COMMENTARY

Circulating microRNAs: novel biomarkers for early detection of colorectal cancer

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Article on page XXX.

Differential expression of circulating miRNAs according to severity of colorectal neoplasia

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Colorectal cancer (CRC) is the third most common cancer in the United States,[1] and about 1.2 million individuals are diagnosed each year with CRC worldwide.[2] Although tumor resection is the most common curative treatment option for about two-thirds of patients with CRC, recurrence rates are very high (28%–50%) and pose a serious challenge to reducing mortality in these individuals.[3] Five-year survival of patients with localized CRC is 90% after surgery.[4] About 50% of patients with CRC develop metastasis, after which the 5-year survival rate drops to 60% in these individuals contributing to the increased rate of mortality.[5] In the absence of a specific risk factor for this disease, prognosis is typically based on the extent of tumor at diagnosis. The detection of early stage disease and improved surveillance has reduced mortality rates, as shown recently in a 30-year follow-up study.[6] Therefore, early detection is critical to effectively treating CRC, and novel biomarkers are urgently needed for this purpose.

MicroRNAs (miRNAs) are a unique class of short noncoding RNA molecules (19–24 nucleotides long) that are implicated in numerous cancers.[7] They exert their effects by regulating gene expression primarily at the post-transcriptional level, where they either induce mRNA degradation or translational inhibition. miRNAs are often dysregulated in CRC; and both overexpression and downregulation of specific miRNAs have been shown to be associated with CRC.[8-10] Profiling of miRNAs in CRC cell lines and patient samples have shown that a large number of them were aberrantly expressed.[8-11] Although it is not entirely clear how the dysregulation of miRNAs occurs in CRC, a number of potential mechanisms have been proposed, including epigenetic modifications and various cellular signaling cascades.[11] In addition, putative targets of some of these miRNAs have been identified.

Seminal discovery of circulating placenta-specific miRNAs in the maternal plasma[12] has led to numerous studies on the identification of miRNAs in various body fluids, such as saliva, urine, and amniotic fluid.[13,14] This subsequently resulted in the establishment of an miRNA database termed “miRandola” on circulating miRNAs found in various diseases.[15] This database originally contained 581 miRNAs from 21 sample types and was expanded recently to include information on the function, diagnostic potential, and drug effects on cellular

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Table I. Circulating microRNAs identified in patients with colorectal cancer

Sample type	MicroRNA	Reference
Serum	miR-17-3p, miR-29a, miR-92a, miR-135b	Faltejskova et al[24]
	miR-20a, miR-130, miR-145, miR-216, miR-372	Zhang et al[39]
	miR-21	Wang and Zhang[40]
	miR-21	Kanaan et al[41]
	miR-21, miR-92a	Liu et al[20]
	miR-21, miR-29a, miR-34a, miR-92a, miR-103 miR-106a, miR-107, miR-143, miR-146a miR-151-5p, miR-155, miR-191, miR-199a-3p miR-210, miR-221, miR-320a, miR-378, miR-382 miR-409-3p, miR-423-3p, miR-423-5p, miR-425 miR-484, miR-652, miR-720, let7d	Hofsli et al[38]
	miR-27b, miR-106a, miR-130b, miR-148a miR-326, miR-484	Kjersem et al[42]
	miR-29a	Wang and Gu[21]
	miR-21, miR-29a, miR-30b, miR-30c, miR-30d miR-146a, miR-486	Ho et al[37]
	miR-92, miR-17-3p	Ng et al[17]
	miR-141	Cheng et al[35]
	miR-200c	Toiyama et al[30]
	miR-601, miR-760	Wang et al[22]
	let7a, miR-21, miR-23a, miR-150, miR-223 miR-1229, miR-1246	Ogata-Kawata[43]
Plasma	miR-15b, miR-19a, miR-19b, miR-29a, miR-335 miR-18a (only in adenoma patients)	Giráldez et al[44]
	miR-15b, miR-17, miR-142-3p, miR-195, miR-331 miR-532, miR-532-3p, miR-652	Kanaan et al[25]
	miR-23a, miR-193a-3p, miR-338-5p	Yong et al[29]
	miR-29a, miR-92a	Huang et al[19]
	miR-92	Ng et al[17]
	miR-221	Pu et al[36]
Stool	miR-21, miR-92a	Wu et al[32]
	miR-135b	Wu et al[33]
	miR-221, miR-18a	Yau et al[34]

and circulating miRNAs.[16] A number of studies have also reported the presence of miRNAs in high concentrations in body fluids and stool of patients with CRC.[17-36] These miRNAs could potentially act as novel biomarkers for noninvasive diagnosis of CRC. Most of these miRNAs were identified using standard methods of microarray and real-time reverse transcription–polymerase chain reaction (RT-PCR) approaches. In this issue of *Translational Research*, Ho et al[37] used a novel, cutting-edge technology of next-generation sequencing (NGS) to profile miRNAs in serum samples of 5 patients with colorectal neoplasia. These findings strongly support other reports that certain miRNAs are downregulated in CRC.[22,38,39]

NGS allows for the identification of novel miRNAs, including those with sequence changes and variants such as iso-miRs. In addition, downregulated or silenced miRNAs are interesting candidates, in that they could potentially function as tumor suppressor agents. Combinations of miRNAs (both upregulated and downregulated) and current diagnostic methods have recently been shown to dramatically improve the detection of CRC.[22] In that study, a combination of miR-92a, miR-29a, and miR-760 together with carcinoembryonic antigen (CEA) analysis significantly enhanced early detection of CRC. Among the so-called downregulated miRNAs reported in the literature as potential biomarkers for CRC are miR-601, miR-760, miR-106a, miR-143, miR-103, miR-199a-3p, miR-151-5p, miR-107, miR-191, miR-423-3p, let7d, miR-409-3p, miR-652, miR-20a, miR-130, miR-145, miR-216, and miR-372[22,38,39] (Table I).

In their study, Ho et al[37] have identified miR-30 family (miR-30b, miR-30C, and miR-30d), and miR-146a as putative candidate circulating biomarkers for the early detection of colorectal neoplasia. However, these miRNAs are not novel for CRC studies. MiR-30a was previously shown to function as a tumor suppressor by targeting the Akt/mTOR pathway,[45] and insulin receptor substrate 2[46] in colon cancer cell lines and tissues. Interestingly, a polymorphism (rs2690164) in the miR-146a was found to be associated with susceptibility