Long non-coding RNA Fer-1-like protein 4 suppresses oncogenesis and exhibits prognostic value by associating with miR-106a-5p in colon cancer

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A new long non-coding RNA (lncRNA) that is called Fer-1-like protein 4 (FER1L4) has been confirmed to play crucial regulatory roles in tumor progression. It exerts an impact on tumor suppression and functions as a competing endogenous RNA (ceRNA) by sponging miR-106a-5p in gastric cancer. However, its clinical significance in colon cancer is completely unknown. The aim of the present study was to annotate the role of FER1L4 and its clinical value in colon cancer. The results showed the aberrant expression of FER1L4 and miR-106a-5p in colon cancer tissues. In addition, significant negative correlation between FER1L4 and miR-106a-5p expression levels was observed. Among the colon cancer cell lines, FER1L4 levels were relatively lower, with concurrent high levels of miR-106a-5p. Restoration of FER1L4 decreased the expression of miR-106a-5p, and had a significant influence on colon cancer cell proliferation, migration and invasion. The FER1L4 expression was correlated with depth of tumor invasion, lymph node metastasis, vascular invasion and clinical stage. Moreover, striking differences in overall survival and disease-free survival were observed for the cases with both low FER1L4 expression and high miR-106a-5p expression compared with cases with high FER1L4 expression and low miR-106a-5p expression. Circulating FER1L4 and miR-106a-5p levels were decreased and increased, respectively, in colon cancer patients after surgery. Our findings indicated that FER1L4 could exert a tumor suppressive impact on colon cancer, which at least, in part, through suppressing miR-106a-5p expression, and depletion of FER1L4, alone or combined with overexpression of miR-106a-5p, is predictive of poor prognosis in colon cancer and may play a crucial role in cancer prevention and treatment.
are one pair of ceRNA that show reciprocal repression to each other, there are currently no published investigations on the possible association of their expression with colon cancer progression. In the present study, the expression levels of FER1L4 and miR-106a-5p in colon cancer tissues and cell lines were determined. Then, the colon cancer cells were treated with pcDNA3.1-FER1L4, and cell proliferation, migration and invasion were analyzed. The correlations between FER1L4 and miR-106a-5p and their clinicopathological significance in colon cancer were investigated. Finally, in human plasma, the expression level of FER1L4 was examined.

**Material and Methods**

**Specimens.** A total of 176 tissue samples were collected from Shanghai Jiao Tong University Affiliated First People’s Hospital, China, from October 2005 to June 2007. The 70 fresh colon cancer tissues and matched adjacent nontumorous tissues and another 36 lymph node metastatic tissues were obtained from the Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). The remaining samples were obtained from the Shanghai Institute of Biochemistry and Cell Biology. A total of 176 tissue samples were collected from Shanghai Jiao Tong University Affiliated First People’s Hospital. The 70 fresh colon cancer tissues and matched adjacent nontumorous tissues and another 36 lymph node metastatic tissues were obtained from the Shanghai Institute of Biochemistry and Cell Biology. A total of 176 tissue samples were collected from Shanghai Jiao Tong University Affiliated First People’s Hospital, China, from October 2005 to June 2007. The 70 fresh colon cancer tissues and matched adjacent nontumorous tissues and another 36 lymph node metastatic tissues were obtained from the Shanghai Institute of Biochemistry and Cell Biology. The remaining samples were obtained from the Shanghai Institute of Biochemistry and Cell Biology.

**Serological tumor marker analysis.** Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured using an Elecsys 2010 machine (Roche Diagnostics, Basel, Switzerland). The cutoff values for CEA and CA19-9 were 5 ng/mL and 35 U/mL, respectively.

**Statistical analysis.** All statistical analyses were set with a significance level of \( P < 0.05 \). Data were performed using Statistical Program for Social Sciences (SPSS) 19.0 software (SPSS, Chicago, IL, USA). The paired \( t \)-test, the two-independent sample \( t \)-test, one-way ANOVA, the \( \chi^2 \)-test and the Kruskal–Wallis test were used as appropriate. All graphs were plotted using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA).

**Results**

**Expression of Fer-1-like protein 4 and miR-106a-5p in colon cancer.** The expression levels of FER1L4 and miR-106a-5p were examined in 70 pairs of colon cancer and matched adjacent normal tissues by qRT-PCR, and the results showed that FER1L4 was downregulated in 60.3% (44/70) of colon cancer tissues compared with the matched adjacent normal tissues (\( P < 0.001 \), Fig. 1a). Inversely, the levels of miR-106a-5p were increased in 60.1% (43/70) of cancer tissues. Furthermore, miR-106a-5p levels were increased with concurrent decreased levels of FER1L4 in 31 paired colon cancer tissues (\( P < 0.001 \), Fig. 1a). An inverse correlation between FER1L4 and miR-106a-5p was also observed in colon cancer tissues (\( P < 0.01 \), \( R^2 = 0.318 \), Fig 1b). In addition, FER1L4 and miR-106a-5p expression levels were assayed in five colon cancer cell lines, RKO, Lovo, HCT116, SW480 and SW620, and all the levels were normalized to the level in NCM460, a normal colon mucosal epithelial cell line. Among all the cancer cell lines, FER1L4 levels were lower with concurrent high levels of miR-106a-
5p (Fig. 1c), consistent with the expression of FER1L4 and miR-106a-5p in colon cancer tissues. It is noteworthy that FER1L4 was downregulated in 86.1% (31/36) of lymph node metastatic tissues, with significant means between lymph node metastatic tissues and primary cancer tissues (Table 1).

Fer-1-like protein 4 inhibits proliferation, migration and invasion of colon cancer cells. According to the findings that

Table 1. Expression of FER1L4 and miR-106a-5p in colon cancer tissues and lymph node metastatic tissues

|                     | FER1L4       | miR-106a-5p |
|---------------------|--------------|-------------|
|                     | High n (%)   | Low n (%)   | High n (%) | Low n (%) |
| Cancer tissue       | 70           | 26 (37.1)   | 44 (62.9)  | 43 (61.4)  | 27 (38.6)  |
| Lymph node metastatic tissue | 36           | 5 (13.9)    | 31 (86.1)  | 29 (80.6)  | 7 (19.4)   |

*P < 0.05 indicates a significant difference in the expression of Fer-1-like protein 4 (FER1L4) and miR-106a-5p between primary colon cancer and lymph node metastatic tissues.
Fig. 2. Confirmation of FER1L4 transfection and its effect on colon cancer cell proliferation, migration and invasion. (a) FER1L4 transfection was validated by quantitative RT-PCR and the empty vector pcDNA3.1 transfected cells were used as controls. Reduction of MiR-106a-5p was consequent upon FER1L4 reintroduction. (b) Compared with control, FER1L4 exhibited a significant inhibition of colon cancer cell proliferation by CCK-8 assay, (c) migration and (d) invasion by Transwell assays. The experiments were repeated in triplicate. Data represent means and SD. Differences among the two groups were analyzed by ANOVA. Graphics were the representative presentations of cell migration and invasion from three independent experiments. *P < 0.05, **P < 0.01.
Expression of FER1L4 and miR-106a-5p in HCT116 and RKO cells were more significantly downregulated than in the other colon cancer cell lines, the HCT116 and RKO cells were treated with pcDNA3.1-FER1L4, respectively. As a result, FER1L4 expression levels were effectively restored; meanwhile, the FER1L4 reintroduction-induced reduction of miR-106a-5p was also observed (Fig. 2a). Using the Cell Counting Kit-8 assay, FER1L4-enhanced cells exhibited a significant proliferation inhibition compared with the control (Fig. 2b). Moreover, in the Transwell migration assay, pcDNA3.1-FER1L4 impeded the migratory ability of HCT116 and RKO cells effectively when compared to cells treated with pcDNA3.1 normal control (Fig. 2c). Similar results were observed in the invasion assay (Fig. 2d).

Correlation between Fer-1-like protein 4 expression and clinicopathological characteristics in colon cancer. Based on the above findings, whether FER1L4 and miR-106a-5p expression levels were associated with the clinicopathological features of patients with colon cancer were further analyzed. As in a previous report in which IncRNA FENDRR in tumor tissues were categorized as high or low according to the median value of FENDRR expression, \(^{(17)}\) in the present study, the colon cancer patients of this study were divided into two groups in relation to the median value of relative FER1L4 and miR-106a-5p expression levels. As shown in Table 2, the FER1L4 expression level demonstrated a negative association with depth of tumor invasion (pT stage, \(P = 0.011\)), lymph node metastasis (pN stage, \(P = 0.003\)), vascular invasion (\(P = 0.019\)) and AJCC stage (\(p < 0.001\)). MiR-106a-5p was positively associated with pT stage (\(P = 0.013\)), pN stage (\(P = 0.009\)), AJCC stage (\(P < 0.001\)) and vascular invasion (\(P = 0.010\)).

Downregulation of Fer-1-like protein 4 alone or combined with overexpression of miR-106a-5p predicts poor prognosis. A total of 48 of the 70 (68.6\%) patients who underwent curative operations experienced recurrent disease. The Kaplan–Meier plot showed that striking differences in OS and DFS were observed between the low FER1L4 expression group and the high FER1L4 expression groups (Fig. 3a). Meanwhile, miR-106a-5p showed no correlation with OS but was significantly associated with DFS (Fig. 3b). Notably, the patient group with both low FER1L4 and high miR-106a-5p expression exhibited a significant difference in prognosis compared with the patient group with high FER1L4 and low miR-106a-5p expression (Fig. 3c). Univariate and multivariate analysis demonstrated that decreased tumor FER1L4 expression was a significant independent prognostic factor for decreased survival and increased disease recurrence. In contrast, miR-106a-5p alone was not a prognostic indicator; however, it appeared to be an independent prognostic factor for OS and DFS when combined with FER1L4 in colon cancer (Table 3).

Expression of Fer-1-like protein 4 and miR-106a-5p in human plasma. Using the blood samples, the existence of FER1L4 and miR-106a-5p in human plasma was observed in the present study, and then the relationship between their expression levels with colon cancer patients was analyzed. From a total of 150 blood samples, including 50 preoperative colon cancer blood samples, 50 postoperative colon cancer blood samples one month after surgery and 50 healthy blood samples, we found that there was no difference of circulating FER1L4 between preoperative patients and healthy persons, and decreased levels of circulating FER1L4 in 70% (35/50) of colon cancer patients one month after surgery (\(P < 0.01\), respectively). As a result, FER1L4 expression levels were effectively restored; meanwhile, the FER1L4 reintroduction-induced reduction of miR-106a-5p was also observed (Fig. 2a). Using the Cell Counting Kit-8 assay, FER1L4-enhanced cells exhibited a significant proliferation inhibition compared with the control (Fig. 2b). Moreover, in the Transwell migration assay, pcDNA3.1-FER1L4 impeded the migratory ability of HCT116 and RKO cells effectively when compared to cells treated with pcDNA3.1 normal control (Fig. 2c). Similar results were observed in the invasion assay (Fig. 2d).

Table 2. Association between clinicopathologic features and FER1L4 or miR-106a-5p expression

| Feature                  | Expression of FER1L4 | P-value | Expression of miR-106a-5p | P-value |
|--------------------------|----------------------|---------|---------------------------|---------|
| Age (years)              |                      |         |                           |         |
| <65                      | 12 23                | 0.621   | 24 11                     | 0.220   |
| ≥65                      | 14 21                |         | 19 16                     |         |
| Gender                   |                      |         |                           |         |
| Male                     | 17 25                | 0.480   | 23 19                     | 0.160   |
| Female                   | 9 19                 |         | 20 8                      |         |
| Location                 |                      |         |                           |         |
| Right                    | 16 20                | 0.193   | 21 15                     | 0.584   |
| Others                   | 10 24                |         | 22 12                     |         |
| pT stage                 |                      |         |                           |         |
| T1                       | 9 5                  | 0.011*  | 4 10                      | 0.013*  |
| T2                       | 8 7                  |         | 8 7                       |         |
| T3                       | 6 14                 |         | 14 6                      |         |
| T4                       | 3 18                 |         | 17 4                      |         |
| pN stage                 |                      |         |                           |         |
| N0                       | 14 8                 | 0.003*  | 10 12                     | 0.009*  |
| N1                       | 7 15                 |         | 11 11                     |         |
| N2                       | 5 21                 |         | 22 4                      |         |
| AJCC stage               |                      |         |                           |         |
| I                        | 14 4                 | -0.001* | 5 13                      | -0.001* |
| II                       | 5 9                  |         | 6 8                       |         |
| III                      | 4 18                 |         | 19 3                      |         |
| IV                       | 3 13                 |         | 13 3                      |         |
| Differentiation          |                      |         |                           |         |
| Well                     | 11 13                | 0.371   | 12 12                     | 0.350   |
| Moderate                 | 8 12                 |         | 13 7                      |         |
| Poor                     | 7 19                 |         | 18 8                      |         |
| Vessel invasion          |                      |         |                           |         |
| No                       | 17 16                | 0.019*  | 15 18                     | 0.010*  |
| Yes                      | 9 28                 |         | 28 9                      |         |
| Serum CA19-9             |                      |         |                           |         |
| Negative                 | 13 26                | 0.459   | 22 17                     | 0.333   |
| Positive                 | 13 18                |         | 21 10                     |         |
| Serum CEA                |                      |         |                           |         |
| Negative                 | 15 19                | 0.241   | 19 15                     | 0.354   |
| Positive                 | 11 25                |         | 24 12                     |         |

*P < 0.05 indicates a significant association among the variables.
AJCC, American Joint Committee On Cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; FER1L4, Fer-1-like protein 4.

Discussion

In the present study, we verified for the first time the association of FER1L4 and miR-106a-5p expression with colon cancer progression. As a tumor suppressor, FER1L4 exhibits its clinical significance in colon cancer. We find that FER1L4
Fig. 3. Kaplan–Meier curves based on FER1L4, miR-106a-5p and their combined expression levels of 70 colon cancer patients. (a) The overall survival (OS) and disease-free survival (DFS) of the FER1L4 low group (n = 44) was significantly shorter than that of the high expression group (n = 26). (b) The DFS of the miR-106a-5p high group (n = 43) was significantly shorter than that of the low expression group (n = 27), but the OS was no different. (c) The OS and DFS of the FER1L4 low combined with the miR-106a-5p high expression group (FER1L4 low/miR-106a-5p high, n = 30) was significantly shorter than that of the FER1L4 high/miR-106a-5p low group (n = 15).
exerts tumor suppressive effects on colon cancer by mediating miR-106a-5p repression, and might serve as a novel biomarker for prognosis of colon cancer when evaluated with miR-106a-5p expression.

Although over the past decade research on microRNA in maintaining malignant disorders has dominated the field of non-coding RNA regulation, the effects of lncRNA on the tumorigenesis of colon cancer are still not completely known. A growing number of reports suggest that plenty of lncRNA could be used as diagnostic biomarkers and therapeutic targets in human cancers and play oncogenic or tumor suppressor roles in human cancer pathogenesis. For instance, colon cancer-associated transcript-1 (CCAT 1) was upregulated in gallbladder cancer tissues and cell lines, and suppression of CCAT

### Table 3. Univariate and multivariate analysis of overall survival and disease-free survival after surgery

|                      | Overall survival |                      | Disease-free survival |                      |
|----------------------|------------------|----------------------|-----------------------|----------------------|
|                      | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate |
|                      | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age                  |              |          |              |          |              |          |              |          |
| <65                  | –           |          | –           |          | –           |          | –           |          |
| ≥65                  | 0.83 (0.44, 1.55) | 0.558     | 1.06 (0.52, 2.07) | 0.611     | –           |          | –           |          |
| Gender               |              |          |              |          |              |          |              |          |
| Male                 | –           |          | –           |          | –           |          | –           |          |
| Female               | 0.95 (0.51, 1.80) | 0.684     | 1.16 (0.63, 1.98) | 0.475     | –           |          | –           |          |
| Location             |              |          |              |          |              |          |              |          |
| Right                | –           |          | –           |          | –           |          | –           |          |
| Other                | 1.03 (0.81, 1.96) | 0.711     | 1.21 (0.68, 1.92) | 0.536     | –           |          | –           |          |
| T stage              |              |          |              |          |              |          |              |          |
| T1                   | 1.16 (0.81, 1.68) | 0.419     | 1.27 (0.73, 1.81) | 0.504     | –           |          | –           |          |
| T2                   | 0.91 (0.54, 1.46) | 0.206     | 0.94 (0.49, 1.51) | 0.323     | –           |          | –           |          |
| T3                   | 0.68 (0.29, 1.19) | 0.015*    | 0.72 (0.31, 1.35) | 0.032*     | –           |          | –           |          |
| T4                   | –           |          | –           |          | –           |          | –           |          |
| N stage              |              |          |              |          |              |          |              |          |
| N0                   | –           |          | –           |          | –           |          | –           |          |
| N1                   | 3.28 (1.97, 5.48) | <0.001*   | 2.82 (0.81, 4.83) | 0.007*     | 3.05 (1.65, 4.96) | <0.001*   | 2.34 (0.63, 4.26) | 0.019*   |
| N2                   | 14.37 (6.83, 25.88) | <0.001*   | 7.25 (2.52, 33.89) | <0.001* | 14.64 (7.44, 28.67) | <0.001* | 5.56 (1.72 30.88) | <0.001* |
| AJCC stage           |              |          |              |          |              |          |              |          |
| I                    | –           |          | –           |          | –           |          | –           |          |
| II                   | 3.32 (0.75, 11.01) | 0.404     | 2.59 (0.66, 9.98) | 0.357     | 3.01 (0.63, 9.25) | 0.335     | 2.38 (0.51, 8.40) | 0.406    |
| III                  | 9.12 (2.28, 37.46) | 0.009*    | 7.81 (1.97, 32.69) | 0.024*     | 8.27 (1.84, 30.55) | 0.006* | 6.41 (1.56, 29.77) | 0.029*    |
| IV                   | 26.21 (11.32, 101.43) | <0.001*   | 21.83 (8.95, 89.24) | <0.001* | 22.56 (9.57, 98.27) | <0.001* | 20.55 (8.18, 82.40) | <0.001* |
| Differentiation      |              |          |              |          |              |          |              |          |
| Well                 | –           |          | –           |          | –           |          | –           |          |
| Moderate             | 1.17 (0.75, 1.93) | 0.703     | 0.89 (0.40, 1.75) | 0.682     | –           |          | –           |          |
| Poor                 | 1.59 (1.03, 2.98) | 0.425     | 1.13 (0.87, 2.59) | 0.303     | –           |          | –           |          |
| Vascular invasion    |              |          |              |          |              |          |              |          |
| No                   | –           |          | –           |          | –           |          | –           |          |
| Yes                  | 3.06 (1.54, 5.85) | 0.014*    | 3.48 (1.77, 6.12) | 0.004*     | –           |          | –           |          |
| FER1L4               |              |          |              |          |              |          |              |          |
| Low                  | 10.25 (5.09, 24.04) | <0.001*   | 3.99 (1.67, 9.01) | 0.021*     | 8.87 (4.39, 19.65) | <0.001* | 4.51 (1.99, 9.02) | 0.032*    |
| High                 | –           |          | –           |          | –           |          | –           |          |
| miR-106a-5p          |              |          |              |          |              |          |              |          |
| Low                  | –           |          | –           |          | –           |          | –           |          |
| High                 | 2.07 (1.22, 3.85) | 0.073     | 2.21 (1.46, 4.11) | 0.034*     | –           |          | –           |          |
| FER1L4/miR-106a-5p   |              |          |              |          |              |          |              |          |
| High/Low             | –           |          | –           |          | –           |          | –           |          |
| Low/High             | 13.31 (4.86, 37.23) | <0.001*   | 7.39 (3.13, 18.45) | <0.001* | 12.30 (4.96, 33.55) | <0.001* | 9.09 (3.75, 25.88) | <0.001* |

*P < 0.05 indicated that 95% CI of HR was not including. HR, hazard ratio; 95% CI, 95% confidence interval.
Fer-1-like protein 4 is a novel long non-coding RNA which was first published as occurring in gastric cancer tissues. In the current study, attenuation of FER1L4 was a frequent event in colon cancer tissues. It is noticeable that miR-106a-5p has recently been reported in several cancers; however, it has a controversial role and exerts oncogenic or suppressive impacts on different tumors. Our findings indicated that increased expression of miR-106a-5p was assessed in 60.1% (43/70) of colon cancer tissues, and its levels were found to be negatively correlated with FER1L4 expression. To our knowledge, it is the first study analyzing miR-106a-5p levels in colon cancer tissues. In addition, FER1L4 levels were lower in concurrent upregulation of miR-106a-5p in colon cancer cell lines, which is consistent with the results in cancer tissues.

Recent evidence demonstrated that some clinicopathological characteristics such as tumor clinical stage, histologic grade and distant metastasis can be used to predict tumor progression and as an independent prognostic factor on survival; however, optimal prognostic biomarkers for colon cancer have not been established until now. Therefore, the relationships among FER1L4, miR-106a-5p expression levels and clinicopathological characteristics were further explored. In our study, FER1L4 expression was significantly associated with tumor invasion depth, lymph node metastasis, distant metastasis and AJCC stage. Moreover, we found that colon cancer patients

miR-106a-5p free to bind to other targets, such as RB1 mRNA. However, whether there exist some other target genes except for RB1 participating in the FER1L4–miR-106a-5p ceRNA network in colon cancer needs to be further explored.

FER1L4 mediated miR-106a-5p repression in colon

Fig. 4. The comparison of FER1L4 and miR-106a-5p expression in plasma of preoperative and postoperative colon cancer patients (n = 50) and healthy controls (n = 50). (a) Plasma FER1L4 was significantly decreased (70%, 35/50) and (b) plasma miR-106a-5p was significantly increased (56%, 28/50) in postoperative blood samples compared with the matched preoperative ones. The different levels of plasma FER1L4 and miR-106a-5p were also obvious between the postoperative groups and healthy controls, but there were no differences between preoperative groups and healthy controls. The quantitation was calculated by using the ΔCt method and higher ΔCt means lower expression levels. *P < 0.05, **P < 0.01.
with low tumor FER1L4 expression were strongly linked to increased risk of poor survival and tumor recurrence. Univariate and multivariate analysis indicated that FER1L4 expression alone or combined with miR-106a-5p expression could be served as an independent prognostic factor for OS and DFS in colon cancer.

Recent studies demonstrated that some biomarkers, including lncRNA and microRNA, exist in human plasma. Therefore, FER1L4 and miR-106a-5p expression levels were detected in human plasma, among preoperative patients, postoperative patients and healthy persons. Although there was no difference in circulating FER1L4 between preoperative patients and healthy persons, it is noteworthy that circulating FER1L4 was significantly decreased in 70% (35/50) of colon cancer patients in the 1 month following surgery. In contrast, circulating miR-106a-5p revealed no statistical difference between healthy blood samples and preoperative blood samples; however, its levels had increased after surgery in 56% (28/50) of postsurgical patients. Based on this truth, we assumed that circulating FER1L4 expressed poorly in postsurgical colon cancer patients and its attenuation may be due to some oncogenic factors which could be secreted by micrometastatic circulating tumor cells (CTC), and miR-106a-5p, which might be released into peripheral blood by CTC mainly rather than primary tumor cells in view of the level changes among preoperative patients, postoperative patients and healthy persons. All these findings underscored the predictive potential of circulating FER1L4 and miR-106a-5p in colon cancer. It is possible that attenuation of circulating FER1L4 in colon cancer correlates with disease recurrence and metastasis, which needs to be verified in a larger prospective clinical investigation.

Collectively, based on the evidence that FER1L4 suppresses carcinogenesis via interaction with miR-106a-5p in colon cancer, we confirmed that colon cancer patients who had low FER1L4 expression and high miR-106a-5p expression tended to have a poor prognosis. It is possible that the reciprocal modulation of FER1L4 and miR-106a-5p may also involve other factors and signaling pathways. Thus, further investigations are warranted to advance our understanding of their effects in colon cancer. FER1L4 plays a crucial regulatory role in colon cancer, at least in part, by suppressing miR-106a-5p expression, and restoration of FER1L4 may provide a promising therapeutic option for suppressing colon cancer progression.

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Disclosure Statement

The authors have no conflict of interest to declare.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Relationship of circulating FER1L4 and miR-106a-5p level changes (ΔΔCt) after surgery with clinicopathological factors of colon cancer patients.