Abstract. Colon cancer is the third most common cancer worldwide, and lymphatic metastasis is one of the principal factors affecting patient prognosis. Recent studies have revealed that long non-coding RNAs (lncRNAs) serve as important regulators in the pathogenesis of colon cancer, therefore affecting patient survival rates. In the present study, colon cancer-associated lncRNAs were screened based on their influence on patient survival. A number of survival-associated lncRNAs (and their potential mechanisms of action) were identified, with the strongest candidate being MIR210HG. Gene expression correlation and protein-protein interaction (PPI) network analyses were performed to identify MIR210HG-associated genes. Various bioinformatics analyses (including gene ontology and Kyoto Encyclopedia of Genes and Genomes analyses) were conducted to investigate the prognostic role of MIR210HG and its associated genes, in colon cancer. Higher expression levels of MIR210HG were associated with shorter overall survival in patients with colon cancer, which was significant in 373 candidates. Multiple findings indicated that MIR210HG may exert its effects in colon cancer through the modulation of energy metabolism and cell adhesion. Further predictions suggested that MIR210HG may affect colon cancer via transcription and post-transcriptional processing. Collectively, these results provided evidence of a transcriptional regulatory network of MIR210HG in colon cancer, and suggested its potential role as a novel biomarker and therapeutic target for colon cancer.

Introduction

Colon cancer is the third most common type of cancer, and the leading cause of cancer-related mortality worldwide (1). There is increasing evidence to suggest that the progression of colon cancer is a multiple-step process, involving genetic and epigenetic abnormalities (2). By comparison, epigenetic alterations are more frequently observed, and carry greater effects compared with gene mutations. For example, the silencing micro RNA-137 can target and decrease the expression level of >500 protein coding genes (3).

Long non-coding RNAs (lncRNAs) are a type of non-coding transcript of >200 nucleotides in length. lncRNAs have been associated with a number of physiological and pathological processes in various human diseases, regulating gene expression via epigenetic, transcriptional and post-transcriptional modification (4). Recent studies revealed that lncRNA was an important regulator in colon cancer pathogenesis, modulating numerous processes including cell proliferation, differentiation, tumor migration, invasion and angiogenesis. It has been reported that IncRNA SUMO1P3 stimulated the proliferation, metastasis and angiogenesis of colon cancer cells, suggesting it's potential as a novel prognostic indicator and therapeutic target for the disease (5).

lncRNAs can target different steps in the transcription process, regulating the activation or regression of gene transcription by modulating different transcriptional components, including RNA polymerase (RNAP) II and the DNA duplex (6). These IncRNAs may be part of the regulatory network that, together with transcription factors, regulate the level of gene expression. Reportedly, certain lncRNAs acted as regulators of general transcription factors which were required for the activity of RNAP II (7). These transcription factors, in addition to components of the initiation complex, assemble at promoter regions and participate in transcription elongation and the regulation of cis elements (8); it was reported that an
IncRNA transcribed from the dihydrofolate reductase (DHFR) gene was able to form a RNA-DNA triplex in the promoter region of DHFR, inhibiting its transcription by blocking the binding of transcription initiation factor IIB (9). Furthermore, the gene coding IncRNA ANRIL is able to run antisense, silencing P15 with which it overlaps.

However, survival-related IncRNAs, particularly in colon cancer remained to be identified. In order to select therapeutically relevant IncRNAs, a linear regression model was used to identify survival-related IncRNAs in colon cancer and further detect MIR210HG-related genes. Gene regulatory network and pathway analyses revealed that MIR210HG may exert its effects in colon cancer through the regulation of cancer cell metabolism and adhesion. Furthermore, bioinformatics predictions indicated that MIR210HG may affect colon cancer by regulating transcription and post-transcriptional processing.

Materials and methods

Screening of survival-related IncRNAs in colon cancer. The RNA-seq data of colon cancer-associated IncRNAs, which consisted of 471 tumor samples and 41 normal samples, were downloaded from The Cancer Genome Atlas (TCGA) data portal (https://cancergenome.nih.gov/) (10). The data were divided into high and low expression groups according to a cut-off of 75 and 25%, respectively. Homo sapiens. GRCh38.84 was used for annotation. The RNA-seq data of other gastrointestinal cancers, including esophageal cancer (162 tumor and 11 normal samples), rectal cancer (167 tumor and 10 normal samples) and stomach cancer (375 tumor and 32 normal samples), were also downloaded, and assigned into high and low expression groups using the same classification criteria as in colon cancer. The association between IncRNA expression and patient survival was determined using the Kaplan-Meier method, and evaluated using the log-rank test. The R package survival (https://github.com/therneau/survival) was used to perform these statistical analyses. P<0.05 was set as the significance threshold.

Genes significantly associated with MIR210HG expression in colon cancer. Based on the above screening, the most significant survival-related IncRNA in colon cancer was identified as MIR210HG; this IncRNA was therefore selected for use in further analysis. Associations between the expression of MIR210HG and other genes were calculated using a linear regression model. It was hypothesized that genes whose expression levels were linearly associated with MIR210HG were likely to be located nearby, upstream or downstream. This method was widely used to screen target-related genes. RNA expression was processed using log2(counts +1) prior to analysis. Subsequently, multiple selection criteria (P-value and adj.r²) were applied to determine the most appropriate candidates. P<0.05 and adj.r²>0.16 were set as the significance threshold. R was used to perform these statistical analyses.

Functional and pathway enrichment analysis. Gene ontology (GO) enrichment analysis (http://www.geneontology.org/) was used to detect biological processes, molecular functions and cellular components. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis(http://www.kegg.jp/), which is used for pathway investigations, was performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID; https://david.ncifcrf.gov/, version 6.8) (11-13). P<0.05 was set as the significance threshold.

Investigation of the correlation between MIRE210HG expression and lymphatic metastasis. All clinical data were obtained from TCGA. A normality test, the Kolmogorov-Smirnov test, was performed and a Mann Whitney U test was subsequently used to assess the association between MIRE210HG expression and metastasis in colon cancer. P<0.05 was considered to indicate a statistically significant difference. SPSS Statistics 22.0 (IBM Corp.) was used to perform statistical analysis.

Protein-protein interaction (PPI) network construction and identification of hub genes. All MIR210HG-related genes were imported into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) to construct a PPI network (14). A combined score ≥0.4 was set as the significance threshold. The network was visualized using Cytoscape (version 3.5.1, http://www.cytoscape.org/) (15). The top 10 hub genes were filtered using cytoHubba, an app in Cytoscape, using the Maximal Clique Centrality (MCC) method (16).

Module analysis of the PPI network. To investigate the most significant modules, Clustering with Overlapping Neighborhood Expansion (ClusterONE), an app in Cytoscape, was used to screen modules within the PPI network with a minimum size of 6, and the minimum density set to auto (17). P<0.05 was considered to indicate a statistically significant difference. GO and KEGG analyses of genes in the screened modules were performed using DAVID.

Transcription and post-transcriptional modulation prediction. To further investigate the mechanism of MIR210HG in colon cancer, known MIR210HG-protein interactions were summarized using starBase v2.0 (http://starbase.sysu.edu.cn/index.php) (18). Novel IncRNA-protein interactions between MIR210HG and its associated transcription factors were also predicted using RPISeq (http://pridb.gdcb.iastate.edu/RPISeq/index.html) (19). Candidates with a Random Forest classifier value >0.5 and Support Vector Machine classifier value >0.5 were considered to be positive results.

Interaction probabilities generated using RPISeq range between 0 and 1. In performance evaluation experiments, predictions with probabilities >0.5 were considered ‘positive’, indicating that the corresponding RNA and protein were likely to interact. Neighboring mRNAs located within 1 Mbps of the MIR210HG loci were investigated to predict possible cis target genes of MIR210HG. Candidate gene information was downloaded from USCS (GRCh38) (20).

Results

MIR210HG expression correlates with survival in patients with colon cancer. IncRNAs have been reported to contribute to patient survival in multiple cancers, including colon cancer (20), breast cancer (21) and larynx squamous cell carcinoma (22), and therefore, in the present study, survival-related
IncRNAs in colon cancer were investigated. RNA-seq and clinical data from colon cancer cohorts (obtained from TCGA) were analyzed to assess the association between various IncRNAs and patient survival. A total of 226 survival-related IncRNAs were selected using P<0.05 as the cut-off threshold (The top 10 survival-related IncRNAs are presented in Table I). A number of IncRNAs were reported to contribute to tumor promotion, including MIR210HG (P=1.19x10^{-3}; log-rank test), which is a diagnostic biomarker in glioma (23). A high expression level of MIR210HG was significantly associated with shorter overall survival in patients with colon cancer, suggesting a potential prognostic role for MIR210HG in the disease (Fig. 1A). However, MIR210HG showed a weak association with survival from esophageal, rectal and stomach cancers, indicating that this particular effect of MIR210HG overexpression is specific to colon cancer (Fig. 1).

Investigation of MIR210HG-related genes in colon cancer. TCGA RNA-seq expression data for MIR210HG was downloaded, and the correlation between MIR210HG expression and other genes in colon cancer was calculated using a linear regression model. A total of 373 genes with P<0.05 and adj.r² >0.16 were filtered out for further analysis (Fig. 2). The top 10 genes significantly associated with MIR210HG expression in colon cancer are presented in Table II. A total of 231 and 142 genes were positively, and negatively associated with MIR210HG expression in colon cancer, respectively. Additionally, the known PPIs among these MIR210HG-related candidates were detected using STRING (Fig. 3). A total of 359 nodes were noted in the network, and their interactions are presented in Fig. 3A. To identify the key nodes that most affected this network, MCC analyses were conducted to rank the strongest hub genes. Hub genes act as cores within the regulatory network, and the results revealed complex and strong links with various MIR210HG-related candidates. It was speculated that the expression of these hub genes may be directly regulated by MIR210HG or its downstream targets, and the results of linear regression analysis showed a significant correlation between the expression of the 10 hub genes and MIR210HG (Table III). Modules were regarded as a group of proteins that participate in the same biological process, or composition of the same complex (24). Modularity analysis was conducted, and 2 modules were selected from the constructed PPI network, as illustrated in Fig. 3B and C. GO and KEGG analysis indicated that module 1 may be associated with glycolysis and cell adhesion (e.g. triosephosphate isomerase 1, GAPDH, enolase 2, mucin 1, cell surface associated, egf-9 family hypoxia inducible factor 3, Bardet-Biedl syndrome 10, and phosphofructokinase, liver type), while module 2 may be associated with ubiquitination (e.g. kelch like family member 42, anaphase promoting complex subunit 2, F-box and WD repeat domain containing 5, and F-box and leucine rich repeat protein 15) (Figs. 4B and C; 5B).

MIR210HG may impact colon cancer by targeting energy metabolism and cell adhesion. In order to determine the possible mechanism of MIR210HG in colon cancer, GO and KEGG pathway analyses were conducted. The GO results revealed that MIR210HG expression was strongly associated with energy metabolism in colon cancer, as evidenced by the enrichment of genes involved in canonical glycolysis (P=1.15x10^{-3}), glycolytic process (P=2.78x10^{-5}) and gluconeogenesis (P=0.001) (Fig. 4A). Additionally, the KEGG results revealed that MIR210HG was significantly associated with the biosynthesis of glycolysis or gluconeogenesis (P=8.33x10^{-4}) and central carbon metabolism in cancer (P=0.003) (Fig. 5A). Furthermore, cell-cell adhesion (P=3.99x10^{-5}), cell-cell adherens junction (P=0.002) and cadherin binding involved in cell-cell adhesion (P=0.001) were notably enriched in biological process, cellular component and molecular function analysis, respectively. A recently published paper suggested that MIR210HG facilitates cancer cell invasion and metastasis in osteosarcoma (25), which is consistent with the findings of the present study. These findings suggest that MIR210HG may exert its effects in colon.
cancer by modulating energy metabolism and cell adhesion, which are closely associated with the prognosis of patients with colon cancer. Furthermore, a Mann Whitney U test was performed to verify the association between lymphatic metastasis and MIR210HG expression in colon cancer, and a strong association was identified (P=0.02; Fig. 6). These results suggest that MIR210HG may be a modulator of colon cancer cell metastasis, and are consistent with the results of the GO and KEGG enrichment analyses.

MIR210HG may influence colon cancer via transcription and post-transcriptional processing. To further investigate the mechanism of MIR210HG in colon cancer, various possible interactions between MIR210HG and screened MIR210HG candidates were predicted. Known MIR210HG-protein interactions were summarized using starBase v2.0. Specific genes associated with RNA splicing and degradation were detected (Table IV), including FUS RNA binding protein (FUS). These genes may therefore serve as post-transcriptional regulators in colon cancer. Novel IncRNA-protein interactions were also predicted using RPISeq. Since transcription factors are considered to be important regulators of gene expression, the focus was on their association with MIR210HG (Table V). Predictions for Mediator of RNA polymerase II transcription (MED)15, MED16 and B-cell lymphoma 3 protein (BCL3; probabilities >0.5) were considered to be ‘positive’. It was observed that MED16 and BCL3 were connected to hub genes within the MIR210HG regulatory network, suggesting that they may modulate the network by stimulating these genes.

IncRNAs also interacted with other cis acting elements of promoters or co-expressed genes, thus regulating gene expression via transcription or post-transcriptional processes. We therefore investigated neighboring mRNAs located within 1 Mbps of the MIR210HG locus to predict possible cis target genes. A total of 13 genes were identified (Table VI), 5 of which were members of the MIR210HG regulatory network. One of these genes was HRAS, which is known to be involved
in central carbon metabolism in cancer. HRAS is a member of the Ras superfamily of GTPases, which are involved in the regulation of cell division in response to growth factor stimulation. Activated mutant HRAS (Hras-V12) is able to initiate irreversible cell cycle arrest and increase the expression of the tumor suppressors p16 and p53 (26).

Discussion

Lymphatic metastasis is one of the principal factors to affect the prognosis of patients with colon cancer (27). The survival rates of patients with lymphatic metastasis is significantly lower compared with that of patients without lymphatic metastasis (28). Furthermore, it has been identified that metastasis-related factors may be used as prognostic biomarkers or potential therapeutic targets for improving the survival rates of patients with colon cancer (29-31).

In the present study, candidate lncRNAs were screened based on the effects of lncRNA expression on the survival rate of patients with colon cancer. The employed screening method may be more suitable for clinical practice compared with traditional selection methods, and is more likely to be applied to treatment. The same method was used to screen survival-related lncRNAs in breast cancer, and a co-expressed gene network of the lncRNA with the greatest effect, LINC00704 (data not shown), was also constructed. The results of GO and KEGG analyses suggested that LINC00704-related genes are associated with the regulation of cell proliferation, which is in agreement with a previous report (32).

Glycolysis is the primary method by which tumor cells generate energy, even under normoxic conditions (33). Glycolysis provides energy for tumor cells, and so targeting glycolysis may have potential as a method to control tumor proliferation. Changes in glycolysis in tumor cells are associated with resistance to anticancer drugs. For instance, Song et al (34) reported that increased glycolytic activity and low phosphorylation efficiency increases chemoresistance in patients with acute myeloid leukemia. This may be regulated by glycolysis-related molecules, including hypoxia-inducible factor 1α, hexokinase II, glucose transport 1 and lactate dehydrogenase (34).

Table III. Top 10 hub genes in protein-protein interaction networks.

| No. | Hub genes | P-value | Adj.r.squared |
|-----|-----------|---------|---------------|
| 1   | PKM       | 6.14x10^-26 | 0.21         |
| 2   | TPI1      | 1.01x10^-20 | 0.17         |
| 3   | PFKL      | 1.18x10^-25 | 0.21         |
| 4   | PFKP      | 9.47x10^-27 | 0.22         |
| 5   | GAPDH     | 1.65x10^-21 | 0.17         |
| 6   | ENO2      | 7.55x10^-27 | 0.22         |
| 7   | LDHA      | 1.88x10^-29 | 0.24         |
| 8   | ALDOA     | 1.43x10^-50 | 0.38         |
| 9   | ALDOC     | 1.09x10^-46 | 0.35         |
| 10  | PFKFB4    | 3.23x10^-42 | 0.33         |

PKM, pyruvate kinase M1/2; TPI1, triosephosphate isomerase 1; PFKL, phosphofructokinase, liver type; PFKP, phosphofructokinase, platelet; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; ENO2, enolase 2; LDHA, lactate dehydrogenase A; ALDOA, aldolase, fructose-bisphosphate A; ALDOC, aldolase, fructose-bisphosphate C; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4.

Table IV. Known MIG210HG-protein interactions via starBase v2.0.

| Name | IncRNA   | Target sites | BioComplex | ClipReadNum |
|------|----------|--------------|------------|-------------|
| eIF4AII | MIR210HG | 12            | 2           | 31          |
| FUS   | MIR210HG | 1            | 1           | 5           |
| SFRS  | MIR210HG | 1            | 1           | 800         |
| U2AF65| MIR210HG | 1            | 1           | 2           |

BioComplex is the number of supporting experiments. ClipReadNum is the read number of CLIP-Seq. IncRNA, long non-coding RNA; eIF4AII, Eukaryotic initiation factor 4A-II; FUS, FUS RNA binding protein; SFRS, Serine/arginine-rich splicing factor 1; U2AF65, U2 small nuclear RNA auxiliary factor 2.
Table V. Prediction of IncRNA-protein interactions between MIR210HG and candidate transcription factors through RPIseq.

| Transcription factors | Isoform | Gene names                        | RF classifier | SVM classifier |
|-----------------------|---------|-----------------------------------|---------------|---------------|
| MED15                 | 1       | Mediator complex subunit 15       | 0.9           | 0.57          |
| MED15                 | 2       | Mediator complex subunit 15       | 0.9           | 0.59          |
| MED15                 | 3       | Mediator complex subunit 15       | 0.9           | 0.62          |
| MED16                 | 1       | Mediator complex subunit 16       | 0.8           | 0.61          |
| MED16                 | 2       | Mediator complex subunit 16       | 0.75          | 0.61          |
| MED16                 | 3       | Mediator complex subunit 16       | 0.75          | 0.6           |
| MED16                 | 4       | Mediator complex subunit 16       | 0.8           | 0.54          |
| MED16                 | 5       | Mediator complex subunit 16       | 0.8           | 0.48          |
| CDK9                  | 1       | Cyclin dependent kinase 9         | 0.85          | 0.55          |
| CDK9                  | 2       | Cyclin dependent kinase 9         | 0.85          | 0.51          |
| BCL3                  | 1       | B-cell CLL/lymphoma 3             | 0.75          | 0.53          |
| PPPIR13L              | 1       | Protein phosphatase 1 regulatory subunit 13 like | 0.85 | 0.49 |

RF, Random forest; SVM, Support Vector Machine.

Figure 2. Genes significantly associated with MIR210HG expression in colon cancer.
The possible mechanism of interaction between MIR210HG and its co-expressed genes was also predicted. Reports have indicated that MIR210HG may affect colon cancer via transcription and post-transcriptional processing. Certain genes associated with RNA splicing and degradation, including FUS, were reported to interact with MIR210HG, suggesting that they may serve as post-transcriptional regulators in colon cancer. mRNA splicing is a vital step in post-transcriptional regulation, as it can trigger translation and functionally diversify proteins. In part of a study by Zarnack et al (37) experimental verification was carried out and reported a correlation between MIR210HG and U2AF65 (supplementary material; summary by starBase v2.0 database: http://starbase.sysu.edu.cn/index.php). While, according to the present study, MIR210HG and U2AF65 also showed associations (probabilities >0.5 using RPISeq: http://pridb.gdcb.iastate.edu/RPISeq/index.html), which is consistent with Zarnack’s experimental results. However, in order to develop novel treatment methods to improve the prognosis of patients with colon cancer, we must improve our understanding of the molecular mechanisms of lncRNAs. In the present study, novel lncRNA-protein interactions were detected using RPISeq, and numerous transcription factors (including MED15, MED16 and BCL3) were considered to be positive candidates. In particular, MED16 and BCL3...
were connected to hub genes within the MIR210HG regulatory network, reinforcing our prediction that MIR210HG serves as a transcriptional modulator in colon cancer. Although there is a lack of evidence indicating the specific molecular association between the selected transcription factors and candidates, it was revealed that some transcription factors (including MED15 and Angiopoietin-related protein 4, BCL3 and GAPDH, Cyclin-dependent kinase 9 and HRAS) interact with the hub genes and are strongly correlated with MIR210HG. A total of 5 selected transcription factors were associated with cancer metastasis. Decreased MED15 expression can suppress the transforming growth factor-β/Smad signaling pathway, thereby downregulating the metastasis of highly invasive breast cancer cells (38). BCL3 can also reduce cancer cell metastasis by influencing cell motility (39). Furthermore, neighboring mRNAs located within 1 Mbps of the MIR210HG loci were investigated to predict possible cis element target genes of MIR210HG. A total of 13 genes were identified, 5 of which, including HRAS, were members of the MIR210HG regulatory network. These results provide new information as how MIR210HG regulates the regulatory network and affects survival in patients with colon cancer.

In summary; in the present study survival-related lncRNAs in colon cancer were screened and bioinformatics analyses were performed to investigate the prognostic potential of MIR210HG and its related genes in colon cancer. The findings indicated that MIR210HG may exert its effects in colon cancer by modulating energy metabolism and cell adhesion. Further predictions suggested that MIR210HG may also affect colon cancer via transcription and post-transcriptional processing. Together, these results provide evidence of the transcriptional regulatory network of MIR210HG in colon cancer, and
suggest that MIR210HG may serve a potential role as a novel biomarker and therapeutic target. Despite the multiple bioinformatic and statistical methods used in the present study, it does have some limitations, and further studies are required to verify these results. Experimental evidence will be provided in future studies; for example, the high expression level of MIR210HG may regulate the expression levels of screened MIR210HG-related genes, or induce the phenotype obtained with bioinformatics analyses (such as the metastasis of colon cancer cells), which will be assessed using cell-based assays with colon cancer cell lines.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL and ZR designed the study. ZR, ZX and ZL performed the data analyses. All authors contributed significantly in writing the manuscript and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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