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Review Article

Fascin-1 and Digestive System Carcinoma

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Abstract

Invasion and metastasis are major reason for poor prognosis of digestive system carcinoma patients. Motility and migratory capacity are important in contributing to tumor cells' invasion and metastasis. Fascin is one of actin cross-linking proteins and can participate in forming parallel actin bundles in cell protrusions. Fascin-1 is consequently involved in cell adhesion, motility, and signaling. In cultured cells, over-expression of fascin-1 can increase migration and invasion capacity of cells. Many studies show up-expressions of fascin-1 are significantly associated with worse prognosis, poor differentiation, TNM stage, positive for lymph node metastasis, and positive for distant metastasis in digestive system carcinoma patients. So fascin-1 may have prognostic value as an early biomarker for more aggressive digestive system carcinoma. This review provides detailed account of preclinical studies conducted to determine the utility of fascin-1 as a therapeutic and predictive agent in invasion and metastasis of carcinomas.

Keywords: Fascin; Invasion; Metastasis; Carcinoma; Digestive System

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Introduction

Motility and migratory capacity are important to tumor cells, which maybe tumor cells' invasion and metastasis potential. It will make the malignant cells gain the ability to migrate that the rearrangements of the actin cytoskeleton facilitated by actin binding proteins [1]. Fascin is one of actin cross-linking proteins and can participate in forming parallel actin bundles in cell protrusions. Fascin-1 is consequently involved in cell adhesion, motility, and signaling. In cultured cells, over-expression of fascin-1 can increase

migration and invasion capacity of cells [2, 3]. Fascin-1 is often expressed in normal mesenchymal, endothelial, dendritic and neuronal cells, but not in normal epithelia cells [4]. In contrast, increased fascin-1 protein has been detected in a variety of carcinomas, including lung [5], bladder [6], breast [7], esophageal [8], pancreatic [9], colon [1], ovary [10]and stomach [11]cancer. Furthermore, studies also found high expression of fascin-1 protein was often correlated with poor prognosis in some carcinomas because it can facilitate invasion and metastasis of cancer cells [4, 5]. This review provides detailed account of preclinical studies conducted to determine the utility of fascin-1 as a therapeutic and predictive agent in invasion and metastasis of carcinomas.

Fascin structure and function

Fascin was discovered in the 1970s as a 55 kDa actin-bingding protein that was purified from cytoplasmic extracts of sea urchin oocytes or coelomocytes [12, 13]. Fascin has been shown to play a role in the organizating of actin-based structures that regulate adhesion and migration of cell. Three fascin-related gene products have been cloned in human. Fascin-1, commonly referred to as fascin, widely expresses in mesenchymal tissues and nervous system; Fascin-2 expresses in retinal photoreceptor cells; and fascin-3 is testis specific [2, 3]. Human fascin-1 gene, *FSCN1*, is located at chromosome 7q22 [14]. Fascin-1 belongs to the β-trefoil group of proteins and is predicted to be composed of four β-trefoil domains by structural alignment [15]. The most highly conserved region is between residues 11 and 50 in all fascins and these regions contain a consensus motif for phosphorylation by protein kinase C (PKC) that is present in all fascins. Expression and subcellular localization of fascin-1 in cultured cells have been studied primarily with vertebrate fascin-1 and fascin-1 is not uniformly expressed in different cell types. It presents to be low or absent in T cells and several epithelial cell lines, but expresses at high levels in neurons, glial cells, skeletal and smooth muscle cells, endothelial cells and some epithelial tumour cells [16-19]. By studies of actively migrating cultured cells, fascin functions in cell protrusions have been reinforced, where fascin-1 localizes in microspikes and ruffles at the leading edges of motile and post-mitotic cells [18, 20-22]. The role of fascin-1 in cell migration has been investigated by direct perturbation of the actin-binding domains of fascin-1. Fascin-1 has also been linked to the organization of cell-cell adhesive contacts. In fascin-positive epithelial tumour lines fascin-1 localizes at cell-cell adherens junctions [23]. Over-expression of fascin-1 in epithelial cells correlates with disorganization of adherens junctions and reduced cell-cell attachment activity [20, 23, 24]. The mechanism of these effects is believed to involve an interaction between fascin-1 and β-catenin that could affect the function of β-catenin in cadherin- and occluding-dependent adhesion complexes [23, 24].

Fascin-1 and Carcinoma of Digestive System, and Fascin-1 and Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) is one of the most common head and neck cancers and is associated with a high potential of tumor recurrence and metastasis, leading to poor prognosis. Down-regulation of fascin-1 protein by using siRNA directly led to changes of cell surface protrusions and resulted in suppression of migration, invasion and increase of adhesion in OSCC and down-regulation of fascin-1 expression also resulted in alterations of E-cadherin, beta-catenin and Twist at certain level, implicative of an association with epithelial-mesenchymal transition (EMT). These results suggested that expression of fascin-1 protein may play an essential role in regulation of progression of OSCC and contributes to the event of EMT in the early aggressiveness of OSCC [25]. Further, fascin-1 over-expression was found in OSCC clinical samples and its expression was significantly associated with nodal metastasis, tumor recurrence and poor patients' overall survival. Consistently, fascin-1 proteins were detected in OSCC cell lines with the expression level corresponding to the invasion ability. Over-expression

of fascin-1 might enhance OSCC aggressiveness by interacting with E-cadherin because fascin-1 was negatively correlated with E-cadherin expression [26].

Fascin-1 and Esophageal Squamous Cell Carcinoma

In esophageal squamous cell carcinoma (ESCC), the intensity of fascin-1 expression was usually increased in the carcinoma compared with that in normal epithelium. Over-expression of fascin-1 was significantly associated with a poor prognosis, extent of the tumor and lymph node metastasis. Multivariate analysis showed that fascin-1 expression intensity was an independent prognostic factor [8]. Univariate survival analysis showed high scores of fascin-1 are significantly associated with worse prognosis, poor differentiation, T4 stage, positive for lymph node metastasis, and positive for distant metastasis in patients [27]. In addition, up-regulation of fascin-1 mRNA was found in 60% of patients and in vitro study revealed that KYSE170, one of the over-expressed fascin-1 cells, decreased its motile and invasive properties after down-regulation of fascin-1 expression [28]. The effect of fascin-1 on cell invasiveness correlated with the activation of matrix metalloproteases (MMP) such as MMP-2 and MMP-9. These results suggested that fascin-1 might play crucial roles in regulating neoplasm progression of ESCC [29]. Down-regulation of fascin-1 by using RNA interference (RNAi) resulted in a suppression of cell proliferation and as well as a decrease in cell invasiveness [29, 30]. Forced expression of fascin-1 in immortalized esophageal epithelial cells accelerated cell proliferation and invasiveness. Expression of either CYR61 or CTGF led to a recovery of the suppression of cellular proliferation and invasiveness induced by down-regulation of fascin-1 expression; the protein level of CYR61 and CTGF were up-regulated in ESCCs and their expression pattern correlated with fascin-1 overexpression. Fascin-1 affected the expressions of CYR61 and CTGF through transforming growth factor (TGF)-beta pathway [30]. In ESCC transcription factor Sp1 can regulate expression of fascin-1 through binding FSCN1 promoter. Fascin-1 expression is enhanced by Sp1 over-expression and blocked by Sp1 RNAi knockdown. Specific inhibition of ERK1/2 decreased phosphorylation levels of Sp1, and thus suppressed the transcription of the *FSCN1*, resulting in the down-regulation of fascin-1. Stimulation with EGF could enhance fascin-1 expression via activating the ERK1/2 pathway and increasing phosphorylation levels of Sp1 [31].

Fascin-1 and Gastric Carcinoma

Gastric carcinoma is one of the most common digestive malignancies in the world and lymph node metastasis is a major prognostic factor in gastric carcinomas. Malignant gastric tissues expressed high levels of fascin-1 compared with normal gastric tissues [32]. By immunohistochemistry, increased fascin-1 was found in gastric carcinoma and adenoma than in adjacent non-neoplastic mucosa. Among the poorly differentiated gastric adenocarcinomas, it exhibited moderate or strong fascin-1 expression [11]. Most of the gastric carcinoma cell lines showed expression of fascin-1 at different levels. Silencing of fascin-1 resulted in altered cancer cell morphology, decreased cell motility, and reduced malignant cell invasion [32]. Univariate analysis indicated the cumulative survival rate of patients with positive fascin-1 expression to be lower than without its expression even stratified according to the depth of invasion [33]. Some previous studies also showed fascin-1 expression was correlated with age, serosal invasion, positive lymph node metastasis, histopathological grading, TNM stage and recurrence and those with fascin-positive tumors had a significantly poorer prognosis than those with fascin-negative tumors [11, 34]. Other study also showed that high expression of fascin-1 protein was observed in gastrointestinal stromal tumor and fascin-1 over-expression was significantly correlated with shorter disease-free survival time and several aggressive pathological factors, including tumor size, mitotic counts, risk grade, blood vessel invasion and

mucosal ulceration. Fascin-1 might be a direct target of miR-133b and down-regulation of miR-133b made the expression of fascin-1 increase in gastrointestinal stromal tumor [35].

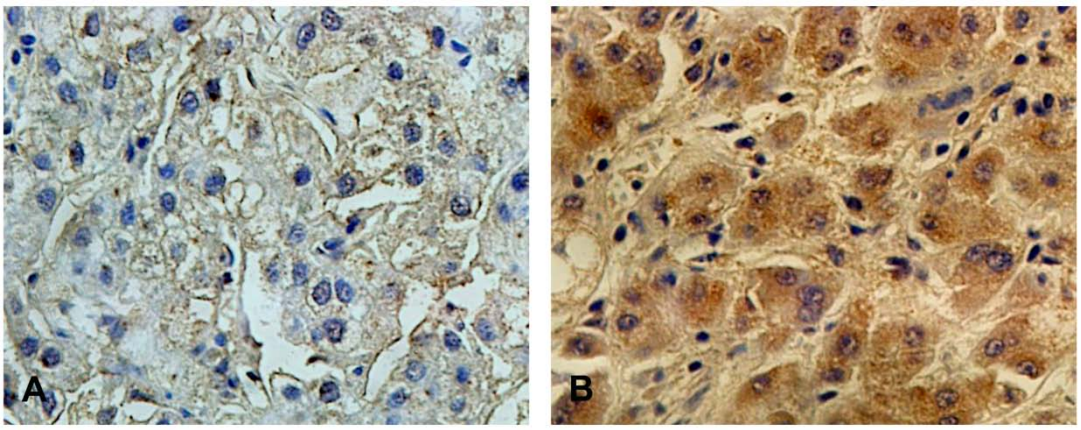
Fascin-1 and Colon Carcinoma

Fascin-1 was not expressed by the normal colonic epithelium. In the clinically-annotated tumors, fascin-1 immunoreactivity was more common in tumors located in the proximal colon [36]. For both central tumor tissue and the invasive front, it was found that the percentage of stained cells was a sufficient measure of fascin-1 expression [37]. Fascin-1 was exclusively localized at the invasive front of tumors also displaying nuclear beta-catenin. Forced expression of fascin-1 in colorectal cancer cells increased their migration and invasion in cell cultures and caused cell dissemination and metastasis in vivo, whereas suppression of fascin-1 expression by small interfering RNA reduces cell invasion. Although expression of fascin-1 in primary tumors correlated with the presence of metastases, fascin-1 was not expressed in metastases. Moreover, the expression of fascin-1 is down-regulated when tumor cells reach their metastatic destination where migration ceases and proliferation is enhanced [38]. Clinical research showed there was a significant independent association between high fascin-1 expression and diminished survival [37]. Patients with stage III/IV adenocarcinomas with strong fascin-1 immunoreactivity had a worse prognosis than patients with low or absent fascin-1. Strong and diffuse expression was seen in a subset of advanced colorectal adenocarcinomas that correlated with shorter survival in stage III and IV patients [36]. Other research also showed that five-year survival rate was significantly low, whereas the distant recurrence rate was significantly high in patients with fascin-positive stage III colorectal cancer and there was no significant correlation between fascin-1 expression and clinicopathologic factors such as tumor size, nodal metastasis, pathologic stage. Fascin-1 expression was an independent prognostic factor in multivariate analysis [39]. So fascin-1 may have prognostic value as an early biomarker for more aggressive colorectal adenocarcinomas.

Fascin-1 and Hepatocellular Carcinoma

Using immunohistochemically, Iguchi T *et al.* showed in patients with hepatocellular carcinoma (HCC), tumors showing fascin-1 expression were larger and less differentiated than those showing no fascin-1 expression. Our research also showed hepatocellular carcinoma tissues expressed high levels of fascin-1 compared with adjacent non-cancerous hepatic tissues (Fig.1). Portal venous invasion, bile duct invasion, and intrahepatic metastasis were detected significantly more frequently in fascin-positive group. In addition, high alpha-fetoprotein (AFP) levels were significantly associated with the fascin-1 expression in HCC. Fascin-positive patients had significantly poorer outcomes than fascin-negative group and Fascin-1 can be as an independent prognostic factor for disease-free survival [40]. One mechanism may be that fascin-1 was involved in EMT and increases invasiveness, thus serving as a promoter of cancer aggressiveness. Immunohistochemical analysis revealed that fascin-1 expression in 19% of primary HCCs was associated with repression of E-cadherin expression, indicating EMT. In vitro, HLE cells showed high fascin-1 expression, loss of E-cadherin, and efficient invasion through matrigel. Knockdown of fascin-1 significantly repressed invasiveness of the HLE cells and slightly induced E-cadherin expression. In contrast, Huh7 cells had low fascin-1 levels, high E-cadherin expression, and were expectedly non-invasive. However, forced overexpression of fascin-1 conferred only modest invasiveness without E-cadherin repression, indicating that fascin-1 alone cannot effectively stimulate invasiveness or EMT. Fascin-1 overexpression dramatically increased the migratory potential of Huh7 cells. Other mechanism may be that MMP 2 and 9 was involved in this process. Significant MMP secretion was only found in HLE cells. Although MMP levels were not elevated in fascin-1-overexpressing Huh7 cells, their invasiveness was remarkably augmented by coculture with HLE cells, and was suppressed in the presence of an MMP inhibitor. In conclusion, it

proposed that fascin-1 primarily acts as a migration factor associated with EMT in HCC cells and facilitates their invasiveness in combination with MMPs [41].



Figue 1 The expression of fascin-1 protein in HCC and adjacent non-cancerous hepatic tissues. (A) Adjacent non-cancerous hepatic tissues, (B) HCC tissues

Fascin-1 and Biliary Tract Carcinoma

Fascin-1 expression was absent or sporadic in normal biliary epithelium, whereas high expression was found in dysplasias and intrahepatic biliary tract carcinoma [42]. Fascin-1 localized to the cytoplasm and membrane compartment of the carcinomas of the biliary tract. Fascin-1 is up-regulated during progression from in situ to infiltrating gallbladder and biliary tract carcinoma [43]. High expression of fascin-1 was correlated with poorly differentiated tumors and among poorly differentiated intrahepatic cholangiocarcinoma, larger tumors (>5 cm) were more likely than smaller lesions to have high fascin-1 expression. Patients whose tumors expressed fascin-1 abundantly had a poorer outcome, and fascin-1 over-expression was an independent prognostic factor [42].

Fascin-1 and Pancreas Carcinoma

Through evaluating fascin-1 expression in surgical specimens, Yamaguchi H *et al.* found fascin-1 expression was significantly higher in borderline neoplasms and carcinomas than in adenomas, but no difference was observed between borderline neoplasms and carcinomas. With regard to the subclassification, intestinal-type neoplasms were more frequently positive for fascin-1 than gastric-type neoplasms. Two oncocytic-type neoplasms were both fascin-negative. Fascin-1 mRNA expression seemed to be higher in moderately to severely dysplastic epithelium than in mildly dysplastic epithelium [44]. Other study also indicated overexpression of fascin-1 was restricted to the cytoplasm and membrane of carcinoma of the epithelial cells. Fascin-1 showed up-regulation of expression with transition from carcinoma in situ to invasive carcinoma, implicating a role for these markers in neoplastic progression [43].

Conclusions

Fascin-1 exhibited important roles in an expanding area of cytoskeletal and cell biology researchs. Growing knowledge of the roles of fascin-1 in human carcinoma focuses attention on their possible value as therapeutic targets. During the last ten years, fascin-1 has emerged as a novel biomarker with general applicability to aggressive carcinomas from digestive system. With the identification of migrastatin as a tumour-suppressive small molecule inhibitor of actin bundling by fascin-1, interest in the regulation of fascin-1 as a candidate target in tumour metastasis is

poised to grow over the next years.

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