

Paradoxical roles of FAK in tumor cell migration and metastasis

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Focal adhesion kinase (FAK), as a key mediator of signaling induced by integrins, plays an instrumental role in many cellular functions, including cell survival and proliferation. Many studies have reported that FAK is a positive regulator of normal cell migration and cancer cell metastasis. However, emerging evidence shows that FAK—under certain oncogenic signaling, such as that initiated by activated Ras and some growth factor receptor kinases—negatively regulates cancer cell migration. Activated Ras may promote tumor cell migration by dephosphorylation of FAK at Y397 and facilitation of focal adhesion turnover at the leading edge of cells.

Introduction

Tumor invasion and metastasis are responsible for most cancer deaths. The invasive and metastatic stages of cancer progression are associated with poor clinical prognosis and unsuccessful treatment.¹ Thus, understanding the fundamental mechanisms underlying tumor cell migration, invasion and metastasis holds the promise of improving therapeutic approaches for cancer. The key to understanding the invasion and metastasis of tumors is to elucidate the basis for the initiation and maintenance of the aberrant motility of tumor cells. Cell migration is a highly integrated and dynamic multistep process of leading-edge protrusion, turnover of focal adhesions, generation of tractional forces, and tail retraction and detachment, which involves precise regulation of cell-cell adhesion and cell-to-extracellular matrix (ECM) adhesion.² Functional regulation

of the molecules involved in cell adhesion signaling is a key process in tumor cell motility.

Focal adhesions are formed at ECM-integrin junctions that bring together integrin receptors, signaling protein complexes, structural proteins and cytoskeletal proteins.^{3,4} Focal adhesion kinase (FAK) is a ubiquitously expressed 125-kDa non-receptor protein tyrosine kinase that localizes at focal adhesion complexes. At focal adhesions, FAK acts as a protein-protein-interaction adaptor and also transmits adhesion- and growth-factor-dependent signals into the cell interior.⁵ FAK can exert control over the rate of cell adhesion turnover and, therefore, cell motility in this unique signaling position.^{4,6,7} Integrin activation by ECM ligands stimulates rapid tyrosine phosphorylation and activation of FAK and the formation of focal adhesions.

In normal cells, FAK is highly phosphorylated at multiple tyrosine sites, including tyrosines 397, 407, 576, 577, 861 and 925.^{4,6} The level of tyrosine phosphorylation of FAK regulates its kinase activity.⁶ The best-characterized FAK phosphorylation event is the molecular interaction between the integrin β 1 C-terminal region and the FAK N-terminal region that results in kinase autophosphorylation of FAK at tyrosine 397, which replaces Src Y527 binding to the SH2 domain of Src thereby relieving the auto-inhibitory interaction and activating Src.^{6,8} In addition to being phosphorylated at multiple tyrosines, FAK is also phosphorylated at serine residues.^{9,10} A number of phosphorylated serine residues of FAK, such as S722, S732, S843 and S910, have been identified.

Key words: FAK, Ras, phosphorylation, dephosphorylation, cell migration, metastasis

Abbreviations: FAK, focal adhesion kinase; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; PIN1, protein interacting with NIMA (never in mitosis A)-1; EGFR, epidermal growth factor receptor; TGF β 1, transforming growth factor- β 1; IGF-1, insulin-like growth factor 1; PTP 1B, protein-tyrosine phosphatase 1B

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Phosphorylation of these residues has been implicated in the regulation of FAK function.¹¹⁻¹⁶ FAK has been demonstrated to be a positive regulator of nonmalignant cell migration, cell survival and proliferation.^{6,8} However, the role of FAK in cancer cell migration and metastasis remains controversial. Paradoxical evidence has been reported regarding the role of FAK in tumor invasion and metastasis.

Evidence for FAK as a Positive Regulator of Tumor Cell Migration and Metastasis

Many studies have implicated FAK as a positive regulator of tumor cell migration and invasion.⁸ Immunohistochemical and immunoblotting analyses have detected increased levels of FAK in human cancers of the prostate, breast, thyroid, colon, rectum, head and neck, oral epithelium and ovary.⁵ In addition, increased tyrosine phosphorylation of FAK is observed in lung, cervical and ovarian cancers.¹⁷⁻¹⁹ Elevated expression of FAK in human tumors has been correlated with increased malignancy and invasiveness.^{5,20,21} Mouse transgenic studies show that conditional *fak* deletion in the epidermis suppresses chemically induced skin tumor formation, and this effect was linked to increased cell apoptosis.²² Furthermore, mammary epithelial-specific disruption of *fak* partially blocked polyoma-virus middle T antigen-induced mammary tumorigenesis, which correlated with impaired mammary epithelial proliferation.²³ In addition, many cell-based studies have shown that FAK is a positive regulator of tumor cell migration, which has been comprehensively reviewed.^{5,6,8,24}

Evidence for FAK as a Negative Regulator of Tumor Cell Migration and Metastasis

In contrast to the observation that FAK plays a positive role in cell motility, new insights suggest that under some conditions FAK actually inhibits cell migration and invasion.^{25,26} Weak expression of FAK in patients with cervical cancer has been correlated with pelvic lymph node metastasis, recurrent disease and poor

survival.²⁷ In another study, expression of FAK was lower in liver metastases than in matched primary human colorectal adenocarcinomas.²⁸ In addition, a low level of FAK expression in intrahepatic cholangiocarcinoma was correlated with large tumor size, poor differentiation, lymph node metastasis, vascular invasion and intrahepatic metastasis.²⁹ In chemical carcinogen-induced colon cancers in mice, FAK expression levels correlated with the grade of tumor cell differentiation, with high FAK expression being associated with highly differentiated tumor cells.³⁰ In line with these findings, three studies of different human colon cancer cell lines (Caco-2, HT-29 and Colo 201) all showed increased levels of FAK expression as the cancer cells were subjected to conditions promoting better differentiation.³¹⁻³³

Previously, we and other groups have shown that epidermal growth factor receptor (EGFR) activation induces tyrosine dephosphorylation of FAK, p130Cas and paxillin;³⁴⁻³⁷ inhibition of FAK activity; and increased tumor cell motility, invasion and metastasis in various human carcinoma cells that overexpress EGFR.³⁵ This finding was supported by the observation that constitutively active RhoA results in activation of EGFR, tyrosine dephosphorylation of FAK, and increased motility of breast cancer cells.³⁸ Inhibition of EGF-induced tyrosine dephosphorylation of FAK reduced cellular morphology changes in and motility of breast cancer cells and tumor invasiveness.³⁹ Similar to the effect of EGFR activation on focal adhesions, FAK and p130Cas were tyrosine-dephosphorylated in HER2/ErbB2-overexpressing cells.⁴⁰ In addition, heregulin, a combinatorial ligand for HER3/ErbB3 and HER4/ErbB4 that can activate HER2, HER3 and HER4 by homo- or heterodimeric interactions between HER members, reduces the total level of FAK tyrosine phosphorylation and promotes the migration of breast cancer cells.⁴¹ Likewise, activation of insulin-like growth factor 1 (IGF-1) receptor or stimulation of hepatocarcinoma cells with transforming growth factor (TGF)- β 1, which reduces cell adhesion strength and promotes cell migration, induces rapid tyrosine dephosphorylation of FAK.⁴²⁻⁴⁵

Apart from the activity of receptor protein kinase family members, activation of CaMK-II, a Ca²⁺/calmodulin-dependent protein kinase, promotes the disassembly and turnover of focal adhesions and cell motility by eliminating paxillin from focal adhesions and decreasing the tyrosine phosphorylation levels of both FAK and paxillin.⁴⁶ SHP-2, a non-receptor tyrosine phosphatase, which can be recruited to focal adhesions by interleukin (IL)-1 β , promotes the dephosphorylation of FAK, loss of E-cadherin and migration and metastasis of MCF-7 breast cancer cells.^{47,48} Protein-tyrosine phosphatase 1B (PTP 1B) was also shown, in cooperation with α -actinin, to disrupt the FAK-Src complex, dephosphorylate FAK Y397, and significantly increase cell migration.⁴⁹ Furthermore, the fact that FAK has a negative role in cell migration under some conditions is supported by the following evidence: FAK deficiency promotes v-Src-induced cell migration;⁵⁰ expression of *Helicobacter pylori* CagA reduces the level of FAK tyrosine phosphorylation and results in impaired cell adhesion and increased cell motility, which is associated with the development of gastric adenocarcinoma;⁵¹ and FAK and paxillin inhibit cell migration by negative regulation of Rac1 activity.⁵²

In an effort to decipher the molecular mechanisms of FAK inhibition in response to oncogenic signaling, we recently demonstrated that activation of both H-Ras and K-Ras, which are activated or mutated in more than 30% of human cancers,⁵³ induced Y397 dephosphorylation and inhibition of FAK, which contributed to refractive and spindle-shaped morphological changes, a reduction in cell-ECM contact, and the promotion of cell migration, invasion and metastasis.⁵⁴ We showed that Ras induced Cdc42 activation in a guanine nucleotide exchange factor FGD1-dependent manner, which led to the activation of the PAK1-MEK-ERK kinase cascade. ERK phosphorylates FAK S910 and recruits protein interacting with NIMA (never in mitosis A)-1 (PIN1) and protein tyrosine phosphatase (PTP)-PEST, which colocalize with FAK at the lamellipodia of migrating cells.

Lamellipodia are migratory organelles at the front, leading edge of motile cells that are believed to be the actual motor that pulls the cell forward during the process of cell migration.⁵⁵ PIN1 binding and prolyl isomerization of FAK cause PTP-PEST to interact with and dephosphorylate FAK Y397. The importance of Ras-induced and ERK-dependent FAK inhibition is supported by the finding that levels of ERK activity were inversely correlated with levels of FAK Y397 phosphorylation in 41 human glioblastoma multiforme specimens.⁵⁴ The significance of FAK Y397 levels in tumor development was also shown in an analysis of heterogeneously differentiated human colon cancer, which revealed a correlation between the Y397 phosphorylation level, as well as total FAK expression, and the degree of tumor cell differentiation within colon cancer specimens.⁵⁶ The fact that a low level of FAK Y397 phosphorylation correlates with poorly differentiated cancer cells further supports the negative role of FAK in colon cancer progression.

Insights into the Role of FAK in Tumor Development—Dynamic Regulation of FAK in Tumor Cell Migration

In addition to the evidence described above for either the positive or negative role of FAK in tumor migration, invasion and metastasis, a couple of reports have shown no clear correlation between FAK expression levels and cell motility or metastasis. For instance, FAK expression correlates with pancreatic tumor size, but not with tumor grade, metastasis or overall survival.⁵⁷ FAK overexpression is not restricted to the invasive phenotype of breast carcinomas but rather appears to be a marker for malignant transformation.⁵⁸ These studies suggest that FAK might have different roles in different tumors. For tumors with FAK overexpression or higher FAK activity induced by certain oncogenic signaling, the activated positive FAK-c-Src feedback loop and subsequent activation of tumor-promoting molecules, such as ERK and AKT, might contribute

to malignancy by promoting cell survival and proliferation. This is evidenced by a report showing that activation of both FAK and c-Src, as detected by higher levels of phospho-FAK Y397 and phospho-Src Y416, and overexpression of paxillin correlate with higher malignancy of breast carcinoma.⁵⁹ This is also in line with the finding that FAK is required for the focal adhesion formation that protects cells from anoikis, a type of apoptosis induced by cell detachment from ECM.⁶⁰ However, for tumors such as those harboring a Ras mutation or activation that can activate ERK and AKT without the involvement of FAK (unpublished data), downregulation of FAK activity might promote the disassembly of focal adhesions and cell migration.

There is also evidence that FAK might have different roles at different stages of tumor progression. In human colorectal adenocarcinomas, the FAK expression level increases in primary tumors compared with normal mucosa and decreases in liver metastases to the level of normal

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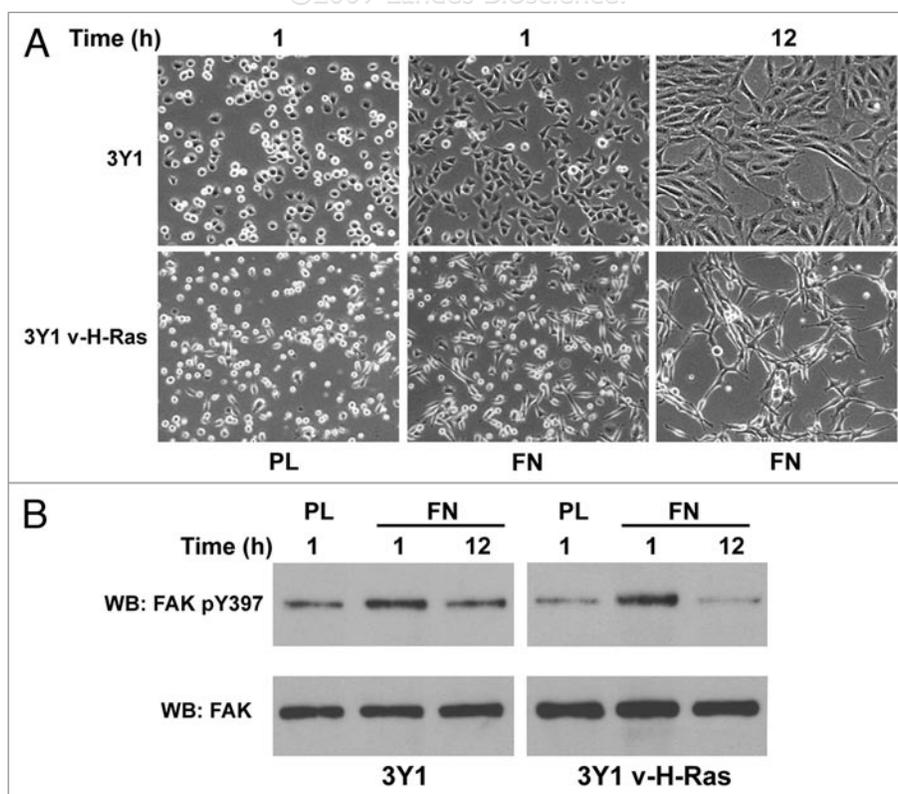


Figure 1. Activated integrin signaling transiently overrides Ras-induced FAK inhibition and promotes cell adhesion and cell spreading. After being trypsinized and kept suspended in DMEM with 0.1% bovine serum albumin for 40 min, 3Y1 cells or 3Y1-v-H-Ras cells were plated onto either fibronectin (FN)-coated or poly-L-lysine (PL)-coated plates for the indicated times. (A) Pictures were taken with a digital camera mounted on a microscope with 100x magnification. (B) Immunoprecipitation and western blotting analyses were performed with the indicated antibodies.

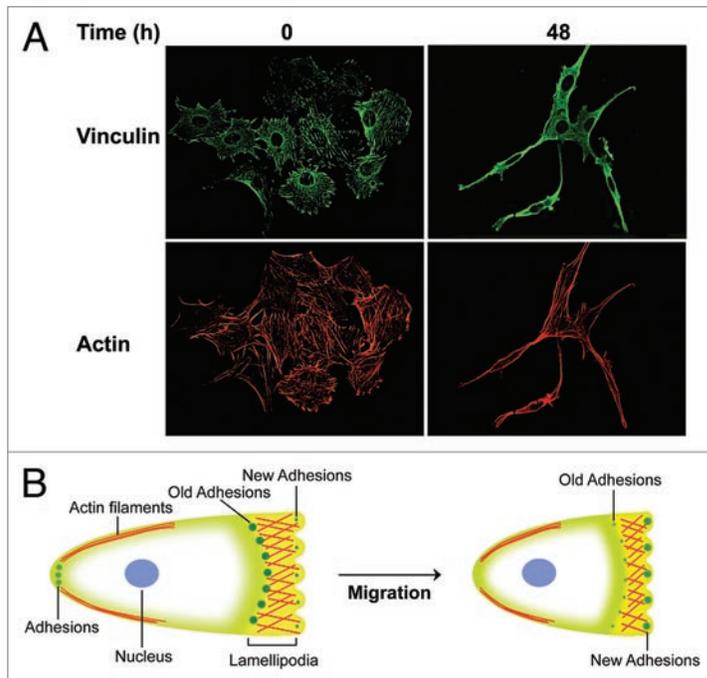


Figure 2. Activated Ras reduced the total number of focal adhesions, and lamellipodial dynamics and turnover of focal adhesion at the leading edge is regulated by the dynamically integrated Ras- and integrin-induced signaling. (A) NIH3T3-v-H-Ras (Tet-off) cells were cultured with or without withdrawal of doxycycline (1 $\mu\text{g/ml}$) for the indicated time and stained for actin with TRITC-labeled phalloidin or for focal adhesion with an anti-vinculin antibody. (B) A model of lamellipodial dynamics and turnover of focal adhesion at the leading edge for activated Ras-induced cell migration. The focal adhesions ("old adhesions") are disassembled by Ras-induced FAK dephosphorylation at Y397, which allows formation of new adhesions induced by activated integrin-FAK signaling. Once the new adhesions mature, the activated Ras will override integrin signaling to inhibit FAK for another round of focal adhesion turnover.

mucosa.²⁸ Colon cancer cells at the migrating front of monolayers exhibited reduced total and activated FAK.⁶¹ In addition, melanoma cells derived from peripheral blood had lost FAK expression, but other melanoma cells isolated from solid metastases from the same patient had not.⁶² Thus, the expression level and activity of FAK can be dynamically regulated.

To understand the mechanism underlying the dynamic regulation of FAK activity, we examined the effect of cross-talk of Ras- and integrin-induced signaling on FAK activity. We seeded 3Y1 or v-H-Ras-expressing 3Y1 rat fibroblast cells on plates coated with either fibronectin or poly-L-lysine. The latter does not bind to integrins and is unable to promote FAK-regulated cell adhesion. One hour after being seeded on fibronectin-coated plates, both 3Y1 and 3Y1-v-H-Ras cells showed a progression of cell adhesion and spreading, while the cells on poly-L-lysine-coated plates maintained a rounded morphology

(Fig. 1A). In line with the status of adhesion progression, integrin engagement with fibronectin phosphorylated and activated FAK to a similar degree in the two different types of cells (Fig. 1B). These results indicated that activated integrin signaling overrides Ras-induced FAK inhibition and promotes cell adhesion and spreading. However, this dominant effect of integrin signaling was transient and occurred only during the early stage of cell adhesion and spreading (Fig. 1B). Twelve hours after seeding, activated Ras induced FAK dephosphorylation at Y397, and this was accompanied by refractile and spindle-shaped morphological changes and reduced cell-ECM contact in cells plated on fibronectin (Fig. 1). Reduction of cell-ECM adhesion is believed to promote cell motility because cells with large integrin clusters/focal adhesions are tightly adherent and typically either nonmigratory or move very slowly.² This result is consistent with our previous report that EGF induces

downregulation of FAK activity, refractile morphological changes, and detachment of cells from the ECM.³⁵ However, once the cells start reattaching to the ECM, FAK activity is restored by activated integrin signaling, which occurs only during the process of adhesion and is downregulated again by EGFR activation thereafter.³⁵

Taking all these findings together, we propose a model of tumor cell migration and metastasis induced by activated Ras and other signaling, such as EGFR, which leads to FAK inhibition: cells with activated Ras (Fig. 2A) or EGFR³⁵ have lower overall FAK activity, leading to fewer focal contacts and facilitating detachment of the cell tail so that cells become less adherent and more motile. At the same time, lamellipodial dynamics and turnover of focal adhesion at the leading edge, which are required for cell migration, are regulated by the dynamically integrated Ras- and integrin-induced signaling (Fig. 2B). When new lamellipodia form, which are driven by actin polymerization and stabilized by adherence to the ECM,² integrin-FAK signaling overrides Ras-induced FAK Y397 dephosphorylation and facilitates the formation of new adhesions, which serve as traction sites for cell migration. However, these newly formed adhesions will be quickly disassembled by Ras-induced signaling, which regains dominance after adhesion formation. This disassembly of mature adhesions will allow new adhesions-protrusions-lamellipodia to form at the leading edge to initiate another round of focal adhesion turnover. These lamellipodial dynamics occur until metastatic tumor cells re-adhere to foreign tissue or organs. At that time, activation of FAK by integrin promotes both the formation of new adhesions and the spread of metastatic tumor cells, which are necessary for the establishment of new metastatic deposits.

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