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FOCAL ADHESION KINASE IN CANCER

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1. ABSTRACT

Focal adhesion kinase (FAK) is a non-receptor cytoplasmic tyrosine kinase that transmits signals important in modulating several cell functions, including proliferation, migration, and survival. Several different types of malignant tumors have been reported to express elevated levels of FAK protein *in vivo*, potentially pointing to a role for FAK in either the progression of tumor cells to malignancy or the pathogenesis of cancer. Considerable knowledge has been gained regarding FAK signaling in non-neoplastic cells, such as fibroblasts, while much less is known regarding FAK signaling in malignant cells. Several studies to date suggest that the regulation of FAK activity and signaling may be different in malignant cells. In this review, we summarize what is known regarding the function and signaling of FAK in cancer cells, and highlight areas that need further study. Evidence is emerging that aberrant FAK expression, activity, and signaling can potentially promote the progression of several types of tumors *in vivo* through its effects on cell function.

2. INTRODUCTION

Focal adhesion kinase (FAK) is a non-receptor cytoplasmic tyrosine kinase that modulates multiple cell functions. Since the identification and cloning of FAK in the early 1990's, the majority of the work published has shown that FAK activity and signaling plays a role in modulating cell proliferation, migration, and survival in non-malignant cells, such as fibroblasts (1, 2). Because of the work in fibroblasts and the implication that FAK regulates cell functions that are likely associated with tumor progression, FAK has become the focus of a number of studies regarding the migration/invasion, proliferation, and survival of cancer cells.

Cancer cells or malignant cells are significantly different from non-malignant cells with regards to their genetic profile, for example loss of function mutations and gain of function mutations occur in these cells (3). In addition, other cellular alterations occur in cancer cells, for example the upregulation or downregulation of specific integrin receptors and the overexpression of the epidermal growth factor receptor (EGFR) (3-6). The influence of these perturbations on FAK signaling and subsequent cell functions can only be understood when *in vitro* studies and *in vivo* animal studies of various types of cancer cells are performed. This signaling in cancer cells is different from the signaling typically described in non-malignant or primary normal cells that are propagated *in vitro*. In this review, we summarize the published work regarding FAK function in tumor cells cultured from spontaneously-derived tumors and in cells transformed with various oncogenes, and we highlight the work that points to a role for FAK signaling in promoting tumor progression through its modulation of various cell functions. We will also point out gaps in our current knowledge regarding the function of FAK in malignant cells and its potential role in tumor progression. Here we limit the use of the term *in vivo* to animal studies or to studies on tissues derived from animals or patient biopsies.

3. FAK AND TUMOR CELL PROLIFERATION *IN VITRO*

Studies investigating the role of FAK in tumor and cancer cell proliferation *in vitro* have been limited. The majority of these studies have focused on the role of FAK in two-dimensional monolayer growth assays where cell surface integrin receptors are engaged, plus/minus growth

factor stimulation. Leyton *et al.* (7) have reported that H1299 non-small cell lung cancer cells treated with bombesin showed increased FAK phosphorylation and increased tumor cell proliferation when propagated as a monolayer. Treatment of these cells with antisense FAK oligonucleotide resulted in decreased proliferation, suggesting a role for FAK in the proliferation of bombesin-stimulated lung cancer cells. Abdel-Ghany *et al.* (8) have reported recently that FAK activity was necessary for B16-F10 melanoma cells to proliferate on endothelial cell-coated plates; these tumor cells attached to the endothelial cell Ca^{+2}-sensitive chloride channel protein through the beta 4 integrin and this ligation lead to the activation of FAK. The proliferation of the B16-F10 melanoma cells appeared to be dependent on FAK signaling to ERK, as expression of a dominant-negative FAK construct (FRNK) decreased ERK activity and correlated closely with decreased BrdU incorporation. FRNK is a splice isoform of FAK found in embryonic chicken cells that encodes the carboxyl-terminal domain of FAK without the amino-terminal and kinase domains (9). This construct competes with FAK for localization to focal adhesions and inhibits FAK signaling (10). FAK activity has also been implicated in growth factor and integrin-mediated proliferation of breast cancer cell lines and malignant hematopoietic cell lines (11-13).

We demonstrated recently that the stable overexpression of FAK in the U-251MG human malignant astrocytoma/glioblastoma cells promoted growth in soft agar (anchorage-independent growth), in a manner dependent on the dosage level of FAK expressed (14). However, we found that cell proliferation as a monolayer in complete media containing 10% serum was not affected by the overexpression of FAK. The mechanism by which FAK promotes growth in soft agar is not clear. Whether growth factor receptors that are upregulated on malignant astrocytoma/glioblastoma cells become activated with autocrine or paracrine growth factor secretion and are responsible for this FAK-promoted growth in soft agar is not known. Roy *et al.* (15) have reported that the expression of FAK in Src-transformed mouse embryo fibroblasts derived from the FAK null mouse did not enhance soft agar growth. This suggests that other alterations are required for FAK to enhance anchorage-independent growth, perhaps the absence of a functional PTEN protein, as is found in the U-251MG cells, or there could be cell-type specificity in FAK function relating to different mechanisms that underlie the transformation of the cells. PTEN is a phosphatase that dephosphosphorylates a subset of inositol phospholipids, and if expressed at stoichiometric concentrations PTEN can dephosphorylate FAK (16).

4. FAK AND TUMOR CELL SURVIVAL *IN VITRO*

One of the earliest pieces of evidence to support a role for FAK in cell survival was provided by the report that transfection into cancer cells of antisense oligonucleotides directed toward FAK resulted in cell detachment from the extracellular matrix and apoptosis (17). While normal cells undergo apoptosis upon detachment from the extracellular matrix (anoikis), studies have shown that in some instances cells can resist anoikis through mechanisms involving FAK (18). In non-malignant or primary normal cells, FAK activation is generally considered to be tightly regulated by integrin-mediated cell attachment or serum stimulation (1, also see the review by Hanks *et al.* in this volume).

FAK signaling to PI3-kinase and Akt are clearly important in promoting cancer cell survival. Tamura *et al.* (19) have shown that the U-87MG malignant astrocytoma/glioblastoma cells and the MDA-MB468 breast cancer cells are resistant to apoptosis in non-adherent suspension culture conditions through a mechanism involving FAK/PI3-kinase/Akt signaling. The U-87MG cell line expresses a mutated PTEN (phosphatase) gene. Re-expression of the wild-type PTEN gene into the U-87MG cells resulted in decreased tumor cell survival and PI3-kinase activity in non-adherent suspension culture conditions through a mechanism involving dephosphorylation of FAK (19). We have reported the increased phosphorylation of FAK at Y397 with the overexpression of FAK in the U-251MG malignant astrocytoma/glioblastoma cells when cultured in aggregate suspension (20), and these cells also lack a functional PTEN gene. In addition, FAK signaling to Akt via PI3-kinase was shown to be necessary for the prevention of apoptosis in the T98G malignant astrocytoma/glioblastoma cells upon exposure to oxidative stress (21). PI3-kinase binds to the phosphorylated Y397 residue in FAK and this association may promote PI3-kinase activity (22). Further evidence that FAK activity (phosphorylation at Y397) is necessary for cancer cell survival is provided by the reports of Sakurai *et al.* (23) and Sonoda *et al.* (24). Expression of a FAK construct mutated at Y397 in the T98G malignant astrocytoma/glioblastoma cells promoted apoptosis by inhibiting PI3-kinase signaling and activating caspase-6, resulting in the proteolysis of endogenous FAK (23, 24).

FAK signaling through p130CAS may also be important in cancer cell survival. Wei *et al.* (25) have demonstrated that lung adenocarcinoma cells are resistant to anoikis through a mechanism involving the constitutive phosphorylation of p130CAS. p130CAS was phosphorylated in these cells cultured in both adherent and suspension conditions, and the expression of a p130CAS construct lacking the substrate domain induced apoptosis. FAK phosphorylation was also detected in these cells under both culture conditions, and FAK activation has been shown to be upstream of p130CAS phosphorylation in other cells (1).

Investigators have begun to determine whether apoptosis induced by the inhibition of FAK-function is due to the activation of the so-called “intrinsic,” or the “death receptor pathway” of apoptosis. Expression of FRNK decreased FAK activity and resulted in the apoptosis of BT474 human breast cancer and C8161 melanoma cells (26). Interestingly, FRNK was able to inhibit FAK function in BT474 cells that were propagated without matrix attachment, on poly-HEMA-coated tissue culture (27). In the BT474 breast cancer cells the apoptosis

induced with expression of FRNK was dependent on the Fas-associated death domain (FADD) and caspase-8, as a dominant-negative version of FADD and a caspase-8 inhibitor blocked apoptosis (27).

FAK is important in promoting cancer cell survival and FAK activity is affected by multiple cellular inputs including, the state of cell attachment or detachment from the matrix, Src activity, and PTEN activity if stoichiometric concentrations of PTEN are available. The identified signals downstream of FAK that can promote the survival of cancer cells include, signaling to PI3-kinase/Akt and p130CAS. A greater understanding of the FAK-mediated mechanisms involved in the ability of tumor cells to resist anoikis are likely important in understanding the process by which tumor cells survive in different environments, such as during tumor cell invasion and metastasis.

5. FAK AND TUMOR CELL MIGRATION/INVASION *IN VITRO*

Integrin receptors mediate cellular migration in large part; the cooperation of other cell surface receptors, such as the urokinase receptor, can also contribute to cell migration (28-30). Much of the work regarding FAK function in malignant tumor cells or cancer cells *in vitro* has focused on FAK signaling that enhances cell migration, likely due to the implication that a role for FAK in modulating cell migration implies a role for FAK in modulating tumor cell invasion. Haptotactic migration (migration toward an insoluble gradient of a matrix protein) and random migration of certain tumor cell lines has been shown to be related to the level of FAK expression. Akasaka *et al.* (31) have reported that in six different human melanoma cell lines the level of FAK expression directly correlated with the motility rate of the cell lines on fibronectin. A similar finding was reported for several prostate cancer cell lines (32). Our laboratory has shown that the overexpression of FAK increased hapototactic migration of the U-251MG malignant astrocytoma/glioblatoma cells toward vitronectin, fibronectin and collagen, but it did not increase random cell migration (14). The FAK family member, Pyk2, has also been shown to promote the migration of malignant astrocytoma/glioblastoma cells on laminin (33).

Investigators utilizing melanoma and prostate cancer cell lines have shown an inhibition of integrin beta 3-mediated migration toward vitronectin by the transfection of FRNK (34, 35). Also, the migration of certain breast cancer cells stimulated with the protease urokinase (binds to the urokinase receptor) was reduced by the expression of FRNK (36). Recently, Giannone *et al.* (37) have shown that FRNK prevented the FAK-promoted disassembly of focal adhesions, which is necessary for cell migration.

FAK likely plays a major role in the coordination of growth factor and integrin receptor inputs into the cell that regulate tumor cell migration and invasion (38). In support of this concept, Hauck *et al.* (39) have reported that anti-sense oligonucleotides directed toward FAK inhibited the invasion of EGF-stimulated A549 lung adenocarcinoma cells through Matrigel. Other investigators have reported that FAK was involved in TGF-beta-stimulated hepatocellular carcinoma cell migration and HGF/SF-stimulated oral carcinoma cell migration on various matrix substrates (40, 41). Also, the EGF-stimulated migration of the LN-401 malignant astrocytoma/glioblastoma cells was reduced by the expression of FRNK (42). In addition, growth factor-simulated prostate cancer cell migration was inhibited by neutral endopeptidase which inactivates growth factors and prevents FAK phosphorylation and Src association with FAK (43).

While a role for FAK in haptotactic and chemotactic migration of tumor cells *in vitro* is becoming well established, the FAK-mediated signaling events involved in the promotion of tumor cell migration are also being elucidated. For a review of FAK signaling in normal cells, see the review of Hanks *et al.* in this volume. FAK signaling to PI3-kinase promoted the migration of the U-251MG malignant astrocytoma/glioblastoma cells and of prostate cancer cells toward multiple extracellular matrix substrates (44, 45). In U-251MG cells, the inhibition of haptotactic cell migration by PI3-kinase inhibitors was shown to be sensitive to the association of a FAK-PI3-kinase complex (44). Likely a FAK/Src/p130CAS complex is also important for tumor cell migration. This complex promoted the directionally persistent migration of the U-87MG malignant astrocytoma/glioblastoma cells (46). Also, Slack *et al.* (32) have shown that the treatment of PC3, DU145, or LNCP prostate cancer cells with a Src kinase inhibitor or the expression of FRNK decreased cell migration.

FAK signaling to the MAP kinase pathways promotes tumor cell migration. Hauck *et al.* (39) have reported that an antisense oligonucleotide directed toward FAK that decreased EGF-stimulated A549 lung adenocarcinoma cell migration also decreased JNK activation through a mechanism involving p130CAS and Src. Moreover, FRNK transfection decreased the motility of the A549 cells and the activation of FAK, ERK and JNK. The urokinase-stimulated migration of MCF-7 breast cancer cells required signaling through the FAK/Shc/ERK pathway (36). Also, hepatocarcinoma cell migration toward laminin appeared to require Grb2 binding to FAK, as decreased Grb2 binding to FAK was correlated with decreased migration (47). (In certain fibroblasts Grb2 binds to the phosphorylated Y925 residue in FAK and promotes ERK activation (48).) We have shown in the U-251MG malignant astrocytoma/glioblastoma cells plated onto vitronectin that the overexpression of FAK resulted in increased Shc association with FAK, Shc phosphorylation, and sustained ERK activation (24 hours) (20); however, the role of this pathway in promoting the migration of these cells is not known.

The above studies examining the signals from FAK that promote cell migration suggest activated FAK serves as a scaffolding protein. Mutation of FAK at Y397 (this phosphorylated site mediates the association of FAK with multiple SH2 domain-containing proteins including,

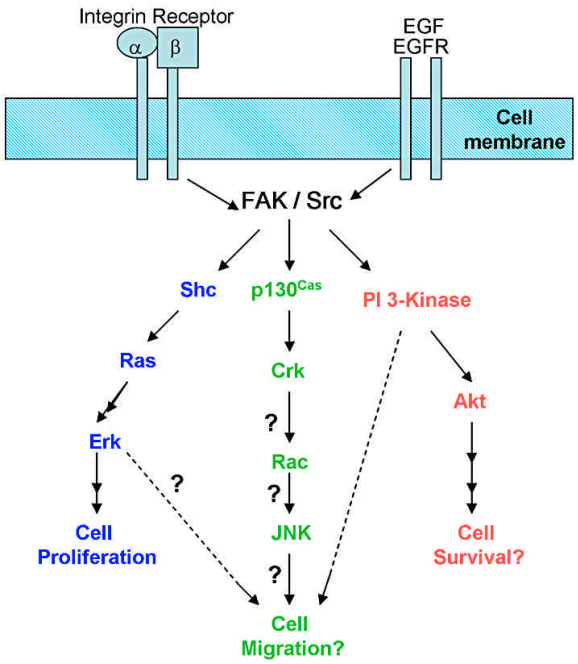

Figure 1. Potential FAK Signaling Pathways Functioning in Malignant Tumors or Cancers *In vivo*. *In vitro* and *in vivo* evidence suggests that FAK promotes the proliferation of certain malignant tumors, such as anaplastic astrocytomas or glioblastomas, by increasing ERK activity. *In vitro* evidence suggests FAK promotes malignant tumor or cancer cell migration and survival.

Src, Shc and PI3-kinase) inhibited cell motility (1). Neutral endopeptidase inhibited prostate cancer cell migration and this inhibition correlated with its ability to compete with FAK for PI3-kinase binding (43). Also, the prevention of an interaction between the plexin homology (PH) domain of Etk and the FERM domain of FAK (at the amino-terminus) disrupted the migration of the PL3M and MB-4355 carcinoma cell lines (49).

FAK is implicated in the regulation of matrix metalloproteinases (MMPs). MMP activity is necessary for matrix protein degradation and tumor cell invasion. As noted above, EGF-stimulated malignant astrocytoma/glioblastoma cell invasion and lung andenocarcinoma cell invasion was inhibited by FRNK expression. FRNK expression inhibited the secretion of MMP-9 (39), suggesting another mechanism by which FAK could regulate tumor cell invasion.

The inability of some malignant cells to regulate FAK activity likely plays a role in promoting tumor cell migration. In malignant astrocytoma/glioblastoma cells that express a mutated PTEN gene, transfection of the wild-type PTEN gene (a phosphatase) decreased tumor cell migration through a mechanism involving FAK dephosphorylation on tyrosine residues (19, 50). Dephosphorylation of FAK by PTEN has also been shown to decrease MMP-9 expression in the U-87MG cells (51). An additional mechanism whereby FAK activity can potentially be regulated is through calpain cleavage of FAK. Carragher *et al.* (52) have shown that v-Src transformed chicken embryo fibroblasts demonstrated increased migration into a wounded monolayer. This promotion of migration appeared to occur through increased focal adhesion turnover that was preceded by calpain-dependent proteolysis of FAK; inhibitors of calpain blocked the increased focal adhesion turnover and the increased cell migration that was observed with v-Src transformation (52).

The above reports suggest that FAK can promote tumor cell migration by 1) signaling to ERK through the association of Shc with FAK, the phosphorylation of Shc, the recruitment of the Grb2/SOS complex and the activation of Ras; 2) signaling to JNK through the FAK/Src/p130CAS pathway; and 3) signaling to PI3-K. Likely the activation of parallel signaling pathways promotes maximal tumor cell migration (see Figure 1).

6. FAK EXPRESSION, ACTIVITY, AND REGULATION IN MALIGNANT TUMORS *IN VIVO*

The majority of work regarding FAK expression *in vivo* has focused on immunohistochemical studies of tumor biopsy samples. Investigators have reported increased FAK expression in tumor biopsy samples from carcinomas of the head and neck, thyroid, prostate, breast and colon, as well as in malignant sarcomas and malignant astrocytomas (anaplastic astrocytomas and glioblastomas) (14, 20, 42, 53-61). Many of these studies reported elevated FAK expression in the tumor as compared to the "normal cell counterpart" or "low grade tumor." Rutka *et al.* (62) have found increased FAK expression in one GBM sample, as compared to normal brain. To confirm our immunohistochemical studies demonstrating elevated FAK expression in malignant astrocytoma tumor biopsy samples, we immunoblotted a series of anaplastic astrocytoma tumor biopsy samples (WHO Grade III) with antibodies directed toward FAK. We found an estimated 2.5-fold increase in the expression of FAK protein in these tumor biopsy samples as compared to normal brain biopsy samples and when normalized to actin (20) (see Figure 2). Also, FAK protein in these tumor biopsy samples migrated with a faster mobility on SDS-PAGE, as compared to FAK protein in normal adult brain (20). Interestingly, FAK protein in rat brain during early development has also been shown to have a faster mobility on SDS-PAGE, suggesting similarities between FAK protein in anaplastic astrocytoma tumors and FAK protein in the developing brain (63). (See the review by Xiong *et al.* in this volume for additional information regarding FAK family members in the nervous system during development.)

Very few studies investigating the mechanism(s) responsible for an elevated FAK expression in tumors *in vivo* have been reported. Weiner *et al.* (57) have reported increased FAK mRNA expression in invasive carcinomas biopsy samples, as compared to "normal" and benign adenomatous biopsy samples. In cell lines propagated *in vitro*, Agochiya *et al.* (64) have reported that the FAK gene locus is amplified in several cancer cell lines, but it is

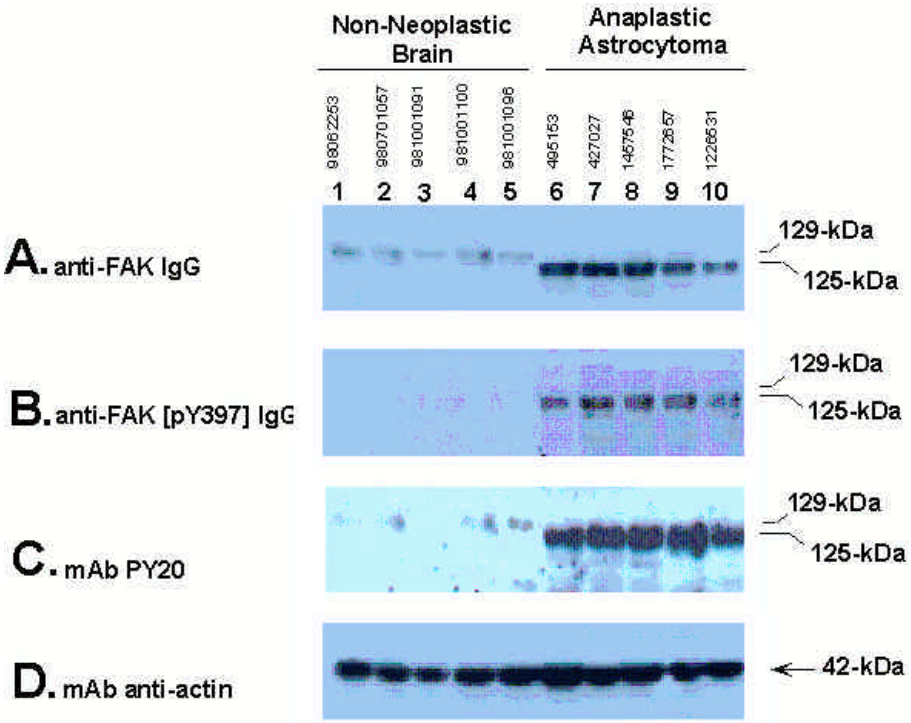

Figure 2. Elevated levels of a hyperphosphorylated FAK, protein in human anaplastic astrocytoma biopsy samples. Human non-neoplastic brain biopsy samples (lanes 1-5) and human anaplastic astrocytoma biopsy samples (lanes 6-10) were detergent lysed, and equivalent microgram of lysate from each sample was subjected to SDS-PAGE, transferred to Immoblion, immunoblotted, stripped, and reprobed. A, Blotted with rabbit anti-FAK IgG; B, blotted with rabbit anti-FAK (pY397) IgG; C, blotted with mAb antiphosphotyrosine; and D, blotted with mAb anti-actin. Reprinted with permission from Hecker *et al.*, *Cancer Research* 2002; 62:2699-2707.

unclear at the present time whether amplification of the FAK gene occurs in tumors *in vivo* and what effect this could have on FAK transcription and expression *in vivo*.

Studies investigating the activity of FAK and its regulation in tumor biopsy samples *in vivo* are also limited. We recently reported increased phosphorylation of FAK on Y397 (an estimated 4-fold increase) and increased overall tyrosine phosphorylation of FAK (an estimated 10-fold increase) in grade III anaplastic astrocytoma tumor biopsy samples, as compared to normal brain biopsy samples and when normalized to actin (20) (see Figure 2). We also found an elevated Src activity that correlated with the increased FAK phosphorylation in these tumor biopsy samples, suggesting the increased Src activity could potentially contribute to the increased FAK activity and phosphorylation *in vivo* (20). Other abnormalities have been described in malignant tumor biopsy samples which could also play a role in regulating FAK activity *in vivo*, such as the upregulation of specific integrin or growth factor receptors and the loss of tumor suppressor genes (e.g. PTEN) (3-6). Furthermore, a new regulator of FAK has been reported. A protein termed FIP200 was identified recently that can prevent FAK from phosphorylating effector molecules; FIP200 directly interacts with the kinase domain of FAK (65). Therefore, current data indicate that integrin receptors, growth factor receptors, Src, FIP200, calpain, and potentially PTEN can regulate FAK activity in tumor cells *in vitro*; however, additional studies are required to understand their role in the regulation of FAK activity in malignant tumors *in vivo*, particularly in animal models.

7. FAK AND MALIGNANT TUMOR CELL FUNCTION *IN VIVO*

The finding that FAK expression is elevated in several different malignant tumors *in vivo* suggests that FAK may modulate tumor cell function *in vivo*. Our lab has reported that the overexpression of wild-type FAK in the U-251MG malignant astrocytoma/glioblastoma cells promotes the proliferation of these cells when injected intracerebrally into the CB17 scid mouse brain (14). This proliferation was independent of a change in cell survival, as the index of apoptosis based on TUNEL assay was unchanged with the overexpression of FAK. In further support of a role for FAK in promoting tumor cell proliferation *in vivo*, Aguirre-Ghiso (66) reported that the expression of FRNK in human Hep3 hepatocellular carcinoma cells prevented the cells from proliferating in the chicken chorioallantoic membrane (CAM), and Abdel-Ghany *et al.* (8) have reported that the expression of FRNK reduced the size of melanoma lesions that metastasized to the lung in C57B1/6 mice. Correlative evidence of a role for FAK in promoting tumor cell proliferation *in vivo* also exist; e.g., agents that inhibit FAK phosphorylation inhibit the growth of tumors in mice (67, 68).

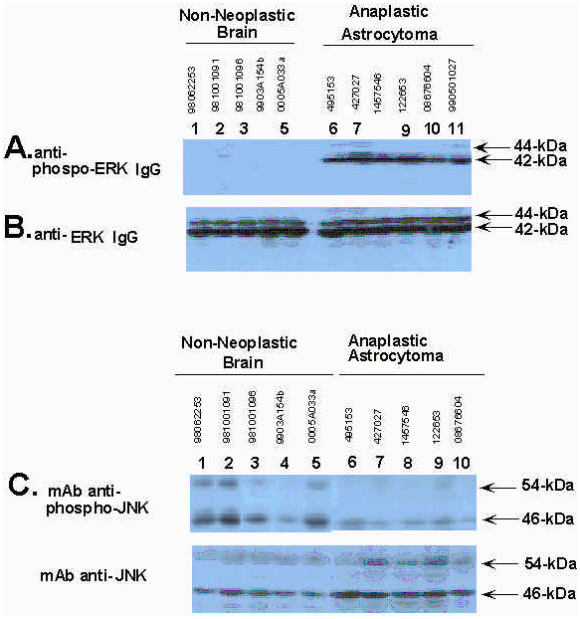

Figure 3. Elevated ERK-2 activity in human anaplastic astrocytoma biopsy samples. Human non-neoplastic brain biopsy samples (lanes 1-5) and human anaplastic astrocytoma biopsy samples (lanes 6-11) were detergent lysed, and equivalent microgram of lysate was subjected to SDS-PAGE, transferred to Immobilon, immunoblotted, stripped, and reprobed. A, blotted with rabbit anti-phospho-ERK IgG; B, blotted with rabbit anti-ERK IgG; C, blotted with mAb anti-phospho-JNK; and D, blotted with mAb anti-JNK. Reprinted with permission from Hecker *et al.*, *Cancer Research* 2002; 62:2699-2707.

A role for FAK in the promotion of tumor cell survival and migration/invasion *in vivo* is largely circumstantial. Investigators have reported increased expression of FAK in tumors that are locally invasive (69), and elevated FAK expression in colorectal carcinoma that has metastasized to the liver (70). As mentioned above, in an animal model of melanoma metastasis investigators have reported that FRNK expression was able to reduce the number of metastatic lung lesions established by the tumor cells (8). Continued investigation and the use of additional models for studying the role of FAK in tumor cell migration/invasion and survival *in vivo* are necessary in order to understand the role of FAK in tumors.

8. FAK SIGNALING IN MALIGNANT TUMOR CELLS *IN VIVO*

Dissecting FAK signaling pathways that modulate tumor cell function *in vivo* has been difficult to address, in part, because of problems inherent in manipulating an *in vivo* system. Aguirre-Ghiso (66) demonstrated that FAK was activated by the engagement of the urokinase and integrin receptors in human carcinoma cells propagated in the chicken CAM. This investigator also reported that the expression of FRNK reduced the growth of these cancer cells in the chicken CAM, and that activated MEK1 mutants could reverse this inhibition. This suggests that FAK signaling to ERK could be important in facilitating the growth of these tumor cells in the chicken CAM model. We reported an *in vivo* correlation between FAK association with Shc, Shc phosphorylation, and elevated ERK activity in anaplastic astrocytoma (WHO Grade III) tumor biopsy samples (20) (see Figure 3). Furthermore, we and others have shown that elevated FAK expression results in increased ERK activity, likely through Shc association with FAK and the phosphorylation of Shc by the FAK/Src complex (20, 36).

Important questions remain to be addressed with regard to FAK signaling in malignant cells *in vivo* and thus additional studies will hopefully be performed. These could include *in vitro* systems that recapitulate the complex microenvironments encountered by tumor cells during malignant progression (71) (e.g., 3-dimensional tumor environments, hypoxic environments, and anchorage-independent conditions). Also, how different environments modulate FAK signaling and thus tumor cell function, and how FAK signaling adapts to meet the demands of different environments are important questions that need to be addressed in order to promote an understanding of the role of FAK in modulating tumor cell behavior *in vivo*.

9. FAK AND ANGIOGENESIS

Angiogenesis is necessary for the progression of malignant tumors (72). Angiogenesis requires endothelial cell sprouting, proliferation and migration; thus, it is not surprising that investigators would consider a role for FAK in this process. *In vitro*, FAK has been shown to be activated in endothelial cells induced to migrate and "sprout" by the pro-angiogenic growth factors, vascular endothelial cell growth factor (VEGF), angiopoietin-1, and Del1 (73-75). Qi and Claesson-Welsh (76) demonstrated that VEGF-induced FAK and PI3-kinase activation were necessary for the migration of brain microvessel endothelial cells, and that endothelial cell transfection with mutant FAK (397F) decreased VEGF-induced PI3-kinase activation. We have reported recently that FRNK transfection inhibited tube formation and branching of mouse brain microvessel endothelial cells cultured in 3-D collagen gels, as well as their haptotactic migration towards collagen and fibronectin (77). Consistent with the above, other investigators have reported that anti-angiogenic agents diminish FAK activation in endothelial cells (78, 79), and that FAK activity is required for VEGF transcription (80). There is less data pointing to a role for FAK in promoting angiogenesis *in vivo*. Recently, Haskell *et al.* (77) reported elevated levels of activated FAK in microvascular endothelial cells in an intracerebral xenograft model of malignant astrocytoma/glioblastoma by immunohistochemical staining.

10. FAK AND THE ETIOLOGY OF MALIGNANCY

The majority of work described above points to the possibility that FAK expression could contribute to the progression of tumors. Can aberrant FAK expression and activity cause normal cells to become malignant? This question is beginning to be addressed, and some evidence

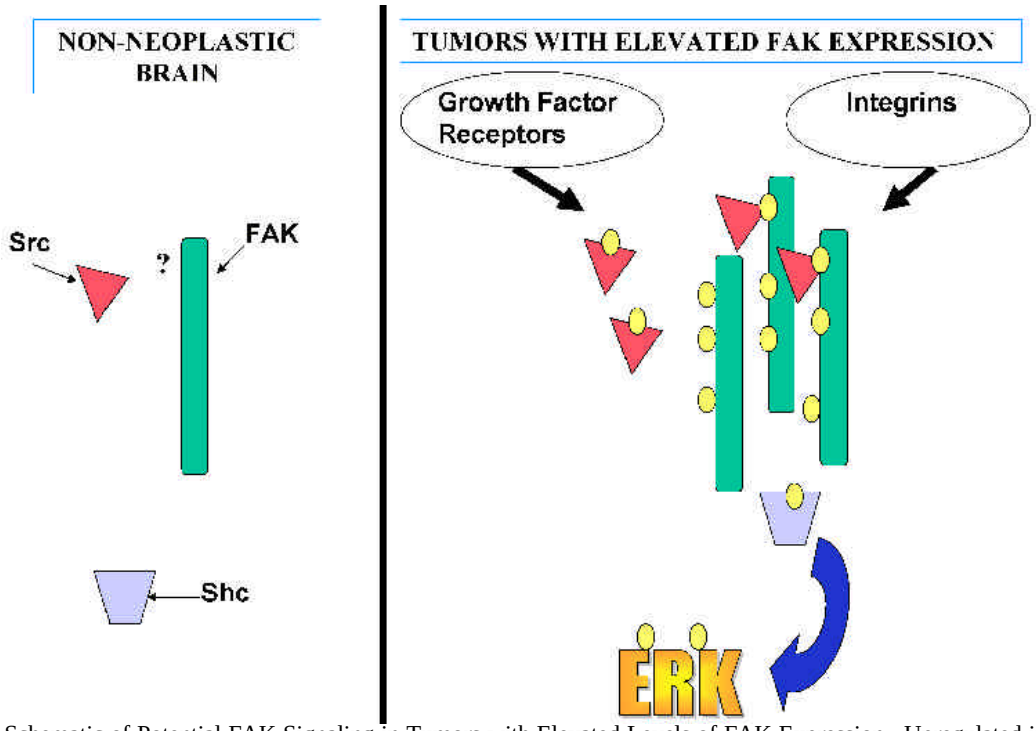

Figure 4. Schematic of Potential FAK Signaling in Tumors with Elevated Levels of FAK Expression. Upregulated integrin and growth factor receptor expression in tumors could increase the activation of FAK. Increased Src kinase activity could also contribute to an elevated FAK activity and increased FAK phosphorylation. Shc binds to the phosphorylated Y397 site in FAK, which in some cells leads to the phosphorylation of Shc, the recruitment of the Grb2/SOS complex, the activation of Ras and the activation of ERK.

points to a role for FAK in the etiology of tumors. Chan *et al.* (81) have reported that the overexpression of FAK in Madin-Darby canine kidney epithelial cells rendered them susceptible to transformation by HGF stimulation. Moreover, FAK promoted sustained activation of ERK, JNK, and Akt in these cells when treated with HGF. McLean *et al.* (82) have reported that fak -/+ mice showed less skin papilloma formation than fak +/+ mice when exposed to a mutation-inducing agent. Interestingly, no difference in the conversion of the papillomas to carcinomas was found in these two mouse lineages. Additional questions to consider include, does FAK overexpression initiate tumor formation, does FAK overexpression play a role in promoting the progression of tumors to a malignant state, does FAK only contribute to tumor cell proliferation, survival and invasion once a malignancy is already established, and is the contribution of FAK to malignancy cell-type specific?

11. SUMMARY

In conclusion, evidence is mounting that supports a role for FAK in promoting the malignant phenotype (deregulated cell proliferation, survival, and migration) of various malignant tumor cells or cancer cells *in vitro* (see Figure 4, potential model of FAK signaling in cells with elevated FAK expression). More extensive studies and the development of relevant *in vitro* and *in vivo* models are required to understand the role of FAK signaling in tumor progression, and to determine whether FAK could contribute to the etiology of different types of tumors *in vivo*. Nevertheless, current studies suggest that FAK may be an important therapeutic target in some tumors, and is likely an important target for anti-angiogenic therapy.

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Abbreviations: FAK, focal adhesion kinase; PTEN a phosphatase and a tumor suppressor gene located on human chromosome 10q23; EGF, epidermal growth factor; EGF receptor; PDGF, platelet-derived growth factor; PDGFr, PDGF receptor; PI3-kinase, phosphatidylionsytol 3-hydroxyl kinase; WHO, world health organization.

Key Words: FAK, Focal adhesion kinase, Erk, Akt, Cancer, Glioma, Glioblastoma, Astrocytoma, Review

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