Correlation between expression levels of lncRNA FER1L4 and RB1 in patients with colorectal cancer

Marjan Ostovarpour1 · Mohammad Khalaj-Kondori1 · Tayyebeh Ghasemi1

Received: 1 March 2021 / Accepted: 8 June 2021 / Published online: 16 June 2021
© The Author(s), under exclusive licence to Springer Nature B.V. 2021

Abstract
Colorectal cancer (CRC) is a major life-threatening malignancy. Studies demonstrated the lncRNA fer-1 like family member 4 (FER1L4) was downregulated in different cancers and its expression was positively correlated with the retinoblastoma 1 (RB1) mRNA in a competing endogenous RNAs network. We investigated expression levels of FER1L4 and RB1 in patients with colorectal cancer. 50 paired colorectal tumors and non-tumor marginal tissues, 30 paired adenomatous colorectal polyps (ACPs) and matched adjacent normal tissues were obtained from the patients. Total RNA was extracted from the samples and cDNAs were synthesized. Their expression was quantified by qRT-PCR. Correlation between FER1L4 and RB1 expression levels was analyzed by Pearson correlation test. Finally, ROC curve analysis was used to evaluate their biomarker potency. We observed significant downregulation of FER1L4, but upregulation of RB1 in the colorectal tumors compared with non-tumor and the polyp tissues. However, RB1 expression was positively correlated with FER1L4 expression both in the tumor and polyp samples. ROC curve analysis showed both FER1L4 and RB1 expression levels could discriminate tumor from non-tumor and tumor from polyp samples. None of the clinicopathological characteristics of patients were associated with FER1L4 or RB1 expression levels. Despite the downregulation of FER1L4 and upregulation of RB1 in tumors compared with non-tumor tissues, the expression of RB1 was positively correlated with the expression of FER1L4 in the colorectal tumor as well as in the polyp tissues. FER1L4 expression level might be considered as a potential biomarker for colorectal cancer development.

Keywords Colorectal cancer · Gene expression · Upregulation · Downregulation · FER1L4 · RB1

Introduction
Colorectal cancer (CRC) as a gastrointestinal malignancy is the third most common cancer and also the second leading cause of cancer-related deaths in the world [1, 2]. In recent decades, the incidence rate of CRC is increasing due to lifestyle changes including dietary habits, obesity, smoking, inflammatory bowel disease, diabetes mellitus, and lack of physical activity [2–4]. Distant metastasis and recurrence of disease are the cause of most CRC-related deaths [5]. Therefore, it is essential to identify novel biomarkers for early stages and to understand the molecular mechanisms of CRC to discover new therapeutic target [5, 6].

Long non-coding RNAs (lncRNAs) are a class of RNAs with a length longer than 200 nucleotides and less than 1 Mb, but they have little ability to code protein [7, 8]. LncRNAs participate in many biological functions, including cell proliferation, apoptosis, metastasis, and gene expression regulation; thus, they could play crucial roles in cancer biology [8–11]. Different cancer types have been reported to be associated with aberrant expression of lncRNAs and the related dysregulation of mRNAs [5, 8, 12]. In colorectal cancer, some lncRNAs have been demonstrated to play a role as a tumor suppressor or oncogene, implying their potential as a diagnostic marker or therapy target for CRC [13–15].

Fer-1-like family member 4 (FER1L4) is a long non-coding RNA that is located on chromosome 20 [16]. This lncRNA has been confirmed to be involved in tumorigenesis and tumor development [17]. LncRNA FER1L4 expression has been reported to decrease in various cancers, including gastric cancer [16], colorectal cancer [6], osteosarcoma [18], endometrial carcinoma [19],
and hepatocellular carcinoma [20]. However, there is little published data about the involvement of FER1L4 in colorectal cancer [6]. On the other hand, the retinoblastoma gene, RB1, acts as a tumor suppressor gene in different tumor types, but its expression has been reported to increase in colorectal cancer [21–28]. The lncRNA FER1L4 and RB1 cooperate in a competing endogenous RNAs (ceRNAs) network involving cancer biology, where, the expression of FER1L4 positively correlates with the RB1 expression. This study aimed to evaluate FER1L4 and RB1 expression levels in colorectal tumor versus paired marginal non-tumor tissues as well as in adenomatous colorectal polyps (ACPs) versus their matched adjacent normal tissues. Finally, the correlation between FER1L4 and RB1 expression levels in colorectal cancer was further explored.

### Materials and methods

#### Study subjects

A total of 160 specimens, including 50 colorectal tumors, 50 corresponding adjacent non-tumorous tissues, 30 adenomatous colorectal polyps, and 30 polyps’ matched adjacent normal tissues were obtained from the Shahid Mahallati Hospital (Tabriz, Iran). The study was approved by the Research Ethics Committee of the University of Tabriz (Tabriz, Iran) and written consents were collected from all patients. All specimens were confirmed by a pathologist as polyp or tumor and included in the study. Exclusion criteria were receiving of clinical treatments such as radiotherapy, chemotherapy, or immunotherapy by the patients before surgery or colonoscopy. Clinicopathological features of patients were reported in Tables 1 and 2.

### Table 1 Association between FER1L4 or RB1 expression (2−ΔCt) and different clinicopathological features in CRC patients

| Clinicopathological features | No. of cases (Percent) | FER1L4 relative expression (Mean ± SD) | P value | RB1 relative expression (Mean ± SD) | P value |
|-----------------------------|------------------------|--------------------------------------|---------|-------------------------------------|---------|
| Gender                      |                        |                                      |         |                                     |         |
| Male                        | 39 (78)                | 0.21 ± 0.41                          | 0.21    | 0.90 ± 1.48                         | 0.52    |
| Female                      | 11 (22)                | 0.03 ± 0.03                          | 0.03    | 0.58 ± 0.45                         | 0.58    |
| Age (years)                 |                        |                                      |         |                                     |         |
| < 65                        | 19 (38)                | 0.09 ± 0.24                          | 0.173   | 0.82 ± 1.74                         | 0.175   |
| ≥ 65                        | 31 (62)                | 0.22 ± 0.42                          | 0.173   | 0.84 ± 1.07                         | 0.175   |
| Smoking status              |                        |                                      |         |                                     |         |
| Ever and current            | 35 (70)                | 0.15 ± 0.28                          | 0.753   | 0.95 ± 1.50                         | 0.935   |
| Never                       | 15 (30)                | 0.22 ± 0.55                          | 0.753   | 0.43 ± 0.34                         | 0.935   |
| Histological grade          |                        |                                      |         |                                     |         |
| Well                        | 40 (80)                | 0.19 ± 0.40                          | 0.53    | 0.97 ± 1.46                         | 0.084   |
| Moderately, poorly          | 10 (20)                | 0.10 ± 0.14                          | 0.53    | 0.30 ± 0.37                         | 0.084   |
| Tumor stage                 |                        |                                      |         |                                     |         |
| I/II                        | 31 (62)                | 0.16 ± 0.42                          | 0.734   | 0.85 ± 1.17                         | 0.859   |
| III                         | 19 (38)                | 0.18 ± 0.32                          | 0.734   | 0.81 ± 1.58                         | 0.859   |
| Lymph node metastasis       |                        |                                      |         |                                     |         |
| Negative                    | 27 (54)                | 0.17 ± 0.43                          | 0.777   | 0.81 ± 1.17                         | 0.989   |
| Positive                    | 23 (46)                | 0.17 ± 0.31                          | 0.777   | 0.86 ± 1.54                         | 0.989   |
| Vascular invasion           |                        |                                      |         |                                     |         |
| Absent                      | 11 (22)                | 0.04 ± 0.04                          | 0.961   | 1.24 ± 2.45                         | 0.569   |
| Present                     | 39 (78)                | 0.20 ± 0.40                          | 0.961   | 0.73 ± 1.01                         | 0.569   |
| Tumor size (cm)             |                        |                                      |         |                                     |         |
| < 5                         | 18 (36)                | 0.06 ± 0.11                          | 0.44    | 0.65 ± 0.98                         | 0.095   |
| ≥ 5                         | 32 (64)                | 0.22 ± 0.43                          | 0.44    | 0.91 ± 1.48                         | 0.095   |
| Location                    |                        |                                      |         |                                     |         |
| Rectum                      | 15 (30)                | 0.04 ± 0.04                          | 0.873   | 0.95 ± 1.38                         | 0.565   |
| Colon                       | 35 (70)                | 0.20 ± 0.41                          | 0.873   | 0.79 ± 1.35                         | 0.565   |
RNA extraction, cDNA synthesis, and expression analysis

RNX-plus Reagent (SinaClone, Iran) was used to isolate total RNA from tissues according to the manufacturer’s instructions. The quality and quantity of isolated RNAs were measured using agarose gel electrophoresis and NanoDrop® ND-1000 UV–Vis Spectrophotometer (Thermo Fisher). A total of 1000 ng RNA was reverse transcribed into cDNA in a volume of 10 µL using PrimeScript RT Reagent kit (TaKaRa) following the manufacturer’s protocol. Primers were: RNU6 Forward: 5'-CTCGCCTTCGAGGAGGAGTGGTCCTGTT-3' and Reverse: 5'-GGAACGCTCGAGAATTTGCTGC-3', FER1L4 Forward: 5'-CGGTGTCTCAGGAGGACCACTGTTGGAGG-3' and Reverse: 5'-GGCAAGTCCACTGTCAGATGTC-3', RB1 Forward: 5'-GGGTGCTCGCTCTGCTGACGTCAGATGTC-3' and Reverse: 5'-AGCCATGCAAGGATTCACAGGAACGCTCGAGAATTTGCTGC-3'. The gene expression levels were quantified by qRT-PCR using Master Mix Green (RealQ plus 2x, AMPLIQON) in a StepOnePlus™ Real-Time PCR System (Applied Biosystems). All reactions were performed in a total volume of 20 µL in duplicate format. The reaction conditions were: Initial denaturation at 95 °C for 10 min, followed by 40 repeats of a cycling stage consisting of 20 s at 95 °C (denaturation), 30 s at 58 °C (RB1), at 65 °C (FER1L4), at 65 °C (RNU6) (primer annealing) and 20 s at 72 °C (extension). Data were normalized to RNU6 and the relative expression of FER1L4 and RB1 were calculated by the 2-ΔΔCt method.

Statistical analysis

Data were analyzed using GenEx 7, SPSS v25, and GraphPad Prism v8 software programs. Kolmogorov–Smirnov, one-way analysis of variance test, Kruskal–Wallis, independent samples T test, and Mann–Whitney U test were used as appropriate. The Kolmogorov–Smirnov test was used to determine the normality of the data. Expression levels in tumor and polyp tissues and their margins were assessed by

| Clinicopathological features | No. of cases (Percent) | FER1L4 relative expression Mean± SD | P value | RB1 relative expression Mean± SD | P value |
|-----------------------------|------------------------|-----------------------------------|---------|----------------------------------|---------|
| Gender                      |                        |                                   |         |                                  |         |
| Male                        | 16 (53.33)             | 0.32±0.32                         | 0.434   | 0.36±0.44                        | 0.159   |
| Female                      | 14 (46.66)             | 0.35±0.21                         |         | 0.30±0.74                        |         |
| Age (years)                 |                        |                                   |         |                                  |         |
| <58                         | 16 (53.33)             | 0.29±0.40                         | 0.071   | 0.47±0.77                        | 0.942   |
| ≥58                         | 14 (46.66)             | 0.32±0.35                         |         | 0.16±0.11                        |         |
| Smoking status              |                        |                                   |         |                                  |         |
| Ever and current            | 12 (40)                | 0.27±0.30                         | 0.177   | 0.33±0.44                        | 0.767   |
| Never                       | 18 (60)                | 0.40±0.24                         |         | 0.34±0.69                        |         |
| Size of ACP                 |                        |                                   |         |                                  |         |
| 1–5 mm                      | 9 (30)                 | 0.53±0.30                         | 0.202   | 0.69±1.04                        | 0.15    |
| 6–9 mm                      | 18 (60)                | 0.29±0.26                         |         | 0.17±0.22                        |         |
| 10 mm or more               | 3 (10)                 | 0.16±0.02                         |         | 0.42±0.55                        |         |
| Location                    |                        |                                   |         |                                  |         |
| Anal, rectum                | 8 (26.66)              | 0.29±0.31                         | 0.933   | 0.27±0.38                        | 0.896   |
| Sigmoid, descending colon   | 15 (50)                | 0.36±0.26                         |         | 0.39±0.72                        |         |
| Transverse colon            | 2 (6.66)               | 0.22±0.01                         |         | 0.05±0.07                        |         |
| Ascending colon, cecum      | 5 (16.66)              | 0.34±0.38                         |         | 0.36±0.59                        |         |
| Polyp type                  |                        |                                   |         |                                  |         |
| Tubular                     | 24 (80)                | 0.37±0.29                         | 0.344   | 0.38±0.65                        | 0.685   |
| Tubulillus                  | 6 (20)                 | 0.15±0.02                         |         | 0.14±0.13                        |         |
| Indications for referral    |                        |                                   |         |                                  |         |
| Abdominal pain              | 10 (33.33)             | 0.40±0.29                         | 0.164   | 0.49±0.90                        | 0.339   |
| Constipation                | 9 (30)                 | 0.23±0.20                         |         | 0.16±0.11                        |         |
| Bleeding per rectum         | 6 (20)                 | 0.12±0.14                         |         | 0.07±0.07                        |         |
| Anemia                      | 3 (10)                 | 0.77±0.11                         |         | 0.86±0.66                        |         |
| Diarrhea                    | 2 (6.66)               | 0.57±0.13                         |         | 0.19±0.12                        |         |
ANOVA test. The clinicopathological features in the two groups by independent samples $T$ test and Mann–Whitney $U$ test were evaluated in normal and abnormal data, respectively. Non-normal data in more than two groups were analyzed first by the Kruskal–Wallis test and then ANOVA test. A receiver operating characteristic (ROC) curve was established to evaluate the diagnostic value. Also, the Pearson test was used to investigate the correlation between FER1L4 and RB1. The data were presented as the mean ± SD and $P < 0.05$ was considered statistically significant.

**Results**

**Study subjects**

Clinicopathological characteristics of the study subjects are shown in Tables 1 and 2. Briefly, 80 patients with colorectal cancer or polyp were assessed. 78% of patients with the tumor were male while 22% were female. 62% of the patients with tumors were recognized as stage I or II, and 38% as stage III. Of the patients with a polyp, 53.33% were men, and 46.66% women. The average age of patients in the CRC and Polyp groups were 65 and 58 years, respectively. So, we simply divided each group into two subgroups of upper and lower than of the average.

**LncRNA FER1L4 is downregulated in colorectal cancer**

We analyzed the expression level of FER1L4 in 50 paired CRC tumor and non-tumor tissues as well as in 30 paired ACPs and their adjacent normal tissues by qRT-PCR. The results indicated that the expression level of lncRNA FER1L4 was significantly reduced in the colorectal cancer tissues compared with their matched adjacent non-tumor tissues ($P = 0.0027$, Fold change: 0.268), however, there was no significant difference between its expression in ACPs and their matched adjacent normal tissues ($P = 0.99$, Fold change: 0.930). Comparing its expression between the tumor and polyp tissues revealed a significantly decreased expression in tumor tissues ($P = 0.00029$, Fold change: 0.159) (Fig. 1a).

Additionally, ROC curve suggested a significant diagnostic ability for FER1L4 in CRC patients. The results demonstrated that the area under the ROC curve (AUC) was 0.764 (99% confidence interval 0.5993–0.9310; $P = 0.0003$) for the paired tumor versus marginal tissues, and 0.907 (99% confidence interval 0.7716–1.0000; $P < 0.0001$) for the tumor versus polyp tissues (Fig. 2).

The association of FER1L4 expression level in CRC, as well as in polyp tissues, with the clinicopathological features of the patients including gender, age, smoking status, size,
location, histological grade, and TNM stage, was further analyzed. The results showed no association between its expression level neither in the CRC nor in the polyp tissues with the clinicopathological features (Tables 1 and 2).

**RB1 is upregulated in colorectal cancer**

The RB1 expression level was also compared between tumor and non-tumor as well as between polyp and their adjacent normal tissues. As shown in Fig. 1b, the expression level of RB1 was significantly higher in the tumor tissues compared with the corresponding adjacent non-tumor tissues (P = 0.00065, Fold change: 3.678), however, there was no significant difference between polyps and matched normal tissues (P = 0.90, Fold change: 1.317). Comparing RB1 expression levels between tumor and polyp tissues revealed that its expression was significantly increased in tumor tissues (P = 0.01343, Fold change: 3.067).

ROC curve analysis identified an area under the curve (AUC) of 0.766 (99% confidence interval 0.6202–0.9117; P < 0.0001) for tumor versus non-tumor and an AUC of 0.708 for tumor versus polyp analyzes (99% confidence interval 0.5388–0.8779; P = 0.0040) (Fig. 2).

![ROC curves](image-url)
Furthermore, the association between clinicopathological characteristics of the patients and the RB1 expression level was analyzed. As shown in Tables 1 and 2, none of the clinicopathological characteristics showed a significant association with its expression in the tumor or polyp groups.

**RB1 expression positively correlates with FER1L4 expression**

Correlation between FER1L4 and RB1 expression levels both in tumor samples and in polyp samples was investigated. We observed a statistically significant positive correlation between FER1L4 and RB1 expression levels in tumor (R = 0.407, P = 0.023) and in polyp samples (R = 0.518, P = 0.033) (Fig. 3).

**Discussion**

Over 1.8 million patients are diagnosed annually with colorectal cancer [1]. So, identification of the pathogenic molecular pathways and determination of therapeutic targets are needed. It has been recognized that mutations within the noncoding genome and deregulation of noncoding RNAs play critical roles in human diseases [14]. LncRNA, as a novel molecular target, impacts cancer pathogenesis [29]. As an example, LncRNA FER1L4 has been confirmed to retard tumor progression [6]. It is downregulated in several cancers, including gastric cancer [16], osteosarcoma [18], endometrial carcinoma [19], hepatocellular carcinoma [30], esophageal squamous cell carcinoma [31], and lung cancer [32]. However, its expression in glioma is upregulated [17]. Furthermore, the expression level of FER1L4 significantly associates with lymph node metastasis, distant metastasis, and TNM stage of diverse cancers [6, 16, 18, 19]. Previous experimental studies determined that FER1L4 could suppress proliferation, migration, and invasion but induce apoptosis [6, 20, 31–34]. FER1L4 functions as a ceRNA to regulate the expression of PTEN through miR-106a-5p and miR-18a-5p in gastric cancer and Osteosarcoma [10, 35]. It also interacts with RB1 which is mediated by miR-106a-5p. Both RB1 and FER1L4 are targets of miR-106a-5p. It was reported that knockdown of FER1L4 by siRNA could decrease both FER1L4 and RB1 levels in gastric cancer. FER1L4 knockdown elevates miR-106a-5p level that provides more chance to bind to other targets, such as RB1 and PTEN mRNAs [36].

To reveal if the lncRNA FER1L4 deregulates in CRC, here we analyzed its expression level in 50 pairs of colorectal tumors and their non-tumor marginal tissues as well as in 30 pairs of adenomatous colorectal polyps and their adjacent normal tissues. Furthermore, the expression level of RB1 as a ceRNA of FER1L4 was also investigated. The results showed that FER1L4 was significantly downregulated in the colorectal tumor tissues, but there was no significant difference between the polyps and their adjacent normal tissues (Fig. 1a). Consistent with these findings, Yue et al. observed that FER1L4 significantly downregulated in colorectal tumors compared with the marginal non-tumor tissues [6]. Interestingly, as Fig. 1a shows, we observed a significant difference between FER1L4 expression in the colorectal tumor and polyp tissues. This observation implies that deregulation of FER1L4 might have occurred after the transformation of adenomatous polyps to colorectal tumors. Furthermore, ROC curve analysis confirmed that FER1L4 expression level can significantly discriminate colorectal tumors from non-tumor tissues, as well as from adenomatous polyps, which implies its potential as a biomarker for colorectal cancer development. Although Yue et al. reported association of FER1L4

![Fig. 3](image_url) Correlation between FER1L4 and RB1 expression levels in (a) tumor and (b) polyp samples.
expression with clinicopathological features including depth of tumor invasion, lymph node metastasis, vascular invasion, and clinical stage [6] we did not observe any significant association with the clinicopathological features. These different observations may result from common study limitations such as heterogeneity of subjects, genetic background of the study population, limited number of samples used in different studies, and sampling errors. Furthermore, multifactorial nature of cancer with diverse drivers and molecular signaling pathways implies that every tumor might have a unique pathogenesis.

RB1 is one of the first described tumor suppressor genes in a wide variety of human cancers, but its involvement and function in colorectal cancer are largely controversial. Some researchers reported its downregulation [37, 38], but, others observed its upregulation in CRC [21–24, 26–28]. Here we also observed significant upregulation of RB1 in the colorectal tumor compared with their matched marginal nontumor tissues. However, its expression was not significantly different between polyps and their matched normal tissues. As stated above, miR-106a-5p targets the RB1 mRNA and regulates its function in a ceRNA network. Sponging miR-106a-5p by the lncRNA FER1L4 improves RB1 level and its appropriate tumor suppressor function [36]. As a general role, this ceRNA interaction network suggests that downregulation of FER1L4 should result in the downregulation of RB1 mRNA, implying a positive correlation between their expression levels. Despite downregulation of FER1L4 and upregulation of RB1 that we and some other researchers [21–28, 37] observed in colorectal tumors compared with their corresponding non-tumor tissues, a positive correlation between their expressions levels was identified when their expressions were analyzed just in tumor or polyp tissues in our study. This observation was consistent with their molecular relationship in the ceRNA network. Probably, the RB1 upregulation which was observed by us and some other researchers might be explained by its increased gene copy number and infrequent allelic loss at the RB1 locus in colorectal cancer [21, 39–41]. Lai et al. observed allelic imbalance (AI) of RB1 in colorectal carcinomas and suggested that AI was indicative of allelic loss [26]. So in this situation, the remaining allele could increase RB1 expression by dosage compensation or homeostatic mechanisms, because mRNA and protein of RB1 were observed in all samples with AI [26]. Furthermore, RB1 mRNA, Rb protein, and Rb Phosphorylation were reported to be increased in colorectal carcinoma compared with paired normal colonic tissue [23–25, 27, 28]. RB1 commonly performs its tumor suppressor role by restraining E2F transcription factors, but this inhibition is abolished by phosphorylation of the Rb protein. Rb phosphorylation as an oncogenic driver leads to increased proliferation and decreased apoptosis in CRC [22, 23].

LncRNAs have been revealed to associate with all major types of malignancies. They involve in tumorigenesis and tumor metastasis by impacting gene expression at both the transcriptional and translational levels [42]. Importantly, having critical roles in the regulation of antigen presentation, they allow tumor cells to escape immune surveillance [43]. Ever-increasing number of lncRNAs entering to the clinical trials [44] provides promised implications of them for the future cancer diagnosis, prognosis and therapy. In the present study, our results suggested that FER1L4 and RB1 might be considered as potential molecular biomarkers for diagnosis and progression of colorectal cancer, however, further studies are needed to confirm these findings.

**Conclusions**

In summary, we observed significant downregulation of lncRNA FER1L4 but overexpression of RB1 in colorectal cancer. However, their expression was positively correlated both in the tumor and polyp samples. Neither FER1L4 nor RB1 expression levels were associated with the clinicopathological characteristics of the patients. However, both FER1L4 and RB1 expression levels could discriminate colorectal tumor from non-tumor tissues, as well as from the adenomatous polyps, highlighting their potential as a biomarker for colorectal cancer development.

**Acknowledgements** This study was supported by the Research and Technology deputy of the University of Tabriz.

**Author contributions** MO: Conceptualization, Methodology, Writing—Original draft preparation, Data analysis, Investigation. MKK: Conceptualization, Methodology, Writing—Review & Editing, Resources, Validation, Project administration. TG: Writing—Review & Editing, Methodology.

**Declarations**

**Conflict of interest** The authors declare they have no conflict of interest.

**Ethical approval** This study was approved by the Ethics Committee of the University of Tabriz (Approved Number: IR.TABRIZU.REC.1398.013) and informed written consent was obtained from patients.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Consent for publication** Author Declaration and Consent to Publish agreement available.

**References**

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality
2. Lin K, Jiang H, Zhang LL et al (2018) Down-regulated LncRNA-HOTAIR suppressed colorectal cancer cell proliferation, invasion, and migration by mediating p21. Dig Dis Sci 63:2320–2331. https://doi.org/10.1007/s10620-018-5127-z

3. Cho YA, Lee J, Oh JH et al (2019) Genetic risk score, combined lifestyle factors and risk of colorectal cancer. Cancer Res Treat 51:1033–1040. https://doi.org/10.4143/crt.2018.447

4. Yan Q, Guo K, Feng G et al (2018) Association between the overexpression of Her3 and clinical pathology and prognosis of colorectal cancer: a meta-analysis. Medicine. https://doi.org/10.1097/MD.0000000000012317

5. Luo J, Xu LN, Zhang SJ et al (2018) Downregulation of LncRNA-RP11-317J10.2 promotes cell proliferation and invasion and predicts poor prognosis in colorectal cancer. Scand J Gastroenterol 53:38–45. https://doi.org/10.1080/0365521.2017.1392597

6. Yue B, Sun B, Liu C et al (2015) Long non-coding RNA Fer-1-like protein 4 suppresses oncogenesis and exhibits prognostic value by associating with miR-106a-5p in colon cancer. Cancer Sci 106:1323–1332. https://doi.org/10.1111/cas.12759

7. Latge G, Poulet C, Bours V et al (2018) Natural antisense transcripts: Molecular mechanisms and implications in breast cancers. Int J Mol Sci 19:1–23. https://doi.org/10.3390/ijms19101123

8. Wu Z, Liu X, Liu L et al (2014) Regulation of IncRNA expression. Cell Mol Biol Lett 19:561–575. https://doi.org/10.2478/s11658-014-0212-6

9. Peng WX, Koirala P, Mo YY (2017) LncRNA-mediated regulation of cell signaling in cancer. Oncogene 36:5661–5667. https://doi.org/10.1038/onc.2017.184

10. Fei D, Zhang X, Liu J et al (2018) Long noncoding RNA FER1L4 suppresses tumorigenesis by regulating the expression of PTEN targeting miR-18a-5p in osteosarcoma. Cell Physiol Biochem 51:1364–1375. https://doi.org/10.1159/000495554

11. Ghasemi T, Khalaj-Kondori M, Hosseinpour Feizi MA, Asadi P (2020) IncRNA-miRNA-mRNA interaction network for colorectal cancer; an in silico analysis. Comput Biol Chem 89:107370. https://doi.org/10.1016/j.compbiolchem.2020.107370

12. Ding F, Tang H, Nie D, Xia L (2017) Long non-coding RNA Fer-1-like family member 4 is overexpressed in human glioblastoma and regulates the tumorigenicity of glioma cells. Oncol Lett 14:2379–2384. https://doi.org/10.3892/ol.2017.4033

13. Sun Z, Liu J, Chen C et al (2018) The biological effect and clinical application of long noncoding RNAs in colorectal cancer. Cell Physiol Biochem 46:431–441. https://doi.org/10.1159/000488610

14. Yang Y, Zhao L, Lei L et al (2017) LncRNAs: the bridge linking RNA and colorectal cancer. Oncotarget 8:12517–12532. https://doi.org/10.18632/oncotarget.13573

15. Jahangiri B, Khalaj-kondori M, Asadollahi E, Sadeghizadeh M (2019) Cancer-associated fibroblasts enhance cell proliferation and metastasis of colorectal cancer SW480 cells by provoking long noncoding RNA UCA1. J Cell Commun Signal 13:53–64. https://doi.org/10.1007/s12079-018-0471-5

16. Liu Z, Shao Y, Tan L et al (2014) Clinical significance of the low expression of FER1L4 in gastric cancer patients. Tumor Biol 35:9613–9617. https://doi.org/10.1007/s13277-014-2259-4

17. Xia L, Nie D, Wang G et al (2019) FER1L4/miR-372/E2F1 works as a ceRNA system to regulate the proliferation and cell cycle of glioma cells. J Cell Mol Med 23:3224–3233. https://doi.org/10.1111/jcmm.14198

18. Chen ZX, Chen CP, Zhang N, Wang TX (2018) Low-expression of IncRNA FER1L4 might be a prognostic marker in osteosarcoma. Eur Rev Med Pharmacol Sci 22:2310–2314. https://doi.org/10.26355/eurrev-201804-14820

19. Kong Y, Ren Z (2018) Overexpression of IncRNA FER1L4 in endometrial carcinoma is associated with favorable survival outcome. Eur Rev Med Pharmacol Sci 22:8113–8118

20. Wang X, Dong K, Jin Q et al (2019) Upregulation of IncRNA FER1L4 suppresses the proliferation and migration of the hepatocellular carcinoma via regulating PI3K/AKT signal pathway. J Cell Biochem 120:6781–6788. https://doi.org/10.1002/jcb.27980

21. Gope R, Christensen MA, Thorson A et al (1990) Increased expression of the retinoblastoma gene in human colorectal carcinomas relative to normal colonic mucosa. J Natl Cancer Inst 82:310–314

22. Kang DW, Lee SW, Hwang WC et al (2017) Phospholipase D1 acts through Akt/TopBP1 and RB1 to regulate the E2F1-dependent apoptotic program in cancer cells. Cancer Res 77:142–152. https://doi.org/10.1158/0008-5472.CAN-15-3032

23. Vasaikar S, Huang C, Wang X et al (2019) Proteogenomic analysis of human colon cancer reveals new therapeutic opportunities. Cell 177:1035-1049.e19. https://doi.org/10.1016/j.cell.2019.03.030

24. Schlicker A, Michaut M, Rahman R, Wessels LFA (2016) OncoScape: exploring the cancer aberration landscape by genomic data fusion. Sci Rep 6:1–11. https://doi.org/10.1038/srep28103

25. Kucherlapati MH, Yang K, Fan K et al (2008) Loss of RB1 in the gastrointestinal tract of Apc1638N mice promotes tumors of the cecum and proximal colon. Proc Natl Acad Sci U S A 105:15493–15498. https://doi.org/10.1073/pnas.0802933105

26. Lai PS, Cheah PY, Kadam P et al (2006) Overexpression of RB1 transcript is significantly correlated with 3q14 allele imbalance in colorectal carcinomas. Int J Cancer 119:1061–1066. https://doi.org/10.1002/ijc.21945

27. Yamamoto H, Soh JW, Monden T et al (1999) Paradoxical increase in retinoblastoma protein in colorectal carcinomas may protect cells from apoptosis. Clin Cancer Res 5:1805–1815

28. Cui X, Shirai Y, Wakai T et al (2004) Aberrant expression of pRb and p16INK4a, alone or in combination, indicates poor outcome after resection in patients with colorectal carcinoma. Hum Pathol 35:1189–1195. https://doi.org/10.1016/j.humpath.2004.06.010

29. Liang W, Zou Y, Qin F et al (2017) sTLR4/MD-2 complex inhibits colorectal cancer migration and invasiveness in vitro and in vivo by IncRNA H19 down-regulation. Acta Biochim Biophys Sin 49:1035–1041. https://doi.org/10.1093/abbs/mx105

30. WU J, Huang J, Wang W et al (2017) Long non-coding RNA Fer-1-like protein 4 acts as a tumor suppressor via miR-106a-5p and predicts good prognosis in hepatocellular carcinoma. Cancer Biomark 20:55–65. https://doi.org/10.3233/1073CBM-170090

31. Ma W, Zhang CQ, Li HL et al (2018) LncRNA FER1L4 suppresses cancer cell growth and invasion in esophageal squamous cell carcinoma. Eur Rev Med Pharmacol Sci 22:2638–2645. https://doi.org/10.26355/eurrev_201805_14958

32. Gao X, Wang N, Wu S et al (2019) Long non-coding RNA FER1L4 inhibits cell proliferation and metastasis through regulation of the PI3K/AKT signaling pathway in lung cancer cells. Mol Med Rep 20:182–190. https://doi.org/10.3892/mmr.2019.10219

33. Ma L, Zhang L, Guo A et al (2019) Overexpression of FER1L4 promotes the apoptosis and suppresses epithelial-mesenchymal transition and stemness markers via activating PI3K/AKT signaling pathway in osteosarcoma cells. Pathol Res Pract 215:1. https://doi.org/10.1016/j.prp.2019.04.004

34. Qiao Q, Li H (2016) LncRNA FER1L4 suppresses cancer cell proliferation and cycle by regulating PTEN expression in endometrial carcinoma. Biochem Biophys Res Commun 478:507–512. https://doi.org/10.1016/j.bbrc.2016.06.160

35. Xia T, Chen S, Jiang Z et al (2015) Long noncoding RNA FER1L4 suppresses cancer cell growth by acting as a competing endogenous RNA and regulating PTEN expression. Sci Rep 5:1–9. https://doi.org/10.1038/srep13445
36. Xia T, Liao Q, Jiang X et al (2014) Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. Sci Rep 4:1–7. https://doi.org/10.1038/srep06088
37. López-Urrutia E, Coronel-Hernández J, García-Castillo V et al (2017) MiR-26a downregulates retinoblastoma in colorectal cancer. Tumor Biol 39:1–9. https://doi.org/10.1177/1010428317695945
38. Poller DN, Baxter KJ, Shepherd NA (1997) p53 and Rb1 protein expression: are they prognostically useful in colorectal cancer? Br J Cancer 75:87–93. https://doi.org/10.1038/bjc.1997.14
39. Muleris M, Salmon RJ, Dutrillaux AM et al (1987) Characteristic chromosomal imbalances in 18 near-diploid colorectal tumors. Cancer Genet Cytogenet 29:289–301. https://doi.org/10.1016/0165-4608(87)90239-1
40. Reichmann A, Martin P, Levin B (1981) Chromosomal banding patterns in human large bowel adenomas. Int J Cancer 28:431–440. https://doi.org/10.1007/BF00389453
41. Vogelstein B, Fearon ER, Kern SE et al (1989) Allelotype of colorectal carcinomas. Science 244:207–211. https://doi.org/10.1126/science.2565047
42. Jiang M-C, Ni J-J, Cui W-Y et al (2019) Emerging roles of lncRNA in cancer and therapeutic opportunities. Am J Cancer Res 9:1354–1366
43. Egranov SD, Hu Q, Lin C, Yang L (2020) LncRNAs as tumor cell intrinsic factors that affect cancer immunotherapy. RNA Biol 17:1625–1627. https://doi.org/10.1080/15476286.2020.1767455
44. Qian Y, Shi L, Luo Z (2020) Long non-coding RNAs in cancer: implications for diagnosis, prognosis, and therapy. Front Med 7:1–8. https://doi.org/10.3389/fmed.2020.612393

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.