Journal of Molecular and Genetic Medicine

Huang et al., J Mol Genet Med 2017, 11:3
DOI: 10.4172/1747-0862.1000274

Review Article OMICS International

Circulating MicroRNAs in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) poses a serious threat to the health of global populations. Screening for the early detection of CRC is important to improve patient survival. Circulating microRNAs (miRNAs, miRs), as nucleic acid markers, play variety of important roles in early screening, diagnosis, TNM stage and prognosis of CRC. In this review, an overview covers recent researches on the roles of circulating miRNAs and their variety potential values correlated with CRC. Studies on the detectable marker values of circulating miRNAs for CRC will help making a global consensus of procedures and standardized protocols to make their clinical transformation more reliable.

Keywords: Colorectal cancer; Biomarkers; Circulating MiRNAs

Introduction

With increasing incidence, colorectal cancer (CRC) remains the second most common cancer in women and the third in men, despite the improved screening techniques, most patients diagnosed CRC are at late stage, CRC is the second leading cause of cancer-related death worldwide [1]. Complete tumor resection by surgery is the main therapeutic modality, it was reported that 5-year survival rates were in range from 93.2% for the earliest stage to 6.6% for advanced disease at diagnosis according to Duke's stage. So, good prognosis of CRC is linked to stage at earlier diagnosis. However, due to asymptomatic in early stage of CRC, many cases were detected at late stage. In clinical practice, colonoscopy is used in the diagnosis and treatment of CRC, but has not yet been wide-used as a screening tool because of some limitations, such as the requirements of bowel preparation, cost burden and perforation risk [2]. In addition, fecal occult blood test (FOBT), some convenient circulating blood biomarkers, including the most frequently used marker carcinoembryonic antigen (CEA), carbohydrate antigens, CA125, CA153 and CA199, are lack of sufficient sensitivity or specificity. For example, the specificity of FOBT is about 95%, while the sensitivity of is around 70% to 75% [3], the sensitivity and specificity of CEA is 60% and 34%, respectively [4]. Therefore, new strategies and novel biomarkers with the characters of detection, staging and prediction of outcome are highly desirable and being explored in order to make optimized treatment prescription and to improve prognosis for CRC patients.

A growing number of researches focus on small non-coding RNA molecules, microRNAs (miRNAs, miRs), which play multiple roles in variety of biological processes, including cancer [5-7]. Since 2008, tumor-derived miRNAs were described present stablely in circulating blood, as circulating-based markers for cancer detection [8]. Consider the detection of circulating miRNAs have the advantages of simple, inexpensive and noninvasive, combined with the remarkable stability characteristics of mature miRNAs due to the miRNA-Argonaute-protein complex, the discovery of circulating miRNAs as novel biomarkers for cancer intervention has been widely explored [9,10]. Growing evidences have indicated that aberrant expression of circulating miRNAs has an association with cancer including CRC. The diagnostic and prognostic value of circulating miRNAs exhibited in screening and monitoring, predicting recurrence or metastasis including lymph node, vessel, peritoneal invasion or distant metastasis, stratification by TNM stage or even histological differentiation grade, and few are associated with drug resistance, chemoradiosensitivity, tumor size and gender. This review covers recent researches in circulating miRNAs and their variety potential values correlated with CRC (Figure 1).

Experiment Flow

Experiment flow for the identification of CRC-related circulating miRNAs apply step-wise strategy. First experiment samples are selected according to different experimental purpose, microarray-based screening is used for expression profiling. Following is usually the training phase, after an extended scale validation by qRT-PCR, the results obtained from the screening phase are obtained. To the interesting results obtained from the training phase, qRT-PCR is used for further validation, correlation analysis is explored for identifying and verifying target miRNAs relevant to CRC.

Main circulating miRNAs in CRC diagnosis

Early diagnosis and surgical intervention is the most effective treatment and benefit for prognosis improvement of CRC patients. Review of previous studies, we recruited 35 of 46 articles encompassed more than 45 circulating miRNAs, which can be used as biomarker for discriminating CRC patients from control subjects (Table 1). Most miRNAs, including let-7a, let-7g, miR-15b, miR-17, miR-18a, miR-19a, miR-20a, miRNA-21, miR-23a, miR-24, miR-27a-3p, miR-29a, miR-106a, miR-125b, miR-133a, miR-139-3p, miR-141, miR-142-5p, miR-143, miR-152, miR-182, miR-193a-3p, miR-200c, miR-210, miR-221, miR-223, miR-320a, miR-338-5p, miR-372, miR-376c-3p, miR-378, miR-423-5p, miR-431, miR-1229, miR-1246 and miR-1290 were increased in plasma or serum source from CRC, while some miRNAs, including miR-26a-5p, miR-29b, miR-31, miR-142-3p, miR-181b, miR-194, miR-195, miR-601 and miR-760 were decreased in circulating blood of CRC than healthy participants. Interestingly, few miRNAs, such as miR-34a, miR-92, miR-145, miR-150, miR-203, presented contradictory results in different studies.

In a study blood samples of 63 CRC patients and 45 controls were collected, expression of 7 target miRNAs was measured using qRT-PCR, the results showed that miR-34a was significantly reduced in CRC [11].

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Received June 16, 2017; **Accepted** July 06, 2017; **Published** July 10, 2017

Citation: Huang Q, Ge B, Hu M, Zhou J, Bai X (2017) Circulating MicroRNAs in Colorectal Cancer. J Mol Genet Med 11: 274 doi:10.4172/1747-0862.1000274

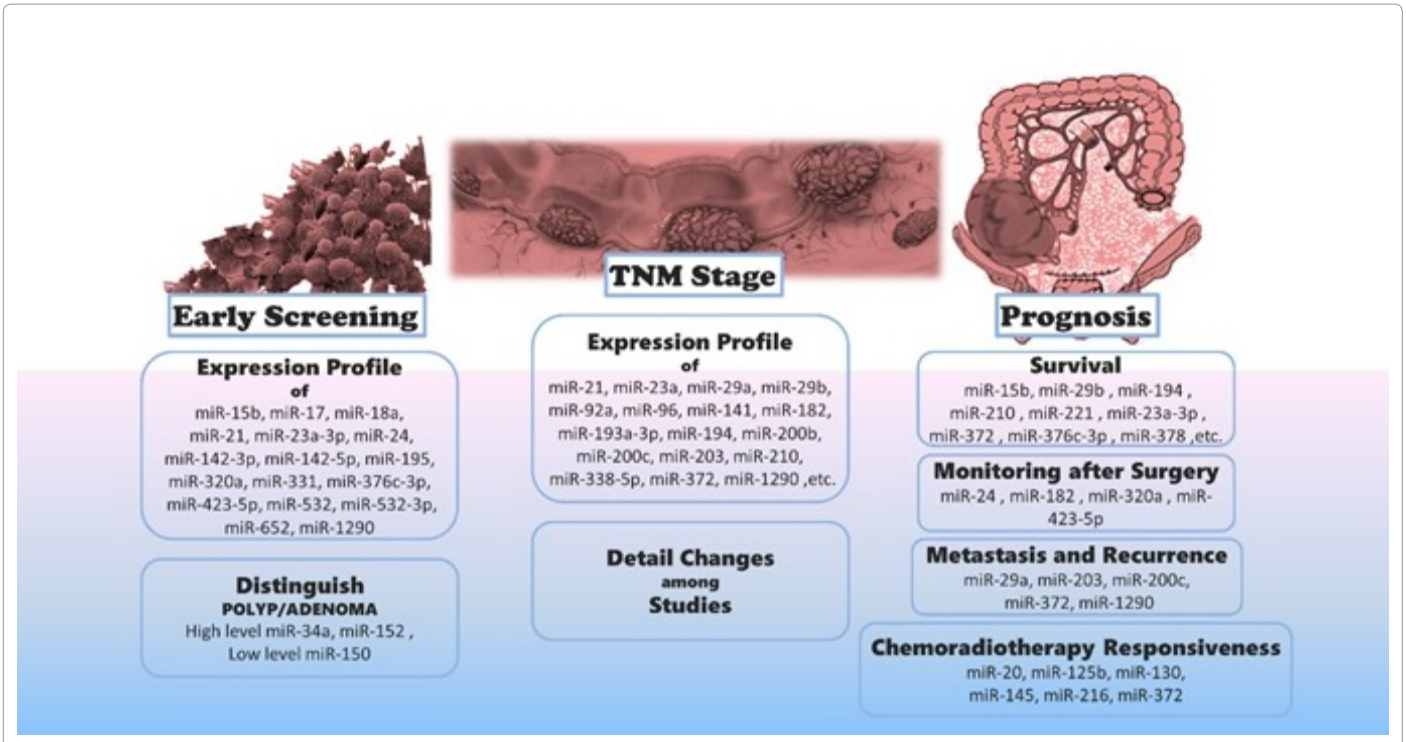

Figure 1: Circulating miRNAs and their variety potential values correlated with CRC.

miRNAs	Sources	Relationship	Country	Group	Aim	Assay	Objective	References
miR-203	serum	+	Japan	186 CRC, 24control	Prognosis	qRT-PCR	Human	[20]
miR-23a-3p, miR-27a-3p, miR-142-5p, miR-376c-3p	serum	+	Czech	427 colon cancer, 276 control	Diagnosis and Prognosis	Sequencing, RT-PCR	Human	[32]
miR-1290	serum	+	Japan	12 stage IV CRC, 12 adenoma, 12 control	Detection and Prognosis	microRNA array	Human	[25]
miR-15b	plasma	+	China	212 CRC, 156 control	Diagnosis and Prognosis	RT-PCR	Human	
miR-17, miR-19a, miR-20a, miR-223	serum	+	Egypt	30 CRC, 24 control	Diagnosis	miScript miRNA PCR	Human	
miR-125b	serum	+	Italy	34 CRC	Biomarker	qRT-PCR	Human	
miR-96, miR-203, miR-141, miR-200b	plasma	+	USA	40 CRC, 10 control	Prognosis	TaqMan Array	Human	[54]
miR-223, miR-92a	plasma	+	China	62 CRC, 62 control	Detection	multiplex qRT-PCR	Human	[16]
miR-194, miR-29b	serum	_	Iran	55 CRC, 55 control	Diagnosis and Prognosis	qRT-PCR	Huamn	
miR-210	serum	+	China	268 CRC, 102 control	Diagnosis and Prognosis	qRT-PCR	Human	
miR-21, miR-152	plasma	+	Chicago	31 CRC, 33 adenomatous polyps, 52 control	Diagnosis	RT-PCR	Human	[34]
miR-29, miR-92, miR-145, miR-195	plasma	+, -	Saudi	20 CRC	Diagnosis	qRT-PCR	Human	[19]
miR-372	serum	+	China	199 CRC/CPL, 30 control	Detection and Prognosis	qRT-PCR	Human	[24]
\miR-18b, miR-20a	plasma	+	Germany	42 rectal cancer	Chemoradiosensitivity Lymph Node Status	qPCR	Human	
miR-103, miR-720	serum	+	Japan	10 CRC	TNM Stage	Microarray qRT-PCR	Human	
miR-21, miR-29a, miR-125b	Serum	+	Japan	160 CRC, 77 control	Diagnosis	RT-PCR	Human	
miR-24, miR-320a, miR-423-5p	plasma	-	China	111 cancer, 59 adenoma 24 polyps, 29 IBD, 130 control	Diagnosis and Prognosis	qRT-PCR	Human	[29]
miR-21	serum	+	Australia	253 adenomatous colon polyps and control	Biomarker	PCR	Human	[28]
miR-21-5p	plasma	+	Italy	20 CRC, 20 control	Biomarker	EvaGreen ddPCR	Human	

miR-106a, miR-20a	blood	+	China	100 CRC, 79 control	Detection	qRT-PCR	Human	
miR-142-3p, miR-26a-5p	plasma	_	Iran	61 CRC, 24 control	Detection	qRT-PCR	Human	
miR-34a, miR-150	plasma	+, -	Czech	8 normal, 8 polyp, 16 adenoma, 8 stage I/II, 8 stage III/IV	Diagnosis	RT-PCR	Human	[12]
miR-199a-3p	serum	+	Japan	10 paired CRC	TNM Stage	microarray qRT-PCR	Human	
miR-21	serum	+	Iran	40 CRC, 40 control	Diagnosis and Prognosis	qRT-PCR	Human	[27]
miR-182	plasma	+	Italy	51CRC, 10 control	Prognosis	qRT-PCR	Human	
let-7a, miR-1229, miR-1246, miR-150, miR-21, miR-223, miR-23a	serum exosome	+	Japan	88 CRC, 11 control	Diagnosis	microarray qRT-PCR	Human	[46]
miR-200c	Serum	+	Japan	182 CRC, 42 control	Prognosis	qRT-PCR	Human	[56]
miR-21, let-7g, miR-31, miR-92a, miR-181b, miR-203	Serum	+, -	China	30 CRC, 30 control	Diagnosis	qRT-PCR	Human	[18]
miR-20, miR-130, miR-145, miR-216, miR-372	serum	nonresponder+	China	93 responders, 80 nonresponders	Chemosensitivity	array and qRT-PCR	Human	
miR-378	plasma	+	Italy	46 CRC, 70control	Prognosis	qRT-PCR	Human	
miR-21	serum	-	Spain	102 CRC	Prognosis	qRT-PCR	Human	
miR-431, miR-15b, miR-139-3p	plasma	+	USA	20CRC, 12 control, 9 adenoma	Diagnosis	RT-PCR	Human	
miR-92a	plasma	+	Japan	13 tumor, 13 control	Tumor Growth	qRT-PCR	Mice	[13]
miR-18a, miR-29a	serum	+	Spain	30 CRC, 26 control	Diagnosis	qRT-PCR	Human	
miR-193a-3p, miR-23a, miR-338-5p	blood	+	Malaysia	42 CRC, 18 control	Detection	microarray RT-PCR	Human	
miR-18a, -20a, -21, -29a, -92a, -106b, -133a, -143, 145	plasma	+	German	50 CRC, 50 control	Detection and Diagnosis	microRNA array qRT-PCR	Human	[36]
miR-29a	serum	+	Czech	100 CRC, 30 control	Detection in TNM Stage	qRT-PCR	Human	[52]
miR-34a	blood	-	Ireland	63 CRC, 45 control	Diagnosis	qRT-PCR	Human	[11]
miR-21	serum	+	China	174 cancer, 39 control	Diagnosis	RT-PCR	Human	
miR-21	plasma	+	USA	20 CRC, 20 control	Diagnosis	RT-PCR	Human	
miR-601, miR-760	plasma	-	China	90 CRC, 58 control	Detection	qRT-PCR	Human	[56]
miR-29a	serum	+	China	38 metastasis, 36 non-metastasis	Detection	RT-PCR	Human	
miR-141	plasma	+	China	102 CRC	Diagnosis and Prognosis	qRT-PCR	Human	[42]
miR-221	plasma	+	China	103 CRC, 37 control	Diagnosis and Prognosis	qRT-PCR	Human	
miR-29a, miR-92a	plasma	+	China	120 CRC, 37 adenoma, 59 control	Detection	qRT-PCR	Human	[17]
miR-92	plasma	+	China	90CRC, 50control	Diagnosis	RT-PCR	Human	[41]

Table 1: Potential circulating microRNA biomarkers for CRC.

Meanwhile, the result of a step-wise study yield plasma samples showed miR-34a was significantly up-regulated in CRC [12]. Another miRNA appeared contradictory was miR-92. Based on circulating plasma of mice bearing human colon cancer xenografts, the level of miR-92a was significantly increased [13]. A three-phase (marker discovery; marker selection and validation; large-scale validation) study showed miR-92 is significantly elevated in plasma of patients with CRC [14]. In a study of developing a multi-marker blood based test for diagnosis of CRC, miR-92a was found to be upregulated in pools of plasma samples of CRC patients compared with neoplasm-free controls [15]. Based on 62 paired-plasma samples, using stepwise approach, miR-92a was found over-expressed in CRC and performed best as biomarkers for detecting CRC [16]. Expression of 12 miRNAs in plasma samples was measured using RT-PCR, and the result showed that miR-92a was upregulated in patients with advanced colorectal neoplasia than healthy controls [17]. In a two-phase case-control test designed to identify serum miRNAs as candidate biomarkers for CRC diagnosis, miR-92a was down-regulated in CRC than control samples [18]. The similar contradictory results were also observed in the circulating miRNAs miR-145, miR-150 and miR-203[19-22].

Values of circulating miRNAs as diagnostic biomarkers

The serum or plasma miRNA (single or panel) to detect CRC yielded an area under the receiver operating characteristic curve (ROC) (AUC) value of 0.67-1.00, with a sensitivity of 47.5% to 100% and a specificity of 41% to 100%, some of which was more sensitive than biomarkers used in clinic, such as serum CEA was reported previously had 60% sensitivity and 34% specificity, the population level use of non-invasive stool DNA tests and the FOBT recommend by guidelines had sensitivities vary from 60% to 95% [23]. CEA, CA125 and CA199 have been reported with the restriction of low specificity and sensitivity, data from à single center study showed that the AUC of serum miRNA for

early CRC diagnosis was significantly higher than that of combined tumor markers (CEA, CA125 and CA199) (0.854 vs. 0.613) [24]. It was worth mentioning that serum miR-1290 could discriminate CRC patients from healthy control, yielded an AUC value of 1.00, sensitivity of 100%, specificity of 100% [25]. In this study designed step by step, the expression of serum miR-1290 was examined in 12 CRC patients, 12 adenoma patients and 12 healthy control subjects in the training step. The results showed higher levels of serum miR-1290 in CRC patients than healthy controls and adenoma patients ($p < 0.0001$ and 0.0027, respectively). ROC analyses showed that levels of serum miR-1290 could distinguish CRC patients from control subjects, with an AUC value of 1.00, sensitivity of 100% and specificity of 100%, furthermore, serum miR-1290 levels could effectively differentiate bewteen adenoma patients and control subjects, with an AUC value of 0.722, sensitivity of 50.0%, specificity of 100%. As a robust biomarker, there was a significant association between serum miR-1290 and aggression and invasion of CRC, moreover, high serum miR-1290 expression in CRC was associated with worse prognosis, tumor size, vessel invasion, T Stage, lymph node metastasis, liver metastasis, peritoneal metastasis, distant metastasis, and Tumor-Nodes-Metastasis (TNM) stage.

Circulating miRNAs in early screening

The above miRNAs in circulating can distinguish between CRC and normal controls. It is widely accepted that CRC mainly develop from precancerous lesions, i.e., polyps and adenomas after many transition stages of malignancy. It has been reported that if CRC patients were diagnosed at an early stage, more benefit would get from curative surgery [26]. As a result, circulating miRNAs aim to screen for the detection of CRC should have an efficiency at delineating the earlier lesions. Combined the above miRNAs, a unique serum or plasma expression profile of miR-15b, miR-17, miR-18a, miR-21, miR-23a-3p, miR-24, miR-142-3p, miR-142-5p, miR-195, miR-320a, miR-331, miR-376c-3p, miR-423-5p, miR-532, miR-532-3p, miR-652 and miR-1290 could distinguish benign colorectal polyp or adenoma lesions from healthy controls with good accuracy or high AUC values [27-33]. High levels of circulating miR-34a, miR-152 and low miR-150 levels were associated with the distinguish of patients with polyps or adenomas from those with CRC (AUC from 0.537 to 0.904) [34]. Distinguish the polyp or adenoma group from the normal group and the benign lesions group is important to improve patient survival and facilitate cancer prevention through the detection and removal of polyps or adenomas.

Circulating miRNAs in TNM stage

Currently, the TNM staging system is remain a useful tool for clinicians, which can be used to estimate tumor burden, guide curative surgical intervention and predict prognosis of patients. Many studies involved circulating miRNAs reported that there was an association between the aberrant expression profiles in circulating blood of CRC and TNM stage. In the previous studies involved in this review, more than 25 circulating miRNAs were reported had an association between clinical TNM stage (including separate analysis of depth of tumor invasion and lymph node status) of CRC and expression levels of circulating miRNAs. These miRNAs contained miR-15b, miR-18a, miR-18b, miR-20, miR-21, miR-23a, miR-29a, miR-29b, miR-92a, miR-96, miR-139-3p, miR-141, miR-152, miR-181b, miR-182, 193a-3p, miR-194, miR-200b, miR-200c, miR-203, miR-210, miR-338-5p, miR-372, miR-431, miR-601, miR-760 and miR-1290. However, the increasing or decreasing trend closely related with the advancement of cancer TNM I-IV stages existed in circulating miR-21, miR-23a, miR-29a, miR-29b, miR-92a, miR-96, miR-141, miR-182, 193a-3p, miR-194, miR-200b, miR-200c, miR-203, miR-210, miR-338-5p, miR-372 and miR-1290. The others were associated with either depth of tumor invasion or lymph node status, or between a certain stage and normal.

In terms of the same miRNA, inconsistent results were observed in different studies, such as miR-18a, miR-21 and miR-29a. Expression levels of serum miR-18a and miR-29a were able to distinguish stage III CRC patients from controls in a set of 30 CRC patients and 26 healthy controls [35]. In a study of validation set recruited 224 plasma cases in total from 80 CRC samples and 144 neoplasm-free individuals, higher expression levels of miR-18a, miR-21 and miR-29a were observed in the plasma of CRC samples than in neoplasm-free subjects, but lack of any significant association between the miRNAs and tumor stage [36]. In a study recruited 40 colorectal adenocarcinoma patients and 40 control subjects, expression levels of serum miR-21 were measured using qRT-PCR assay, the results showed high expression level of serum miR-21 was associated with high clinical stages in the patients. Similar results were found in miR-29a in a study recruited 100 sera of patients with CRC and 30 sera of healthy donors [37]. Some miRNAs can distinguish TNM stage in CRC tissue samples, but failed in circulating miRNAs. Take miR-92a as an example, though miR-92a was previously reported to be correlate with TNM stage as to the relationship between the clinicopathologic characteristics and miR-92a expression, based on plasma from 90 patients with CRC, miR-92 levels of individual tumor stage had significant differences when compared to the controls, but it did not vary significantly across the stage in another study [38]. It has been reported that the 5-year survival rate range from 93.2% for stage I to 8.1% for stage IV. Consequently, a reliable treatment plan according to TNM stage may lead to vastly different clinical outcomes [39]. As a more convenient and accurate diagnostic tool, circulating miRNAs have the potential to positively link early diagnosis and treatment of CRC to higher patient survival rates.

Circulating miRNAs related to prognosis

The quality of life is closely related to prognosis of patients with CRC. Besides circulating miRNAs related to TNM staging system, which currently be used as a tool for predicting prognosis and survival. Several circulating miRNAs have been proposed and verified to be used as an important predictive parameter, through which can improve patients' quality of life by choosing the best combination of treatment modalities, such as surgery, radiation, and/or chemotherapy. Researches about circulating miRNAs independent of TNM stage related to prognosis may focus on predict postoperative survival, early recurrence and metastasis. Kaplan–Meier curve was used for overall survival, relapse free survival and disease free survival analysis according to the levels of circulating miRNAs, such as miR-15b, miR-29b, miR-194, miR-210, miR-221, miR-23a-3p, miR-372, miR-376c-3p and miR-378, aberrant expression led to a worse survival. Based on the difference of preoperative and postoperative expression levels of circulating miRNAs, take miR-24, miR-182, miR-320a and miR-423-5 as examples, circulating miRNAs will be provided with potential prognosis values for CRC progression monitoring after surgery. As important prognostic related factors, metastasis and recurrence are major cause of deaths in patients with CRC, based upon logistic regression analysis, Cox proportional hazards regression analyses and ROC analysis, miR-29a, miR-203, miR-200c, miR-372 and miR-1290 were reported as potential biomarkers. Moreover, the application of pre- and post-operative chemoradiotherapy was also factors influencing the prognosis of patients, circulating miR-20, miR-125b, miR-130, miR-145, miR-216 and miR-372 had been reported to be used as predictive biomarker of the chemoradiotherapy responsiveness.

Discussion

It has been estimated that over 95% CRC patients will benefit from

radical operation to the cases diagnosed at early stage. Several early detection procedures by colonoscopy, barium enema, stool- and blood-based tests have been widely used in clinic, due to the restriction of low specificity and sensitivity and invasive nature, the minimally invasive blood based test appears to be more attractive. Circulating miRNAs are stable owing to protection from endogenous ribonuclease, with the superiority characteristics of ease to detect, relative noninvasive and reliable, make these molecules potential to be candidates as biomarkers to reflect various states in CRC progression [40]. Numerous circulating miRNAs have been reported and being explored in identifying as screening, diagnostic and prognostic biomarkers for CRC, but few have moved into clinical translation and widely available in the clinic, before entering clinical arena, numerous obstacles need to be overcome [41].

It has been suggested that tumor-derived miRNAs can be present in circulation based on the variation of circulating miRNAs' expression level pre- and post-operation, reflect from the expression levels of circulating miRNAs down-regulated after surgical resection of primary tumors. However, the expression level of the same miRNA is not always inconsistent in tissues with that in circulating system. In a study of miR-141 predicts prognosis as circulating biomarker, plasma level of miR-141 was significantly higher in CRC patients than in controls, but the results also showed that miR-141 level was not significantly higher in tumor specimens than in paired adjacent normal controls [42]. It has also been suggested that miRNAs are secreted from tumor-independent cells, such as immune and inflammatory cells, which occur coincidentally at primary lesions, or secreted into body fluids, including blood, urine, and so on, via be packaged into exosomes [43-46]. To the pathways of miRNAs into circulating system, several studies demonstrated that different potential ways, such as direct leakage passive from broken tumor cell, regulation of chemokines expression and function in tumor microenvironment, selective activation and secretion, similar to the release of cytokines and hormones, microvesicle-embedded secretion [47-50].

Limit the clinical application of circulating miRNAs is also reflected in the inconsistent results. Tracing it to the cause of these conflicting conclusions of circulating miRNAs in diagnosis, early screening, TNM stage and prognosis, may be attributed to the following factors: (1) genetic variations among different region, ethnic groups and different environmental and dietary factors, (2) difference of sample collection procedures or processing conditions, the source choice of plasma, serum or whole blood (3) uniform inclusion and exclusion criteria of subjects (i.e., early or late stages of cancers) to the same research purpose (diagnosis or TNM stage), (4) usage of pooled samples, (5) different internal controls including miR-16, RNU6B or cel-miR-39, and variety ways of data normalization and analysis in the quantification of RNA levels with qRT-PCR, (6) different miRNA expression levels between tissue and plasma, (7) sample size, screening method, and so on [51-56].

Another limitation with the use of circulating miRNAs as biomarkers is that they are not unique for CRC, but act as broad-spectrum biomarker for many other cancers or non-oncological diseases, such as lung, gastric, ovarian, pancreatic cancers and ulcerative colitis. Therefore, an effective and special diagnostic method should be considered for the clinical application target CRC.

Conclusion

This review examines issues and advantages of afflicted circulating miRNAs as biomarkers for CRC. Highlight the clinical significance need a global consensus of procedures and standardized protocols to make their clinical transformation more reliable.

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Citation: Huang Q, Ge B, Hu M, Zhou J, Bai X (2017) Circulating MicroRNAs in Colorectal Cancer. J Mol Genet Med 11: 274 doi:10.4172/1747-0862.1000274