ROLE OF FOCAL ADHESION KINASE INHIBITORS AS ANTI-CANCER AGENTS

Madhuri Harakial Jain and Rakesh Ravindra Somani*

Department of Pharmaceutical Chemistry, Vivekanand Education Society’s College of Pharmacy, Chembur (E), Mumbai: 400074. India.

ABSTRACT

Focal adhesion kinase (FAK) is a cytoplasmic protein tyrosine kinase that enables activation by integrins or growth factor receptors in different types of human cancers. It is overexpressed and activated in cancer. FAK mediates metastasis and tumour proliferation. FAK mediates metastasis and tumour proliferation. The kinase-dependent and kinase-independent role of FAK controls cell invasion, movement, gene expression, survival and self-renewal of cancer stem cell. FAK activation and overexpression are usually investigated in metastatic or primary cancers which are correlated with the poor clinical outcome. It highlights FAK as potential portent marker and anticancer target. Various FAK inhibitors target FAK-scaffolding functions and FAK kinase activity which impairs cancer development in preclinical or clinical trials. FAK inhibitors decreases metastasis and growth of tumour in many preclinical models and have shown biological activity with less number of adverse reactions. In this review, we give an overview of different FAK signaling pathways in cancer, its role in cellular function that provide rationale and support for future therapeutic approach in cancer treatment.

KEYWORDS: Angiogenesis, Cell adhesion, Cell invasion, Cell proliferation, Cell survival, Focal adhesion kinase.

INTRODUCTION

Focal adhesion kinase (FAK) is a non-receptor or cytoplasmic tyrosine kinase protein its molecular mass of 125-kDa. It is encoded by FAK gene on human chromosome 8q24. It is found at integrin clusters, which are so-called focal adhesions. And hence named as FAK. It functions as a scaffold and switch for the transduction of signals from diverse stimuli,
including integrin’s and growth factor receptors.\[1\] FAK plays important role in various biological processes like cell growth, cell survival, cell proliferation and cell migration. FAK functions in protein-protein interaction at sites of cell attachment to the extracellular matrix (ECM), thus contributing to focal adhesion ‘scaffolding’ and it also helps in adhesion dependent and growth-factor-dependent signals into the interior of cell. In relation to cancer, the synergistic signaling between FAK and growth-factor receptors might be relevant since they are up-regulated in tumour cells. Signaling from growth-factor receptors and action of FAK together control the alter growth of tumour cells as well as their responses to paracrine or autocrine factors.\[2\] FAK also influences the dynamic regulation of integrin associated adhesions and actin cytoskeleton which is tethered there through diverse molecular interactions. This leads to regulation of cell migration by controlling the focal-complex assembly and disassembly cycle leading to lamellipodia i.e. delicate sheet like extensions of cytoplasm that form transient adhesions with the cell substrate and wave gently, enabling the cell to move along the substrate. Adhesions and actin dynamics are co-ordinately regulated with survival and growth signaling in focal adhesions through FAK dependent actions. FAK plays a critical role in the biological processes of normal and cancer cells and thus FAK has been proposed as a potential target in cancer therapy.\[3\]

**FAK STRUCTURE**

FAK is a non-membrane and cytoplasmic associated protein tyrosine kinase (PTK). It consists of three major domains. The central domain consists of catalytic kinase flanked by C-terminal consisting of focal adhesion targeting (FAT) domain and a large N-terminal consisting of FERM (band four point one, ezrin, radixin, moesin) domain. Long linkers of about 220 (catalytic kinase-FAT) and 50 (FERM-kinase) residues separate these domains. For FAK about 50 ligands have been reported thus each linker and domain region has its own set of ligands.\[4\] (Fig. 1).

![Fig. 1: Structure of FAK, FERM: band four point one, ezrin, radixin, moesin PRP: Proline rich region FAT: Focal adhesion targeting](image-url)
C-TERMINAL OF FAK
C-terminal is a non-catalytic domain of FAK and it is rich in protein-protein interaction sites. C-terminal consists of 2 regions, consisting of focal adhesion targeting (FAT) sequence and two rich sequence of proline with its proximity to catalytic domain. C-terminal is around 15.5-kDa. FAK is directed to the newly formed adhesion complexes by the FAT sequence. Proteins such as paxillin and talin which are associated to adhesions bind at the FAT site. The FAT domain also consists of two hydrophobic patches that bind to the FAK-associated proteins containing the leucine-rich domain (LD). The α- helix 1 of the FAT domain contains tyrosine 861 and tyrosine 925. Specific functions of the C-terminal domain of FAK include association of the FAT domain to integrins and localization of FAK to focal adhesion complexes, which is required for migration of cells. Additionally, tyrosine 861 and tyrosine 925 upon phosphorylation by Src family kinases (SFKs) recruit Grb2 (Growth Factor Receptor-bound) via the Grb2 SH2 (Src Homology 2) domain, leading to activation of the Ras/Raf/MAPK/ERK proliferation pathway.\[5\]

N-TERMINAL OF FAK
N-terminal contains approximately 300 amino acids which show sequence homology FERM. The FERM helps in mediating protein-membrane interactions as well as protein-protein interactions. It contains tyrosine 397 which is an auto-phosphorylation site. FERM domain interacts with p53, which regulates tumor survival of tumor cells. It also interacts with Src protein which helps in auto phosphorylation of FAK. This domain facilitates interaction of FAK with other receptor tyrosine kinases such as Hepatocyte Growth Factor Receptor Precursor (MET), Epidermal Growth Factor Receptor (EGFR), Platelet-Derived Growth Factor Receptor (PDGFR) and also some integrins. These interactions are required to activate signaling cascades that promote migration, as well as invasion, proliferation, survival, anti-apoptosis and adhesion.\[6\]

KINASE DOMAIN
Kinase Domain is the primordial conserved domain related to all protein tyrosine kinases. The crystal structure of FAK kinase domain reveals a bilobed structure with the N-terminal lobe containing a single α-helix with a five-stranded β-sheet and the larger C-terminal lobe that is mostly α-helical. In the kinase domain itself are three tyrosine phosphorylation sites (Y-407, Y-576 and Y577). Phosphorylation of these sites results into formation of a β-hairpin loop confirmation, as observed in other active kinases.\[7\]
ROLE OF FAK IN CANCER

FAK overexpression is been reported in various tumor cells, including pancreatic, cervical, breast, melanoma, neuroblastoma, osteosarcoma, lung, kidney, brain, prostate, oral, thyroid, head, colon and neck cancer indicating that FAK plays important role in tumor progression. FAK overexpression correlates with increased malignancy of tumor, since FAK plays important role in cell survival, proliferation, invasion, migration and growth.[8] Levels of FAK mRNA are increased in invasive and metastatic tumors and premalignant adenomatous tissues. There is increased regional expression of FAK at the invasive tumor edge, implicating FAK in tumor invasion. It functions with growth factor receptors and integrins to promote cell survival-dependent kinase activity. FAK also promotes cell survival and proliferation through FERM enhanced p53 degradation independent kinase activity.[9] (Fig. 2).

REGULATION OF CANCER CELL SURVIVAL

FAK-mediated signaling has an important role in the regulation of cancer cell survival. Over expression of FAK leads to resistance of cell detachment- induced cell death i.e. anoikis it is a type of programmed cell death resulting from ECM-cell interactions, in which FAK activity is lost and therefore leads to apoptosis of cell. Increased in Src-FAK complex leads to activation of both MEK-extracellular signal regulated ½(ERK1/2) and AKT-PI3K signal transductions, thereby resulting in cancer cell growth and survival in a cell detached condition. In addition to this signal transduction several upstream signals also leads to resistance in FAK-mediated anoikis in cancerous cells. Transforming growth factor-β (TGF-β) results in activation of AKT and FAK via p38 MAPK and SMAD3, respectively, this in turn leads to resistance to anoikis and tumor progression. Fibronectin-mediated integrin αV activation results in FAK phosphorylation at Y397 prevent tumor suppressor p53-mediated...
anoikis in squamous cell sarcoma (SCC). FAK overexpression results in blockage of the caspase-3-mediated apoptosis. Thus inhibition of FAK leads to cancer cells apoptosis. By RNA interference inhibition of FAK overexpression leads to inhibition of metastasis of pancreatic cancer and anoikis. Binding of FAK to the Death domain kinase receptor-interacting protein (RIP), leads to suppression of apoptosis by inhibiting the death domain of RIP.

**REGULATION OF CANCER CELL PROLIFERATION**

Cell proliferation means increase in number of cells by cell division and growth. Various findings related to FAK overexpression and phosphorylation of FAK proved correlation with cell cycle proliferation by modulating cell cycle-relative molecules, thus proving that FAK functions as key regulator in promoting cancer cell proliferation. Over expression of FAK leads increase in cyclin D1 expression and decrease in cyclin-dependent kinase (CDK) inhibitor p21 expression thus increasing the rate of transition from G1 phase to S phase. Mutated FAK leads to inhibition of cell cycle progression from G1 phase. FAK was known to modulate E26 transformation-specific (ETS) binding site which is present in cyclin D1 promoter which leads to regulation of transcriptional activation of cyclin D1 and thus promotes proliferation of cancer cell. FAK consistently promotes cancer cell proliferation by reducing the expression of CDK inhibitors in concert with increased in expression of cyclin E and cyclin D1. FAK enhances cancer cell proliferation by suppressing tumor suppressor p53-mediated inhibition of p53 transcriptional activity and apoptosis. It is been proposed that FAK exerts its FERM domain as a scaffold to stabilize ubiquitin E3 ligases Mdm2 in the nucleus and p53, which thus enhances the Mdm2-dependent p53 ubiquitination and subsequently leading to degradation and polyubiquitination of p53. In simple words it means, FERM domain of nuclear FAK enables mediating turnover of p53 in regulation of cell survival and proliferation. Loss of p53 expression leads to mammary tumor malignancy.

**REGULATION OF CELL MIGRATION**

FAK promotes cell migration through integrins signaling. This was studied by correlative studies observed by activation and increased expression of FAK during epidermal wound healing in the migrating keratinocytes. Studies of FAK knockout reported an early embryonic lethal phenotype with increased mesodermal deficiency. When FAK C-terminal recombinant protein (FRNK) was microinjected in the mice, it leads to inactivation of FAK and decreased
in migration of both ECs and fibroblasts. Various downstream signaling pathways of FAK which promoted cell migration through phosphorylation and association of p130cas by the Src/FAK complex. Cell migration can be reduced by inhibiting the FAK binding to p130cas or Src which in turn inhibits phosphorylation at multiple sites. When the tyrosine group on p130cas is phosphorylated it associates with various protein containing SH2 including Crk. Formation of Cas/Crk complex plays a critical role in regulating cell migration through Rac. Paxillin, a cytoskeletal and adaptor protein, is the substrate of FAK-Src kinase complex and its phosphorylation at Y118 and Y31 could recruit Crk same as Cas. Other pathway which mediates promotion cell migration by FAK involves interaction with PI3K and Grb7 which is an adaptor molecule. Mutated FAK selectively inhibits its binding to Grb7 and PI3K, but it retains its binding to Src and induces phosphorylation of Cas, but failed to promote migration. Through downstream effector Rac which is an important regulator of cortical lamellipodia and actin, activated PI3K which in turn stimulated cell migration. Grb7 association with phosphatidylinositol is facilitated by increased D3-phosphoinositides through PH domain in the plasma membrane.[15] There is conformational change in Grb7 when phosphatidylinositol phosphates bind to Grb7, which in turn leads to Grb7 phosphorylation by FAK. Studies have proved that binding of FAK and phosphorylation of Grb7 are important for initiation of cell migration. Independent binding of FAK to Grb7 and PI3K is observed which promotes cell migration in a cooperative manner.[16] Thus FAK helps in cell migration.

ROLE IN CELL ADHESION

Regulation of cell migration, proliferation, invasion and survival is achieved by adhesion of cells to ECM. All of the above cellular functions are very important for the maintenance, development and repair of architecture of tissue. Adhesion to the ECM is mediated predominantly by the integrin receptors. Integrins are present on cell surface as heterodimers and they consists of α- and β- subunits which are associated with each other. These subunits are type I transmembrane proteins which consists of large extracellular domain which helps in binding to the cytoplasmic part and ECM ligands. Clustering of integrins is induced by binding of cells to ECM on the cell surface. Binding of the scaffold/ adaptor and signaling proteins is mediated by cytoplasmic part of the integrins which are clustered in the inner surface of plasma membrane, which leads to the formation of focal adhesions. Here example of scaffold/ adaptor and signaling proteins is paxillin and talin which is a part of C-terminal of FAK helps in formation of strong linkages to the actin cytoskeleton which in turn helps in
firm binding of cells to the ECM. This firm binding helps in generation of tension which is required for altering the morphology of cells and also provides the traction required for the movement of cell during cell migration. FAK and Src plays important role in integrin mediated signaling cascades. As such integrins have no intrinsic activity but these protein tyrosine kinases helps in transmitting signals by phosphorylating various integrin-associated proteins from Focal adhesions to the cells. Hence, Src and FAK both act as a molecular switch that initiates multiple cellular responses like cell migration, proliferation, invasion and survival via focal adhesion complexes. Talin act as an important regulator in the initial Focal adhesion assembly step. Talin consists of head and rod domain which are quite unique. The rod domain consists of various sites for binding of adhesome proteins which includes 2 sites for actin, multiple sites for vinculin and 1 for cytoplasmic part of β-integrin. And the head part helps in binding the cytoplasmic part of the β-subunit of integrin. Talin act as a platform which helps in increasing extracellular structural framework by forming a dimer through its terminal carboxy helix. Talin is a cytoskeletal protein which is concentrated in areas of cell-substratum and cell-cell contacts. It plays a significant role in the assembly of actin filaments and in spreading and migration of cells.  

**Fig. 3** FAK- ECM mediated cellular functions  

**ROLE IN CELL INVASION**  
Cancer cell invasion is an important event for spreading of tumor malignancy. Multiple studies prove that FAK helps in the promotion of cancer cell invasion. FAK-Src complex is formed by the action of various integrins which leads to recruitment of Crk-Dock180-ELMO complex by FAK signaling through p130Cas which in turns lead to activation of Rac1.
leads to production of Matrix metalloproteinases (MMPs) through activation of JNK protein and this result in ECM proteolysis. ECM proteolysis through MMPs plays an important role in cancer cell invasion through FAK-Src complex. Before cancer cell invasion starts there is a morphological and developmental alternation which is epithelial mesenchymal transition (EMT). EMT is a process through which epithelial cells transdifferentiate into mobile mesenchymal cells. During the happening of EMT, degradation of Epithelial cadherin (E-cadherin) which is a major molecule present in the epithelial adherent junctions, leads to release of cell-cell restriction and hence promotes cancer cell invasion. FAK is phosphorylated at Tyr407 and Tyr861 by the formation of FAK-Src complex which promotes degradation of E-cadherin. Simultaneously, transforming growth factor-β (TGF-β) promotes EMT because of degradation of E-cadherin which is mediated by FAK-Src complex. Thus FAK plays important role in cancer cell invasion.\[19\][20]

**ROLE IN ANGIOGENESIS**

Angiogenesis means formation of new blood vessels from pre-existing blood vessels, which plays vital role in survival of cancerous cell. During angiogenesis in response to various proangiogenic growth factors, endothelial cells (ECs) proliferate and migrate. Initial step of angiogenesis is ECs sprouting and it requires cell migration into the ECM present beneath the basement membrane. Various studies prove that angiogenesis is mediated by signals from integrins and growth factor receptor. FAK plays vital role in integrin mediated signal transduction pathways. FAK on activation by integrin-mediated cell adhesion, gets associated with multiple SH2 domain containing proteins like Src which belongs to family of kinase, Grb7, p85 subunit of PI3K and phospholipase C-g.\[21\] FAK on interaction with all these proteins leads to inhibition of various pathways which regulates multiple cellular functions. FAK binds to epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor and platelet-derived growth factor receptor (PDGFR) receptors through its N-terminal. Vascular endothelial growth factor (VEGF) is an proangiogenic factor, which is released from cells that are exposed to hypoxia and partly because of transcription, thus leading to binding of VEGF to VEGFR. This causes dimerization of the receptor and phosphorylation of FAK, which in turn leads to FAK mediated angiogenesis.\[22\] Platelet-derived growth factor (PDGF) is also a proangiogenic factor. When PDGF binds to PDGFR it leads to phosphorylation of FAK Ser-910 site. This causes activation of endothelial cells, stromatal cells and circulating endothelial progenitor cells (CEPs), which secrete several enzymes including matrix metalloproteinases that break down the ECM and allows
endothelial cells to invade surrounding tissue. Thus FAK functions simultaneously in signaling pathways stimulated by growth factor receptors and integrins, which are important in maintaining multiple cellular functions related to angiogenesis.\[^{23}\]

**PATHWAYS IN WHICH FAK IS INVOLVED**

![](image)

**Fig. 4: Various signalling pathways involving FAK**

\(? = \text{mechanism is still not known clearly}\)

Multiple proteins which are FAK associated have been studied and the signal transduction pathways arising from the interactions are known. Knowledge of multiple signaling pathways involving FAK provides information of how FAK contributes to regulation of cell adhesion, migration, invasion, angiogenesis and proliferation.\[^{24}\][\[^{25}\]\n
Proteins associated with FAK are MAPKs, ERK and JNK, Rho family GTPases like RAC1 and AKT. For cell migration FAK downstream two pathways: 1) FAK association with PI3K and 2) phosphorylation of FAK mediated by Src which is associated with p130Cas and it also requires Crk downstream of p130Cas. For cell proliferation three pathways are described: 1) Downstream of MAPKs by FAK-Src complex leads cell proliferation.\[^{26}\] 2) It promotes Grb2/Shc association by unknown mechanism\[^{27}\]\ and 3) FAK binding to Grb2 and p130Cas.\[^{28}\]\n
FAK prevents apoptosis by down streaming AKT and PI3K. It promotes cell invasion by phosphorylation of paxillin which is Src dependent. FAK phosphorylation by Src not only regulates kinase activity but also E-cadherin and integrin mediated adhesion, formation of protein complexes which are phosphorylation-dependent and cellular invasion and motility. Phosphorylation of FAK Tyr925 is by Src leads to EMT which causes cell migration.\[^{29}\]\n
Invasive pathway which is mediated by FAK involves RAC1, JNK and MMPs (**Fig. 4**). Binding of p53 with FAK promoter leads to inhibition of its promoting activity. FAK inhibits apoptotic signaling and
p53-transcriptional activity by sequestering p53.\textsuperscript{[30]} It promotes p53 ubiquitination and degradation binding to Mdm-2. P53 inhibits Nanog and maintains the Mdm-2. Further Nanog inhibits p53 which helps in maintaining cancer stem cell pool and inhibits apoptosis and thus promotes tumor growth by cell growth and survival.\textsuperscript{[31]} FAK is promoted by Nanog which helps in phosphorylation of Nanog by FAK and this cross-linked signaling promotes cell invasion and motility and plays a vital role in tumor metastasis.\textsuperscript{[32]}

**STRATEGIES TO INHIBIT FAK**

Knowing the vital role played by FAK in cellular activities, it has been proposed as a therapeutic target for cancer.\textsuperscript{[33]} Various FAK inhibitors have been mentioned below.

**PF-573,228:**

PF-573,228 (Fig. 5) is first FAK directed drug developed by Pfizer which is a ATP-competitive inhibitor of FAK. It inhibits FAK phosphorylation and downregulates effector paxillin which results in inhibition of cell adhesion and migration with IC50 of 4 nM.\textsuperscript{[34]} It is not highly effective on cell growth and survival in cell lines of prostate cancer. Inspite of its potent FAK inhibition it has shown limited antineoplastic effects due to the compensatory role of Pyk2 which a FAK homologue.\textsuperscript{[35]}

![Fig. 5: PF 573,228, Tetrahydroquinolinone analogue](image)

**TAE-226**

TAE-226 a pyrimidine analogue (Fig. 6), is an orally bioavailable pre-clinical compound is an ATP competitive inhibitor of FAK. It is very potent inhibitor of FAK with IC50 value of 5 nM. It has shown potent antitumor activities against ovarian, esophageal, pancreatic cancer, neuroblastoma, glioma, oral squamous cell carcinoma and imanitib-resistant GIST.\textsuperscript{[36]} When TAE-226 was treated with esophageal cancer and tongue squamous cell carcinoma cell lines, it exhibited abnormal cell attachment, growth inhibition which was time and dose dependent and inhibition of caspase mediated apoptosis. Despite of these inspiring results in pre-clinical
finding it was stalled because of drug failing in clinical trials for some undisclosed reasons.\cite{37}

![Fig. 6: TAE-226, Pyridine analogue](image)

**Y15**

Y15 a 1,2,4,5-tetraaminobenzene hydrochloride salt (Fig. 7), is an allosteric FAK inhibitor developed by Roswell Park Cancer Institute. It robustly inhibits Tyr397 autophosphorylation in the concentration range of 25nM-1μM. It’s mechanism of action is different from ATP competitive FAK inhibitors that binds to the ATP-binding domain and targets the Tyr397 site of FAK.\cite{38} It does not inhibit other protein tyrosine kinases such as EGFR, Src and PYK2.\cite{39}

Pancreatic cancer cells on treatment with Y15 produced inhibition of cell adhesion and attachment in a dose dependent manner and induced apoptosis by decreasing cell survival. Y15 decreased tumor growth in colon, pancreatic, breast cancer, neuroblastoma, impaired liver metastasis of neuroblastoma cells and glioblastoma. But still its clinical studies are under process.\cite{40}

![Fig. 7: Y15, Aminobenzene analogue](image)

**GSK-2256098**

GSK-2256098 is a small molecule FAK inhibitor developed by GlaxoSmithKline (Fig. 8). Two pre-clinical yet so far has been reported. Antitumor activity of GSK-2256098 in ovarian cancer cells was enhanced in presence of Pazopanib which is an PDGFR and VEGFR inhibitor.\cite{41} Through matrigel GSK2256098 inhibited cell invasion and migration in eight of twenty-six glioblastoma cell lines. Clinical studies proved that it was well tolerated in the body.\cite{42}
BI 853520

BI 853520 inhibits phosphorylation of Tyr397 of FAK in prostate cancer cells with EC50 of 1nM. It is 1000-times more selective for FAK over PYK2. In several tumor xenograft models daily oral dose of 50mg/kg of BI 853520 caused marked suppression of tumor. Currently, it is been tested in two clinical trials and they are under phase I studies to determine its tolerability and safety and MTD of the compound for patients.\textsuperscript{[43]}

VS-4718

VS-4718 (Fig. 9) is a substituted pyridine which was earlier known as PND-1186 and it is acquired by Verastem.\textsuperscript{[45]} It is an orally bioavailable FAK inhibitor with potent antineoplastic activity. It inhibits FAK by suppressing fibronectin-stimulated FAK autophosphorylation of Tyr397.\textsuperscript{[44]} It also prevents the integrin mediated stimulation of several downstream signal transduction pathways, including ERK, MAPK/JNK and PI3K/Akt. Thus this results in reduction of cancer stem cells. It is a potent reversible inhibitor of FAK with IC50 of 1.5 nM in cultured carcinoma cells. Initial preclinical studies exhibited little effects on cell adhesion and proliferation, whereas it showed marked inhibition of phosphorylation of FAK and p130Cas resulting in activation of caspase-3 activation and apoptosis.\textsuperscript{[46]}

PF-562.271

PF-562.271 (Fig. 10) is an orally administered drug which is a dual inhibitor of FAK and FAK homologue is Pyk2. It was developed by Pfizer but now acquired by Verastem,
therefore known as VS-6062.\textsuperscript{[47]} It is 100-times more selective for FAK and Pyk2 from other non-target protein tyrosine kinase with IC50 value of 1.5 nM for FAK and 14 nM for Pyk2. Therefore, it is more potent than PF-573,228. It inhibits phosphorylation of FAK Tyr397 in a dose dependent manner.\textsuperscript{[48]}

![Fig. 10: PF-562271, Pyridopyrimidine analogue](image)

**DEFACTINIB**

Defactinib is an ATP competitive FAK inhibitor (Fig. 11), which is also known as VS-6063 developed by Pfizer and recently acquired by Verastem. Its pharmacodynamics profile is much better than PF-562,271. There are total three phase II clinical trials are been done on defactinib. Phase I clinical trials showed marked tolerance in patients with advanced non-hematologic malignancies.\textsuperscript{[49]}

![Fig. 11: Defactinib, Pyridopyrimidine analogue](image)

FAK inhibitors are potential therapeutic target for cancer. However, in development of FAK inhibitors there are still some obstruction. Inhibition of kinase domain by FAK inhibitors leads to downstream signaling cascades. But FAK alone is not essential for regulation of various pathways.

**CONCLUSION**

This review explains how overexpression of tumors leads to cell migration, proliferation, angiogenesis, survival, growth and invasion. Inhibitors which are used to inhibit FAK signaling act by blocking ATP binding site, autophosphorylation and protein interaction can
be future therapy approach. FAK can function with growth factor receptors and integrins which promotes cell survival-dependent kinase activity. FAK stimulates cell survival and proliferation through FERM initiated p53 degradation independent kinase activity. Still, whether signaling of FAK within the tumor is a key event in promoting tumor progression and mechanism of the role of FAK in tumor cell generation is still not known; hence future work is needed to explore these issues.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflicts of interest.

ABBREVIATIONS
FAK: Focal Adhesion Kinase,
ECM: Extracellular matrix,
FERM: band four point one, ezrin, radixin, moesin,
FAT: Focal adhesion targeting,
Grb-2: Growth factor receptor bound,
MAPK: Mitogen-activated protein kinase.
ERK: Extracellular signal-regulated kinases,
Akt: A serine/threonine kinase
PI3K: Phosphoinositide 3-kinase
DOCK 180: Dedicator of cytokinesis,
JNK: c-Jun N-terminal kinases

REFERENCES


