focal adhesion kinase. Biochim. Biophys. Acta 1692, 77-102.

Schmitz K.J., Grabellus F., Callies R., Otterbach F., Wohlschlaeger J., Levkau B., Kimmig R., Schmid K.W. and Baba H.A. (2005). Specific induction of pp125 focal adhesion kinase in human breast cancer. Br. J. Cancer 93, 694-698.

Schneider G.B., Kurago Z., Zaharias R., Gruman L.M., Schaller M.D. and Hendrix M.J.C. (2002). Elevated focal adhesion kinase expression facilitates oral tumor cell invasion. Cancer 95, 2508-2515.

Sheta E.A., Harding M.A., Conaway M.R., and Theodorescu D. (2000). Focal adhesion kinase, Rap1, and transcriptional induction of vascular endothelial growth factor. J. Natl. Cancer Inst. 92, 1065-1073.

Siciliano J.C., Toutant M., Derkinderen P., Sasaki T. amd Girault J.A. (1996). Differential regulation of proline-rich tyrosine kinase 2/cell adhesion kinase beta (PYK2/CAKbeta) and pp125(FAK) by glutamate and depolarization in rat hippocampus. J. Biol. Chem. 271, 28942-28946.

Smith C.S., Golubovskaya V.M., Peck E., Xu L.H., Monia B.P., Yang X. and Cance W.G. (2005). Effect of focal adhesion kinase (FAK) downregulation with FAK antisense oligonucleotides and 5-fluorouracil on the viability of melanoma cell lines. Melanoma Res. 15, 357-362.

Sonoda Y., Kasahara T., Yokota-Aizu E., Ueno M. and Watanabe S. (1997). A suppressive role of p125FAK protein tyrosine kinase in hydrogen peroxide-induced apoptosis of T98G cells. Biochem. Biophys. Res. Commun. 241, 769-774.

Sonoda Y., Watanabe S., Matsumoto Y., Aizu-Yokota E. and Kasahara T. (1999). FAK is the upstream signal protein of the phosphatidylinositol 3-kinase-Akt survival pathway in hydrogen peroxide-induced apoptosis of a human glioblastoma cell line. J. Biol. Chem. 274, 10566-10570.

Sood A.K., Coffin J.E., Schneider G.B., Fletcher M.S., DeYoung B.R., Gruman L.M., Gershenson D.M., Schaller M.D. and Hendrix M.J.C. (2004). Biological significance of focal adhesion kinase in ovarian cancer: role in migration and invasion. Am. J. Pathol. 165, 1087-1095.

Sorenson C.M. and Sheibani N. (1999). Focal adhesion kinase, paxillin, and bcl-2: analysis of expression, phosphorylation, and association during morphogenesis. Dev. Dyn. 215, 371-382.

Sorenson C.M. and Sheibani N. (2002). Altered regulation of SHP-2 and PTP 1B tyrosine phosphatases in cystic kidneys from bcl-2 -/- mice. Am. J. Physiol. Renal Physiol. 282, F442-450.

Su J.M, Gui L., Zhou Y.P. and Zha X.L. (2002). Expression of focal adhesion kinase and alpha5 and beta1 integrins in carcinomas and its clinical significance. World J. Gastroenterol. 8, 613-618.

Tai Y.Z., Podar K., Catley L., Tseng Y.H., Akiyama M., Shringarpure R., Burger R., Hideshima T., Chauhan D., Mitsiades N., Richardson P., Munshi N.C., Kahn C.R., Mitsiades C. and Anderson K.C. (2003). Insulin-like growth factor-1 induces adhesion and migration in human multiple myeloma cells via activation of beta1-integrin and phosphatidylinositol 3'-kinase/AKT signaling. Cancer Res. 63, 5850-5858. Erratum in: Cancer Res. 63, 7543.

Takahashi R., Sonoda Y., Ichikawa D., Yoshida N., Eriko A.Y. and Tadashi K. (2007). Focal adhesion kinase determines the fate of death or survival of cells in response to TNFalpha in the presence of actinomycin D. Biochim. Biophys. Acta 1770, 518-526.

Tamura M., Gu J., Danan E.H.J., Takino T., Miyamoto S. and Yamada K.M. (1999). PTEN interactions with focal adhesion kinase and suppression of the extracellular matrix-dependent phosphatidylinositol 3-kinase/Akt cell survival pathway. J. Biol. Chem. 274, 20693-20703.

Tamura M., Gu J., Matsumoto K., Aota S., Parsons R. and Yamada K.M. (1998). Inhibition of cell migration, spreading, and focal

adhesions by tumor suppressor PTEN. Science 280, 1614-1617.
Tamura M., Gu J., Takino T. and Yamada KM. (1999). Tumor suppressor PTEN inhibition of cell invasion, migration, and growth: differential involvement of focal adhesion kinase and p130Cas. Cancer Res. 59, 442-449.
Tamura M., Gu J., Tran H. and Yamada K.M. (1999). PTEN gene and integrin signaling in cancer. J. Nat. Cancer Inst. 91, 1820-1828.
Tanaka C. and Nishizuka Y. (1994). The Protein Kinase C Family for Neuronal Signaling. Annu. Rev. Neurosci. 17, 551-567.
Tani T., Von Koskull H. and Virtanen I. (1996). Focal adhesion kinase pp125FAK is associated with both intercellular junctions and matrix adhesion sites in vivo. Histochem. Cell. Biol. 105, 17-25.
Ten Klooster J.P., Jaffer Z.M., Chernoff J. and Hordijk P.L. (2006). Targeting and activation of Rac1 are mediated by the exchange factor ß-Pix. J. Cell Biol. 172, 759-769.
Thamilselvan V. and Basson M.D. (2004). Pressure activates colon cancer cell adhesion by inside-out focal adhesion complex and actin cytoskeletal signaling. Gastroenterology 126, 8-18.
Thamilselvan V. and Basson M.D. (2005). The role of the cytoskeleton in differentially regulating pressure-mediated effects on malignant colonocyte focal adhesion signaling and cell adhesion. Carcinogenesis 26, 1687-1697.
Theocharis S.E., Kouraklis G.P., Kakisis J.D., Kanelli H.G., Apostolakou F.E., Karatzas G.M. and Koutselinis A.S. (2003). Focal adhesion kinase expression is not a prognostic predictor in colon adenocarcinoma patients. Eur. J. Surg. Oncol. 29, 571-574.
Toker A., Meyer M., Reddy K.K., Falck J.R., Aneja R., Aneja S., Parra A., Burns D.J., Ballas L.M. and Cantley LC. (1994). Activation of protein kinase C family members by the novel polyphosphoinositides PtdIns-3,4-P2 and PtdIns-3,4,5-P3. J. Biol. Chem. 269, 32358-32367.
Tremblay L., Hauck W., Aprikian A.G., Begin L.R., Chapdelaine A. and Chevalier S. (1996). Focal adhesion kinase (pp125FAK) expression, activation and association with paxillin and p50CSK in human metastatic prostate carcinoma. Int. J. Cancer 68, 164-71.
Tsai Y.T., Su Y.H., Fang S.S., Huang T.N., Qiu Y., Jou Y.S., Shih H.M., Kung H.J. and Chen R.H. (2000). Etk, a Btk family tyrosine kinase, mediates cellular transformation by linking Src to STAT3 activation. Mol. Cell. Biol. 20, 2043-2054.
Tsuda T., Kusui T. and Jensen R. (1997). Neuromedin B receptor activation causes tyrosine phosphorylation of p125FAK by a phospholipase C independent mechanism which requires p21rho and integrity of the actin cytoskeleton. Biochemistry 36, 16328-16337.
Vadlamudi R.K., Adam L., Nguyen D., Santos M. and Kumar R. (2002). Differential regulation of components of the focal adhesion complex by heregulin: role of phosphatase SHP-2. J. Cell. Physiol. 190, 189-199.
Vadlamudi R.K., Sahinn A.A., Adam L., Wang R.A. and Kumar R. (2003). Heregulin and Her2 signaling selectively activates c-Src phosphorylation at tyrosine 215. FEBS Lett. 2003 543: 76-80.
Van Nimwegen M.J. and Van de Water B. (2007). Focal adhesion kinase: A potential target in cancer therapy. Biochem. Pharmacol. 73, 597-609.
Wang D., Grammer J.R., Cobbs C.S., Stewart J.E. Jr, Liu Z., Rhoden R., Hecker T.P., Ding Q. and Gladson C.L. (2000). p125 focal adhesion kinase promotes malignant astrocytoma cell proliferation in vivo. J. Cell. Sci. 113, 4221-4230.
Wang F.M., Liu H.Q., Liu S.R., Tang S.P., Yang L. and Feng G.S. (2005). SHP-2 promoting migration and metastasis of MCF-7 with loss of E-cadherin, dephosphorylation of FAK and secretion of MMP-9 induced by IL-1beta in vivo and in vitro. Breast Cancer. Res. Treat. 89, 5-14.
Wang H., Radjendirane V., Wary K.K. and Chakrabarty S. (2004). Transforming growth factor beta regulates cell-cell adhesion through extracellular matrix remodeling and activation of focal adhesion kinase in human colon carcinoma Moser cells. Oncogene 23, 5558-5561.
Wang W.J., Kuo J.C., Yao C.C. and Chen RH. (2002). DAP-kinase induces apoptosis by suppressing integrin activity and disrupting matrix survival signals. J. Cell Biol. 159, 169-179.
Wang X.Y., Liu T., Zhu C.Z., Li Y., Sun R., Sun C.Y. and Wang AX. (2005). Expression of KAI1, MRP-1, and FAK proteins in lung cancer detected by high-density tissue microarray. Ai Zheng. 24, 1091-1095.
Watermann D.O., Gabriel B., Jager M., Orlowska-Volk M., Hasenburg A., zur Hansen A., Gitsch G. and Stickeler E. (2005). Specific induction of pp125 focal adhesion kinase in human breast cancer. Br. J. Cancer 93, 694-698.
Weiner T.M., Liu E.T., Craven R.J. and Cance W.G. (1993). Expression of focal adhesion kinase gene and invasive cancer. Lancet 342, 1024-1025.
Weiner T.M., Liu E.T., Craven R.J. and Cance W.G. (1994). Expression of growth factor receptors, the focal adhesion kinase, and other tyrosine kinases in human soft tissue tumors. Ann. Surg. Oncol. 1, 18-27.
Westhoff M.A., Serrels B., Fincham V.J., Frame M.C. and Carragher N.O. (2004). SRC-mediated phosphorylation of focal adhesion kinase couples actin and adhesion dynamics to survival signaling. Mol. Cell. Biol. 24, 8113-8133.
Yu F., Dong Y., Jiao Y., Zhang H., Li X., Liang Z. and Xie J. (2004). Expression of focal adhesion kinase in laryngeal carcinoma. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 18, 149-151.
Yu H.G., Schrader H., Otte J.M., Schmidt W.E. and Schmitz F. (2004). Rapid tyrosine phosphorylation of focal adhesion kinase, paxillin, and p130Cas by gastrin in human colon cancer cells. Biochem. Pharmacol. 67, 135-146.
Yu H.G., Tong S.L., Ding Y.M., Ding J., Fang X.M., Zhang X.F., Liu Z.J., Zhou Y.H., Liu Q.S., Luo H.S. and Yu J.P. (2006). Enhanced expression of cholecystokinin-2 receptor promotes the progression of colon cancer through activation of focal adhesion kinase. Int. J. Cancer 119, 2724-2732.
Zachary I., Sinnett-Smith J., Rozengurt E. (1992) Bombesin, vasopressin, and endothelin stimulation of tyrosine phosphorylation in Swiss 3T3 cells. Identification of a novel tyrosine kinase as a major substrate. J. Biol. Chem. 267, 19031-19034.
Zachary I. (1997). Focal adhesion kinase. Int. J. Biochem. Cell. Biol. 29, 929-934.
Zeng Z.Z., Lia Y., Hahn N.J., Markwart S.M., Rockwood K.E. and Livant D.L. (2006). Role of focal adhesion kinase and phosphatidylinositol 3'-kinase in integrin fibronectin receptor-mediated, matrix metalloproteinase-1-dependent invasion by metastatic prostate cancer cells. Cancer Res. 66, 8091-8099.
Zhang L., Yu Q., He J. and Zha X. (2004). Study of the PTEN gene expression and FAK phosphorylation in human hepatocarcinoma tissues and cell lines. Mol. Cell. Biochem. 262, 25-33.

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