Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Research Article **DOI: 10.26479/2021.0706.05**

STRUCTURAL AND FUNCTIONAL CHARACTERISTICS OF MiRNA IN COLON CANCER AND THE IDENTIFICATION OF TARGETS BY INSILICO METHODS

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ABSTRACT: MicroRNAs (miRNA) are single-stranded RNA molecules with a length of 21-23 nucleotides that inhibit mRNA translation and promote mRNA degradation. miRNA is an endogenous regulator of gene expression that is involved in cancer biology processes such as cell growth, proliferation, differentiation, and apoptosis. Dysregulation of miRNA has been linked to colorectal cancer in several studies. Depending on the cellular context in which they are expressed, certain microRNAs can behave as suppressors or oncogenes. MicroRNA expression is changed in Colorectal Cancer (CRC), and the patterns of expression are linked to diagnosis, prognosis, and treatment outcome (CRC). MicroRNAs might be used as molecular classifiers, early detection biomarkers, and therapeutic targets for CRC, according to these findings. We'll go over the evidence that microRNAs have a role in CRC in this section. The goal of this research was to describe the miRNA profiles of serum exosomes and find out which ones were changed in colorectal cancer patients (CRC). The connection between particular exosomal miRNA levels and pathological changes in patients, including disease stage and tumor resection, was investigated to see if they might be used as diagnostic biomarkers. MicroRNA has an important part in the development of malignancies. These noncoding RNAs' specific expressions can also be used as biomarkers for early colorectal cancer detection, although molecular identification is difficult and costly.

Keywords: miRNA, colon cancer, quantitative real-time PCR, Colon cells line encyclopedia, Insilico Drug Discovery.

Article History: Received: Oct 26, 2021; Revised: Nov 04, 2021; Accepted: Nov 18, 2021.

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1. INTRODUCTION

Tumor recurrence is one of the most prevalent aspects of all cancers, occurring in roughly half of all cases of colorectal cancer, the third most common disease in the United States [1-6]. This might be because traditional chemotherapy mainly targets the rapidly dividing cells that make up the majority of the tumor, and while chemotherapy can lower the tumor size, the benefits are typically ephemeral and do not increase the patient's survival rate [7-16]. To do so, we looked at the role of miRNA (miRNA) in colon CSCs. MiRNAs are a kind of endogenous RNA with a length of 19–22 nucleotides that suppress the expression of target genes by cleaving messenger RNA (mRNA) or by translation repression [16-25] MicroRNA21 (miR21) has been reported to be over expressed in the majority of epithelial tumors, and is thus thought to play a key role in the advancement of a variety of cancers, including lung, breast, stomach, prostate, colon, brain, head and neck, esophageal, and pancreatic cancers [25-34]. Systematic approaches for diagnosing pathological disorders may help to increase the diagnosis rate of individuals with CRC at an early stage, lowering death rates [35-42]. The use of screening tools such as the fecal occult blood test and flexible sigmoidoscopy has lowered CRC mortality [43-54].miRNA dysfunction is present in a variety of malignancies, and endogenous miRNA expression patterns can be utilized to categorize cancer types [55-59]. Several miRNAs with high levels of expression in cancer tissues have been proposed as diagnostic or prognostic indicators [60-62]. Exosomes leak miRNAs from numerous cells, including cancer cells, into bodily fluids such as blood, urine, breast milk, and saliva, according to recent research [63-64]. The majority of CRC research has previously focused on the function of genetic and epigenetic alterations in protein-coding genes in CRC start and development. MicroRNAs are a type of tiny noncoding RNA that has recently gained attention. Based on factors such as evolutionary conservation, predicted effects on protein structure, and observed recurrence in existing cancer datasets, several computational approaches exist and have been implemented to predict the functional impact of mutations, and even predict whether the specific mutation is a driver of the carcinogenesis process [65].

2. MATERIALS AND METHODS

Sample collections and Cell Culture

From 2003 to 2004, the National Cancer Center Hospital Biobank, Japan (Tokyo, Japan) donated serum samples from 88 CRC patients (aged 35 to 65 years) having a primary tumor. From 2003 to 2004, serum samples were obtained from 29 patients after surgical excision of the main tumor. In 2009, the National Cancer Center Hospital Biobank in Japan donated blood samples from 13 distinct CRC patients (aged 45 to 70 years) with a primary tumor for qRT-PCR confirmation. Patients treated at Teikyo University Hospital (Tokyo, Japan) provided surgical specimens of primary colon cancer and surrounding non-cancerous tissues [66]. The human colon cancer cell line (SW1116) was obtained from the Cell Bank, Shanghai Institute of Life Science, Chinese Academy of Sciences, and

kept in RPMI-1640 medium (Invitrogen, Carlsbad, CA, United States) supplemented with 10% fetal bovine serum (Gibco BRL, United States), penicillin G (1 105 U/L), and streptomycin (100 mg/L) at 37 °C in a 50 mL/L CO2 atmosphere.

Quantitative reverse transcriptase Polymerase Chain Reaction

DNase I was used to treat the whole RNA, which was then purified using phenol-chloroform. At an optical density of 260 nm, the concentration of RNA was determined spectrophotometrically. The GeneAmp RNA PCR Kit was used to perform quantitative reverse transcription-polymerase chain reaction (qRTPCR) (Applied Biosystems, Foster City, CA). SYBR Green Quantitative PCR Master Mix was used to amplify five microliters of complementary DNA (cDNA) products (Applied Biosystems). The following primers were used in the polymerase chain reaction (PCR): 5#-TGAGACTGATGTTGACTGTTGAA -3# and 5#TGTCAGACAGCCCATCGAC -3#; b-actin forward, 5#CCCAGCACAATGAAGATCAA-3# and reverse, 5#-TGTCAGACAGCCCATCGAC -3# TGFbR2 forward 5#-ACATCTGCTGGAAGGTGGAC -3#, 5# AAATGGAGGCCCAGAAAGAT 3#, and reverse 5#ACTTGACTGCACCGTTGTTG -3#. The Applied Biosystems 7500 Real-time PCR System was used to perform the reactions. Briefly, the TaqMan MicroRNA reverse transcription kit was used to create cDNA (Applied Biosystems). Applied Biosystems provided the miRNA reverse transcription–PCR primers for miR-21 and the endogenous control RNU6B. The Applied Biosystems 7500 Realtime PCR System was used to perform real-time qRT–PCR analyses. The TaqMan 2 Universal PCR Master Mix PCR mix was processed as follows: 95°C for 10 minutes, then 95°C for 15 seconds, 60°C for 60 seconds for up to 40 cycles.

Colon Cancer cells growth

We created CR human colon cancer HCT-116 and HT-29 cell lines by exposing them to 5-FU oxaliplatin at clinically appropriate dosages and regimens for four months to better understand the molecular pathways behind colon cancer recurrence. We used a cell viability experiment with 250 lM 5-FU 6.25 lM oxaliplatin to assess the degree of resistance of FOLFOX-resistant cells (CR cells) to 5-FU oxaliplatin (.10-fold the IC50,half-maximal inhibitory concentration, of both drugs). The chemotherapeutic mixture suppressed the cellular proliferation of parental HCT-116 and HT-29 cells considerably. We propose that CR-HCT-116 and CR-HT-29 cells are enriched in CSCs because CSCs are resistant to death by conventional chemotherapy. This implies that CSCs are abundant in CR cells.

Expression of miRNA in Colon Cancer

More than twenty studies have looked at miRNA expression patterns in CRC to date, and they've all found that microRNAs are consistently and reliably changed in this illness.These investigations employed a range of methodologies, ranging from global miRNA expression profiling using deep sequencing [66] or miRNA microarrays to quantitative reverse transcriptase Polymerase chain

reaction to examine the expression of specific microRNAs (qRT-PCR). This suggests that in CRC, microRNAs may have more oncogenic than tumor-suppressive properties. The findings that microRNAs are over-represented in regions of the genome that show copy number gain while under-represented in regions that show copy number loss in CRC correspond to the findings that microRNAs are over-represented in regions of the genome that show copy number gain while under-represented in regions that show copy number loss in CRC [66]. Regardless of these findings, functional investigations show that certain microRNAs have key oncogenic roles while others have important tumor suppressor capabilities, and these functions must be examined separately for each miRNA in the context of the relevant tissue/tumor type.

Cancer Insilico Drug Discovery

CiDD (Cancer InSilico Drug Discovery) begins with selecting CCLE cell lines depending on tissue types provided by the user. CiDD then interrogates CCLE mutation data taken from either targeted sequencing of common cancer genes or Oncomap 3.0, an SNP array that genotypes samples at known cancer-related locations, to identify cell lines that have user-specified mutations. Using mutation and RNA-sequencing data from The Cancer Genome Atlas (TCGA) colon and rectum projects, we used CiDD to find potential medicines to treat CRCs with BRAF V600E mutations. We also found cell lines are characteristic of colorectal cancers with BRAF mutations in the Cancer Cells Lines Encyclopedia (CCLE), making them eligible for in vitro drug testing.

3. RESULTS AND DISCUSSION

Over-expression of miRNA in Colon Cancer

The pCMV/miR-21 plasmid (OriGene) was stably transfected in HCT-116 cells to assess the probable functional features of miR-21. Four miR-21 positive clones were chosen based on miR-21 expression as indicated by the qRT–PCR (real-time PCR) study. When clone 1 was compared to an empty vector, miR-21 expression was found to be.240-fold greater. For following investigations, the miR-21 over-expressing clone 1 and/or pooled clone were employed. When compared to vector-transfected controls, the levels of TGFbR2, PDCD4, and PTEN, which are targets of miR-21 [66], were lower in miR-21 over-expressing clone 1 as well as the pooled clone.

Regulating Stemness in miRNA

Many cancers, including colorectal cancer, are known to activate the Wnt/b-catenin signaling pathway [61]. This signaling pathway is also important in controlling the growth of CSCs (Kanwar S.S et.al., 2010). When comparing total b-catenin, C-Myc, and Cyclin-D1 expression in miR-21 over-expressing HCT-116 cells to the vector-treated control, Western blot analysis revealed a 28–100% increase in total b-catenin, C-Myc, and Cyclin-D1 expression, but a 60% drop in axin levels.

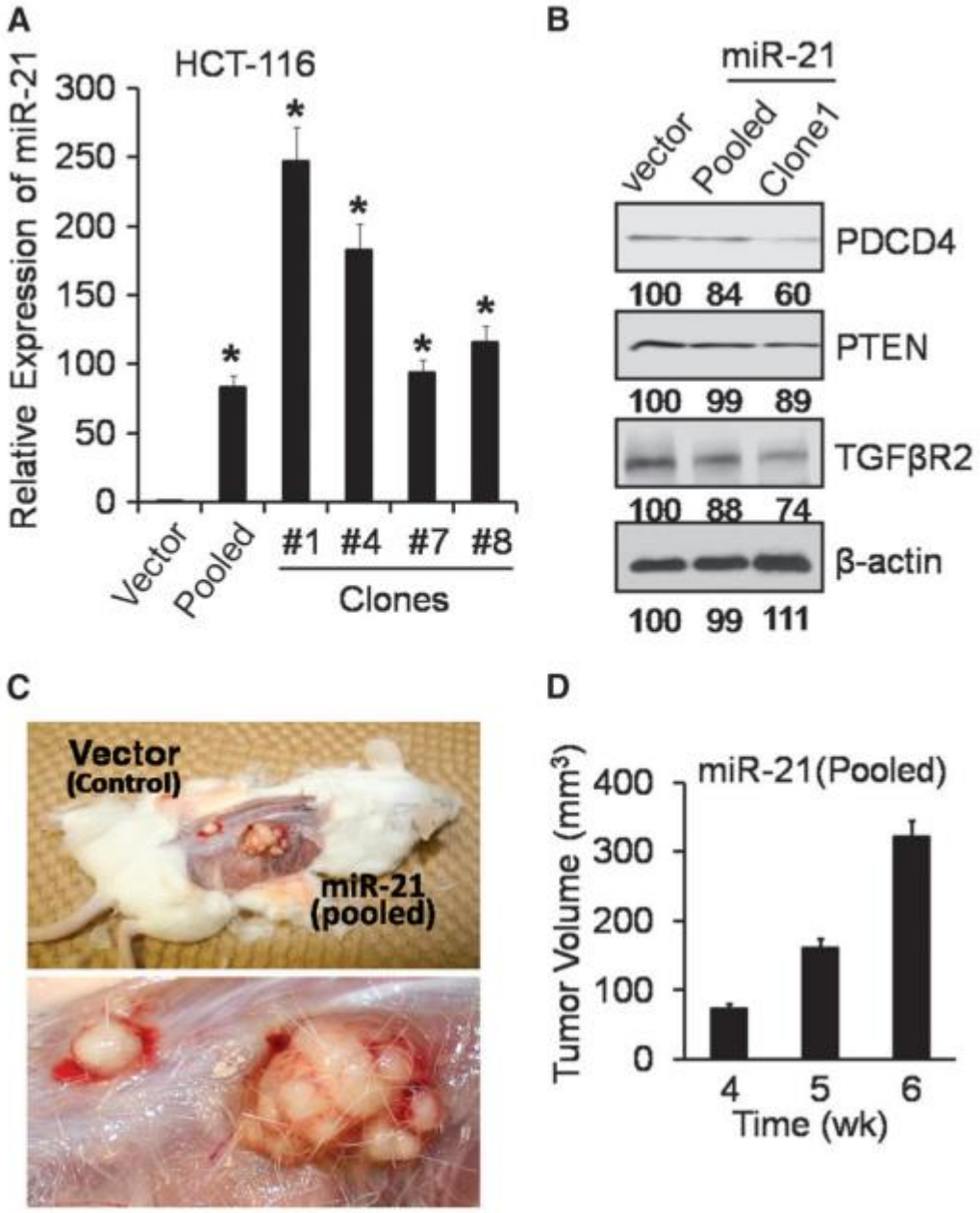

Fig 1. miRNA 21 over-expression in human colon cancer HCT116 cells.

A) Up-regulation of mature miRNA-21 in HCT116 cells by qRT-PCR

B) Western blotting showing down-regulation

C) the anatomical intact xenograft tumor in female SCID mice

D) Xenograft tumors volume

CRC is still a serious public health concern as well as a life-threatening condition. The goal of this study was to find candidate microRNAs and their related target genes that may be used as CRC diagnostic biomarkers. Currently, surgery and chemotherapy are the only two effective options for advanced colorectal cancer treatment. To be more successful, chemotherapy treatment usually comprises a mix of medications. FOLFOX is a combination of 5-FU, leucovorin, and oxaliplatin used to treat advanced colorectal cancer.

The study of the molecular pathways involved in cancer genesis and progression has sparked a lot

of interest in miRNAs. Secreted miRNAs incorporated in exosomes may be diagnostic biomarkers for cancer detection, in addition to their crucial physiological roles. Long primary miRNA transcripts produce mature functional miRNAs with roughly 22 nucleotides that influence gene expression at the posttranscriptional level by degrading or inhibiting target mRNAs. The abnormal expression of certain miRNAs in cancer has been widely established.

4. CONCLUSION

With the help of insilico Methods, miRNAs with seven prominent target genes have been identified. Patients with modifications in the miRNA prioritized target genes had considerably higher overall survival than patients without these alterations, according to the patterns of expression obtained in their target genes relative to their microRNAs and their prognostic values. The current study's findings reveal that miR21 over-expression is linked to stemness induction via down-regulation of TGFbR2, a direct target of miR-21, and augmentation of the b-catenin TCF/LEF signaling pathway. miRNAs have an important role in the onset and development of CRC. Many studies have found that miRNA expression patterns or related polymorphisms are linked to CRC diagnosis or prognosis, suggesting that they might be used as early detection markers or predictive/prognostic classifiers.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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