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EDITORIAL

Inhibiting focal adhesion kinase: A potential target for enhancing therapeutic efficacy in colorectal cancer therapy

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Abstract

Focal adhesion kinase (FAK) is a major integrin-dependent tyrosine phosphorylated protein, recently, FAK association with colorectal cancer (CRC) has gained attention. The various cancer-promoting mechanisms that associated with FAK can be implicated in the progression of CRC. The interactions between structural features of FAK and various kinases could be closely related to growth, survival, and metastasis in CRC cells. These interactions include human epithelial growth factor receptor, c-Met, platelet-derived growth factor receptor, vascular endothelial growth factor receptor, and Src. Such interactions can trigger the survival signaling of CRC cells and are also involved signaling downstream of phosphatidylinositol 3-kinase, AKT, and the extracellular regulated kinase. Based on this scientific background, many pharmaceutical companies are taking efforts to develop FAK inhibitors to treat solid cancer including CRC. Although the anti-cancer efficacies have been noted in many studies, the commercial drugs have not been developed yet. Therefore, the FAK research on CRC is expected to gain momentum and be highly appreciated as a potential field for developing the new drugs. Therefore, the studies on FAK that effect on the progression of human CRC s would be possible to suggest various approaches to CRC treatment, and FAK could be a potential target as an anticancer candidate for CRC therapies.

Key words: Colorectal cancer; Focal adhesion kinase; Focal adhesion kinase inhibitor; Anticancer effect

Core tip: Despite ongoing development in treatment for colorectal cancer (CRC), effective markers for treatment of CRC have not been elucidated. FAK association with various kinases for progression and invasion of CRC has recently gained attention. The possibility for this association is accounted that FAK is interactions with integrins, growth factor receptors, and adjacent kinase domain. Targeting FAK is possible to explain the mechanism at

the upstream level by which can mediate the expression of various survival signaling and inhibition of oncosuppressor genes as well as inducing migration and invasion of the CRC cells. Therefore, FAK could be a prognostic marker and a potential candidate target for CRC therapies.

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Focal adhesion kinase (FAK) is a major integrin-dependent tyrosine phosphorylated protein and a non-receptor tyrosine kinase that is localized to cellular focal adhesions[1]. Although there have been many studies on the role of FAK in breast cancer, its association with colorectal cancer (CRC) has recently gained attention. FAK, known as protein tyrosine kinase 2, is related to other tyrosine kinases, such as Src kinase[2]. FAK comprises a central kinase domain between an N-terminal FERM domain and a C-terminal domain that includes the focal adhesion sequence. The construction of the N-terminal FERM domain is similar to that of cytoskeletal proteins and several tyrosine phosphatases and tyrosine kinases. This domain mediates FAK interactions with integrins and growth factor receptors and interacts with the adjacent kinase domain in FAK. The C-terminal domain contains proline-rich sequences for SH3 domain-containing proteins and acts to recruit additional signaling proteins[3,4].

The interactions between structural features of FAK and various kinases could be closely related to cancer growth, survival, and metastasis. FAK is activated by the direct interaction of the Src kinase with the integrin β cytoplasmic domain[4]. Integrin can trigger the survival signaling of cancer cells at locations further downstream of phosphatidylinositol 3-kinase (PI3K), AKT, and the extracellular regulated kinase (ERK)[1,5]. The kinase complex with Src is reportedly affected in the activation of these survival pathways. In addition, FAK interacts with several receptor tyrosine kinases, including human epithelial growth factor receptor, c-Met, platelet-derived growth factor receptor, and vascular endothelial growth factor receptor (VEGFR), which also mediates the survival pathway of cancer cells[2,6]. The detailed mechanism of PI3K signaling is as follows. The PI3K/AKT pathway induces the expression of apoptosis inhibitory proteins through nuclear factor kappa (NF-κ) B and protects the cells from stress-induced apoptosis. It is also associated with expression of cancer suppressor genes[5,6]. FAK promotes cell survival via suppression of p53 activation. This is mediated by the kinase-independent FAK FERM domain, and it suppresses the transcriptional activation of target genes that is mediated by p53 activation. Therefore, FAK can enhance cell survival through both kinase-dependent and-independent mechanisms[7]. Further, the expression of an active mutant of ERK has indicated a direct role of FAK in promoting cancer growth. It is suggested that FAK signaling through the ERK pathway is needed to maintain cancer cell development[8]. Furthermore, the kinase activity of FAK is estimated to be significant for the invasive phenotype and for cancer metastasis. FAK reportedly promotes cancer cell invasion through the regulation of matrix metalloproteinases (MMPs)[1,9]. In v-Src transformed cells, the Rac1 and JNK is activated in FAK/Src complex and is induced the MMP2 and MMP9 expression. Thus, FAK promotes increased invasiveness of cancer cells[10].

Of course, the various cancer-promoting mechanisms associated with FAK described above could also be implicated in the progression of CRC. Colon cells including epithelial and fibrous cells increases the FAK expression at early stages of carcinogenesis, even before the cancer has formed[1,11]. The up-regulation of FAK promotes the adhesive properties of CRC cells and their survival[11]. FAK signaling is associated with the binding of the Rho guanine nucleotide exchange factor, and this signaling complex promotes the local invasion of colon carcinoma. The increase in FAK activation is thus related to elevated tyrosine phosphorylation and an adaptor protein, such as paxillin, involved in the growth of the CRC cells[1,2,12]. Further, FAK signaling contributes to epithelial-mesenchymal transition (EMT) profile change in CRC cells. FAK scaffolding increases, thus leading to alterations in EMT markers, including MMP-induced motility of CRC cells. Therefore, FAK acts to affect the dynamic internalization of E-cadherin in CRC cells[2,13]. Furthermore, FAK FERM overexpression can reduce steady-state p53 levels in CRC cells, particularly HCT-116 cells. As increased FAK expression is often found in early-stage CRCs, the FAK FERM-mediated cell survival pathway is expected to have an important function in the survival of CRC cells[7,14]. During cancer progression and metastasis, an anchorage-independent pathway can facilitate the spread of cells from the primary cancer site. Under these conditions, the cancer cells that show higher levels of FAK may be more resistant to apoptosis by non-integrin-associated FAK to translocate to the nucleus and prevent excessive p53 activation[2,7,15]. It is associated with that alternative-spliced transcripts encompassing the N-terminal FERM domain without the FAK kinase or C-terminal regions would be related to the progression of CRC[2,7].

Based on this scientific background, many pharmaceutical companies are taking efforts to develop FAK inhibitors. TAE-226 by Novartis exhibits nanomolar inhibitory activity toward FAK and protein tyrosine kinases and has anti-cancer activity. It particularly blocks cell proliferation and invasion and showed increased apoptosis in many xenograft animal models[7]. Further, TAE-226 in combination with docetaxel, a microtubule stabili-

zer, significantly decreases angiogenesis and cancer cell invasion[15]. Pfizer has developed PF-228 that shows more specific FAK inhibitory activity. It inhibits cancer cell migration *in vitro*. Pfizer has also developed PF-573, 228 compound, and the results indicated cancer growth inhibition in the colon xenograft cancer model[16]. In addition, several other FAK inhibitors have been developed, including GSK2256098 by GlaxoSmithKline as a formulation for oral intake and VS-4718 by Poniard as an improved version of the previous product, PND-1186[17,18]. Although efficacy has been noted in non-clinical and early-stage clinical trials, the drugs have not been commercialized yet. Therefore, the FAK research on CRC is expected to gain momentum and be highly appreciated as a potential field for developing the new drugs.

The kinase-dependent function and kinase-independent ability of FAK are essential for cancer development[19]. Multifunctional characteristics of FAK have been highlighted has modulators of numerous signal transductions in CRC cells. The established role of FAK in cancer progression and metastasis has obviously proposed that increase in FAK expression contributes a very important part in CRC development. Various inhibitors by small-molecules for targeting inhibition of FAK kinase and autophosphorylation have been produced by many pharmaceutical companies. Although some clinical trials have already been undergoing and potential efficacy has been noted, further studies must be needed to confirm if FAK expression has important role in a progression of human CRC and elaborates on the clear mechanisms and downstream effectors in the context of carcinogenicity. Taken together, based on the clinical observations, the over-expression of FAK at both transcriptional and translational levels in human CRCs would imply that targeting FAK could be a prognostic marker and a potential anticancer candidate for CRC therapy.

REFERENCES

1 **Yoon H**, Dehart JP, Murphy JM, Lim ST. Understanding the roles of FAK in cancer: inhibitors, genetic models, and new insights. *J Histochem Cytochem* 2015; **63**: 114-128 [PMID: 25380750 DOI: 10.1369/0022155414561498]

2 **Sulzmaier FJ**, Jean C, Schlaepfer DD. FAK in cancer: mechanistic findings and clinical applications. *Nat Rev Cancer* 2014; **14**: 598-610 [PMID: 25098269 DOI: 10.1038/nrc3792]

3 **Lietha D**, Cai X, Ceccarelli DF, Li Y, Schaller MD, Eck MJ. Structural basis for the autoinhibition of focal adhesion kinase. *Cell* 2007; **129**: 1177-1187 [PMID: 17574028 DOI: 10.1016/j.cell.2007.05.041]

4 **Dunty JM**, Gabarra-Niecko V, King ML, Ceccarelli DF, Eck MJ, Schaller MD. FERM domain interaction promotes FAK signaling. *Mol Cell Biol* 2004; **24**: 5353-5368 [PMID: 15169899 DOI: 10.1128/MCB.24.12.5353-5368.2004]

5 **Bianconi D**, Unseld M, Prager GW. Integrins in the Spotlight of Cancer. *Int J Mol Sci* 2016; **17**: pii: E2037 [PMID: 27929432 DOI: 10.3390/ijms17122037]

6 **Mitra SK**, Schlaepfer DD. Integrin-regulated FAK-Src signaling in normal and cancer cells. *Curr Opin Cell Biol* 2006; **18**: 516-523 [PMID: 16919435 DOI: 10.1016/j.ceb.2006.08.011]

7 **Lim ST**, Mikolon D, Stupack DG, Schlaepfer DD. FERM control of FAK function: implications for cancer therapy. *Cell Cycle* 2008; **7**: 2306-2314 [PMID: 18677107 DOI: 10.4161/cc.6367]

8 **Zheng Y**, Xia Y, Hawke D, Halle M, Tremblay ML, Gao X, Zhou XZ, Aldape K, Cobb MH, Xie K, He J, Lu Z. FAK phosphorylation by ERK primes ras-induced tyrosine dephosphorylation of FAK mediated by PIN1 and PTP-PEST. *Mol Cell* 2009; **35**: 11-25 [PMID: 19595712 DOI: 10.1016/j.molcel.2009.06.013]

9 **Prifti S**, Zourab Y, Koumouridis A, Bohlmann M, Strowitzki T, Rabe T. Role of integrins in invasion of endometrial cancer cell lines. *Gynecol Oncol* 2002; **84**: 12-20 [PMID: 11748970 DOI: 10.1006/gyno.2001.6410]

10 **Van Slambrouck S**, Grijelmo C, De Wever O, Bruyneel E, Emami S, Gespach C, Steelant WF. Activation of the FAK-src molecular scaffolds and p130Cas-JNK signaling cascades by alpha1-integrins during colon cancer cell invasion. *Int J Oncol* 2007; **31**: 1501-1508 [PMID: 17982677 DOI: 10.3892/ijo.31.6.1501]

11 **Owen KA**, Abshire MY, Tilghman RW, Casanova JE, Bouton AH. FAK regulates intestinal epithelial cell survival and proliferation during mucosal wound healing. *PLoS One* 2011; **6**: e23123 [PMID: 21887232 DOI: 10.1371/journal.pone.0023123]

12 **Deakin NO**, Pignatelli J, Turner CE. Diverse roles for the paxillin family of proteins in cancer. *Genes Cancer* 2012; **3**: 362-370 [PMID: 23226574 DOI: 10.1177/1947601912458582]

13 **Bolós V**, Gasent JM, López-Tarruella S, Grande E. The dual kinase complex FAK-Src as a promising therapeutic target in cancer. *Onco Targets Ther* 2010; **3**: 83-97 [PMID: 20616959 DOI: 10.2147/OTT.S6909]

14 **Golubovskaya VM**, Ho B, Zheng M, Magis A, Ostrov D, Morrison C, Cance WG. Disruption of focal adhesion kinase and p53 interaction with small molecule compound R2 reactivated p53 and blocked tumor growth. *BMC Cancer* 2013; **13**: 342 [PMID: 23841915 DOI: 10.1186/1471-2407-13-342]

15 **Paoli P**, Giannoni E, Chiarugi P. Anoikis molecular pathways and its role in cancer progression. *Biochim Biophys Acta* 2013; **1833**: 3481-3498 [PMID: 23830918 DOI: 10.1016/j.bbamcr.2013.06.026]

16 **Golubovskaya VM**, Figel S, Ho BT, Johnson CP, Yemma M, Huang G, Zheng M, Nyberg C, Magis A, Ostrov DA, Gelman IH, Cance WG. A small molecule focal adhesion kinase (FAK) inhibitor, targeting Y397 site: 1-(2-hydroxyethyl)-3, 5, 7-triaza-1-azoniatricyclo [3.3.1.1(3,7)]decane; bromide effectively inhibits FAK autophosphorylation activity and decreases cancer cell viability, clonogenicity and tumor growth in vivo. *Carcinogenesis* 2012; **33**: 1004-1013 [PMID: 22402131 DOI: 10.1093/carcin/bgs120]

17 **Zhang J**, He DH, Zajac-Kaye M, Hochwald SN. A small molecule FAK kinase inhibitor, GSK2256098, inhibits growth and survival of pancreatic ductal adenocarcinoma cells. *Cell Cycle* 2014; **13**: 3143-3149 [PMID: 25486573 DOI: 10.4161/15384101.2014.949550]

18 **Kolev VN**, Tam WF, Wright QG, McDermott SP, Vidal CM, Shapiro IM, Xu Q, Wicha MS, Pachter JA, Weaver DT. Inhibition of FAK kinase activity preferentially targets cancer stem cells. *Oncotarget* 2017; **8**: 51733-51747 [PMID: 28881682 DOI: 10.18632/oncotarget.18517]

19 **Tai YL**, Chen LC, Shen TL. Emerging roles of focal adhesion kinase in cancer. *Biomed Res Int* 2015; **2015**: 690690 [PMID: 25918719 DOI: 10.1155/2015/690690]

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