World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i34.5615

World J Gastroenterol 2013 September 14; 19(34): 5615-5621
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

MicroRNA-21 as a potential colon and rectal cancer biomarker

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Received: May 25, 2013 Revised: July 15, 2013
Accepted: July 18, 2013
Published online: September 14, 2013

Abstract

Colorectal cancer (CRC) is one of the most common malignant diseases worldwide and the prognosis is still poor although much progress has been achieved in recent years. In order to reduce CRC-related deaths, many studies are aimed at identifying novel screening- and prognosis-related biomarkers. MicroRNAs (miRNAs) are a class of 18-27-nucleotide single-stranded RNA molecules that regulate gene expression at the post-transcriptional level. It has been demonstrated that miRNAs regulate a variety of physiological functions, including development, cell differentiation, proliferation, and apoptosis. They play important roles in various physiologic and developmental processes and in the initiation and progression of various human cancers. It has been shown that miRNAs can critically regulate tumor cell gene expression, and evidence suggests that they may function as both oncogenes and tumor suppressor genes. In CRC, miRNAs-21 is one of the most important miRNAs and is rapidly emerging as a novel biomarker in CRC, with good potential as a diagnostic and therapeutic target. In this review, we summarize the latest research findings of the clinicopathological relevance of miRNAs-21 in CRC initiation, development, and progress, highlighting its potential diagnostic, prognostic, and therapeutic application, as well as discussing future prospects.

Key words: Colorectal cancer; MicroRNA; Diagnosis; Treatment; Chemotherapy

Core tip: We summarize the latest study findings about microRNA-21 in colorectal cancer through a systematic review of literature. We recommend microRNA-21 as one of the most important microRNAs, which is rapidly emerging as a novel biomarker, with good potential as a diagnostic and therapeutic target.

Li T, Leong MH, Harms B, Kennedy G, Chen L. MicroRNA-21 as a potential colon and rectal cancer biomarker. *World J Gastroenterol* 2013; 19(34): 5615-5621 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i34/5615.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i34.5615

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death in the United States. It was estimated that there were about 142570 new cases diagnosed and 51370 deaths in 2010[1]. Progress in diagnosis and treatment has had a positive effect in improving overall survival, with more patients being diagnosed in the early stage of the disease, but the outcomes of patients diagnosed with advanced stage disease remains quite poor[2]. Long-term survival and better prognosis of patients depend on the stage of the tumor at the time of detection. Fecal occult blood testing and tumor markers (*e.g.*, carcinoembryonic antigen) are used as the primary screening tools, with colonoscopy reserved for patients testing positive. However, they are generally considered to lack the desired convenience, sensitivity and specificity[3]. There are currently no tests or biomark-

ers that precisely predict the presence of early tumors, recurrence, sensitivity to chemotherapy and long-term survival. It is clear that improvements in early detection of primary and recurrent disease are required.

MicroRNAs (miRNAs) are a family of small, non-coding RNAs (19-22 nucleotides) which post-transcriptionally regulate gene expression. In general, miRNAs are transcribed as a group called the pri-miRNA complex, which is cleaved in the nucleus to form the pre-miRNA which is then translocated to the cytoplasm where they undergo final maturation into a functional miRNA[4]. Once in the cytoplasm, the miRNAs regulate gene expression by binding to the 5'-untranslated region of their target mRNA resulting in degradation of the double-stranded mRNA mediated by the Dicer complex. More than 700 miRNAs have thus far been identified in plants, viruses, animals and humans, and this number continues to increase (www.mirbase.org). Studies have shown that about 30% of human genes are regulated by miRNAs[5]. This wide regulation has implications in many important cellular functions including development, differentiation, proliferation, and programmed cell death[6-8]. Given the critical regulatory roles miRNAs serve, it is no surprise that they have been shown to be associated with many cancers[9]. CRC is a complex genetic disease characterized by uncontrolled proliferation, migration, invasion, and failure of apoptotic cell death, due to oncogene activation and tumor suppressor gene defects[10]. Many miRNAs which mediate cell growth and tumor progression have been found to be upregulated in CRC including miR-20, miR-21, miR-17-5p, miR-15b, miR-181b, miR-191 and miR-200c[9,11-14]. While lower levels of mature miRNAs such as miR-34a, miR-126, miR-143, miR-145 and miR-342 are also found, suggesting that they act as tumor suppressor miRNAs[15-18]. This deregulation of various miRNAs has been associated with tumor diagnosis and prognosis indicating that they might be potential biomarker in clinical application[3,19-21]. Multiple studies have identified that miR-21 plays a significant role in cancer biology, diagnostics and prognosis. In this article, we review the literature demonstrating the importance of miR-21 in CRC, summarize the association of miR-21 expression level with CRC diagnosis and prognosis, and discuss the potential therapeutic implications for the future.

MIR21 IN COLORECTAL CANCER

Human miR-21 (hsa-miR-21) was cloned from HeLa cell total RNA and is highly conserved among species including human, rat, mouse, fish and frog[22]. It is located on chromosome 17q23-1 overlapping with the TMEM49 gene, a human homologue of rat vacuole membrane protein-1. MiR-21 encodes a single hairpin and is regulated by its own promoter containing binding sites for AP-1 and PU.1 transcription factors[23]. Experimental data has shown that miR-21 functions in many cell types as an anti-apoptotic and pro-survival factor and plays a significant role in cancer biology and prognosis[24-26]. Asangani *et al*[26] transfected Colo206f cells with miR-21 and found significant suppression of PDCD4 proteins *in vitro*. Resected normal and tumor tissues of 22 CRC patients demonstrated that miR-21 expression has a direct correlation with tumor invasion and metastasis.

Table 1 Current screening methods and guidelines for colorectal cancer

Method	Sensitivity	Interval	Society
Fecal tests			
FOBT		Yearly	USPSTF, ASGE, USMSTF
FIT	65.8%[32,33]	Yearly	
Fecal DNA	50%-60%[34]	Unspecified	USMSTF
Serum markers			
CEA	30%[35]		
CA19-9			
Imaging tests			
DCBE	85%-97%[36]	Every 5 years	USMSTF
CTC	55%-94%[37]	Every 5 years	USMSTF
Optical tests			
FS		Every 5 years Every 10 years	USPSTF, ASGE, USMSTF
FC			USPSTF, ASGE, USMSTF

FOBT: Fecal occult blood test; FIT: Fecal immunochemical based stool tests; CEA: Carcinoembryonic antigen; DCBE: Double-contrast barium enema; CTC: Computed tomography colonography; FS: Flexible sigmoidoscopy; FC: Flexible colonoscopy; USPSTF: United States Preventive Services Task Force; ASGE: American Society for Gastrointestinal Endoscopy; USMSTF: Multi-Society Task Force on Colorectal Cancer.

miR-21 in adenomas

It is clear that the majority of CRCs begin as benign adenomas, and through a series of accumulated genetic events, end up as invasive tumors. However, not all polyps will progress to invasive carcinomas. In fact, it is estimated that up to 20% of benign, subcentimeter adenomas will ultimately regress[27,28]. Therefore, it seems that the key to preventing polyps from progressing to malignant carcinomas is being able to determine which ones have the potential to progress and removing them at the benign stage. Interestingly, increased expression of several miRNAs such as miR-21, miR-31, miR-96, miR-221, miR-191, miR-19a, and miR-135b has been shown to correlate with the presence of adenomas[29,30]. In fact, Yamamichi *et al*[31] analyzed miR-21 expression patterns in different stages of CRC development using *in situ* hybrization, and found higher miR-21 expression in precancerous adenomas but not in non tumorigenic polyps. Furthermore, the frequency and extent of miR-21 expression increased during the transition from precancerous colorectal adenoma to advanced carcinoma. This demonstrates that expression of miR21 in benign colon adenomas may represent an early event in the progression to carcinoma.

Expression of miR-21 as a screening test for colorectal cancer

Current recommendations for CRC screening are found in Table 1[32-37]. Fecal occult blood testing is a widely used test but its low specificity and sensitivity limits its clinical

use, particularly for early detection. Newer screening tests are taking advantage of the presence of stem cells from human exfoliated deciduous teeth cells in the stool and are using various molecular tests to examine these cells for genetic events consistent with malignant changes. Expression levels of miRNAs offer attractive new potential biomarkers as they are uniquely stable and may represent some of the earliest changes in adenomas. Ng *et al*[38] reported high expression levels of miRNAs in colorectal tumors and plasma. Of the panel of 95 miRNAs analyzed by real-time polymerase chain reaction (PCR), five were upregulated in both plasma and tissue. The results were again validated using the plasma of 25 patients with CRC and 20 healthy controls. In these studies, the miRNAs 21, 17-3p, and 92 were elevated in patients with CRC ($P < 0.0005$). The authors further demonstrated that the plasma levels of these markers were significantly reduced after surgery in 10 patients with CRC ($P < 0.05$) suggesting that the high levels specifically indicate the presence of a carcinoma. Kristina *et al* tested the levels of 15 miRNAs in stool and colorectal tissue samples from 15 patients with CRC and five healthy individuals[39]. Although, variability was more pronounced among the stool samples than the tissue samples, the authors concluded that specific miRNA expression profiles could be defined, suggesting that stool is yet another biological material in which miRNAs are preserved and are amenable for early diagnosis of CRC. A stage-independent, sensitive, and specific marker for CRC in plasma or stool would be clinically important, and clearly these promising results support further assessment of miRNAs as potential biomarkers both in adenoma and extracellular fluids.

miR-21 expression levels and prognosis

The prognosis of patients with CRC is associated with tumor stage and phenotypic characteristics of resected cancer specimens such as tumor grade, positive lymph nodes, and angiolymphatic invasion[40]. Unfortunately, recently identified genomic and proteomic biomarkers, tumor cell mutations, and microsatellite instability cannot be recommended for routine clinical use because of insufficiently available data[41]. However, markers of prognosis are needed to help stratify patients into high risk thereby identifying patients who are likely to benefit from further therapy. Many studies on tumor biomarkers have been undertaken[42]. However, no study has identified a new marker that has been validated in clinical trials. The miRNAs represent particularly attractive markers as they seem to be micromanagers of cellular gene expression and may represent the earliest events responsible for carcinogenesis. In fact, studies have shown that the expression levels of different miRNAs, such as miR-21, miR-320, miR-498, miR-106a and miR-200c, correlate with disease-free and overall survival[43].

miR-21 may be a particularly attractive target as it has been shown to regulate the expression of many genes thought to be important in carcinogenesis. Target validation studies on putative miR-21 targets in breast cancer samples and CRC cells have demonstrated a link between miR-21 expression levels and the p53 tumor suppressor, and also demonstrated that the tumor suppressors PDCD4 and maspin are targets of miR-21[44]. Consistent with the importance in the process of carcinogenesis, Staby *et al*[45] demonstrated that higher miR-21 expression levels were correlated with advanced cancer stages, worse outcome, poor response to therapy, and shorter disease-free survival. Additionally, they found that miR-21 levels were positively correlated with cancer stage, lymph node involvement, and development of distant metastasis.

The most comprehensive analysis of miRNA expression in CRC performed to date tested two cohorts of 197 colon cancer patients by utilizing microarrays containing 389 miRNAs probes[46]. This analysis revealed 37 miRNAs which were differentially expressed in stage Ⅱ colonic adenocarcinoma compared with adjacent normal tissue using a test set and two validation cohorts. In one of the cohorts, miR-20a, miR-21, miR-106a, miR-181b, and miR-203 were found to be overexpressed in tumor tissues with high tumor to normal ratios, as well as being associated with poor overall survival. However, the prognostic relevance could be confirmed in the validation set for only one of the candidates, miR-21, and the clinical and biological implications of differential expression of the remaining miRNAs were unclear. Similar conclusions were drawn from a study of 29 tumor samples, in which miR-21 expression was associated with poor survival and therapeutic outcome in stage Ⅱ and Ⅲ CRC[46]. Nielsen *et al*[47] reported the expression of miRNA-21 in 130 colon and 67 rectal stage Ⅱ cancer specimens using high-affinity locked nucleic acid (LNA) probes. High levels of miR-21 correlated with shorter disease-free survival (hazard ratio: 1.28; 95% confidence interval: 1.06-1.55; $P = 0.004$) in the stage Ⅱ colon cancer patient group, whereas no significant correlation with disease-free survival was observed in the stage Ⅱ rectal cancer group.

miR-21 expression and implications for treatment

miR-21 and response to chemotherapy: The current treatment for CRC involves a multidisciplinary approach including surgery supplemented with chemotherapy and radiation therapy in certain instances. In general, patients with node-positive disease benefit from chemotherapy. However, there may be a subgroup of patients with node-positive disease who are at low risk of recurrence, as nearly 40% of patients randomized to a no-treatment arm in chemotherapy trials did not develop a recurrence[48]. In addition, it is clear that some patients with node-negative disease who have advanced T-stage tumors are at high risk of developing recurrences[49]. A test that would allow for the accurate stratification of patients with stage Ⅱ and Ⅲ disease into low and high risk would be very clinically useful. Recently, the role of miRNAs in predicting the response to 5-fluorouracil (5-FU)-based chemotherapy in CRC treatment has been explored. A significant focus has been placed on the value of miR-21 expression levels and their abilities to predict both response to and need for chemotherapy[50].

Rossi *et al*[51] utilized two subclones from the human

Table 2 MicroRNA-21 expression in colorectal cancer

Ref.	Regulation	Biological material tested	Detection method	Clinical relevance	Comment
Tumor development					
Fassan *et al*[60]	Up	300 polypoid lesions of the colon mucosa	RT-PCR ISH	Significant miR-21 upregulation in preneoplastic/neoplastic samples	High miR-21 expression is consistent with PDCD4 downregulation
Yantiss *et al*[61]	Up	24 patients < 40 years 45 patients ⩾ 40 years	RT-PCR	Significantly higher expression	
Tumor diagnosis					
Link *et al*[62]	Up	Stool samples	RT-PCR	Higher expression in patients with adenomas and CRCs	May be an excellent candidate of a noninvasive screening test for colorectal neoplasms
Tumor prognosis					
Chang *et al*[63]	Up	48 colorectal tumors, 61 normal tissues , 7 polyps	RT-PCR	Disease recurrence	miR-21 post-transcriptionally modulates PDCD4 *via* mRNA degradation
Nielsen *et al*[47]	Up	130 stage Ⅱ colon and 67 stage Ⅱ rectal cancer specimens	ISH	Shorter disease-free survival in colon cancer, but not in rectal cancer	
Kulda *et al*[64]	Up	46 paired tissue samples 30 tissue samples with live metastasis	RT-PCR	Disease-free interval	
Schetter *et al*[46]	Up	196 paired tissues	RT-PCR	Association with cancer-specific mortality, including stage Ⅱ patients alone	miR-21 expression are independent predictors of colon cancer prognosis and may provide a clinically useful tool to identify high-risk patients
Schetter *et al*[46]	Up	US cohort: 84 patients; Hong Kong cohort: 113 patients	MicroRNA microarray, RT-PCR	Poor survival and poor therapeutic outcome	

RT-PCR: Reverse transcription-polymerase chain reaction; ISH: *In situ* hybridization; PDCD4: Programmed cell death protein 4.

CRC cell lines HT29 and HCT116 to investigate the effect of 5-FU on miRNA expression and also to determine patterns of expression that correlated with response to therapy. Quantitative real-time PCR revealed that 5-FU upregulated 19 and downregulated three miRNAs. While some changes in miRNA expression were consistent with the antitumor effects of the drug, others were not, such as upregulation of miR-21 and the polycistronic miR-17-92 cluster (which include miR-19a and miR-20). In fact, a number of miRNAs that are already overexpressed in neoplastic tissues, including miR-21, have been shown to be upregulated in colon cancer cell lines treated with 5-FU[51]. Tomimaru *et al*[52] found that hepatocellular carcinoma cells transfected with pre-miR-21 were significantly resistant to 5-FU, while the 5-FU sensitivity of transfected anti-miR-21 was weakened by transfection with siRNAs of the target molecules, PTEN and PDCD4. This finding may be a cell-specific defense mechanism to survive 5-FU treatment. Svoboda *et al*[53] found significant changes in miRNA expression in 35 patients with rectal carcinoma undergoing preoperative capecitabine chemoradiation therapy. Tumor biopsies were taken before starting therapy and after 2 wk of therapy. The extent of the tumor response to the therapy was investigated microscopically by an experienced pathologist according to Mandard's tumor regression criteria. In addition, the levels of miRNAs were evaluated using real-time PCR. The authors found dramatic changes in the expression levels of many miRNAs including miR-21, miR-10a, miR-145, miR-212, miR-339, miR-361. However, only two miRNAs, miR-125b and miR-137, were found to be significantly increased after 2 wk of therapy and these miRNA expression levels had a positive correlation with a poorer tumor regression response[53]. These types of studies highlight the potential for using miRNA expression profiles to predict the response to chemotherapy. However, verification of the targets in adequately designed clinical panels is the important next step that has yet to be taken.

miR-21 maybe a potential therapeutic target in colorectal cancer treatment: miRNAs are important regulators of gene expression and may present potentially interesting therapeutic targets in cancer. The synthesis, maturation and activity of miRNAs can be manipulated with various oligonucleotides that encode the sequences complementary to mature miRNAs. By influencing particular miRNAs, a cascade of pathways could be modified to inhibit tumor growth.

Wong *et al*[54] reported the application of 20-*O*-methyl- and/or DNA/LNA-mixed oligonucleotides to specifically inhibit miR-21 in cultured glioblastoma and breast cancer cells suppressed cell growth *in vitro* in association with increased caspase-mediated apoptosis[55]. Suppression of miR-21 also significantly reduced invasion and lung metastasis in MDA-MB-231 metastatic breast cancer[56]. Although there are at present no clinical reports describing therapy targeting miR-21 in CRC treatment,

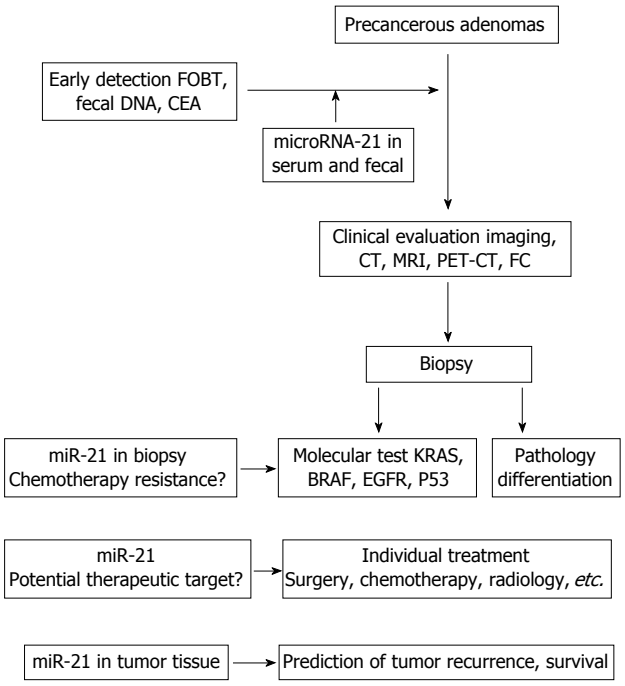

Figure 1 miR-21 as a potential biomarker in colon and rectal cancer. CT: Computed tomography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography-computed tomography; FC: Fiber colonscopy; FOBT: Fecal occult blood test; CEA: Carcinoembryonic antigen.

most seem to have optimistic views on the future utility of miR-21 as therapeutic targets but further studies are clearly needed[57-59]. Expression of microRNA-21 and the clinical relevance in CRC are summarized in Table 2.

FUTURE PERSPECTIVES

The role of miRNAs in CRC presents potentially exciting new opportunities for future investigations to determine the use of miRNAs as potential biomarkers for prognosis at the time of diagnosis as well as to determine their ability to predict the response to chemotherapy. In addition, the potential for miRNAs to serve as targets for new chemotherapeutic treatments has yet to be realized. Among the many miRNAs that have been associated with clinical outcomes, miR-21 has been consistently shown to be dysregulated in CRC. Many of the early studies relating miR-21 to CRC have been performed *in vitro* on established cell lines. In addition, studies using human tumor tissue have been performed in a retrospective fashion, which limits the conclusions because of inherent study bias. If these micromanagers of cell processes are to be useful tools in the diagnosis or treatment of colon cancer, we will have to study them in well-designed prospective trials. It remains to be discovered if these types of molecular expression profiles will be used in clinical practice (Figure 1).

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ISSN 1007-9327
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