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# miRNAs are Stable in Several Severe Storage Conditions and Useful for Molecular Diagnostics

**Yoshikatsu Koga***

*Division of Developmental Therapeutics, National Cancer Center, Japan*

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***Corresponding author:** Yoshikatsu Koga, Division of Developmental Therapeutics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Japan, Tel: +81-4-7134-6866; Email: ykoga@east.ncc.go.jp

**Abstract**

To date, several miRNAs have been reported as good biomarkers for cancer detection and tumor recurrence. In these reports, miRNA stored at severe conditions, such as feces or FFPE tissue, was used because of its stability. Fecal miRNA expressions in colorectal cancer patients were first reported in 2010. Since then, several miRNAs were considered to be good biomarkers for detection of colorectal cancer. Combined method with FOBT and fecal miRNA test was one of the candidates for colorectal cancer screening. To identify a high risk group in stage II colorectal cancer patients is important for adjuvant treatment. Six-miRNA-based classifier and miR-181c were good predictive biomarkers of tumor recurrence in stage II colorectal cancer patients. miRNA might be stable in several severe storage conditions and useful for molecular diagnostics.

**Keywords:** miRNA; Fecal sample; FFPE sample; Colorectal cancer

**Abbreviations:** miRNA: MicroRNA; mRNA: Messenger RNA; FFPE: Formalin-Fixed Paraffin-Embedded; FOBT: Fecal Occult Blood Test

## Introduction

MicroRNAs (miRNAs) are known as small non-coding RNA molecules and down-regulator for specific mRNA expressions. In the oncology area, miRNAs play important roles such as carcinogenesis, invasion, and metastasis. To date, several studies have clarified that circulating miRNA in plasma (serum) was a potential marker for colorectal cancer detection [1,2], and was remarkably stable in plasma due to its protection from endogenous RNase activity [3]. Moreover, miRNAs can be preserved in severe storage conditions, such as fecal samples [4] and formalin-fixed paraffin-embedded (FFPE) tissues [5]. In a clinical laboratory examination related to colorectal cancer, not only blood samples but also tissue and fecal samples are used for cancer detection and screening. Thus, miRNAs extracted from these samples were useful for biomarkers for detection of colorectal cancer or prediction of tumor recurrence by using miRNA microarray and real-time RT-PCR analyses. Several miRNA analyses of colorectal cancer using fecal and FFPE samples were shown in this mini review.

## Discussion

Fecal miRNA expressions in colorectal cancer patients were first reported in 2010. Link et al. [6] reported that miR-21 and miR-106a were highly expressed in patients with colorectal neoplasia including non-advanced adenoma, advanced adenoma, and cancer compared with individuals without colorectal neoplasia. At the same time, we reported miRNA expression profiling [7] using miRNA extracted from fecal colonocytes isolated by anti-human EpCAM mAb conjugated magnetic beads [8]. We found the expression of miR-17-92 cluster, miR-21, and miR-135 was significantly higher in colorectal cancer tissues compared with normal adjacent tissues. The overall sensitivity and specificity by using miRNA expression in 316 participants were 74.1% and 79.0%, respectively. Although the accuracy of fecal miRNA expression was lower than that of fecal occult blood test (FOBT), fecal miRNA might have a potential to detect colorectal cancer.

FOBT is widely used for colorectal cancer screening. However it does not have a high sensitivity to detect colorectal cancer. Yamazaki et al. [9] investigated the applicability of fecal miRNA test using FOBT residual samples. Fecal miRNA stored at 4 °C for up to 5 days had a sufficient quality for real-time RT-PCR analysis. Then, we reported a new colorectal cancer screening method combining FOBT and fecal miRNA test to improve the sensitivity compared with FOBT alone [10]. Approximately 2μg RNA could be extracted from 10mg fecal pellet of FOBT residua, and this amount of miRNA was enough for miRNA analysis because only 5ng RNA was required for real-time RT-PCR analysis. Levels of fecal miR-106a expression in FOBT positive colorectal cancer

patients and FOBT negative colorectal cancer patients were significantly higher than that in individuals without colorectal neoplasia. Although the sensitivity of FOBT was 60.7%, that of combination method with FOBT and fecal miRNA test was 70.9%. Fecal miRNA test combined with FOBT might improve the sensitivity to detect colorectal cancer.

Chang et al. [11] reported miRNA expressions of blood, feces, and tissue samples in same colorectal cancer patients. Although the miRNA expressions in plasma and fecal samples were lower than that in tissue sample, positive correlations were observed in paired tissues, plasma, and fecal samples. miRNAs highly expressed in colorectal cancer tissues were also highly expressed in plasma and fecal samples; however, miRNAs expressed at a higher level should be targeted in fecal samples for real-time RT-PCR analysis.

A standard treatment for stage II colorectal cancer is surgical resection without adjuvant chemotherapy. However, the recurrence rate of stage II colorectal cancer patients who underwent surgery alone was reported about 20%. Therefore, the investigation for the adequate biomarkers was considered to be important for stage II colorectal cancer patients to select a high risk group. Zhang et al. [12] reported six-miRNA-based classifier, which contained miR-21-5p, miR-20a-5p, miR-103a-3p, miR-106b-5p, miR-143-5p, and miR-215, was a prognostic and a predictive biomarker for tumor recurrence in stage II cancer patients. More recently, Yamazaki et al. [13] reported the higher expression of miR-181c in FFPE samples was detected as an independent predictive biomarker of tumor recurrence in stage II colorectal cancer patients. The miRNAs reported by Zhang et al. [12] were selected using cancer tissue and normal adjacent tissue in stage II colorectal cancer patients. Whereas, tissue miR-181c reported by Yamazaki et al. [13] was selected as follows; miRNAs which were expressed higher in the cancer tissues rather than those in the adjacent normal tissues were initially selected, and the miRNAs which were expressed higher in the cancer tissues of the patients with recurrence than those without recurrence were finally obtained.

## Conclusion

miRNA is stable in several severe storage conditions, such as fecal and FFPE samples. Thus, fecal miRNA might be a good biomarker for colorectal cancer screening and miRNA extracted from FFPE tissues could be useful for a predictive biomarker of tumor recurrence in stage II colorectal cancer patients.

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