Focal Adhesion Kinase

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Contributor: Frank Aboubakar Nana

Small-cell lung cancer (SCLC) represents 15% of all lung cancers and it is clinically the most aggressive type, being characterized by a tendency for early metastasis, with two-thirds of the patients diagnosed with an extensive stage (ES) disease and a five-year overall survival (OS) as low as 5%. There are still no effective targeted therapies in SCLC despite improved understanding of the molecular steps leading to SCLC development and progression these last years.

Keywords: focal adhesion kinase ; small-cell lung cancer ; targeted therapy

1. Introduction

Lung cancer, which arises from lung epithelial cells, is histologically divided into two main types: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which represent 15% and 85% of the cases, respectively [1]. As opposed to SCLC, oncogenic drivers with sensitivity to targeted therapies have been discovered in NSCLC. Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, or other oncogenic abnormalities have brought remarkable improvements in the outcome of oncogenic-driven NSCLC patients [2]. Immunotherapy with anti-programmed death-(ligand) 1 (PD-(L)1) immune checkpoint inhibitors (ICIs) has also significantly improved the survival of NSCLC patients without oncogenic drivers [3][4][5][6][7][8][9]. Clinically, SCLC is the most aggressive type of lung cancer, being characterized by a high growth rate, a fast doubling time, and a tendency for early metastasis, with two-thirds of the patients diagnosed with an extensive stage (ES) disease [10][11]. While a good initial response to chemotherapy and/or radiation therapy is observed in most patients, they typically recur or progress rapidly after the primary treatment, with a median overall survival (OS) of 24–38 months in limited stage (LS) [12] [13] and 7–10 months in ES [14], and a five-year OS as low as 5% [1].

Despite improvements in the understanding of the molecular steps that lead to SCLC development and progression these last years, there are still no effective targeted therapies in SCLC. Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate (pyrrolobenzodiazepine (PBD)-dimer cytotoxic) that is directed against Delta-like 3 (DLL3), an inhibitory NOTCH ligand, which has been shown to be overexpressed on the surface of SCLC cells [15]. Despite encouraging preclinical and early clinical results, targeted therapy with Rova-T underperformed in the phase II TRINITY trial, including pretreated SCLC patients with high levels of DLL3 on tumor cell surface [15][16]. After four decades, the only modest improvement in the OS of patients suffering from ES-SCLC has recently been shown in a trial combining atezolizumab, an anti-PD-L1 ICI, with carboplatin and etoposide, chemotherapy agents [17]. In this trial, the OS was 10.3 months in the chemotherapy alone arm, while it was 12.3 months in the chemotherapy plus immunotherapy arm. Based on this positive trial, atezolizumab that is associated to carboplatin an etoposide recently became the new standard of care in the first-line treatment of ES-SCLC [17]. At relapse or progression after a first-line treatment, a rechallenge with platinum and etoposide is proposed to tumors that are considered to be sensitive to platinum (relapse or progression within 60 or 90 days of completion of chemotherapy) [18], while a second-line chemotherapy with topotecan is proposed to tumors platinum-refractory (relapse or progression before three to six months). However, the response rates are poor and OS ranges from 1.2 months to 7.6 months based on systematic reviews of real-world data 15 [19]. These disappointing results highlight the need for novel therapies.

Focal adhesion kinase (FAK) is a 125 kDa non-receptor protein tyrosine kinase that is known to be overexpressed and activated in several cancers, including SCLC [20][21][22][23][24][25][26][27][28]. Unlike receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR), non-RTKs, such as FAK, are cytoplasmic enzymes that lack transmembrane and extracellular domains [29]. FAK localizes to focal adhesions and it is triggered off by extracellular signals, such as integrin-mediated adhesion and some growth factors [30]. Therefore, FAK plays a central role in the interaction between cells, including cancer cells and their microenvironment. The FAK structure includes an NH2-terminal Protein4.1-ezrin-radixin-moesin (FERM) domain, a central kinase domain, two proline-rich motifs, and a COOH-terminal focal adhesion targeting (FAT) domain. FAK is maintained in an inactive state by the binding of the FERM domain to the kinase domain,

which blocks access to the catalytic site and sequesters the activation loop, as well as the key autophosphorylation site tyrosine 397 (Tyr397) (**Figure 1**). The engagement of integrins with the extracellular matrix (ECM) or growth factors leads to signals that displace the FERM domain, resulting in rapid autophosphorylation of Tyr397, which is a critical event in signal transduction by FAK [30][31]. Tyr397 phosphorylation provides a binding site that recruits and activates Src through the SH2 domains of Src family kinases. The FAK-Src complex therefore maintains Src and FAK in their activated states, creating a functional kinase complex [32].

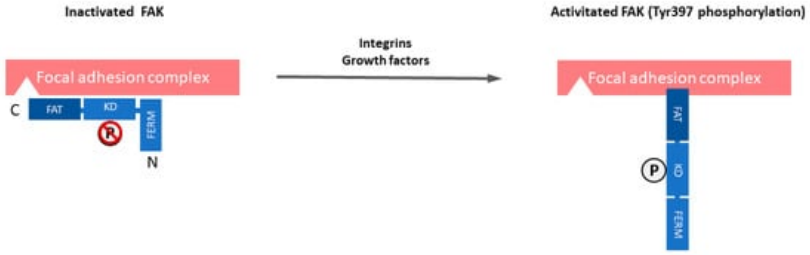

Figure 1. The domain organization and activation of focal adhesion kinase (FAK). FAK is composed of a central kinase domain (KD), an amino-terminal side that is flanked by a protein band 4.1-ezrin-radixin-moesin (FERM) homology domain, and a carboxy-terminal focal adhesion targeting (FAT) domain flanked by proline-rich regions (PRRs). FAK localizes to focal adhesions and is triggered off by extracellular signals such as integrin-mediated adhesion and some growth factors. FAK is maintained in an inactive state by the binding of the FERM domain to the kinase domain, which blocks access to the catalytic site and sequesters the activation loop, as well as the key autophosphorylation site tyrosine 397 (Tyr397). Engagement of integrins with the extracellular matrix (ECM) or growth factors leads to signals that displace the FERM domain, resulting in rapid autophosphorylation of Tyr397, which is a critical event in signal transduction by FAK.

Based on FAK overexpression and/or increased activity in cancer and its known function in multiple biological processes that play a role in the development and progression of cancers, such as crosstalk between cell and his microenvironment, cell growth, survival, adhesion, spreading, migration, invasion, angiogenesis, DNA damage repair, radioresistance, and regulation of cancer stem cells, it has been suggested that increased the expression and/or activity of FAK may have a critical role in cancer development and progression [33]. Therefore, FAK is a potential target for anti-cancer therapy, especially in SCLC, being known to be a highly invasive cancer. Small-molecule inhibitors targeting the FAK kinase domain and preventing FAK activation (Tyr397 autophosphorylation) have been developed. Phase I trials with GSK2256098 [34][35][36], VS-6062 [37], defactinib (VS-6063) [38][39][40], or BI853520 [41][42][43] have shown an acceptable safety profile and favorable pharmacokinetics. Most frequent treatment-related adverse events included digestive disorders (nausea, diarrhea, vomiting), headaches, reversible proteinuria, and unconjugated hyperbilirubinemia [34][35][36][37][38][39][40][41][42]. With GSK2256098, the best response of stable disease was observed in 37% of glioblastoma (three patients, median PFS 5, seven weeks) [36] and in 45% of advanced solid cancers (28 patients) [35]. With VS-6062, 34% of patients (31 patients) with advanced solid tumors exhibited stable disease at six weeks, including one case of SCLC for ≥6 cycles cycles [37]. VS-6063 led to the stabilization of advanced solid tumors in 43% of Caucasian patients (six cases) after six weeks of treatment [38] and in 33% of Asian patients (three cases) during more than 24 weeks (median PFS of 63 days) [40]. Recently, the combination of the FAK inhibitor GSK2256098 and the MEK inhibitor trametinib in recurrent advanced pancreatic ductal adenocarcinoma did not provide significant clinical activity in a phase II trial (PFS of 1.6 month and OS of 3.6 months) [44]. In malignant pleural mesothelioma, defactinib in maintenance after first-line chemotherapy in a phase II trial did not provide any benefit either (PFS of 4.1 months with defactinib vs 4.0 months with placebo, and OS of 12.7 months with defactinib vs. 13.6 months with placebo) [45]. Preoperative administration of defactinib in the ongoing phase II clinical trial NCT02004028 appears promising, with therapeutic activity (13% objective partial response, 67% stable disease, 17% tumor progression) and beneficial modification of the tumoral microenvironment [46]. Several clinical trials with defactinib associated with immunotherapy (NCT02758587, NCT03727880, NCT02943317), RAK/MEK inhibitor (NCT03875820), or chemotherapy (NCT02546531) are ongoing, with some of them being open to SCLC inclusion (**Table 1**) [34][35][36][37][39][40][41][42][43][44][45][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61]. Other small-molecules targeting the protein-protein interactions between FAK and other proteins, such as VEGFR-3, called scaffolding inhibitors, have been developed and shown to induce antitumoral effects in preclinical studies. Further research is needed to find predictive biomarkers of response to FAK TKI alone or, probably more promising, in association with another drug.

Table 1. FAK inhibitors with anti-tumor activity in preclinical studies and clinical trials.

Name	Type	Specificity	Cancers Targeted	Study Phase	References
TAE-226 Novartis	Kinase inhibitor ATP competitive	FAK, IGF-IR, c-Met, Pyk2	Glioma, ovarian	Preclinical	[47][62]
PF-573,228 Pfizer	Kinase inhibitor ATP competitive	FAK	Prostate, breast	Preclinical	[48]
GSK2256098 GlaxoSmithKline	Kinase inhibitor ATP competitive Reversible	FAK, UGT1A1	Solid tumors (ovarian, pancreatic, meningioma, glioblastoma, malignant pleural mesothelioma)	Clinical: phase I & II	[34][35][36][44][49] NCT00996671, NCT02523014
NVP-TAC544	Kinase inhibitor ATP competitive	FAK	N/A	Preclinical	[50]
VS-4718 (PND-1186) Verastem	Kinase inhibitor ATP competitive Reversible	FAK, Pyk2	Solid tumors (pancreas, breast, ovarian), acute myeloid leukemia, B-cell acute lymphoblastic leukemia	Clinical: phase I	[51]
VS-6062 (PF-562271 and PF271) Verastem	Kinase inhibitor ATP competitive Reversible	FAK, CDK2/CyclinE, CDK3/CyclinE, CDK1/CyclinB, Pyk2	Prostate, pancreatic, head and neck	Clinical: phase I	[37][52]
VS-6063 (Defactinib) Verastem	Kinase inhibitor ATP competitive	FAK, Pyk2	NSCLC, pancreatic cancer, ovarian, malignant pleural mesothelioma, hematologic	Clinical: phase I/Ib & II	[38][39][40][45][53] NCT02758587 NCT02004028 NCT03875820 NCT03727880, NCT02943317, NCT02913716, NCT02465060, NCT02546531
1H-Pyrrolo(2,3-b) Merk Serono	Kinase inhibitor non-ATP competitive	Hinge region of FAK	N/A	Preclinical	[54]
C4 CureFAKtor Pharmaceuticals	Scaffold inhibitor	FAK /VEGFR-3	Neuroblastoma, pancreatic, breast	Preclinical	[55][56][57]
Compound R2 (Roslins) CureFAKtor Pharmaceuticals	Scaffold inhibitor	FAK, p53	Colon, reast	Preclinical	[58]
Y11 CureFAKtor Pharmaceuticals	Scaffold inhibitor	FAK Y397 site	Colon, breast	Preclinical	[59]
BI853520	ATP competitive inhibitor	FAK	Malignant pleural mesothelioma, non-hematologic malignancies	Preclinical, clinical	[42][43][60]

Abbreviations: CDK: Cyclin-dependent kinases 1, 2, 3; FAK: focal adhesion kinase; IGF-IR: insulin-like growth factor 1 (IGF-1) receptor; N/A: data not available; Pyk2: proline-rich tyrosine kinase 2; UGT1A1: UDP-glucuronosyltransferase 1-1; VEGFR-3: vascular endothelial growth factor receptor 3.

2. FAK Role in Proliferation, Cell Cycle, and Survival

FAK activation during cell adhesion protects cells from anoikis, a form of apoptosis that is induced by cell detachment from ECM, favouring cancer growth and metastasis [63]. FAK is implicated in several pathways that contribute to cell survival. Phosphorylated FAK at Tyr397 can bind PIK3R2, which leads to the activation of AKT that inhibits apoptosis by regulating various molecules. Among other mechanisms, there is the suppression of apoptosis by FAK through c-JUN kinase activation downstream of CAS [33] and the inhibition of RIP interaction with the death receptor complex [64].

FAK also induces cell proliferation through the stimulation of cell cycle progression. One of the mechanisms is the formation of FAK/Src complex that allows for Src to phosphorylate FAK at Tyr925 and mediate its interaction with Grb2, which leads to the activation of the RAS-MAPK signaling pathway [40]. Another mechanism involves the FAK-induced increased expression of cyclin D1 and decreased expression of cycline-dependent kinase (Cdk) inhibitor p21 [65][66][67][68]. Other cell cycle regulators, such as cyclin E, Cdk inhibitor p27, and Skp2, also mediate FAK regulation of cell cycle progression [69][70][71][72]. Moreover, FAK is important for tumor cell-induced remodeling of the tumor matrix, which produces a rigid microenvironment and facilitates cell proliferation [73].

Specifically, in SCLC cell lines, it has been shown that the inhibition of FAK activity with PF-573,228, a FAK TKI, decreased proliferation, DNA synthesis, induced cell-cycle arrest in G2-M phases, and increased apoptosis in the NCI-H82, NCI-H146, NCI-H196, and NCI-H446 SCLC cell lines [74]. Treatment with increasing concentrations of PF-228 (0.1 to 10 µM) dose-dependently decreased the FAK phosphorylation (Tyr397) in these four cell lines, without modifying total FAK expression, and the inhibition of FAK activity with 1 to 10 µM PF-228 significantly decreased their proliferation, also dose-dependently ($p < 0.001$ for all tested concentrations beside 1 µM in NCI-H196), as assessed by a WST-1 assay. Cell cycle analysis showed that PF-228 inhibited progression through cell cycle by significantly reducing the S phase and inducing cell cycle arrest in the G2/M phases in the four cell lines after 24h-treatment, dose-dependently ($p < 0.001$). PF-228 at concentrations of 1 to 5 µM also significantly induced apoptosis in the four cell lines, as demonstrated by a dose-dependent increase of PARP p85 expression by WB after 48h-treatment. This was confirmed by flow cytometry in NCI-H82 and NCI-H446 cell lines, with a significant increase of BrdU-positive and activated Caspase 3-positive cells after 48h-treatment ($p < 0.001$ for all tested concentrations, except 1 µM in NCI-H446 in the Caspase-3 assay). Genetic inhibition of FAK through stable transduction with FAK shRNA and/or FAK-related non-kinase (FRNK), a splice variant lacking the N-terminal and kinase domains of FAK, revealed that the FAK-targeting (FAT) domain (attached to focal adhesion complex, where it inhibits pro-proliferative proteins) was necessary to inhibit proliferation, cell cycle progression, and survival [74]. Indeed, FAK shRNA transduction did not affect these functions, while the restoration of FAT domain by FRNK transduction inhibited proliferation, DNA synthesis, and induced apoptosis in the evaluated SCLC cell lines. Additionally, while FAK shRNA transduction increased the active Rac1 level, FRNK re-expression in cells that were previously transduced with FAK shRNA decreased it. Therefore, this study not only suggested that FAK is important in SCLC biology, but also that targeting its kinase domain might have a therapeutic potential, while targeting its FAT domain might have Rac1-mediated pro-tumoral activity and thus should be avoided.

3. FAK Role in Adhesion, Migration, and Invasion

FAK induces morphological changes in cells, including the formation of podosomes or invadopodia, contributing to cell migration [75][76][77]. Moreover, cancer cells overexpressing FAK are able to invade tissues [78]. FAK overexpression contributes to the metastatic phenotype of cancer cells by promoting cell migration and invasion.

Cell migration is a complex process that consists of several coordinated events, including protrusion of the leading edge, adhesion of the leading edge to the substrate [79], translocation of the cell body, and release of the trailing edge [80]. Thus, a strict regulation of tension at specific times and in specific areas of the cell is required for cell migration [81][82], where FAK plays an important role by sensing the mechanical forces that are generated in or exerted on cells [83], and modulating cell responses to environmental stimuli. Once activated by integrins, G protein-coupled receptors ligands, or growth factors, FAK is autophosphorylated at Tyr397 and activates proteins, such as Src, p130CAS, paxillin, and PIK3R2 [84], to regulate adhesion turnover at the cell front, a process that is central to migration [84][85][86][87][88]. FAK is indeed required for the organization of the leading edge in migrating cells [89]. The formation of a complex between FAK and Src, leading to the phosphorylation of the adaptor molecule CAS by the FAK/Src complex [90][91][92][93][94], is one of the best characterized downstream signaling pathways that mediate FAK-stimulated cell migration. A second mechanism involves FAK interaction with PIK3 and an adaptor molecule, Grb7 [95][96]. A third mechanism involves the modulation of the assembly and disassembly of actin cytoskeleton through the effect of FAK on the Rho family GTPases. Among the Rho family GTPases, FAK/Src signaling has, in particular, been implicated in regulating the activities of Rac1 and RhoA.

Besides its role in cell migration, FAK promotes invasion in normal and cancer cells by various mechanisms. In one of them, FAK promotes the formation of the Src-CAS-Crk-Dock180 complex, which activates Rac1 and JNK, and leads to increased expression or activity of metalloproteinases 2 (MMP2) and 9 (MMP9) [75]. MMPs are concentrated and activated at actin-rich cell/ECM contacts, termed podosomes or invadopodia, which are distinct from focal adhesion. In another mechanism, FAK cooperates with Src to disrupt the E-cadherin-based intercellular adherens junctions [97], contributing to EMT and, therefore, to the invasive phenotype of metastatic carcinomas through increased cell migration and remodelling of the ECM microenvironment [98][99][100]. In SCLC cell lines, the pharmacologic inhibition of FAK with PF-573,228 decreased cell adhesion [28], as well as migration and invasion [74]. In NCI-H69, NCI-H146, and NCI-H209 SCLC cell lines,

PF-573,228 induced a dose-dependent decrease of cell adhesion on laminin, with the effect becoming statistically significant at the concentration of 10 µM (NCI-H69: $p = 3 \times 10^{-4}$, NCI-H146, and NCI-H209: $p = 1 \times 10^{-4}$ as compared to DMSO) [28]. Moreover, a wound healing assay combined with time-lapse microscopy showed that PF-573,228 decreased the migration velocity of two SCLC cell lines with an adherent component, from 5 to 2.5 µm/min. in NCI-H196 ($p = 0.0561$) and from 9 to 4 µm/min. in NCI-H446 ($p = 0.0916$)) [75]. Modified Boyden chambers showed that PF-573,228, at a concentration of 3 µM, also inhibited invasion, with the number of invasive cells being able to migrate to the lower side of the insert separating the two Boyden chambers, decreasing from 150 to 50 per field (20× magnification) for NCI-H196 and from 45 to five per field for NCI-H446 [75].

4. FAK in Epithelial to Mesenchymal Transition

Through epithelial-to-mesenchymal transition (EMT), cancer cells acquire a more motile phenotype, promoting invasion, metastasis, but also conferring resistance to chemotherapies and targeted therapies. Epithelial cancers undergoing EMT acquire transient mesenchymal features, like Vimentin and N-cadherin, which are associated with the loss of epithelial markers E-cadherin and β-catenin [101]. EMT is correlated with poor outcomes in SCLC [102], such as in many other cancers. Identified mechanisms inducing EMT in SCLC include inactive Notch signaling [103], activated MET receptor signaling through hepatocyte growth factor [102], and activated TGFβ/Akt signaling [104].

While FAK-mediated EMT has not yet been explored in SCLC, its important role has been demonstrated in other cancers and non-malignant cells [105][106][107][108]. Impaired FAK functions lead to a defective mesenchymal phenotype during EMT. Hence, upon TGF β-induced EMT, hepatocyte cell lines transduced with FRNK, a genomic method for inhibiting FAK, underwent an incomplete mesenchymal transition, exhibiting a lack of mesenchymal markers MMP9 and fibronectin and a persistence of membrane-bound E-cadherin [105]. Mammary tumor cells with deficient FAK scaffolding function due to Pro 878/881 mutation also displayed incomplete mesenchymal phenotype with increased E-cadherin and decreased N-cadherin, Vimentin, and fibronectin in a mice model [106]. It was associated with decreased metastasis potential and decreased expression of EMT-inducing gene Snail 1 [106]. A similar reduction of Snail 1 in embryonic FAK-null cells has been associated with the inability to display mesenchymal cell characteristics, while the reexpression of FAK restored mesenchymal phenotype and Snail 1 level through PI3K/Akt signaling [107]. In ovarian cancer, FAK controls EMT by upregulating transcription factor KLF8 via the PI3K/Akt pathway [108]. It has been shown that transcription factors Snail 1 and KLF8 repress E-cadherin expression, promoting EMT in various normal and malignant cells [109][110][111]. The inhibition of FAK by a genetic or a pharmacologic method decreased the EMT features and aggressiveness in colorectal carcinoma cell lines [112][113] and triple negative breast cancer cell lines in vitro [114], but not in NSCLC cell lines in vitro [115].

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