Hindawi
Disease Markers
Volume 2019, Article ID 2587109, 13 pages
https://doi.org/10.1155/2019/2587109

Review Article

Circulating Noncoding RNAs Have a Promising Future Acting as Novel Biomarkers for Colorectal Cancer

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Received 31 December 2018; Revised 23 April 2019; Accepted 21 May 2019; Published 3 June 2019

Academic Editor: Monica Cantile

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, causing a large number of cancer-related deaths each year. Patients are usually diagnosed at advanced and incurable stages due to the lack of suitable screening methods for early detection. Noncoding RNAs (ncRNAs), including small and long noncoding RNAs (lncRNA), are known to have significant regulatory functions, and accumulating evidence suggests that circulating ncRNAs have potential applications as noninvasive biomarkers for diagnosing CRC, evaluating its prognosis, or predicting chemosensitivity in the general population. In this review, we summarize the origins of circulating ncRNAs and provide details of single and multiple circulating ncRNAs that might have roles as diagnostic and prognostic biomarkers in CRC. We end by discussing circulating ncRNAs that may distinguish patients with resistance to chemotherapy.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors of the gastrointestinal tract and the third most commonly diagnosed cancer in men and the second in women worldwide [1, 2]. Therapeutic methods have improved and new techniques have been developed, but survival rates for CRC patients are still below our expectations as they are usually diagnosed at an advanced stage [3]. Therefore, population-based early screening for CRC detection might help reduce incidence and improve patient survival [4]. Colonoscopy is the current gold standard for CRC detection, but it is not very suitable for population-wide CRC screening because it is invasive and expensive and capacity requirements cannot be met [5, 6].

Hence, it would be useful to discover novel and accurate biomarkers for screening CRC using a less invasive procedure. Recently, blood-based biomarkers such as circulating noncoding RNAs (ncRNAs) have been the subject of intense research since blood samples are easier to retrieve and more acceptable than colonoscopy for patients.

ncRNAs include microRNAs (miRNAs), long noncoding RNAs (lncRNAs), piwi-interacting RNAs (piRNAs), and transfer RNAs (tRNAs), all with no capacity to encode proteins [7–10]. In particular, miRNAs and lncRNAs have been the most widely studied ncRNAs in recent decades. miRNAs are small ncRNAs with approximately 22 nucleotides that can regulate human genes by binding to the $3'$ untranslated region of the target message RNAs [11, 12]. lncRNAs, comprising more than 200 nucleotides, are involved in a wide range of biological processes and diseases including cancer development and metastasis, even though they lack an open reading frame [13–17]. Both miRNAs and lncRNAs can be detected in plasma or serum samples, and they may potentially act as circulating biomarkers for diagnosis, prognosis, and chemosensitivity in various types of cancer. For example, miR-21 was significantly upregulated in pancreatic ductal adenocarcinoma (PDAC) plasma samples compared with healthy controls. The expression of plasma miR-21 was associated with advanced stage, lymph node metastasis, liver metastasis (LM), and poor survival in PDAC patients; patients with higher plasma miR-21 have worse outcome

[18]. Additionally, H19 is a well-known lncRNA found upregulated in the plasma of gastric cancer patients. H19 levels were also reduced in postoperative samples compared with preoperative samples [19]. Moreover, a panel of five miRNAs (miR-20a, miR-130, miR-145, miR-216, and miR-372) might be potential serum biomarkers for predicting the response to oxaliplatin-based chemotherapy [20].

In this review, we summarize the origins of circulating ncRNAs and discuss the current knowledge regarding their potential roles as novel diagnostic, prognostic, and chemosensitive predictive biomarkers, which may improve the effectiveness of treatments and reduce patient mortality.

2. Origins of Circulating ncRNAs

Most studies indicate that ncRNAs are released into the circulation via three possible mechanisms:

(1) Membrane-bound vesicles such as exosomes and microvesicles are the major origin of circulating ncRNAs. These vesicles can participate in cell-cell communication by transferring ncRNAs [21–24]. Exosomes and microvesicles can carry several types of ncRNAs when released from donor cells via membrane blebbing [21, 23, 25]. Studies have shown that exosomes can transfer miRNAs to target cells and protect miRNAs from RNases in the circulation [24]. When these vesicles are received by recipient cells, the ncRNAs can participate in modulating cellular functions, such as angiogenesis, hematopoiesis, exocytosis, and tumorigenesis [21].

(2) Apoptotic bodies can also be the source of circulating ncRNAs. When apoptosis occurs, cell fragments from dying cells are transported in apoptotic bodies, which are engulfed by neighboring living cells via phosphatidylserine signaling. Several miRNAs are carried within the apoptotic bodies when they are released into the circulation [26, 27]. In particular, miR-126 is highly enriched in apoptotic bodies, so uptake of apoptotic bodies by recipient cells can cause transfer of miR-126 which then regulates sprouty-related protein 1, vascular cell adhesion molecule-1, and CXCL12 [26].

(3) RNA-binding proteins (RBPs) can regulate gene expression and are another possible source of circulating ncRNAs. RBPs participate in several components of the messenger RNA (mRNA) maturation process, including pre-mRNA splicing and mRNA export, localization, and translation [28, 29]. Some of the proteins that bind with ncRNAs include high-density lipoproteins (HDLs) and Argonaute 2 (Ago2) [30, 31]. Studies indicate that HDL complexes can transport miRNAs and deliver them to target cells with functional capabilities [30]. Circulating miRNAs such as miR-16, miR-92a, and miR-122 are also present in nonvesicular Ago2 complexes, and it has been suggested that these complexes are responsible for the stability of circulating miRNAs [31].

Research indicates that ncRNAs exhibit high stability in the circulation. Due to their protection in exosomes, microvesicles, apoptotic bodies, and protein complexes, circulating ncRNAs are resistant to harsh conditions such as high temperatures, extremes pH values, or long-term frozen storage [31–35]. Thus, circulating ncRNA concentrations are stable, allowing them to serve as potential biomarkers for several diseases, including CRC [33, 36, 37].

3. Circulating ncRNAs for Diagnostic and Early Screening in CRC

3.1. Single Circulating miRNAs as Diagnostic and Early Screening Biomarkers. miR-21 acts as an oncogene in several cancers [38–40], and a clear upregulation of miR-21 was found in CRC plasma [41, 42]. In a training set comprising 30 CRC patients and 30 healthy controls, the area under the receive operating characteristic (ROC) curve (AUC) value for miR-21 was 0.820 (sensitivity: 90.0%, specificity: 90.0%). In a test set containing 20 CRC patients and 20 healthy controls, the AUC value was 0.910 [41]. This association was supported by Liu et al. who found increased miR-21 in serum from CRC patients compared with colorectal advanced adenoma (CAA) patients and healthy controls, yielding an AUC value of 0.802 with a sensitivity of 65.0% and specificity of 85.0% [43]. Moreover, serum exosomal miR-21 levels could also be used for screening early CRC [44].

A group of 353 individuals (111 CRC patients, 29 inflammatory bowel disease (IBD) patients, 83 patients with benign lesions, and 130 healthy controls) participated in a study where three miRNAs (miR-24, miR-320a, and miR-423-5p) were measured, and all were decreased significantly in CRC plasma samples compared with IBD patients and controls. When miR-24, miR-320a, and miR-423-5p were used to distinguish CRC from controls, the AUC values were 0.822, 0.897, and 0.839, respectively. When these miRNAs were employed to distinguish between CRC and IBD, the AUC values for miR-24 and miR-320a were 0.974 and 0.990, respectively. Furthermore, miR-320a and miR-423-5p both decreased during the progression of colorectal disease from IBD to CRC [45].

Another study also found that circulating miRNAs could separate malignant and benign diseases from healthy controls. In a cohort of 90 CRC patients, 43 CAA patients, and 58 controls, plasma miR-760 and miR-601 levels could differentiate CRC patients from healthy controls with AUC values of 0.788 and 0.747, respectively. The AUC values were 0.682 for miR-760 and 0.638 for miR-601 when discriminating CAA patients from healthy controls. Importantly, both miRNAs decreased in the plasma during CRC progression. Patients with TNM stage IV had significantly lower plasma levels of miR-760 and miR-601 than those with stage I. In addition, ROC curve analysis showed that combining miR-601 and miR-760 with CEA improved diagnostic sensitivity from 29.4% to 80.4% with an AUC of 0.805 [36].

Other circulating miRNAs and their diagnostic value for CRC are listed in Table 1.

3.2. Single Circulating lncRNAs as Diagnostic and Early Screening Biomarkers. Colon cancer-associated transcript 2 (CCAT2) is located at the 8q24 region, and its genomic locus encompasses the SNP rs6983267 which is closely associated with increased risks for many cancers [46, 47]. CCAT2 is overexpressed in many cancer tissues, and it participates in tumor cell proliferation, invasion, and motility [48–50]. Compared with microsatellite-unstable CRC tissues or normal mucosae which lack the chromosomal instability, the expression level of CCAT2 is higher in microsatellite-stable CRC tissues which exhibit chromosomal instability. In addition, CCAT2 can regulate Wnt signaling via the TCF7L2 protein and also regulates the nearby gene MYC via *cis* signaling [51]. Wang et al. found higher circulating CCAT2 in CRC patient serum and exosomes than in healthy subjects. CCAT2 might be protected by exosomes and act as a novel diagnostic biomarker for predicting CRC [52].

HNF1A-AS1 was shown to be upregulated in various cancers including gastric [53], lung [54], and hepatocellular cancers [55]. The expression of HIF1A-AS1 in serum samples from 151 patients with CRC was higher than in samples from 160 healthy individuals. The diagnostic value was very high at 0.960 (sensitivity: 86.8%, specificity: 92.5%). In addition, serum HIF1A-AS1 levels were strongly associated with differentiation degree, tumor size, T stage, N stage, M stage, and TNM stage [56].

NEAT1 was shown to be overexpressed in CRC serum and cancer tissues compared with healthy controls and matched NATs. ROC curve analysis indicated the discriminatory power of NEAT1 levels in tissues with an AUC value of 0.810 [39]. In serum samples, NEAT1 was significantly elevated in 56 CRC patients compared with controls, and the AUC value was 0.947 [57]. Considering the diagnostic relevance of NEAT1, future studies should expand the sample size to hundreds of individuals in further multicenter studies for possible clinical applications.

Colorectal Neoplasia Differentially Expressed (CRNDE), which was originally found aberrantly expressed in CRC, is upregulated in a number of malignant cancers such as pancreatic, lung, and hepatocellular cancers [58–60]. It can promote cell proliferation and chemoresistance by regulating Wnt/β-catenin signaling via miR-181a-5p in CRC [61]. CRNDE is located at human chromosome 16 and many splice variants have been identified, one of which called CRNDE-h was shown to effectively distinguish between colorectal malignancies, benign diseases, and healthy individuals. Serum exosomal CRNDE-h levels were significantly upregulated in CRC patients compared with patients with IBD, hyperplastic polyps, adenoma, or healthy controls. The AUC value was 0.892 for distinguishing CRC patients from a group containing 80 benign disease patients and 80 controls (sensitivity: 70.3%, specificity: 94.4%). The diagnostic value of CRNDE-h was better than that of the conventional tumor biomarker CEA, which alone had an AUC value of 0.688 (sensitivity: 37.16%, specificity: 88.75%). The AUC value improved significantly to 0.913 when exosomal CRNDE-h levels were combined with CEA. The origin of exosomal CRNDE-h has been explored. It was shown that exosomal CRNDE-h could enter the cell culture medium and that expression was clearly elevated in five CRC cell lines (HCT116, SW620, SW480, HT29, and LoVo). Second, the presence of a tumor led to a marked increase in the serum exosomal CRNDE-h level in a xenograft mice model. Third, CRNDE-h expression levels measured in serum samples and matched CRC tissues showed a moderately significant correlation. Finally, serum exosomal CRNDE-h levels were significantly lower in postoperative samples compared with preoperative samples. These findings suggest that the exosomal CRNDE-h detected in the serum is mainly released or leaked from tumor cells. Thus, exosomal CRNDE-h may be a novel serum-based tumor marker for the diagnosis of CRC [62]. Besides CRNDE-h, another splice variant of CRNDE named CRNDE-p might also be a diagnostic biomarker. Yu et al. indicated that serum exosomal CRNDE-p from 410 CRC patients was higher than that in 58 adenoma patients or 175 healthy subjects. The AUC for CRNDE-p discriminating CRC patients from adenoma patients is 0.854, and the AUC is 0.882 when combining serum exosomal CRNDE-p and the traditional biomarker CEA. In addition, high expression of CRNDE-p is closely associated with advanced T stage lymph node metastasis and clinical stages. This suggests that serum exosomal CRNDE-p might be a novel diagnostic biomarker, especially when combined with the traditional biomarker CEA [63].

Hu et al. isolated plasma exosomes by ultracentrifugation from 10 CRC patients and 10 healthy individuals then used microarray to find lncRNAs with differential expression. Among the 1705 significantly differential lncRNAs, they chose the six lncRNAs with the largest increase in expression (LNCV6_116109, LNCV6_98390, LNCV6_38772, LNCV6_108266, LNCV6_84003, and LNCV6_98602) for subsequent analysis. In a larger cohort consisting of 50 CRC patients and 50 healthy subjects, researchers found that the expression levels of all six lncRNAs are significantly higher in CRC than in healthy individuals. These six plasma exosomal lncRNAs might serve as potential biomarkers for early CRC detection. All six lncRNAs are obviously higher in CRC patients with stage I/II than in healthy subjects. AUC values for LNCV6_116109, LNCV6_98390, LNCV6_38772, LNCV6_108266, LNCV6_84003, and LNCV6_98602 are 0.8052, 0.7088, 0.7460, 0.7292, 0.7356, and 0.6800, respectively [64].

ZNFX1 antisense RNA1 (ZFAS1) has been reported to be overexpressed and involved in cell proliferation and metastasis in many cancers [65–67]. Additionally, studies demonstrate that SP-1 can induce ZFAS1 and promote cell cycle progression via the miR-150-5p/VEGFA axis [68]. ZFAS1 also acts as an oncogene by destabilizing p53 and its interactions with the CDK1/cyclin B complex, finally regulating the cell cycle and inhibiting apoptosis in CRC [69]. Fang et al. examined expression levels of ZFAS1 in plasma samples from 105 patients with CRC and 95 healthy subjects and found that ZFAS1 is higher in plasma samples from CRC patients, similar to its change in tissues. When the optimal cutoff value is 10.84, ZFAS1 has an AUC of 0.88 and sensitivity and specificity of 92.38% and 76.84%, respectively. Moreover, its

Table 1: Single circulating ncRNA as diagnostic and early screening biomarkers for CRC.

ncRNAs	Body fluid	Dysregulation	Numbers of CRC	Numbers of healthy control	AUC	Sensitivity	Specificity	Reference
miR-21	Plasma	↑	50	50	0.91	90%	90%	[41]
	Serum	↑	200	80	0.802	65%	85%	[43]
	Serum	↑	200	80	0.786	65.5%	82.5%	[43]
miR-92a	Plasma	↑	120	115	0.885	89%	70%	[108]
	Plasma	↑	120	59	0.838	84.0%	71.2%	[109]
miR-29a	Plasma	↑	120	59	0.844	69.0%	89.1%	[109]
miR-18a	Plasma	↑	78	86	0.804	73.1%	79.1%	[110]
miR-200c	Plasma	↑	78	86	0.749	64.1%	73.3%	[110]
miR-20a	Plasma	↑	100	79	0.59	46.00%	73.00%	[111]
miR-106a	Plasma	↑	100	79	0.605	74.00%	44.40%	[111]
miR-199a-3p	Serum	↑	114	32	0.644	47.60%	75.00%	[112]
miR-223	Serum	↑	130	60	0.838	—	—	[113]
miR-372	Serum	↑	165	30	0.854	81.9%	73.3%	[114]
miR-103	Serum	↑	124	32	0.662	55.9%	75.0%	[115]
miR-720	Serum	↑	124	32	0.63	58.3%	56.3%	[115]
miR-155	Serum	↑	146	60	0.776	58.2%	95.0%	[116]
miR-378	Plasma	↑	65	70	0.796	—	—	[117]
miR-23a	Serum (exosome)	↑	101	19	0.953	—	—	[44]
miR-150	Serum (exosome)	↑	101	19	0.758	—	—	[44]
miR-223	Serum (exosome)	↑	101	19	0.716	—	—	[44]
miR-1246	Serum (exosome)	↑	101	19	0.948	—	—	[44]
miR-221	Plasma	↑	103	37	0.606	86.00%	41.00%	[118]
miR-24	Plasma	↓	111	130	0.839	78.38%	83.85%	[45]
miR-320a	Plasma	↓	111	130	0.886	92.79%	73.08%	[45]
miR-423-5p	Plasma	↓	111	130	0.833	91.89%	70.77%	[45]
miR-601	Plasma	↓	100	68	0.747	69.2%	72.4%	[36]
miR-760	Plasma	↓	100	68	0.788	80.0%	72.4%	[36]
miR-194	Serum	↓	55	55	0.85	72%	80%	[119]
miR-29b	Serum	↓	55	55	0.87	77%	75%	[119]
miR-139-3p	Serum	↓	117	90	0.9935	96.60%	97.80%	[120]
miR-375	Plasma	↓	94	46	0.7489	76.92%	64.62%	[121]
miR-145	Serum	↓	25	10	0.78	80%	68%	[122]
HIF1A-AS1	Serum	↑	151	160	0.96	86.80%	92.5%	[56]
CRNDE-h	Serum (exosome)	↑	148	300	0.892	70.3%	94.4%	[62]
CRNDE-p	Serum (exosome)	↑	410	175	0.854	0.854	—	[63]
HOTAIRM1	Plasma	↓	150	101	0.78	64.0%	76.5%	[71]
ZFAS1	Plasma	↑	105	95	0.88	92.38%	76.84%	[70]
GNAT1-1	Plasma	↓	62	37	0.72	—	—	[72]
BLACAT1	Serum	↑	30	30	0.858	83.3%	76.7%	[123]
CCAT2	Serum (exosome)	↑	100	—	—	—	—	[52]
GAS5	Plasma (exosome)	↓	158	173	0.875	—	—	[76]
LNCV6_116109	Plasma (exosome)	↑	50	50	0.8052	—	—	[64]
LNCV6_98390	Plasma (exosome)	↑	50	50	0.7088	—	—	[64]
LNCV6_38772	Plasma (exosome)	↑	50	50	0.7460	—	—	[64]
LNCV6_108266	Plasma (exosome)	↑	50	50	0.7292	—	—	[64]
LNCV6_84003	Plasma (exosome)	↑	50	50	0.7356	—	—	[64]
LNCV6_98602	Plasma (exosome)	↑	50	50	0.6800	—	—	[64]

Note: ↑, upregulated; ↓, downregulated; —, not mentioned. HIF1A-AS1, hypoxia-inducible factor 1 alpha-antisense RNA 1; CRNDE, colorectal neoplasia differentially expressed; HOTAIRM1, HOX antisense intergenic RNA myeloid 1; GNAT1-1, G protein subunit α transducin 1; BLACAT1, bladder cancer-associated transcript 1; ZFAS1, ZNFX1 antisense RNA1; GAS5, growth arrest specific transcript 5; CCAT2, colon cancer-associated transcript 2.

positive predictive value and negative predictive value are 80.70% and 84.88%, respectively [70]. Thus, ZFAS1 shows potential as a diagnostic biomarker.

HOTAIRM1 is located between the human HOXA1 and HOXA2 genes, and its level was shown to be lower in CRC plasma samples compared with controls. In a training set of 100 CRC patients and 67 controls, the AUC value was 0.780 (specificity: 80.3%, sensitivity: 61.5%). In the validation set comprising 50 CRC patients and 34 controls, the AUC value was 0.771 (specificity: 76.5%, sensitivity: 64.0%) [71].

GNAT1-1 was found downregulated in CRC tissues and plasma samples compared with matched NATs and healthy controls. Lower GNAT1-1 expression was associated with more advanced stages, and patients with TNM stages III and IV have significantly lower plasma GNAT1-1 levels than those with stages I and II. Moreover, GNAT1-1 could discriminate CRC patients from controls with an AUC value of 0.720 [72].

GAS5 is downregulated in CRC tissues compared with matched NATs. Some previous results indicated that GAS5 can inhibit CRC progression via the miR-182-5p/FOXO3a axis and the Wnt/β-catenin signaling pathway [73–75]. In a recent study, Liu et al. found that GAS5 is downregulated in CRC tissues, plasma, and exosomes, with an AUC for tissue GAS5 levels distinguishing CRC and NATs of 0.791 and GAS5 in plasma and exosomes distinguishing 158 patients with CRC and 173 healthy subjects with AUC values of 0.875 and 0.964, respectively [76]. Further research confirms this result, demonstrating an obvious decrease in GAS5 levels in the serum of CRC patients between 109 CRC patients and 99 healthy subjects [77]. These results suggest that GAS5 might be intimately involved in CRC and acts as a biomarker for CRC screening.

Other circulating lncRNAs and their diagnostic values are listed in Table 1.

3.3. Panels of Circulating miRNAs and lncRNAs as Diagnostic and Early Screening Biomarkers. In addition to the single circulating ncRNAs reviewed above, studies have also combined different circulating ncRNAs into panels for detecting CRC. Combinations of several ncRNAs have better diagnostic value than single biomarkers [78]. Based on a cohort comprising control, CRC, CAA, breast cancer, pancreatic cancer, and lung cancer samples, Carter et al. identified some uniquely dysregulated miRNAs specifically for screening CRC. Four miRNAs (miR-21, miR-29c, miR-346, and miR-374a) could distinguish between healthy controls or patients with any type of neoplasia with an AUC of 0.91. Four miRNAs (miR-21, miR-29c, miR-372, and miR-374a) were analyzed in patients with neoplasms, and the AUC value was 0.79 when discriminating patients with colorectal neoplasm from other neoplasms. Subsequently, miR-29c, miR-122, miR-192, and miR-374a were used to distinguish whether patients had CRC or CAA, with an AUC value of 0.98 [79].

Considering the diagnostic relevance of this miRNA signature, further studies are merited before clinical applications. In another study, four plasma miRNAs (miR-21, miR-25, miR-18a, and miR-22) were identified as CRC biomarkers. The combination of these four miRNAs could clearly distinguish CRC patients from controls, with an AUC value of 0.93 (sensitivity: 67%, specificity: 90%) [80]. A microRNA expression profiling assay was used for screening biomarkers to distinguish CRC, CRC precursor lesions, and healthy individuals. Total RNA was obtained from 21 patients with CRC, 20 patients with CAA, and 20 healthy controls for microRNA profiling. Six miRNAs (miR-29a, miR-18a, miR-19a, miR-19b, miR-15b, and miR-335) were significantly upregulated in CRC plasma samples compared with healthy controls. Combining miR-19a and miR-19b showed an AUC value of 0.8194, with sensitivity and specificity of 78.57% and 77.36%, respectively. Combining miR-15b with these two miRNAs increased the discriminative capacity, with an AUC value of 0.8356 (sensitivity: 78.6%, specificity: 79.3%) [78].

Wang et al. combined up- and downregulated miRNAs and established a diagnostic panel for CRC screening. miR-21 and let-7g were both upregulated in CRC serum samples, whereas miR-92a, miR-31, miR-181b, and miR-203 were all downregulated. In a training set comprising 30 CRC patients and 30 healthy controls, this panel of six miRNAs yielded an AUC value of 0.900. Subsequent validation obtained an AUC value of 0.923 when distinguishing 83 CRC patients and 59 controls [81].

Plasma expression levels of HOTAIR and CCAT1 were found to be remarkably upregulated in CRC patients compared with healthy individuals. Combining these two lncRNAs increased diagnostic performance, with an AUC value of 0.954 (sensitivity, 84.3%; specificity, 80.2%). Additionally, the diagnostic positivity rate when combining HOTAIR with CCAT1 for CRC in stage I/II was 85% [82].

Dysregulated lncRNAs were investigated in CRC tissues using genome-wide lncRNA microarrays, and their expression levels were then validated in 80 cancer tissues and 120 serum samples. A panel of four lncRNAs (lnc-BANCR, lnc-NR-026817, lnc-NR-029373, and lnc-NR-034119) obtained an AUC value of 0.881 when discriminating CRC patients and controls (sensitivity: 89.2%, specificity: 75.8%). The corresponding AUC values obtained using this panel for CRC patients with TNM at stage I, stage II, and stage III were 0.774, 0.844, and 0.949, respectively [35].

In another study, Wang et al. found that a three-lncRNA signature could play as a diagnostic marker for CRC screening via stepwise regression analysis. First, they found that 13 of the 17 candidate CRC or gastrointestinal cancer-associated lncRNAs were detectable in a small cohort. Second, five of the 13 lncRNAs were found with significant differential abundance in 30 preoperative CRC patients and 31 healthy individuals. Third, these five lncRNAs were further evaluated in additional serum samples from 30 CRC patients and 30 healthy individuals. Finally, all data from the second and third steps were pooled and analyzed, with results indicating that RP11-462C24.1, LOC285194, and Nbla12061 were significantly upregulated in serum from CRC patients. The AUC value of combining RP11-462C24.1, LOC285194, and Nbla12061 was 0.793 (sensitivity: 68.3%, specificity: 86.9%), obviously higher than that of CEA, CA199, CA125, and CA724. When these three lncRNAs were combined with CEA, CA199, CA125, or CA724, the AUC values further

improved to 0.845, 0.855, 0.798, or 0.824, respectively. Furthermore, expression of the three lncRNAs was significantly reduced after surgery. These results suggest that this combination of three lncRNAs in serum represents a new supplementary method for CRC screening [37]. Panels of circulating miRNAs and lncRNAs that act as diagnostic biomarkers are listed in Table 2.

4. Circulating ncRNA as Recurrence and Survival Evaluation Biomarkers in CRC

4.1. Single Circulating miRNAs as Recurrence and Survival Evaluation Biomarkers. Increased serum miR-21 strongly correlated with poor survival in CRC patients, and it might serve as an independent prognostic factor for overall survival (OS). Furthermore, elevated miR-21 expression in serum samples correlated with tumor size and distant metastases [83]. The same result was obtained by Yin et al. who found elevated serum miR-21 levels in patients with LM and other organ metastasis [84]. Similarly, another study showed that increased exosomal miR-21 in CRC plasma samples significantly correlated with advanced TNM stage and LM. Patients with high levels of exosomal miR-21 had poor OS and relapse-free survival (RFS). Furthermore, plasma exosomal miR-21 levels could serve as an independent prognostic factor for OS and disease-free survival (DFS) in TNM stage II and III patients, and OS in TNM stage IV patients [85]. miR-200c was significantly elevated in TNM stage IV serum samples compared with TNM stage I. High serum miR-200c levels were significantly associated with poor OS, DFS, positive lymph nodes, and LM. miR-200c could serve as an independent prognostic factor for lymph node metastasis, tumor recurrence, and poor OS in CRC patients [86].

Similarly, Hur et al. indicated that miR-885-5p was a significantly upregulated miRNA in the LM group compared with the pCRC group. miR-885-5p expression levels significantly correlated with lymph node metastasis, distant metastasis, and LM. Furthermore, patients with higher serum miR-885-5p expression levels had poor OS and DFS [87]. miR-885-5p might serve as a potential biomarker for CRC prognosis. Yuan et al. demonstrated that miR-183 was significantly overexpressed in CRC plasma samples, and patients with elevated expression levels of miR-183 had a high risk of tumor recurrence. In addition, miR-183 expression could serve as an independent prognostic factor for OS in CRC patients. High plasma miR-183 levels were significantly associated with lymph node metastasis, distant metastasis, and advanced pTNM stage [88].

Another study showed that miR-139-5p might be a CRC recurrence-associated biomarker because miR-139-5p levels were significantly higher in cancer tissues from recurrent patients. A subsequent study demonstrated that miR-139-5p levels in serum samples were significantly higher in recurrent CRC patients compared with nonrecurrence cases, with an AUC value of 0.750, a specificity of 80.0%, and a sensitivity of 64.0%. Furthermore, CRC patients with higher serum levels of miR-139-5p had a significantly shorter RFS than those with lower miR-139-5p expression [89].

Other circulating miRNAs are listed in Table 3, which shows their prognostic value for CRC.

4.2. Single Circulating lncRNAs as Recurrence and Survival Evaluation Biomarkers. lncRNA 91H is an oncogene involved with CRC progression, and it can promote cell proliferation, migration, and invasion [90]. Serum exosomal 91H levels strongly correlate with metastasis and tumor recurrence. Patients with high 91H levels had a higher risk of tumor metastasis and recurrence than other patients. Univariate and multivariate analyses indicated that 91H could serve as an independent prognostic factor for RFS in CRC patients [91].

Increased serum exosomal CRNDE-h was significantly associated with regional lymph nodes and distant metastasis. Furthermore, patients with high exosomal CRNDE-h had poor OS, and expression of exosomal CRNDE-h could serve as an independent factor for OS in CRC patients [62].

As mentioned above, GNAT1-1 is significantly downregulated in CCRC serum samples. The expression of GNAT1-1 expression was significantly lower in LM tissues compared with pCRC tissues. In addition, GNAT1-1 strongly correlated with tumor stage, lymphovascular invasion, tumor depth, and distant metastasis. Patients with decreased GNAT1-1 expression levels have a shorter OS than those with high levels, and GNAT1-1 expression could be used as an independent prognostic factor [72].

5. Circulating ncRNAs as Treatment Response Prediction Biomarkers in CRC

5.1. Circulating miRNAs as Treatment Response Prediction Biomarkers. Chemotherapy is a useful treatment for CRC patients before or after surgical resection. Effective systemic treatment could improve the possibility of survival with advanced stage CRC. However, CRC patients with resistance to chemotherapy fail to benefit from effective chemotherapy and may also suffer from adverse side effects following chemotherapy [20, 92, 93]. To improve CRC treatment, it is necessary to identify new therapeutic biomarkers to discriminate patients who will respond to chemotherapy from those who are resistant. Recently, several studies demonstrated associations between circulating ncRNAs and sensitivity to chemotherapy. The association between ncRNAs and chemosensitivity are listed in Table 4, which shows their prognostic value for CRC.

Studies have identified potential serum biomarkers for predicting the response to oxaliplatin-based chemotherapy (modified FOLFOX6) in patients with CRC. In particular, a study employed TaqMan low-density arrays based on pooled serum samples from 20 responders and 20 nonresponders to chemotherapy to identify differentially expressed miRNAs. The results showed that five serum miRNAs (miR-20a, miR-130, miR-145, miR-216, and miR-372) differed significantly between the two groups. In the training set, the AUC value for these five miRNAs was 0.841, and the positive and negative predictive values were 0.86 and 0.89, respectively. Moreover, in a larger validation set comprising 93 responders and 80 nonresponders, the AUC value was 0.918, and the

Table 2: Panels of circulating miRNAs as diagnostic and early screening biomarkers for CRC.

Panel of ncRNA	Body fluid	Number of ncRNAs	Numbers of patients	Numbers of controls	AUC	Sensitivity	Specificity	Reference
miR-21↑, let-7g↑, miR-31↓, miR-92a↓, miR-181b↓, miR-203↓	Serum	6	113	89	0.923	—	—	[81]
miR-19a↑, miR-19b↑, miR-15b↑	Plasma	3	63	73	0.84	78.57%	79.25%	[78]
miR-409-3p↑, miR-7↓, miR-93↓	Plasma	3	124	117	0.897	82%	89%	[32]
miR-29c↓, miR-122↑, miR-192↓, miR-374a↓	Plasma	4	55	55	0.98 (discriminate CRC from CAA)	—	—	[79]
lnc-CCAT1↑, lnc-HOTAIR↑	Plasma	2	32	32	0.954	—	—	[82]
lnc-LOC285194↑, lnc-RP11-462C24.1↑, lnc-Nbla12061↑	Serum	3	71	70	0.793	68.33%	86.89%	[37]
lnc-BANCR↑, lnc-NR-026817↓, lnc-NR-029373↓, lnc-NR-034119↓	Serum	4	240	240	0.881	89.17%	75.83%	[35]

Note: ↑, upregulated; ↓, downregulated; —, not mentioned. CAA, colorectal advanced adenoma; CCAT1, colon cancer-associated transcript 1; HOTAIR, HOX transcript antisense intergenic RNA; BANCR, BRAF-activated noncoding RNA.

Table 3: Single circulating ncRNAs as recurrence and survival evaluation biomarkers for CRC.

ncRNAs	Body fluid	Numbers of patients	Clinical significance	Application detail	Reference
miR-21	Serum	186	Tumor size, distant metastasis	miR-21↑ → OS↓	[83]
miR-22	Plasma (exosome)	326	Liver metastasis, TNM stage	miR-21↑ → OS↓, DFS↓	[85]
miR-200c	Serum	206	Lymph node, distant metastasis, tumor recurrence	miR-200c↑ → OS↓, DFS↓	[86]
miR-96	Plasma	227	—	miR-96↑ → OS↓	[124]
miR-200b	Plasma	227	—	miR-200b↑ → OS↓	[124]
miR-141	Plasma	227	—	miR-141↑ → OS↓	[124]
miR-885-5p	Serum	169	Lymph node metastasis, distant metastasis, TNM stage, liver metastasis, lymphatic invasion	miR-885-5p↑ → OS↓, DFS↓	[87]
miR-221	Serum	103	—	miR-221↑ → OS↓	[118]
miR-183	Plasma	118	Lymph node metastasis, distant metastasis, pTNM stage (III-IV), tumor recurrence	miR-183↑ → OS↓, DFS↓	[88]
miR-139-5p	Serum	76	TNM stage, tumor recurrence	miR-139-5p↑ → RFS↓	[89]
miR-148a	Serum	26	Tumor recurrence	miR-148a↓ → OS↓, DFS↓	[125]
91H	Serum (exosome)	232	Tumor metastasis, recurrence	91H↑ → RFS↓	[91]
CRNDE-h	Serum (exosome)	148	Lymph nodes metastasis, distant metastasis	CRNDE-h↑ → OS↓	[62]
GNAT1-1	Plasma	62	—	GNAT1-1↓ → OS↓	[72]

Note: ↑, upregulated; ↓, downregulated; —, not mentioned. OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; CRNDE-h, colorectal neoplasia differentially expressed-h; SPRY4-IT1, SPRY4 intronic transcript 1.

positive and negative predictive values were 0.93 and 0.94, respectively. These five serum miRNAs may be potential serum biomarkers for predicting response to chemotherapy in CRC [20].

Another study identified potential biomarkers for predicting outcome in metastatic CRC (mCRC) patients treated with 5-FU and oxaliplatin-based chemotherapy. A cohort comprising 24 mCRC plasma samples (12 responders and 12 nonresponders) was investigated in this study. The top 10 differentially expressed miRNAs were selected for further study in a validation cohort of 150 patients, and three plasma miRNAs (miR-106a, miR-484, and miR-130) were found to be significantly upregulated in mCRC patients with chemotherapy resistance. Patients with elevated expression of these three plasma miRNAs had poor progression-free survival (PFS). These plasma miRNAs might predict the outcome for mCRC patients before treatment with 5-FU and oxaliplatin-based chemotherapy [94].

Similarly, Hansen et al. found significantly elevated plasma miR-126 levels in nonresponding mCRC patients compared with responding patients who received first-line chemotherapy (XELOX) combined with bevacizumab. The change in miRNA-126 also positively correlated with tumor size changes. Thus, there is a relationship between changes in miR-126 and tumor response when receiving first-line chemotherapy combined with bevacizumab in

Table 4: Single circulating ncRNAs as treatment response prediction biomarkers for CRC.

Chemotherapy regimen	ncRNA	Body fluid	Chemotherapy sensitivity	Reference
5-Fluorouracil combined with oxaliplatin	miR-106a, miR-484, miR-130	Plasma	(miR-106a, miR-484, miR-130) ↑ → resistance	[94]
	miR-20a, miR-130, miR-145, miR-216, miR-372	Serum	(miR-20a, miR-130, miR-145, miR-216, miR-372) ↑ → resistance	[20]
Oxaliplatin combined with capecitabine	miR-1914, miR-1915	Plasma	(miR-1914↑, miR-1915) ↑ → responding	[96]
Oxaliplatin, capecitabine combined with bevacizumab	miR-126	Plasma	miR-126↑ → resistance	[95]
5-Fluorouracil	XIST	Serum	XIXT↑ → resistance	[97]
Oxaliplatin	MEG3	Serum	MEG3↑ → resistance	[98]

Note: ↑, upregulated. XIST, X-inactive specific transcript; MMEG3, maternally expressed gene 3.

mCRC patients. Therefore, miR-126 might be a possible biomarker for resistance to antiangiogenic-containing treatments [95].

miR-1914 ∗ and miR-1915 were found to be downregulated in the plasma of chemoresistant CRC patients who received XELOX. The decreased expression of these two miRNAs significantly correlated with poor OS and PFS. miR-1914 ∗ and miR-1915 can reduce the expression of nuclear factor I/X and suppress chemoresistance by regulating cell proliferation, invasion, and apoptosis in CRC [96].

5.2. Circulating lncRNAs as Treatment Response Prediction Biomarkers. lncRNA XIST was shown to be significantly upregulated in both serum and cancer tissues from nonresponding CRC patients. Serum XIST had an AUC value of 0.756 when distinguishing nonresponding cases from responders (sensitivity: 71.7%, specificity: 68.3%). Furthermore, OS and RFS were poor in CRC patients with elevated XIST expression levels who were treated with 5-FU [97].

Serum lncRNA MEG3 levels were significantly lower in oxaliplatin-based chemotherapy resistant CRC patients, with an AUC value of 0.784 when discriminating nonresponders from responders [98].

6. Future Directions

CRC is a leading cause of cancer-related deaths throughout the world [99]. Colonoscopy is the gold standard for diagnosis, but it is expensive and invasive [5, 6]. Thus, novel and accurate biomarkers using less invasive approaches are urgently required to improve CRC detection. In recent decades, studies have shown that ncRNAs can be detected in various bodily fluids, including serum and plasma, and that they are particularly stable [24, 31–34]. Significant progress has been made in investigating the potential roles of ncRNAs in CRC screening.

Several traditional blood-based biomarkers, such as CEA, carbohydrate antigen (CA) 19-9, CA242, and CA724, have been employed widely as clinical diagnostic biomarkers for CRC screening in recent decades, but they are limited in their diagnostic value, sensitivity, and specificity. As discussed above, several circulating ncRNAs have high accuracy in CRC detection, such as CRNDE-h with an AUC value of 0.892, a sensitivity of 70.3%, and specificity of 94.4% when differentiating CRC and controls, and they may potentially be more reliable biomarkers compared with traditional blood-based biomarkers (in the same cohort, the AUC value for CEA was only 0.688 with a sensitivity of 37.16% and a specificity of 88.75%; combining CRNDE-h and CEA improved the AUC value from 0.688 to 0.913) [62]. Also, CEA protein expression levels may be affected by other bowel diseases, such as ulcerative colitis [100]. Some other malignant tumors, including PDAC, breast cancer, and gastric cancer, can also affect levels of these traditional markers [100–102], leading to frequent high false positive rates. This may be avoided using ncRNAs, as Carter et al. found that miR-21, miR-29c, miR-372, and miR-374a could distinguish CRC and other neoplasms with an AUC value of 0.79. miR-29c, miR-122, miR-192, and miR-374a could also distinguish CRC from CAA, with an AUC value of 0.98 [79]. Circulating ncRNAs have remarkable potential as biomarkers for CRC screening. In the future, it will be important to identify further circulating ncRNA biomarkers, possibly in combination with each other or protein biomarkers, and apply them in the clinic.

Many recent studies have focused on lncRNAs and miRNAs, but few have investigated other types of circulating ncRNAs such as circular RNAs (circRNAs) and piRNAs. circRNAs can regulate genome expression levels by acting as miRNA sponges, and they are extremely stable since they lack open linear tails and they are insensitive to exonucleases [103–105]. Yang et al. found upregulated circ-LDLRAD3 in the plasma of patients with pancreatic cancer that could be used as a biomarker in diagnosing pancreatic cancer [106]. The potential use of serum piRNA was also suggested as a diagnostic biomarker for tumor detection. piR-651 was significantly downregulated in classical Hodgkin lymphoma serum samples, and it exhibited an increasing trend in serum samples from complete response patients compared with the diagnostic samples [107]. However, few studies have investigated the diagnostic capacities of circulating circRNAs and piRNAs for CRC detection. Among the human genome, dozens or even hundreds of genes or transcripts may serve as accurate and sensitive biomarkers.

The studies summarized above suggest areas for further improvements. Circulating ncRNAs were often evaluated in small cohorts of serum and plasma samples in these studies. For example, Kanaan et al. investigated miR-21 in a group of 20 CRC patients and 20 healthy subjects, and the AUC value was 0.910 [41], yet this high diagnostic efficacy might accidentally be misattributed due to the small sample size. In future investigations, multicenter studies should be performed and sample sizes must be increased to ensure reliable scientific results.

Some studies have combined multiple circulating ncRNAs into panels for CRC detection. These panels obtained higher AUC values and improved the diagnostic accuracy for CRC detection over most single biomarkers [78]. Exosomal miR-23a and miR-1246 levels were validated in 101 CRC serum samples, and AUC values of 0.953 and 0.948 were obtained, respectively [44]. Considering the high predictive accuracy of these individual circulating miRNAs, combining serum exosomal miR-23a and miR-1246 levels may yield a higher AUC value. Establishing mathematical models and combining multiple biomarkers may be an effective approach for optimizing diagnostic biomarkers. We hypothesize that combining different types of ncRNAs, such as lncRNAs and miRNAs which have known diagnostic capacities, may yield novel and more precise biomarker panels in future research.

Several studies have reported the potential roles of circulating ncRNAs as diagnostic, prognostic, or chemosensitivity predictive biomarkers in CRC, but they may be "the tip of the iceberg." Future research should aim at achieving a deeper understanding of the regulatory mechanisms related to circulating ncRNAs and establish standard protocols for ncRNA detection to establish them as biomarkers for general CRC patients.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by the National Key R&D Program of China (MOST-2016YFC1303200), the Doctoral Scientific Research Startup Foundation of Liaoning Province (20170520024), and the Program for Liaoning Innovative Research Team in University (LT2016005).

Authors' Contributions

Jia-jun Wang and Xin Wang contributed equally to this work. Jia-jun Wang, Xin Wang, and Yong-xi Song contributed to the drafting and editing of the manuscript. Jun-hua Zhao and Jin-xin Shi participated in conceptualizing the idea. Jia-jun Wang, Jing-xu Sun, and Zhong-hua Wu contributed to the literature search. Zhen-ning Wang participated in conceptualizing and coordinating. All authors have read and approved the final manuscript for publication.

References

[1] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2017," *CA: A Cancer Journal for Clinicians*, vol. 67, no. 1, pp. 7–30, 2017.

[2] H. Brenner, M. Kloor, and C. P. Pox, "Colorectal cancer," *The Lancet*, vol. 383, no. 9927, pp. 1490–1502, 2014.

[3] N. Pawa, T. Arulampalam, and J. D. Norton, "Screening for colorectal cancer: established and emerging modalities," *Nature Reviews Gastroenterology & Hepatology*, vol. 8, no. 12, pp. 711–722, 2011.

[4] L. Rasmussen, I. J. Christensen, M. Herzog, J. Micallef, H. J. Nielsen, and Danish Collaborative Group on Early Detection of Colorectal Cancer, "Circulating cell-free nucleosomes as biomarkers for early detection of colorectal cancer," *Oncotarget*, vol. 9, no. 12, pp. 10247–10258, 2018.

[5] F. B. Nicholson and M. G. Korman, "Acceptance of flexible sigmoidoscopy and colonoscopy for screening and surveillance in colorectal cancer prevention," *Journal of Medical Screening*, vol. 12, no. 2, pp. 89–95, 2005.

[6] B. Levin, D. A. Lieberman, B. McFarland et al., "Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology," *CA: A Cancer Journal for Clinicians*, vol. 58, no. 3, pp. 130–160, 2008.

[7] International Human Genome Sequencing Consortium, "Finishing the euchromatic sequence of the human genome," *Nature*, vol. 431, no. 7011, pp. 931–945, 2004.

[8] H. Ling, M. Fabbri, and G. A. Calin, "MicroRNAs and other non-coding RNAs as targets for anticancer drug development," *Nature Reviews Drug Discovery*, vol. 12, no. 11, pp. 847–865, 2013.

[9] W. Chang, "Non-coding RNAs and berberine: a new mechanism of its anti-diabetic activities," *European Journal of Pharmacology*, vol. 795, pp. 8–12, 2017.

[10] L. Elia and M. Quintavalle, "Epigenetics and vascular diseases: influence of non-coding RNAs and their clinical implications," *Frontiers in Cardiovascular Medicine*, vol. 4, p. 26, 2017.

[11] S. D. N. Reddy, R. P. Gajula, S. B. Pakala, and R. Kumar, "MicroRNAs and cancer therapy: the next wave or here to stay?," *Cancer Biology & Therapy*, vol. 9, no. 7, pp. 479–482, 2010.

[12] M. T. Piccoli, S. K. Gupta, and T. Thum, "Noncoding RNAs as regulators of cardiomyocyte proliferation and death," *Journal of Molecular and Cellular Cardiology*, vol. 89, Part A, pp. 59–67, 2015.

[13] M. X. Liu, X. Chen, G. Chen, Q. H. Cui, and G. Y. Yan, "A computational framework to infer human disease-associated long noncoding RNAs," *PLoS One*, vol. 9, no. 1, article e84408, 2014.

[14] M. Sauvageau, L. A. Goff, S. Lodato et al., "Multiple knockout mouse models reveal lincRNAs are required for life and brain development," *eLife*, vol. 2, article e01749, no. 2, 2013.

[15] Y. Yin, P. Yan, J. Lu et al., "Opposing roles for the lncRNA *Haunt* and its genomic locus in regulating *HOXA* gene activation during embryonic stem cell differentiation," *Cell Stem Cell*, vol. 16, no. 5, pp. 504–516, 2015.

[16] J. Ruiz-Orera, X. Messeguer, J. A. Subirana, and M. M. Alba, "Long non-coding RNAs as a source of new peptides," *eLife*, vol. 3, article e03523, 2014.

[17] N. Bushati and S. M. Cohen, "MicroRNA functions," *Annual Review of Cell and Developmental Biology*, vol. 23, no. 1, pp. 175–205, 2007.

[18] M. Abue, M. Yokoyama, R. Shibuya et al., "Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer," *International Journal of Oncology*, vol. 46, no. 2, pp. 539–547, 2015.

[19] X. Zhou, C. Yin, Y. Dang, F. Ye, and G. Zhang, "Identification of the long non-coding RNA H19 in plasma as a novel biomarker for diagnosis of gastric cancer," *Scientific Reports*, vol. 5, no. 1, article 11516, 2015.

[20] J. Zhang, K. J. Zhang, M. S. Bi, X. L. Jiao, D. L. Zhang, and Q. Dong, "Circulating microRNA expressions in colorectal cancer as predictors of response to chemotherapy," *Anti-Cancer Drugs*, vol. 25, no. 3, pp. 346–352, 2014.

[21] H. Valadi, K. Ekström, A. Bossios, M. Sjöstrand, J. J. Lee, and J. O. Lötvall, "Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells," *Nature Cell Biology*, vol. 9, no. 6, pp. 654–659, 2007.

[22] G. Rabinowits, C. Gerçel-Taylor, J. M. Day, D. D. Taylor, and G. H. Kloecker, "Exosomal microRNA: a diagnostic marker for lung cancer," *Clinical Lung Cancer*, vol. 10, no. 1, pp. 42–46, 2009.

[23] M. P. Hunter, N. Ismail, X. Zhang et al., "Detection of microRNA expression in human peripheral blood microvesicles," *PLoS One*, vol. 3, no. 11, article e3694, 2008.

[24] N. Kosaka, H. Iguchi, Y. Yoshioka, F. Takeshita, Y. Matsuki, and T. Ochiya, "Secretory mechanisms and intercellular transfer of microRNAs in living cells," *Journal of Biological Chemistry*, vol. 285, no. 23, pp. 17442–17452, 2010.

[25] J. W. Bess Jr., R. J. Gorelick, W. J. Bosche, L. E. Henderson, and L. O. Arthur, "Microvesicles are a source of contaminating cellular proteins found in purified HIV-1 preparations," *Virology*, vol. 230, no. 1, pp. 134–144, 1997.

[26] A. Zernecke, K. Bidzhekov, H. Noels et al., "Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection," *Science Signaling*, vol. 2, no. 100, article ra81, 2009.

[27] H. D. Halicka, E. Bedner, and Z. Darzynkiewicz, "Segregation of RNA and separate packaging of DNA and RNA in apoptotic bodies during apoptosis," *Experimental Cell Research*, vol. 260, no. 2, pp. 248–256, 2000.

[28] M. J. Moore, "From birth to death: the complex lives of eukaryotic mRNAs," *Science*, vol. 309, no. 5740, pp. 1514–1518, 2005.

[29] J. D. Keene, "RNA regulons: coordination of post-transcriptional events," *Nature Reviews Genetics*, vol. 8, no. 7, pp. 533–543, 2007.

[30] K. C. Vickers, B. T. Palmisano, B. M. Shoucri, R. D. Shamburek, and A. T. Remaley, "MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins," *Nature Cell Biology*, vol. 13, no. 4, pp. 423–433, 2011.

[31] J. D. Arroyo, J. R. Chevillet, E. M. Kroh et al., "Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 12, pp. 5003–5008, 2011.

[32] S. Wang, J. Xiang, Z. Li et al., "A plasma microRNA panel for early detection of colorectal cancer," *International Journal of Cancer*, vol. 136, no. 1, pp. 152–161, 2015.

[33] X. Chen, Y. Ba, L. Ma et al., "Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases," *Cell Research*, vol. 18, no. 10, pp. 997–1006, 2008.

[34] P. S. Mitchell, R. K. Parkin, E. M. Kroh et al., "Circulating microRNAs as stable blood-based markers for cancer detection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 30, pp. 10513–10518, 2008.

[35] D. Han, X. Gao, M. Wang et al., "Long noncoding RNA H19 indicates a poor prognosis of colorectal cancer and promotes tumor growth by recruiting and binding to eIF4A3," *Oncotarget*, vol. 7, no. 16, pp. 22159–22173, 2016.

[36] Q. Wang, Z. Huang, S. Ni et al., "Plasma miR-601 and miR-760 are novel biomarkers for the early detection of colorectal cancer," *PLoS One*, vol. 7, no. 9, article e44398, 2012.

[37] C. Wang, J. Yu, Y. Han et al., "Long non-coding RNAs LOC285194, RP11-462C24.1 and Nbla12061 in serum provide a new approach for distinguishing patients with colorectal cancer from healthy controls," *Oncotarget*, vol. 7, no. 43, pp. 70769–70778, 2016.

[38] F. Yan, C. Wang, T. Li, W. Cai, and J. Sun, "Role of miR-21 in the growth and metastasis of human salivary adenoid cystic carcinoma," *Molecular Medicine Reports*, vol. 17, no. 3, pp. 4237–4244, 2018.

[39] D. D. Xiong, Z. B. Feng, W. L. Cen et al., "The clinical value of lncRNA NEAT1 in digestive system malignancies: a comprehensive investigation based on 57 microarray and RNA-seq datasets," *Oncotarget*, vol. 8, no. 11, pp. 17665–17683, 2017.

[40] H. Sun, P. Wang, Q. Zhang et al., "MicroRNA21 expression is associated with the clinical features of patients with gastric carcinoma and affects the proliferation, invasion and migration of gastric cancer cells by regulating Noxa," *Molecular Medicine Reports*, vol. 13, no. 3, pp. 2701–2707, 2016.

[41] Z. Kanaan, S. N. Rai, M. R. Eichenberger et al., "Plasma miR-21: a potential diagnostic marker of colorectal cancer," *Annals of Surgery*, vol. 256, no. 3, pp. 544–551, 2012.

[42] H. Chen, H. Liu, H. Zou et al., "Evaluation of plasma miR-21 and miR-152 as diagnostic biomarkers for common types of human cancers," *Journal of Cancer*, vol. 7, no. 5, pp. 490–499, 2016.

[43] G. H. Liu, Z. G. Zhou, R. Chen et al., "Serum miR-21 and miR-92a as biomarkers in the diagnosis and prognosis of colorectal cancer," *Tumour Biology*, vol. 34, no. 4, pp. 2175–2181, 2013.

[44] H. Ogata-Kawata, M. Izumiya, D. Kurioka et al., "Circulating exosomal microRNAs as biomarkers of colon cancer," *PLoS One*, vol. 9, no. 4, article e92921, 2014.

[45] Z. Fang, J. Tang, Y. Bai et al., "Plasma levels of microRNA-24, microRNA-320a, and microRNA-423-5p are potential biomarkers for colorectal carcinoma," *Journal of Experimental & Clinical Cancer Research*, vol. 34, no. 1, p. 86, 2015.

[46] Y. Kasagi, E. Oki, K. Ando et al., "The expression of *CCAT2*, a novel long noncoding RNA transcript, and rs6983267 single-

nucleotide polymorphism genotypes in colorectal cancers," *Oncology*, vol. 92, no. 1, pp. 48–54, 2017.

[47] O. G. Shaker, M. A. Senousy, and E. M. Elbaz, "Association of rs6983267 at 8q24, HULC rs7763881 polymorphisms and serum lncRNAs CCAT2 and HULC with colorectal cancer in Egyptian patients," *Scientific Reports*, vol. 7, no. 1, article 16246, 2017.

[48] Z. J. Wu, Y. Li, Y. Z. Wu et al., "Long non-coding RNA CCAT2 promotes the breast cancer growth and metastasis by regulating TGF-β signaling pathway," *European Review for Medical and Pharmacological Sciences*, vol. 21, no. 4, pp. 706–714, 2017.

[49] S. W. Wu, Y. P. Hao, J. H. Qiu, D. B. Zhang, C. G. Yu, and W. H. Li, "High expression of long non-coding RNA CCAT2 indicates poor prognosis of gastric cancer and promotes cell proliferation and invasion," *Minerva Medica*, vol. 108, no. 4, pp. 317–323, 2017.

[50] S. Chen, H. Wu, N. Lv et al., "lncRNA *CCAT2* predicts poor prognosis and regulates growth and metastasis in small cell lung cancer," *Biomedicine & Pharmacotherapy*, vol. 82, pp. 583–588, 2016.

[51] H. Ling, R. Spizzo, Y. Atlasi et al., "*CCAT2*, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer," *Genome Research*, vol. 23, no. 9, pp. 1446–1461, 2013.

[52] L. Wang, W. Duan, S. Yan, Y. Xie, and C. Wang, "Circulating long non-coding RNA colon cancer-associated transcript 2 protected by exosome as a potential biomarker for colorectal cancer," *Biomedicine & Pharmacotherapy*, vol. 113, article 108758, 2019.

[53] Y. Dang, F. Lan, X. Ouyang et al., "Expression and clinical significance of long non-coding RNA *HNF1A-AS1* in human gastric cancer," *World Journal of Surgical Oncology*, vol. 13, no. 1, p. 302, 2015.

[54] Y. Wu, H. Liu, X. Shi, Y. Yao, W. Yang, and Y. Song, "The long non-coding RNA HNF1A-AS1 regulates proliferation and metastasis in lung adenocarcinoma," *Oncotarget*, vol. 6, no. 11, pp. 9160–9172, 2015.

[55] Z. Liu, X. Wei, A. Zhang, C. Li, J. Bai, and J. Dong, "Long non-coding RNA HNF1A-AS1 functioned as an oncogene and autophagy promoter in hepatocellular carcinoma through sponging hsa-miR-30b-5p," *Biochemical and Biophysical Research Communications*, vol. 473, no. 4, pp. 1268–1275, 2016.

[56] W. Gong, M. Tian, H. Qiu, and Z. Yang, "Elevated serum level of lncRNA-HIF1A-AS1 as a novel diagnostic predictor for worse prognosis in colorectal carcinoma," *Cancer Biomarkers*, vol. 20, no. 4, pp. 417–424, 2017.

[57] W. Peng, Z. Wang, and H. Fan, "lncRNA NEAT1 impacts cell proliferation and apoptosis of colorectal cancer via regulation of Akt signaling," *Pathology Oncology Research*, vol. 23, no. 3, pp. 651–656, 2017.

[58] G. Wang, J. Pan, L. Zhang, Y. Wei, and C. Wang, "Long non-coding RNA CRNDE sponges miR-384 to promote proliferation and metastasis of pancreatic cancer cells through upregulating IRS1," *Cell Proliferation*, vol. 50, no. 6, 2017.

[59] H. Jing, H. Xia, M. Qian, and X. Lv, "Long noncoding RNA CRNDE promotes non-small cell lung cancer progression via sponging microRNA-338-3p," *Biomedicine & Pharmacotherapy*, vol. 110, pp. 825–833, 2019.

[60] D. Ji, C. Jiang, L. Zhang et al., "lncRNA CRNDE promotes hepatocellular carcinoma cell proliferation, invasion, and migration through regulating miR-203/ *BCAT1* axis," *Journal of Cellular Physiology*, vol. 234, no. 5, pp. 6548–6560, 2019.

[61] P. Han, J. W. Li, B. M. Zhang et al., "The lncRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR-181a-5p-mediated regulation of Wnt/β-catenin signaling," *Molecular Cancer*, vol. 16, no. 1, p. 9, 2017.

[62] T. Liu, X. Zhang, S. Gao et al., "Exosomal long noncoding RNA CRNDE-h as a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer," *Oncotarget*, vol. 7, no. 51, pp. 85551–85563, 2016.

[63] B. Yu, Q. Du, H. Li et al., "Diagnostic potential of serum exosomal colorectal neoplasia differentially expressed long non-coding RNA (CRNDE-p) and microRNA-217 expression in colorectal carcinoma," *Oncotarget*, vol. 8, no. 48, pp. 83745–83753, 2017.

[64] D. Hu, Y. Zhan, K. Zhu et al., "Plasma exosomal long non-coding RNAs serve as biomarkers for early detection of colorectal cancer," *Cellular Physiology and Biochemistry*, vol. 51, no. 6, pp. 2704–2715, 2018.

[65] T. Li, J. Xie, C. Shen et al., "Amplification of long noncoding RNA ZFAS1 promotes metastasis in hepatocellular carcinoma," *Cancer Research*, vol. 75, no. 15, pp. 3181–3191, 2015.

[66] H. Zhou, F. Wang, H. Chen et al., "Increased expression of long-noncoding RNA ZFAS1 is associated with epithelial-mesenchymal transition of gastric cancer," *Aging*, vol. 8, no. 9, pp. 2023–2038, 2016.

[67] G. Liu, L. Wang, H. Han et al., "lncRNA ZFAS1 promotes growth and metastasis by regulating BMI1 and ZEB2 in osteosarcoma," *American Journal of Cancer Research*, vol. 7, no. 7, pp. 1450–1462, 2017.

[68] X. Chen, K. Zeng, M. Xu et al., "SP1-induced lncRNA-ZFAS1 contributes to colorectal cancer progression via the miR-150-5p/VEGFA axis," *Cell Death & Disease*, vol. 9, no. 10, p. 982, 2018.

[69] N. Thorenoor, P. Faltejskova-Vychytilova, S. Hombach et al., "Long non-coding RNA ZFAS1 interacts with CDK1 and is involved in p53-dependent cell cycle control and apoptosis in colorectal cancer," *Oncotarget*, vol. 7, no. 1, pp. 622–637, 2016.

[70] C. Fang, J. Zan, B. Yue, C. Liu, C. He, and D. Yan, "Long non-coding ribonucleic acid zinc finger antisense 1 promotes the progression of colonic cancer by modulating ZEB1 expression," *Journal of Gastroenterology and Hepatology*, vol. 32, no. 6, pp. 1204–1211, 2017.

[71] M. J. G. Milevskiy, F. Al-Ejeh, J. M. Saunus et al., "Long-range regulators of the lncRNA *HOTAIR* enhance its prognostic potential in breast cancer," *Human Molecular Genetics*, vol. 25, no. 15, pp. 3269–3283, 2016.

[72] C. Ye, Z. Shen, B. Wang et al., "A novel long non-coding RNA lnc-GNAT1-1 is low expressed in colorectal cancer and acts as a tumor suppressor through regulating RKIP-NF-κB-Snail circuit," *Journal of Experimental & Clinical Cancer Research*, vol. 35, no. 1, p. 187, 2016.

[73] Y. Yang, Z. Shen, Y. Yan et al., "Long non-coding RNA GAS5 inhibits cell proliferation, induces G0/G1 arrest and apoptosis, and functions as a prognostic marker in colorectal cancer," *Oncology Letters*, vol. 13, no. 5, pp. 3151–3158, 2017.

[74] K. Cheng, Z. Zhao, G. Wang, J. Wang, and W. Zhu, "lncRNA GAS5 inhibits colorectal cancer cell proliferation via the miR-182-5p/FOXO3a axis," *Oncology Reports*, vol. 40, no. 4, pp. 2371–2380, 2018.

[75] J. Song, H. Shu, L. Zhang, and J. Xiong, "Long noncoding RNA GAS5 inhibits angiogenesis and metastasis of colorectal cancer through the Wnt/β-catenin signaling pathway," *Journal of Cellular Biochemistry*, vol. 120, no. 5, pp. 6937–6951, 2019.

[76] L. Liu, T. Meng, X. H. Yang et al., "Prognostic and predictive value of long non-coding RNA GAS5 and mircoRNA-221 in colorectal cancer and their effects on colorectal cancer cell proliferation, migration and invasion," *Cancer Biomarkers*, vol. 22, no. 2, pp. 283–299, 2018.

[77] Y. Li, Y. Li, S. Huang et al., "Long non-coding RNA growth arrest specific transcript 5 acts as a tumour suppressor in colorectal cancer by inhibiting interleukin-10 and vascular endothelial growth factor expression," *Oncotarget*, vol. 8, no. 8, pp. 13690–13702, 2017.

[78] M. D. Giráldez, J. J. Lozano, G. Ramírez et al., "Circulating microRNAs as biomarkers of colorectal cancer: results from a genome-wide profiling and validation study," *Clinical Gastroenterology and Hepatology*, vol. 11, no. 6, pp. 681–688.e3, 2013.

[79] J. V. Carter, H. L. Roberts, J. Pan et al., "A highly predictive model for diagnosis of colorectal neoplasms using plasma microRNA: improving specificity and sensitivity," *Annals of Surgery*, vol. 264, no. 4, pp. 575–584, 2016.

[80] M. L. Wikberg, R. Myte, R. Palmqvist, B. van Guelpen, and I. Ljuslinder, "Plasma miRNA can detect colorectal cancer, but how early?," *Cancer Medicine*, vol. 7, no. 5, pp. 1697–1705, 2018.

[81] J. Wang, S. K. Huang, M. Zhao et al., "Identification of a circulating microRNA signature for colorectal cancer detection," *PLoS One*, vol. 9, no. 4, article e87451, 2014.

[82] W. Zhao, M. Song, J. Zhang, M. Kuerban, and H. Wang, "Combined identification of long non-coding RNA CCAT1 and HOTAIR in serum as an effective screening for colorectal carcinoma," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 11, pp. 14131–14140, 2015.

[83] Y. Toiyama, M. Takahashi, K. Hur et al., "Serum miR-21 as a diagnostic and prognostic biomarker in colorectal cancer," *Journal of the National Cancer Institute*, vol. 105, no. 12, pp. 849–859, 2013.

[84] J. Yin, Z. Bai, J. Song et al., "Differential expression of serum miR-126, miR-141 and miR-21 as novel biomarkers for early detection of liver metastasis in colorectal cancer," *Chinese Journal of Cancer Research*, vol. 26, no. 1, pp. 95–103, 2014.

[85] M. Tsukamoto, H. Iinuma, T. Yagi, K. Matsuda, and Y. Hashiguchi, "Circulating exosomal microRNA-21 as a biomarker in each tumor stage of colorectal cancer," *Oncology*, vol. 92, no. 6, pp. 360–370, 2017.

[86] Y. Toiyama, K. Hur, K. Tanaka et al., "Serum miR-200c is a novel prognostic and metastasis-predictive biomarker in patients with colorectal cancer," *Annals of Surgery*, vol. 259, no. 4, pp. 735–743, 2014.

[87] K. Hur, Y. Toiyama, A. J. Schetter et al., "Identification of a metastasis-specific microRNA signature in human colorectal cancer," *Journal of the National Cancer Institute*, vol. 107, no. 3, 2015.

[88] D. Yuan, K. Li, K. Zhu, R. Yan, and C. Dang, "Plasma miR-183 predicts recurrence and prognosis in patients with colorectal cancer," *Cancer Biology & Therapy*, vol. 16, no. 2, pp. 268–275, 2015.

[89] J. Miyoshi, S. Toden, K. Yoshida et al., "miR-139-5p as a novel serum biomarker for recurrence and metastasis in colorectal cancer," *Scientific Reports*, vol. 7, no. 1, article 43393, 2017.

[90] Q. Deng, B. He, T. Gao et al., "Up-regulation of 91H promotes tumor metastasis and predicts poor prognosis for patients with colorectal cancer," *PLoS One*, vol. 9, no. 7, article e103022, 2014.

[91] T. Gao, X. Liu, B. He et al., "Exosomal lncRNA 91H is associated with poor development in colorectal cancer by modifying HNRNPK expression," *Cancer Cell International*, vol. 18, no. 1, p. 11, 2018.

[92] C. Tournigand, T. André, E. Achille et al., "FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study," *Journal of Clinical Oncology*, vol. 22, no. 2, pp. 229–237, 2004.

[93] R. M. Goldberg, D. J. Sargent, R. F. Morton et al., "A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer," *Journal of Clinical Oncology*, vol. 22, no. 1, pp. 23–30, 2004.

[94] J. B. Kjersem, T. Ikdahl, O. C. Lingjaerde, T. Guren, K. M. Tveit, and E. H. Kure, "Plasma microRNAs predicting clinical outcome in metastatic colorectal cancer patients receiving first-line oxaliplatin-based treatment," *Molecular Oncology*, vol. 8, no. 1, pp. 59–67, 2014.

[95] T. F. Hansen, A. L. Carlsen, N. H. H. Heegaard, F. B. Sørensen, and A. Jakobsen, "Changes in circulating microRNA-126 during treatment with chemotherapy and bevacizumab predicts treatment response in patients with metastatic colorectal cancer," *British Journal of Cancer*, vol. 112, no. 4, pp. 624–629, 2015.

[96] J. Hu, G. Cai, Y. Xu, and S. Cai, "The plasma microRNA miR-1914∗ and -1915 suppresses chemoresistant in colorectal cancer patients by down-regulating NFIX," *Current Molecular Medicine*, vol. 16, no. 1, pp. 70–82, 2016.

[97] Y. Xiao, U. A. Yurievich, and S. V. Yosypovych, "Long non-coding RNA XIST is a prognostic factor in colorectal cancer and inhibits 5-fluorouracil-induced cell cytotoxicity through promoting thymidylate synthase expression," *Oncotarget*, vol. 8, no. 47, pp. 83171–83182, 2017.

[98] L. Li, J. Shang, Y. Zhang et al., "MEG3 is a prognostic factor for CRC and promotes chemosensitivity by enhancing oxaliplatin-induced cell apoptosis," *Oncology Reports*, vol. 38, no. 3, pp. 1383–1392, 2017.

[99] W. Chen, R. Zheng, P. D. Baade et al., "Cancer statistics in China, 2015," *CA: A Cancer Journal for Clinicians*, vol. 66, no. 2, pp. 115–132, 2016.

[100] H. X. Xu, L. Liu, J. F. Xiang et al., "Postoperative serum CEA and CA125 levels are supplementary to perioperative CA19-9 levels in predicting operative outcomes of pancreatic ductal adenocarcinoma," *Surgery*, vol. 161, no. 2, pp. 373–384, 2017.

[101] S. G. Wu, Z. Y. He, H. Y. Ren et al., "Use of CEA and CA15-3 to predict axillary lymph node metastasis in patients with breast cancer," *Journal of Cancer*, vol. 7, no. 1, pp. 37–41, 2016.

[102] Y. Liang, W. Wang, C. Fang et al., "Clinical significance and diagnostic value of serum CEA, CA19-9 and CA72-4 in

patients with gastric cancer," *Oncotarget*, vol. 7, no. 31, pp. 49565–49573, 2016.

[103] F. A. Karreth, Y. Tay, D. Perna et al., "In vivo identification of tumor- suppressive PTEN ceRNAs in an oncogenic BRAF-induced mouse model of melanoma," *Cell*, vol. 147, no. 2, pp. 382–395, 2011.

[104] B. Y. Zhang, Z. Jin, and Z. Zhao, "Long intergenic noncoding RNA 00305 sponges miR-136 to regulate the hypoxia induced apoptosis of vascular endothelial cells," *Biomedicine & Pharmacotherapy*, vol. 94, pp. 238–243, 2017.

[105] Y. Zhong, Y. du, X. Yang et al., "Circular RNAs function as ceRNAs to regulate and control human cancer progression," *Molecular Cancer*, vol. 17, no. 1, p. 79, 2018.

[106] F. Yang, D. Y. Liu, J. T. Guo et al., "Circular RNA circ-LDLRAD3 as a biomarker in diagnosis of pancreatic cancer," *World Journal of Gastroenterology*, vol. 23, no. 47, pp. 8345–8354, 2017.

[107] A. Cordeiro, A. Navarro, A. Gaya et al., "PiwiRNA-651 as marker of treatment response and survival in classical Hodgkin lymphoma," *Oncotarget*, vol. 7, no. 29, pp. 46002–46013, 2016.

[108] E. K. O. Ng, W. W. S. Chong, H. Jin et al., "Differential expression of microRNAs in plasma of patients with colorectal cancer: a potential marker for colorectal cancer screening," *Gut*, vol. 58, no. 10, pp. 1375–1381, 2009.

[109] Z. Huang, D. Huang, S. Ni, Z. Peng, W. Sheng, and X. Du, "Plasma microRNAs are promising novel biomarkers for early detection of colorectal cancer," *International Journal of Cancer*, vol. 127, no. 1, pp. 118–126, 2010.

[110] G. J. Zhang, T. Zhou, Z. L. Liu, H. P. Tian, and S. S. Xia, "Plasma miR-200c and miR-18a as potential biomarkers for the detection of colorectal carcinoma," *Molecular and Clinical Oncology*, vol. 1, no. 2, pp. 379–384, 2013.

[111] W. Y. Chen, X. J. Zhao, Z. F. Yu et al., "The potential of plasma miRNAs for diagnosis and risk estimation of colorectal cancer," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 6, pp. 7092–7101, 2015.

[112] R. Nonaka, J. Nishimura, Y. Kagawa et al., "Circulating miR-199a-3p as a novel serum biomarker for colorectal cancer," *Oncology Reports*, vol. 32, no. 6, pp. 2354–2358, 2014.

[113] A. R. N. Zekri, A. S. E. D. Youssef, M. M. Lotfy et al., "Circulating serum miRNAs as diagnostic markers for colorectal cancer," *PLoS One*, vol. 11, no. 5, article e0154130, 2016.

[114] J. Yu, L. Jin, L. Jiang et al., "Serum miR-372 is a diagnostic and prognostic biomarker in patients with early colorectal cancer," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 16, no. 4, pp. 424–431, 2016.

[115] R. Nonaka, Y. Miyake, T. Hata et al., "Circulating miR-103 and miR-720 as novel serum biomarkers for patients with colorectal cancer," *International Journal of Oncology*, vol. 47, no. 3, pp. 1097–1102, 2015.

[116] Z. C. Lv, Y. S. Fan, H. B. Chen, and D. W. Zhao, "Investigation of microRNA-155 as a serum diagnostic and prognostic biomarker for colorectal cancer," *Tumour Biology*, vol. 36, no. 3, pp. 1619–1625, 2015.

[117] S. Zanutto, S. Pizzamiglio, M. Ghilotti et al., "Circulating miR-378 in plasma: a reliable, haemolysis-independent biomarker for colorectal cancer," *British Journal of Cancer*, vol. 110, no. 4, pp. 1001–1007, 2014.

[118] X. X. Pu, G. L. Huang, H. Q. Guo et al., "Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression," *Journal of Gastroenterology and Hepatology*, vol. 25, no. 10, pp. 1674–1680, 2010.

[119] G. Basati, A. E. Razavi, I. Pakzad, and F. A. Malayeri, "Circulating levels of the miRNAs, miR-194, and miR-29b, as clinically useful biomarkers for colorectal cancer," *Tumour Biology*, vol. 37, no. 2, pp. 1781–1788, 2016.

[120] L. Ng, T. M. Wan, J. H. Man et al., "Identification of serum miR-139-3p as a non-invasive biomarker for colorectal cancer," *Oncotarget*, vol. 8, no. 16, pp. 27393–27400, 2017.

[121] L. Xu, M. Li, M. Wang, D. Yan, G. Feng, and G. An, "The expression of microRNA-375 in plasma and tissue is matched in human colorectal cancer," *BMC Cancer*, vol. 14, no. 1, p. 714, 2014.

[122] I. Ramzy, M. Hasaballah, R. Marzaban, O. Shaker, and Z. A. Soliman, "Evaluation of microRNAs-29a, 92a and 145 in colorectal carcinoma as candidate diagnostic markers: an Egyptian pilot study," *Clinics and Research in Hepatology and Gastroenterology*, vol. 39, no. 4, pp. 508–515, 2015.

[123] M. Dai, X. Chen, S. Mo et al., "Meta-signature lncRNAs serve as novel biomarkers for colorectal cancer: integrated bioinformatics analysis, experimental validation and diagnostic evaluation," *Scientific Reports*, vol. 7, no. 1, article 46572, 2017.

[124] Y. Sun, Y. Liu, D. Cogdell et al., "Examining plasma microRNA markers for colorectal cancer at different stages," *Oncotarget*, vol. 7, no. 10, pp. 11434–11449, 2016.

[125] H. L. Tsai, I. P. Yang, C. W. Huang et al., "Clinical significance of *microRNA-148a* in patients with early relapse of stage II stage and III colorectal cancer after curative resection," *Translational Research*, vol. 162, no. 4, pp. 258–268, 2013.