SPANDIDOS PUBLICATIONS

Overexpression of the *fibroblast growth factor receptor-1* gene correlates with liver metastasis in colorectal cancer

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Abstract. Expression of the *fibroblast growth factor (FGF)-1, FGF-2, fibroblast growth factor receptor (FGFR)-1,* and *FGFR-2* genes has been reported in various cancers and is associated with poor outcomes in patients with solid tumors. This study examined the relations between the relative expression of the FGF genes and clinicopathological factors, especially invasion and metastasis, in patients with colorectal cancer. We studied surgical specimens of cancer tissue and adjacent normal mucosa obtained from 202 patients with untreated colorectal carcinoma. The relative expression levels of *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* mRNA in cancer and in normal adjacent mucosa were measured by quantitative real-time, reverse-transcription polymerase chain reaction. The relative expression level of the *FGFR-2* gene was higher in normal adjacent mucosa than in cancer, whereas the relative expression levels of the *FGF-1, FGF-2,* and *FGFR-1* genes were similar. *FGFR-1* gene expression levels were higher in the presence than in the absence of liver metastasis. An analysis of the relation between clinicopathological features and gene expression showed that overexpression of *FGFR-1* correlated with liver metastasis. Our results suggested that overexpression of the *FGFR-1* gene might lead to liver metastasis in colorectal cancer. Overexpression of the *FGFR-1* gene may thus be a useful predictor of liver metastasis in patients with colorectal cancer.

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Introduction

Fibroblast growth factors (FGFs) are a family of heparin-binding growth factors. FGFs promote angiogenesis by interacting with various endothelial cell-surface receptors, including tyrosine kinase receptors, heparin-sulfate proteoglycans, and integrins. The relation between angiogenesis and tumor growth is well established, and numerous inducers of angiogenesis have been identified (1). Gospodarowicz (2) discovered FGF-2 in 1974. This protein was found to strongly promote the proliferation of fibroblasts. Since then, 22 structurally-related members of the FGF family and 4 FGF-homologous factors have been identified. FGFs exert their biological activities by binding to high-affinity tyrosine kinase FGF receptors (FGFRs) on the surface of target cells. Angiogenic potential has been assessed for only a limited number of the 22 members of the FGF family *in vitro* and *in vivo*. Most experimental studies have focused on the prototypes FGF-1 and FGF-2 (3).

FGFs exert their biologic activity by interacting with high-affinity FGFRs. Four members of the FGFR family (FGFR-1, FGFR-2, FGFR-3, and FGFR-4) are encoded by distinct genes, and their structural variability is increased by alternative splicing. FGFR-1 is expressed by endothelial cells *in vivo* and *in vitro*. Some cultured endothelial cells can express FGFR-2 (3,4).

Expression levels of the *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* genes have been examined in various cancers, including breast cancer (5-8), brain tumors (9-12), hepatocellular carcinoma (13-15), cervical and esophageal cancers (16-20), and pancreatic cancer (21-23). Correlations between *FGF-1* and *FGFR-1* expression in breast cancer (5) and esophageal cancer (17) and between *FGF-2* and *FGFR-1* in hepatocellular carcinoma (13) have suggested that these factors promote proliferation of cancer cells in an autocrine manner.

Numerous studies have demonstrated that FGFR-1 correlates with angiogenesis and carcinogenesis. Acevedo *et al* (24) reported that FGFR-1 promotes the progression of prostate cancer in a mouse model. Freier *et al* (19) found that increased

Table I. PCR primers and conditions.

Gene	Primer	Annealing temperature (C)	Product size (bp)
FGF-1	5'-CATTACCACGCCTTGACC-3' 5'-AGCCAGTTTCCCTTTCTTTC-3'	58.0	175
FGF-2	5'-AGCGACCCTCACATCAAG-3' 5'-ATCTTCCATCTTCCTTCATAGC-3'	58.0	106
FGFR-1	5'-GGCTGTATGAAAAGGGTGGGAATG-3' 5'-GGTGCGTCGTGAGGTCTGG-3'	62.0	152
FGFR-2	5'-ATCTGCCTGGTCGTGGTC-3' 5'-GCTCTAATGTGGTATCCTCAAC-3'	60.0	82
ß-actin	5'-AGTTGCGTTACACCCTTTCTTGAC-3' 5'-GCTCGCTCCAACCGACTGC-3'	60.0	171

FGFR-1 expression contributes to carcinogenesis during the early development of oral squamous cell carcinoma. Freeman *et al* (25) showed that activation of FGFR-1, but not FGFR-2, led to strong up-regulation of osteopontin, associated with prostate cancer progression and metastasis. Feng *et al* (26) reported that FGFR-2 limits and FGFR-1 accelerates the tumorigenicity of prostate epithelial cells.

Expression of FGFs and FGFRs in colorectal cancer has been reported by various studies. Jang *et al* showed that FGFR-1 is overexpressed in colorectal carcinoma cells and associated with tumorigenesis (27). Galzie *et al* (28,29) demonstrated a relation between FGF-2 production and the invasive potential of human colorectal carcinoma cells. To date, however, few studies have examined the relations between expression levels of *FGFs* and *FGFRs* and clinicopathological features in colorectal cancer.

We measured expression levels of the *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* genes in 202 paired specimens of cancer tissue and adjacent normal mucosa obtained from patients with colorectal cancer. To evaluate the clinical significance of these FGFs, we examined correlations between the relative expression of these genes and clinicopathological features.

Materials and methods

Patients and samples. We studied surgical specimens of cancer tissue and adjacent normal mucosa obtained from 202 patients with untreated colorectal carcinoma. The patients underwent surgery at the Gastroenterological Center, Yokohama City Medical Center, and at Kanagawa Cancer Center between 2002 and 2006. Informed consent was obtained from each patient, and the Ethics Committees of Yokohama City Medical Center and Kanagawa Cancer Center approved the protocol before initiation of the study. Each tissue sample was embedded in O.C.T. compound (Sakura Finetechnical Co., Ltd., Tokyo) and immediately stored at -80˚C until use. No patient had any other malignancies. Tissue specimens were stained with hematoxylin and eosin and examined histopathologically. Sections that consisted of >80% carcinoma cells were used to prepare total RNA.

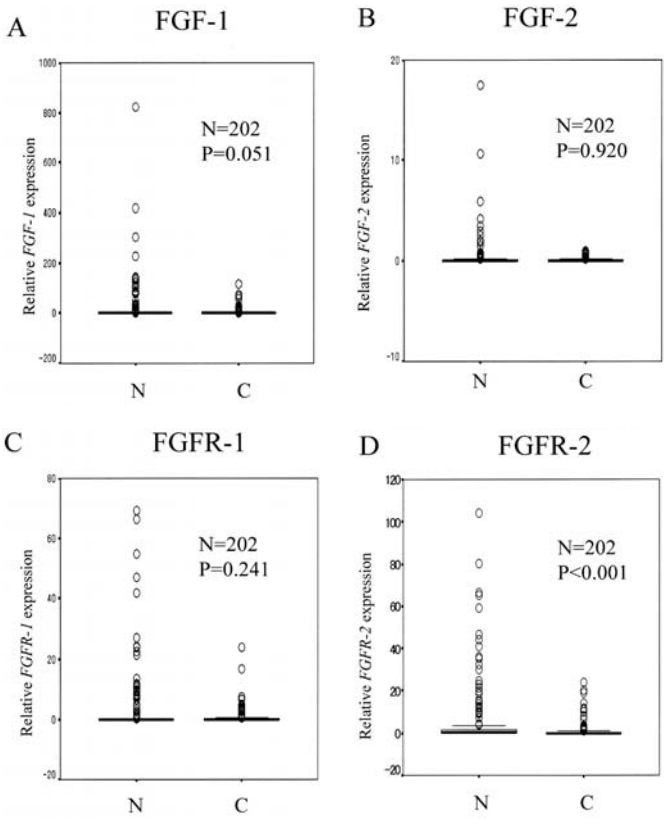
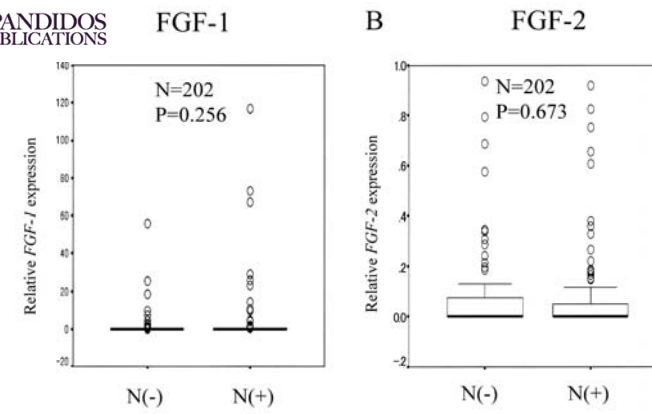


Figure 1. Comparison of *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* mRNA expression between colorectal cancer tissue (C) and adjacent normal mucosa (N). *FGFR-2* gene expression levels were higher in normal adjacent mucosa than in cancer tissue (P<0.001). *FGF-1, FGF-2,* and *FGFR-1* gene expression levels were similar in normal tissue and cancer tissue (P=0.051, P=0.920, P=0.241).

Quantitative real-time, reverse-transcription polymerase chain reaction (PCR). Total RNA isolated from colorectal cancer tissue and adjacent normal mucosa was prepared with the use of Trizol (Gibco, Life Tech, Gaithersburg, MD). Complemetary DNA (cDNA) was synthesized from 2 μg of total RNA with an iScript cDNA synthesis kit (Bio-Rad Laboratories, Hercules, CA). After synthesis, the cDNA was



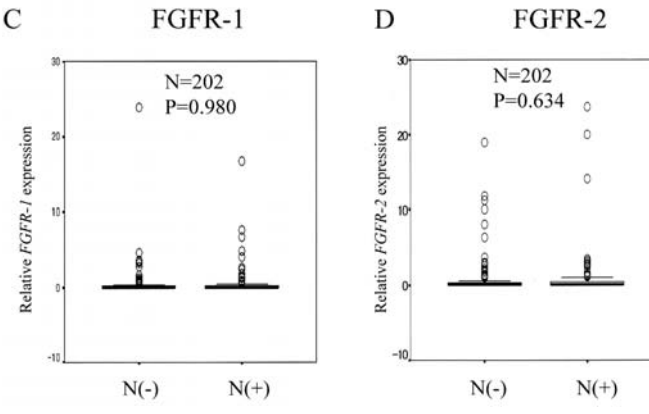
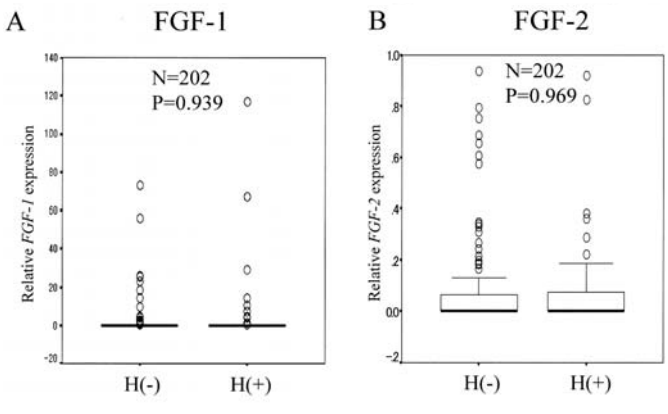


Figure 2. Associations of *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* gene expression with lymph node metastasis in 202 patients with colorectal cancer. There was no significant association between the expression level of any gene and the presence or absence of lymph node metastasis. P-values were calculated by the Mann-Whitney U test.



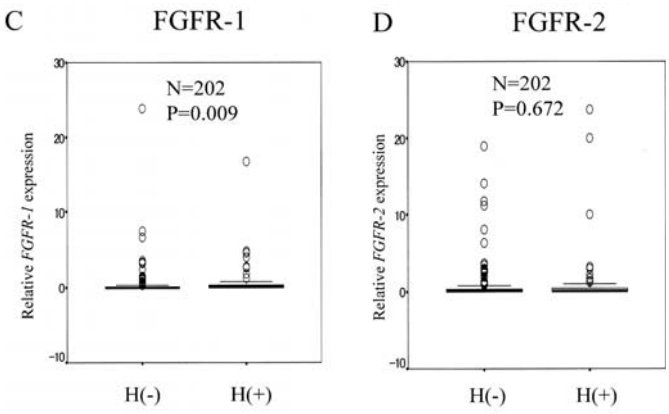


Figure 3. Associations of *FGF-1, FGF-2, FGFR-1*, and *FGFR-2* gene expression with liver metastasis in patients with colorectal cancer. There was no significant association between the expression levels of the *FGF-1, FGF-2*, and *FGFR-2* genes and the presence or absence of liver metastasis (P=0.939, P=0.969, P=0.672) (A, B and D). *FGFR-1* gene expression levels were higher in the presence than in the absence of liver metastasis (P=0.009) (C). P-values were calculated by the Mann-Whitney U test.

diluted 1:4 with water and stored at -20˚C until use. Quantitative real-time PCR was performed with an iQ SYBR-Green Supermix (Bio-Rad Laboratories). PCR reactions were carried out in a total volume of 15 μl, containing cDNA derived from 75 ng of RNA, 0.27 μM of each primer, 7.5 μl of iQ SYBR-Green Supermix containing dATP, dCTP, dGTP, and dTTP at concentrations of 400 μM each, and 50 U/ml of iTag DNA polymerase. The PCR consisted of 10 min at 94˚C, followed by 50 cycles of denaturation of the cDNA for 30 sec at 94˚C, annealing for 30 sec at an appropriate temperature (Table I), and a primer extension for 1 min at 72˚C followed by 72˚C for 10 min. The PCR primer sequences of *FGF-1, FGF-2, FGFR-1, FGFR-2,* and ß-actin, used as an internal control, are shown in Table I.

Statistical analysis. Gene expression levels of colorectal cancer were compared with those of normal adjacent mucosa with the use of the Wilcoxon test. Relations between gene expression and potential explanatory variables, including age, gender, tumor size, histological type, depth of invasion, lymph node metastasis, location, lymphatic invasion, venous invasion, and liver metastasis, were evaluated with the χ^2 test.

Associations between variables were assessed using the Mann-Whitney U test. Correlation coefficients between the different variables were calculated by simple regression analysis. Each statistical analysis was performed using the Dr SPSS II program, version 11.0.1J for Windows (SPSS Inc., Chicago, IL, USA). Two-sided P-values were calculated, and a difference was considered statistically significant at P<0.05.

Results

Comparison of FGF-1, FGF-2, FGFR-1, and FGFR-2 mRNA expression between colorectal cancer tissue and adjacent normal mucosa. *FGFR-2* gene expression levels were higher in normal adjacent mucosa than in cancer tissue (P<0.001) (Fig. 1D). *FGF-1, FGF-2,* and *FGFR-1* gene expression levels were similar in normal tissue and cancer tissue (P=0.051, P=0.920, P=0.241) (Fig. 1A-C).

Associations of FGF-1, FGF-2, FGFR-1, and FGFR-2 gene expression with lymph node metastasis in patients with colorectal cancer. There was no significant association between the expression level of any gene and the presence or absence of lymph node metastasis (Fig. 2).

Associations of FGF-1, FGF-2, FGFR-1, and FGFR-2 gene expression with liver metastasis in patients with colorectal cancer. There was no significant association between the expression levels of the FGF-1, FGF-2, and FGFR-2 genes and the presence or absence of liver metastasis (P=0.939, P=0.969, P=0.672) (Fig. 3A, B and D). FGFR-1 gene

Table II. Relations between the expression of the *FGF-1, FGF-2, FGFR-1*, and *FGFR-2* genes and clinicopathological features.

Variables/categories	FGF-1 expression			FGF-2 expression			FGFR-1 expression			FGFR-2 expression		
	Low (n=101)	High (n=101)	P-value	Low (n=101)	High (n=101)	P-value	Low (n=101)	High (n=101)	P-value	Low (n=101)	High (n=101)	P-value
Age	65.6±10.5	66.2±10.3	0.320	66.6±11.4	64.8±10.2	0.250	67.2±10.5	64.2±10.9	0.053	66.4±10.8	65.0±10.8	0.340
Gender												
Male	54	56	0.888	49	43	0.48	55	55	1.000	54	56	0.888
Female	47		45	52	58		46	46		47	45	
Size												
<5 cm	46	60	0.073	57	55	0.887	58	54	0.671	56	56	1.000
≥5 cm	55	41		44	46		43	47		45	45	
Histological type												
Well differentiated	24	35	0.061	33	26	0.292	30	29	0.987	25	34	0.100
Moderately differentiated	60	55		52	63		57	58		65	50	
Poorly differentiated	17	11		16	12		14	14		11	17	
Depth of invasion												
T1/T2	50	60	0.203	54	56	0.888	56	54	0.888	55	55	1.000
T3/T4	51	41		47	45		45	47		46	46	
Location												
Colon	50	59	0.259	55	54	1.000	57	52	0.572	52	57	0.572
Rectum	51	42		46	47		44	49		49	44	
Lymphatic invasion												
Absent	67	65	0.883	64	68	0.658	68	64	0.658	66	66	1.000
Present	34	36		37	33		33	37		35	35	
Lymph node metastasis												
Absent	45	48	0.778	47	46	1.000	45	48	0.778	44	49	0.572
Present	56	53		54	55		56	53		57	52	
Venous invasion												
Absent	35	40	0.560	33	42	0.244	40	35	0.560	39	36	0.771
Present	66	61		68	59		61	66		62	65	
Liver metastasis												
Absent	69	71	0.879	72	68	0.647	78	62	0.022	70	70	1.000
Present	32	30		29	33		23	39		31	31	

n levels were higher in the presence than in the f liver metastasis (P=0.009) (Fig. 3C)

Relations of FGF-1, FGF-2, FGFR-1, and FGFR-2 gene expression levels to clinicopathological features. Expression levels of the *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* genes were categorized as low or high according to their median values. The relation between the expression of these genes and clinicopathological features was then examined. The expression levels of the *FGF-1, FGF-2* and *FGFR-2* genes were unrelated to age, gender, tumor size, lymph node metastasis, and lymphatic invasion. *FGFR-1* expression correlated with liver metastasis (P=0.022) (Table II).

Discussion

Cancer-cell invasion is associated with tumor stromal fibrosis. Cancer cells interact with surrounding fibroblasts proliferating at the invasion front by producing various factors, thereby promoting cancer-cell proliferation and invasion (1,3). Previous studies have shown that FGFs and FGFRs are overexpressed in cancer cells and fibroblasts (30). We therefore studied expression levels of the *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* genes in colorectal cancer tissue and adjacent normal mucosa.

We first compared the mRNA expression levels of each of these genes between colorectal cancer tissue and adjacent normal mucosa. Bansal *et al* (7) reported that the expression of FGF-1 is lower in breast cancer than in the normal human breast. Myoken *et al* (31) showed stronger expression of FGF-2 in oral squamous cell carcinomas than in normal tissue. Chow *et al* (14) demonstrated strong expression of FGF-1 and FGF-2 in normal liver cells, but weak expression of these factors in cancer cells. Yoshimura *et al* (5) and Jang *et al* (27) reported increased expression of FGFR-1 in cancer cells. Sahadevan *et al* (32) showed significant overexpression of FGFR-1 protein, but not of FGFR-2 protein, in prostate cancer. In our study, the expression level of the *FGFR-2* gene was higher in normal adjacent mucosa, whereas the expression levels of the *FGF-1, FGF-2,* and *FGFR-1* genes did not differ significantly between cancer tissue and normal adjacent mucosa.

Second, we examined whether the expression levels of the *FGF-1, FGF-2, FGFR-1,* and *FGFR-2* genes in cancer tissue were related to clinicopathological factors such as lymph node metastasis and liver metastasis. Sugiura *et al* (17) reported that FGFR-1 expression was not associated with lymph node metastasis. In contrast, Takanami *et al* (33) and Hase *et al* (16) reported that FGFR-1 expression was related to lymph node metastasis. As for liver metastasis, only a few studies have commented on the relation to FGFR-1 expression. Suyama *et al* (34) suggested that synergy between N-cadherin and FGFR-1 alters the duration of Mitogen-activated protein kinase(MAPK)-extracellular signal-regulated kinase (ERK) signals, leading to distant metastasis. In our study, the expression level of the *FGFR-1* gene was unrelated to lymph node metastasis, but was significantly higher in the presence than in the absence of liver metastasis.

We then examined the relation between FGF gene expression levels and clinicopathological features. Among the many studies addressing this topic (1), Sahadevan *et al* (32) found no association of FGFR-1 or FGFR-2 expression levels with clinical stage or distant metastasis in prostate cancer. Han *et al* (35) showed significant correlations of FGF-2 expression with the depth of invasion, clinical stage, and lymph node metastasis in oral squamous cell carcinoma. Mano *et al* (36) demonstrated that T stage and lymph node metastasis were significantly associated with strong FGFR-1 expression in lung cancer. Devilard *et al* (37) also reported that T stage correlated with FGFR-1 expression in prostate cancer. In our study, *FGFR-1* expression was associated with liver metastasis, but the expression levels of the *FGF-1, FGF-2,* and *FGFR-2* genes were not significantly related to any clinicopathological feature examined.

In conclusion, our results suggest that overexpression of the *FGFR-1* gene correlates with liver metastasis in colorectal cancer. High levels of *FGFR-1* gene expression may thus be a novel marker or predictor of liver metastasis.

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