MicroRNAs: Potential Candidates for Diagnosis and Treatment of Colorectal Cancer

Article *in* Journal of Cellular Physiology · January 2017

DOI: 10.1002/jcp.25801

4 authors, including:

Abdullah Moridikia
Baqiyatallah University of Medical Sciences
11 PUBLICATIONS **298** CITATIONS

SEE PROFILE

Hamed Mirzaei
University of Tehran
164 PUBLICATIONS **4,307** CITATIONS

SEE PROFILE

Jafar Salimian
Baqiyatallah University of Medical Sciences
56 PUBLICATIONS **416** CITATIONS

SEE PROFILE

REVIEW ARTICLE

MicroRNAs: potential candidates for diagnosis and treatment of colorectal cancer†

Abdullah Moridikia[1], Hamed Mirzaei[1], Amirhossein Sahebkar[2,3], Jafar Salimian[1*]

[1]Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

[2] Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[3]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

***Corresponding author:**

Jafar Salimian, Assistant Professor in Immunology, Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

E-mail: Jafar.salimian@gmail.com

†This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/jcp.25801]

Received 12 January 2017; Accepted 13 January 2017
Journal of Cellular Physiology

DOI 10.1002/jcp.25801

Abstract

Colorectal cancer (CRC) is known as the third common cancer worldwide and an important public health problem in different populations. Several genetics and environmental risk factors are involved in the development and progression of CRC including chromosomal abnormalities, epigenetic alterations, and unhealthy lifestyle. Identification of risk factors and biomarkers could lead to a better understanding of molecular pathways involved in CRC pathogenesis. MicroRNAs (miRNAs) are important regulatory molecules which could affect a variety of cellular and molecular targets in CRC. A large number of studies have indicatedderegulations of some known tissue-specific miRNAs, e.g. miR-21, miR-9, miR-155, miR-17, miR-19, let-7 and miR-24 as well as circulating miRNAs, e.g. miR-181b, miR-21, miR-183, let-7g, miR-17 and miR-126, in patients with CRC. In the current review, we focus on the findings of preclinical and clinical studies performed on tissue-specific and circulating miRNAs as diagnostic biomarkers and therapeutic targets for the detection of patients at various stages of CRC.

Key word: Colorectal cancer, MicroRNA, Diagnosis, Therapy

Introduction

Colorectal cancer (CRC) is known as one of main types of gastrointestinal cancers which threatens the lives of millions of people globally (Treanor and Quirke 2007; Gharagozloo, Mirzaei et al. 2012). Many genetic and environmental factors or inflammatory conditions could play important roles in the pathogenesis of CRC (Grady and Markowitz 2002).

Several lines of evidences have indicated that identification of various risk factors and biomarkers could contribute to better understanding of cellular and molecular signaling pathways involved in disease processes which could finally lead to a more effective therapy for CRC patients (Tanaka, Tanaka et al. 2010; Schirripa and Lenz 2016; Das, Kalita et al. 2017). Moreover, using powerful diagnostic and prognostic biomarkers allow a better monitoring of response to therapy in patients with CRC (Tanaka, Tanaka et al. 2010; Yiu and Yiu 2016).

Among various proposed biomarkers such as DNAs, RNAs, epigenetic changes, proteins and glycoproteins, microRNAs (miRNA) have emerged as noveldiagnostic, prognostic and therapeutic biomarkers in patients with CRC (Ferracin, Lupini et al. 2016; Trang, Weidhaas et al. 2017). MiRNAs are regulatory non-coding RNAs which are able to exert their effects at the transcriptional or post-transcriptional level (Salarini, Sahebkar et al. 2015; Fathullahzadeh, Mirzaei et al. 2016; Mirzaei, Sahebkar et al. 2016; Simonian, Mosallayi et al. 2016; Mirzaei, Momeni et al. 2017). miRNAs regulate various genes and cellular/molecular targets which have critical tasks in vital processes such as apoptosis, angiogenesis, differentiation, and cell cycle (Mirzaei, Khataminfar et al. 2016; Mirzaei, Naseri et al. 2016; Mohammadi, Goodarzi et al. 2016). Several lines of evidence have revealed that a network of miRNAs is involve in the pathogenesis of CRC (Martín-Subero and Esteller 2017; Trang, Weidhaas et al. 2017). Deregulation of these molecules could lead to inhibition and/or activation of several cellular and molecular targets that trigger development of CRC (Wang, Du et al. 2015).

Several studies have indicated deregulation of a variety of tissue-specific miRNAs e.g. miR-21, miR-181b, miR-155, let-7 and miR-92a and circulating miRNAs e.g. miR-21, miR-26a, miR-126 and miR-203 in CRC patients (Orang and Barzegari 2014; Kijima, Hazama et al. 2017). These miRNAs exert their effects *via* cellular and molecular targets such as p53, c-Met, K-Ras, cox-2, Rb and Bcl2 family (Wang, Du et al. 2015). Being non-invasive and relatively easy assay methods have made miRNAs novel candidates for the diagnosis of CRC. Moreover, exosomes containing miRNAs are one of other biomarkers which could be used for identifying CRC patients (Ogata-Kawata, Izumiya et al. 2014). Exosomes are nano-carriers released from different cells such as tumor cells, stem cells and some normal cells (Mirzaei, Sahebkar et al. 2016; Saadatpour, Fadaee et al. 2016). There vesicles could carry various cargos such as DNA, proteins, mRNAs and miRNAs. Secretion of exosomes could lead to a change in the behavior of receipient cells (Mirzaei, Sahebkar et al. 2016). Therefore, exosomes might be applied as diagnostic biomarkers in CRC patients.

Here, we summarize a variety of tissue-specific miRNAs and circulating miRNAs which could be used as potential diagnostic and therapeutic biomarkers in CRC patients. Moreover, we highlight potential utilization of exosomes containing miRNAs as new diagnostic biomarkers in these patients.

MicroRNA as diagnostic, prognostic and therapeutic biomarkers in CRC

Effective treatment in early stages of CRC could lead to increasing the survival rate of patients (Chi and Zhou 2016). Several lines of evidence have indicated that identification of a sequence of cellular and molecular pathways involved in CRC pathogenesis could have a critical role for the discovery of new diagnostic, prognostic and therapeutic biomarkers in patients with CRC (Dakubo 2017). Among various biomarkers which are employed for the diagnosis of CRC in different stages, miRNAs have emerged as new candidates with several advantages (Dong, Yu et al. 2014). miRNAs are regulatory non-coding RNAs which could regulate a sequence of cellular and molecular targets including EGF receptor (EGFR), TGF, phosphatase and tensin homolog

(PTEN)/phosphatidylinositol-3-kinase (PI3K), and p53 pathways in CRC (Figure 1)(Wang, Du et al. 2015). It has been showed that miRNAs act as regulatory molecules which are capable to regulate the expression of the above-mentioned genes in CRC. These molecular/cellular targets mediate processes such as angiogenesis, apoptosis, survival, cell cycle and differentiation that can lead to CRC upon deregulation (Wang, Du et al. 2015). miRNAs have been found to act as oncogene or tumor suppressor in various cancers such as CRC (Wang, Du et al. 2015). Therefore, deregulation of them changes the behavior of cells and predisposes to cancerous conditions.

Multiple lines of evidence have indicated up- and/or down-regulation of a variety of tissue-specific miRNAs in CRC. Segmental *resection* without adjuvant chemotherapy is the most common therapy for CRC patients at stage II of the disease (Misiakos, Karidis et al. 2011). Nowadays, identification of biomarkers for patients in stage II CRC is an important challenge (Misiakos, Karidis et al. 2011). Yamazaki et al., indicated that deregulation of a set of miRNAs could be used as a diagnostic biomarker in CRC patients with recurrence at stage II (Yamazaki, Koga et al. 2016). Their results indicated that a variety of miRNAs including miR-128a, miR-23c, let-7a, let-7d, let-7e, miR-26b, miR-151-5p, and miR-181c are deregulated in patients with recurrence at stage II. They showed that miR-181c might be a predictive factor for recurrence of the disease. Moreover, the recurrence rate is associated with up-regulation of miR-181c in patients with CRC (Yamazaki, Koga et al. 2016).

CRC could be divided into 2 categories. First, chromosome abnormalities could lead to CRC and second, microsatellite instability (MSI) (Lindblom 2001). These groups could affect on miRNAs expression and lead to deregulation of them in CRC patients. Wen-Jian et al. indicated that chromosomal abnormalities affect the expression of a number of miRNAs including miR-17/92 cluster, and miR-143/145 cluster in CRC patients. They showed that these miRNAs could be used as potential therapeutic and diagnostic biomarkers in CRC patients (Meng, Yang et al. 2015). Earle and colleagues assessed the relationship between miRNA signatures with MSI in CRC patients (Earle, Luthra et al. 2010). Their result indicated that a variety of miRNAs including miR-31, miR-133b, miR-183, miR-20, miR-135a, miR-92, miR-93, miR-25, miR -17, miR-203, and miR-223

were up-regulated while miR-192, miR-196a, miR-215, miR-26b, miR-16, miR-145, miR-191, miR-143, and let-7a were down-regulated in CRC samples. These results indicated that the expression profile of miRNAs could be related to MSI subgroups and might be applied as a diagnostic and prognostic biomarker in these patients (Earle, Luthra et al. 2010).

Given that a number of miRNAs e.g. miR-506, miR-487b, miR-20a, miR-126, miR-31, and miR-33a are down-regulated in CRC and could act as tumor suppressor in this disease which might suggest therapeutic potential of them for CRC patients. Recently, Zu et al. indicated that miR-506 acts as a tumor suppressor in CRC cells and its up-regulation could inhibit progression of CRC cells *via* targeting laminin subunit γ-1 (LAMC1) (Zu, Liu et al. 2016). Hence, miR-506 could be used as a new therapeutic candidate in patients with CRC. LAMC1 is one an important target for CRC and has critical roles in the development of the disease (Peters, Jiao et al. 2013).

In other study, Hata et al., revealed that miR-487b act as tumor suppressor and a negative controller for CRC patients with liver metastasis via KRAS signaling pathway (DOKI, MORI et al. 2016). MiR-487b was down regulated in CRC patients with liver metastasis. Moreover, over expression of miR-487b is related with better prognosis. It has been observed that over expressing of miR-487b is capable to inhibit invasive and cell proliferation of CLL cells. This molecule exerts its effect via down regulation of KRAS and other signaling pathways are associated with KRAS. MiR-487b could also affect on LRP6 which is a receptor for WNT/β-catenin signaling pathway. These findings suggested that miR-487b could be used a potential therapeutic biomarkers in CRC patients with liver metastasis (DOKI, MORI et al. 2016).

ADAMTSs are known as a gene family of secreted proteinases which exert their effect on a number of cellular processes such as adhesion, fusion, migration, and proliferation. It has been observed that up-regulation of ADAMTSs leads to progression of CRC cells (Filou, Korpetinou et al. 2015). IGFBP5 is an important protein which play key role in cell growth and survival and up regulation of it involve in cancer progression (Baxter 2014). Yu et al. indicated that miR-140-5p is capable to

affect the progression of CRC cells via targeting ADAMTS5 , IGFBP5 (Yu, Lu et al. 2016). Down regulation of miR-140-5p and up regulation of ADAMTS5, IGFBP5 are observed in CRC samples which are associated with metastasis and advanced stages in these patients. These results indicated that up regulation of miR-140-5p could inhibit metastasis and invasive effect of CRC cells via down regulation of ADAMTS5, IGFBP5. These data suggested that this miRNAs might be applied as a new therapeutic biomarkers in patients with CRC (Yu, Lu et al. 2016). Table 1 illustrates a large number of miRNAs and their targets that are involve in CRC pathogenesis and could be used as diagnostic, prognostic and therapeutic biomarkers in this disease.

Circulating microRNA in CRC

A wide range of studies have indicated a variety of miRNAs that are released into bloodstream and known as circulating miRNAs (Mirzaei, Sahebkar et al. 2016). These molecules could be protected from unfavorable physiological conditions including handing, storage, high PH and temperature by binding to specific protein complexs and specific vesicles (Mirzaei, Sahebkar et al. 2016). Circulating miRNAs could be a new attractive option for the diagnosis and treatment of several diseases. Various studies have revealed that deregulation of circulating miRNAs can be used as potential diagnostic and therapeutic biomarkers in a variety of cancers such as CRC (Orang and Barzegari 2014).

Wang et al., investigated circulating miRNA expression profile in CRC patients (Wang, Huang et al. 2014). They showed that the expression of some circulating miRNAs e.g. miR-21, let-7g, miR-31, miR-92a, miR-181b, and miR-203 is significantly different between CRC patients and healthy subjects. Their results revealed that the expression of these miRNAs could have high specificity for detecting the CRC patients. This finding suggested that these circulating miRNAs could be employed as attractive option for detecting patients with CRC (Wang, Huang et al. 2014).

Circulating miR-20a is a miRNA which might be applied as a potential therapeutic target in CRC patients (Huang, Chen et al. 2017). It has been shown that up-regulation of miR-20a is associated with survival of CRC cells. TRAIL is one of the main tumor suppressor genes and its expression is related to the induction of apoptosis in CRC cells. It has been found that miR-20a could affect the expression of TRAIL in CRC patients. Down-regulation of miR-20a by inhibitors increases the anti-cancer effect of TRAIL. Moreover, miR-20a could regulate BID which is a member of the Bcl-2 family. These results indicated that miR-20a acts as an oncogene and might be a new therapeutic target in CRC patients (Huang, Chen et al. 2017).

Zekri et al. assessed the possibility of using circulating miRNAs as potential diagnostic candidates in patients with CRC, inflammatory bowel disease (IBD) and colonic polyps (CP) (Wang, Huang et al. 2014). The results indicated that miR-19b and miR-18a are up-regulated in IBD and CP patients by 5.24 and 3.49 folds, respectively. Moreover, a number of circulating miRNAs e.g. miR-223, miR-19a, miR-17, and miR-20a are up-regulated in CRC patients (by 2.35, 3.07, 2.38 and 10.35 folds, respectively). This finding revealed that deregulation of various miRNAs could be involved in CRC pathogenesis and (Wang, Huang et al. 2014).

Luo and colleagues used plasma miRNAs for the diagnosis of CRC in early stages (Luo, Stock et al. 2013). They assessed miRNAexpression in 50 CRC patients and 50 neoplasm-free controls. Validation groups included 80 CRC patients, 80 advanced adenoma patients and 194 neoplasm-free controls. TaqMan MicroRNA array analysis indicated that a number of circulating miRNAs including miR-133a, miR-29a, miR-342-3p, miR-106b, and miR-532-3p are differentially expressed. Moreover, seven circulating miRNAs including miR-92a, miR-18a, miR-21, miR-143, miR-20a, miR-145, and miR-181b were selected for validation. The authors showed that nine of the twelve circulating miRNAs including miR-29a, miR-18a, miR-92a, miR-20a, miR-21, miR-106b, miR-143, miR-133a, and miR-145 are differentially expressed between controls and patients with CRC in the validation samples. The results indicated that this of circulating miRNAs might be used as diagnostic and prognostic biomarkers in CRC patients (Luo, Stock et al. 2013). Table 2

illustrates a number of circulating miRNAs which might be applied as diagnostic and therapeutic biomarkers in CRC patients.

Exosomes in CRC

Exosomes are key contributors to intercellular communication. These nano-carriers are released from different types of cells such as tumor cells, stem cells and some normal cells (Mirzaei, Sahebkar et al. 2016; Saadatpour, Fadaee et al. 2016). Exosomes can carry a number of molecules such as DNAs, mRNAs, proteins and miRNAs to receipt cells (Mirzaei, Sahebkar et al. 2016; Saadatpour, Fadaee et al. 2016). Hence, exosomes and their cargos transfer particular message to recipient cells and change the cell behavior. Several studies have indicated that exosomes released from cancer cells are important players in tumor progression in several diseases such as cancer (Mirzaei, Sahebkar et al. 2016; Saadatpour, Fadaee et al. 2016). Multiple lines of evidence have revealed that these nano-vehicles with particular cargos such as miRNAs could change the behaviors of CRC cells and move them into progression stages (Silva, Garcia et al. 2012). Hence, identification of exosomes and their cargos might be applied as a new approach for detecting CRC in early stages.

Ogata-Kawata et al. investigated the expression of circulating exosomes containing miRNAs in 81 CRC patients and 11 healthy samples which showed relationship between these exosomes with pathogenic events in this disease (Ogata-Kawata, Izumiya et al. 2014). Their results revealed that the level of circulating exosomes containing a number of miRNA, including let-7a, miR-1229, miR-1246, miR-150, miR-21, miR-223, and miR-23a, were up-regulated in the sera of CRC patients. Moreover, these miRNAs were down-regulated after surgical resection of tumors in CRC patients compared with the healthy group. These findings suggested that circulating exosomes containing miRNAs could be a new candidate for the diagnosis of patients with CRC (Ogata-Kawata, Izumiya et al. 2014).

Matsumura and colleagues assessed exosomes containing miRNAs as new candidates for early diagnosis of recurrence in patients with CRC (Matsumura, Sugimachi et al. 2015). They confirmed that the expression of exosomal miR-17-92a cluster was associated with the recurrence disease. Moreover, the expression of exosomal miR-19a was up-regulated in the sera of CRC patients compared with the control group. It has been observed that up-regulation of exosomal miR-19a is associated with a poor prognosis in CRC patients. These results have revealed that exosomal miR-19a and miR-17-92a might be used as diagnostic biomarkers in CRC patients (Matsumura, Sugimachi et al. 2015).

Chiba et al. indicated that exosomes released from CRC cells could carry various cargos such as some proteins and RNAs which could be used as biomarkers in CRC cells (Chiba, Kimura et al. 2012). They showed that exosomal proteins including CD63, CD9 and CD81 are useful biomarkers for the identification of CRC cells. Moreover, they detected other cargos such as mRNA (ACTB, GAPDH), miRNA (miR-21, miR-192 and miR-221) and the natural antisense RNAs (LRRC24, MDM2 and CDKN1A) in exosomes released from CRC cells. Finally, these findings indicated that exosomal proteins, RNAs and miRNAs might be used as potential biomarkers in CRC patients (Chiba, Kimura et al. 2012). Table 3 indicates a number ofexosomal biomarkers released from CRC cells.

Conclusion

CRC is ranked among the most common types of cancer and a leading cause of cancer-related death worldwide. Early diagnosis of CRC is a pre-requisite for proper management of the patient and increasing survival. Several lines of evidence have indicated that patients with CRC have a poor prognosis due to the lack of simple, reliable and non-invasive diagnostic tools for the early stage of the disease. Currently, colonoscopy is the gold standard for early diagnosis of CRC but its invasiveness is a big limitation. MicroRNAs have emerged as non-coding RNAs which have the potential to be used as promising candidates for the diagnosis of CRC patients. Moreover, exosomal

biomarkers including miRNAs, proteins and mRNAs could open new horizons for the diagnosis of CRC.

References

Akao, Y., Y. Nakagawa, et al. (2006). "let-7 microRNA functions as a potential growth suppressor in human colon cancer cells." Biological and Pharmaceutical Bulletin **29**(5): 903-906.

Bauer, K. M. and A. B. Hummon (2012). "Effects of the miR-143/-145 microRNA cluster on the colon cancer proteome and transcriptome." Journal of proteome research **11**(9): 4744-4754.

Baxter, R. C. (2014). "IGF binding proteins in cancer: mechanistic and clinical insights." Nature Reviews Cancer **14**(5): 329-341.

Bi, D.-P., C.-H. Yin, et al. (2016). "miR-183 functions as an oncogene by targeting ABCA1 in colon cancer." Oncology reports **35**(5): 2873-2879.

Bigagli, E., C. Luceri, et al. (2016). "Exosomes secreted from human colon cancer cells influence the adhesion of neighboring metastatic cells: Role of microRNA-210." Cancer Biology & Therapy **17**(10): 1062-1069.

Bu, P., K.-Y. Chen, et al. (2013). "A microRNA miR-34a-regulated bimodal switch targets Notch in colon cancer stem cells." Cell stem cell **12**(5): 602-615.

Cai, K., F. Shen, et al. (2015). "Expression of miR-221 in colon cancer correlates with prognosis." Int J Clin Exp Med **8**(2): 2794-2798.

Cekaite, L., J. K. Rantala, et al. (2012). "MiR-9,-31, and-182 deregulation promote proliferation and tumor cell survival in colon cancer." Neoplasia **14**(9): 868-IN821.

Cha, D. J., J. L. Franklin, et al. (2015). "KRAS-dependent sorting of miRNA to exosomes." Elife **4**: e07197.

Chen, Q., H.-W. Xia, et al. (2013). "Serum miR-19a predicts resistance to FOLFOX chemotherapy in advanced colorectal cancer cases." Asian Pacific Journal of Cancer Prevention **14**(12): 7421-7426.

Chen, Y., Y. Xie, et al. (2017). "Protein content and functional characteristics of serum-purified exosomes from patients with colorectal cancer revealed by quantitative proteomics." International Journal of Cancer.

Cheng, D., S. Zhao, et al. (2016). "MicroRNA-20a-5p promotes colorectal cancer invasion and metastasis by downregulating Smad4." Oncotarget.

Cheng, H., L. Zhang, et al. (2011). "Circulating plasma MiR-141 is a novel biomarker for metastatic colon cancer and predicts poor prognosis." PloS one **6**(3): e17745.

Chi, Y. and D. Zhou (2016). "MicroRNAs in colorectal carcinoma-from pathogenesis to therapy." Journal of Experimental & Clinical Cancer Research **35**(1): 1.

Chiba, M., M. Kimura, et al. (2012). "Exosomes secreted from human colorectal cancer cell lines contain mRNAs, microRNAs and natural antisense RNAs, that can transfer into the human hepatoma HepG2 and lung cancer A549 cell lines." Oncology reports **28**(5): 1551-1558.

Clancy, C., S. Khan, et al. (2016). "Screening of exosomal microRNAs from colorectal cancer cells." Cancer Biomarkers(Preprint): 1-9.

Dakubo, G. D. (2017). Colorectal Cancer Biomarkers in Circulation. Cancer Biomarkers in Body Fluids, Springer**:** 213-246.

Das, V., J. Kalita, et al. (2017). "Predictive and prognostic biomarkers in colorectal cancer: A systematic review of recent advances and challenges." Biomedicine & Pharmacotherapy **87**: 8-19.

Deng, B., B. Wang, et al. (2016). "MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of EIF5A2." Scientific Reports **6**.

Diaz, R., J. Silva, et al. (2008). "Deregulated expression of miR-106a predicts survival in human colon cancer patients." Genes, Chromosomes and Cancer **47**(9): 794-802.

DOKI, Y., M. MORI, et al. (2016). "Identification of microRNA-487b as a negative regulator of liver metastasis by regulation of KRAS in colorectal cancer."

Dong, Y., J. Yu, et al. (2014). "MicroRNA dysregulation as a prognostic biomarker in colorectal cancer." Cancer management and research **6**: 405.

Earle, J. S., R. Luthra, et al. (2010). "Association of microRNA expression with microsatellite instability status in colorectal adenocarcinoma." The Journal of Molecular Diagnostics **12**(4): 433-440.
Eyking, A., H. Reis, et al. (2016). "MiR-205 and MiR-373 Are Associated with Aggressive Human Mucinous Colorectal Cancer." PloS one **11**(6): e0156871.
Fang, Y., X. Gu, et al. (2013). "miR-449b inhibits the proliferation of SW1116 colon cancer stem cells through downregulation of CCND1 and E2F3 expression." Oncology reports **30**(1): 399-406.
Fathullahzadeh, S., H. Mirzaei, et al. (2016). "Circulating microRNA-192 as a diagnostic biomarker in human chronic lymphocytic leukemia." Cancer gene therapy **23**(10): 327-332.
Ferracin, M., L. Lupini, et al. (2016). Circulating Non-coding RNA as Biomarkers in Colorectal Cancer. Non-coding RNAs in Colorectal Cancer, Springer**:** 171-181.
Filou, S., A. Korpetinou, et al. (2015). "ADAMTS Expression in Colorectal Cancer." PloS one **10**(3): e0121209.
Fujino, Y., S. Takeishi, et al. (2016). "Downregulation of miR-100/miR-125b is associated with lymph node metastasis in early colorectal cancer with submucosal invasion." Cancer Sci **29**(10): 13152.
Gao, J., N. Li, et al. (2015). "miR-34a-5p suppresses colorectal cancer metastasis and predicts recurrence in patients with stage II/III colorectal cancer." Oncogene **34**(31): 4142-4152.
Gao, Y., B.-D. Li, et al. (2013). "Effect of miR27a on proliferation and invasion in colonic cancer cells." Asian Pacific Journal of Cancer Prevention **14**(8): 4675-4678.
Gao, Y., Y. Liu, et al. (2015). "Down-regulation of miR-24-3p in colorectal cancer is associated with malignant behavior." Medical Oncology **32**(1): 1-8.
Geng, L., A. Chaudhuri, et al. (2014). "MicroRNA-192 suppresses liver metastasis of colon cancer." Oncogene **33**(46): 5332-5340.
Gharagozloo, M., H. R. Mirzaei, et al. (2012). "Cell cycle analysis of the CD133+ and CD133-cells isolated from human colorectal cancer." Journal of cancer research and therapeutics **8**(3): 399.
Grady, W. M. and S. D. Markowitz (2002). "Genetic and epigenetic alterations in colon cancer." Annual review of genomics and human genetics **3**(1): 101-128.
Hansen, T., A. Carlsen, et al. (2015). "Changes in circulating microRNA-126 during treatment with chemotherapy and bevacizumab predicts treatment response in patients with metastatic colorectal cancer." British journal of cancer **112**(4): 624-629.
He, J., G. Xie, et al. (2014). "Overexpression of microRNA-122 re-sensitizes 5-FU-resistant colon cancer cells to 5-FU through the inhibition of PKM2 in vitro and in vivo." Cell biochemistry and biophysics **70**(2): 1343-1350.
Hiyoshi, Y., A. J. Schetter, et al. (2015). "Increased microRNA-34b and-34c predominantly expressed in stromal tissues is associated with poor prognosis in human colon cancer." PloS one **10**(4): e0124899.
Huang, G., X. Chen, et al. (2017). "miR-20a-directed regulation of BID is associated with the TRAIL sensitivity in colorectal cancer." Oncology Reports **37**(1): 571-578.
Huang, L., X. Wang, et al. (2015). "Hsa-miR-19a is associated with lymph metastasis and mediates the TNF-α induced epithelial-to-mesenchymal transition in colorectal cancer." Scientific reports **5**.
Huang, Z., S. Huang, et al. (2011). "MicroRNA-95 promotes cell proliferation and targets sorting Nexin 1 in human colorectal carcinoma." Cancer research **71**(7): 2582-2589.
Ibrahim, A. F., U. Weirauch, et al. (2011). "MicroRNA replacement therapy for miR-145 and miR-33a is efficacious in a model of colon carcinoma." Cancer research **71**(15): 5214-5224.
Ilm, K., S. Fuchs, et al. (2016). "MACC1 is post-transcriptionally regulated by miR-218 in colorectal cancer." Oncotarget **7**(33): 53443-53458.
Ji, D., Z. Chen, et al. (2014). "MicroRNA-181a promotes tumor growth and liver metastasis in colorectal cancer by targeting the tumor suppressor WIF-1." Molecular cancer **13**(1): 1.
Ji, H., D. W. Greening, et al. (2013). "Proteome profiling of exosomes derived from human primary and metastatic colorectal cancer cells reveal differential expression of key metastatic factors and signal transduction components." Proteomics **13**(10-11): 1672-1686.
Jiang, Y., Q. Meng, et al. (2015). "MiR-497 promotes metastasis of colorectal cancer cells through Nrdp1 inhibition." Tumor Biology **36**(10): 7641-7647.
Jinushi, T., Y. Shibayama, et al. (2014). "Low expression levels of microRNA-124-5p correlated with poor prognosis in colorectal cancer via targeting of SMC4." Cancer medicine **3**(6): 1544-1552.

Karaayvaz, M., T. Pal, et al. (2011). "Prognostic significance of miR-215 in colon cancer." Clinical colorectal cancer **10**(4): 340-347.
Ke, T.-W., P.-L. Wei, et al. (2015). "MiR-92a promotes cell metastasis of colorectal cancer through PTEN-mediated PI3K/AKT pathway." Annals of surgical oncology **22**(8): 2649-2655.
Kijima, T., S. Hazama, et al. (2017). "MicroRNA-6826 and-6875 in plasma are valuable non‐invasive biomarkers that predict the efficacy of vaccine treatment against metastatic colorectal cancer." Oncology Reports **37**(1): 23-30.
Kim, B.-K., H.-I. Yoo, et al. (2015). "FZD6 expression is negatively regulated by miR-199a-5p in human colorectal cancer." BMB reports **48**(6): 360.
Kjersem, J., T. Ikdahl, et al. (2014). "Plasma microRNAs predicting clinical outcome in metastatic colorectal cancer patients receiving first-line oxaliplatin-based treatment." Molecular oncology **8**(1): 59-67.
Knudsen, K. N., B. S. Nielsen, et al. (2015). "microRNA-17 is the most up-regulated member of the miR-17-92 cluster during early colon cancer evolution." PloS one **10**(10): e0140503.
Konishi, H., M. Fujiya, et al. (2015). "microRNA-26a and-584 inhibit the colorectal cancer progression through inhibition of the binding of hnRNP A1-CDK6 mRNA." Biochemical and biophysical research communications **467**(4): 847-852.
Lee, C. G., S. McCarthy, et al. (2014). "MicroRNA-147 induces a mesenchymal-to-epithelial transition (MET) and reverses EGFR inhibitor resistance." PLoS One **9**(1): e84597.
Li, B., Z. Xie, et al. (2016). "miR-152 functions as a tumor suppressor in colorectal cancer by targeting PIK3R3." Tumor Biology: 1-10.
Li, Q., X. Liang, et al. (2016). "miR-139-5p Inhibits the Epithelial-Mesenchymal Transition and Enhances the Chemotherapeutic Sensitivity of Colorectal Cancer Cells by Downregulating BCL2." Scientific reports **6**: 27157.
Li, Q., C. Zou, et al. (2013). "MicroRNA-25 functions as a potential tumor suppressor in colon cancer by targeting Smad7." Cancer letters **335**(1): 168-174.
Li, Y., C. Kuscu, et al. (2015). "miR-181a-5p inhibits cancer cell migration and angiogenesis via downregulation of matrix metalloproteinase-14." Cancer research **75**(13): 2674-2685.
Li, Y., J. Wang, et al. (2015). "miR-451 regulates FoxO3 nuclear accumulation through Ywhaz in human colorectal cancer." American journal of translational research **7**(12): 2775.
Liao, W., C. Gu, et al. (2016). "MicroRNA-33b inhibits tumor cell growth and is associated with prognosis in colorectal cancer patients." Clinical and Translational Oncology **18**(5): 449-456.
Lin, C., X. Li, et al. (2014). "TAp63 suppress metastasis via miR-133b in colon cancer cells." British journal of cancer **110**(9).
Lin, S., Q. Xia, et al. (2016). "miR-124 regulates radiosensitivity of colorectal cancer cells by targeting PRRX1." Nan fang yi ke da xue xue bao= Journal of Southern Medical University **36**(8): 1110.
Lindblom, A. (2001). "Different mechanisms in the tumorigenesis of proximal and distal colon cancers." Current opinion in oncology **13**(1): 63-69.
Ling, H., K. Pickard, et al. (2015). "The clinical and biological significance of MIR-224 expression in colorectal cancer metastasis." Gut: gutjnl-2015-309372.
Liu, S., X. Sun, et al. (2014). "A microRNA 221–and 222–Mediated Feedback Loop Maintains Constitutive Activation of NFκB and STAT3 in Colorectal Cancer Cells." Gastroenterology **147**(4): 847-859. e811.
Liu, T., X. Zhang, et al. (2016). "Exosomal long noncoding RNA CRNDE-h as a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer." Oncotarget **7**(51): 85551-85563.
Long, L., G. Huang, et al. (2013). "Down-regulation of miR-138 promotes colorectal cancer metastasis via directly targeting TWIST2." Journal of translational medicine **11**(1): 1.
Long, L. M., B. F. He, et al. (2015). "microRNA-214 functions as a tumor suppressor in human colon cancer via the suppression of ADP-ribosylation factor-like protein 2." Oncology letters **9**(2): 645-650.
Luo, X., C. Stock, et al. (2013). "Identification and evaluation of plasma microRNAs for early detection of colorectal cancer." PloS one **8**(5): e62880.
Lv, Z.-c., Y.-s. Fan, et al. (2015). "Investigation of microRNA-155 as a serum diagnostic and prognostic biomarker for colorectal cancer." Tumor Biology **36**(3): 1619-1625.
Martín-Subero, J. I. and M. Esteller (2017). Epigenetic Mechanisms in Cancer Development. The Molecular Basis of Human Cancer, Springer**:** 263-275.

Matsumura, T., K. Sugimachi, et al. (2015). "Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer." British journal of cancer **113**(2): 275-281.
Matsuyama, R., D. Okuzaki, et al. (2016). "MicroRNA-27b suppresses tumor progression by regulating ARFGEF1 and focal adhesion signaling." Cancer science **107**(1): 28-35.
Meng, W.-J., L. Yang, et al. (2015). "MicroRNA expression profile reveals miR-17-92 and miR-143-145 cluster in synchronous colorectal cancer." Medicine **94**(32).
Meng, X., J. Wu, et al. (2013). "Genetic and epigenetic down-regulation of microRNA-212 promotes colorectal tumor metastasis via dysregulation of MnSOD." Gastroenterology **145**(2): 426-436. e426.
Migliore, C., V. Martin, et al. (2012). "MiR-1 downregulation cooperates with MACC1 in promoting MET overexpression in human colon cancer." Clinical Cancer Research **18**(3): 737-747.
Mirzaei, H., S. Khataminfar, et al. (2016). "Circulating microRNAs as Potential Diagnostic Biomarkers and Therapeutic Targets in Gastric Cancer: Current Status and Future Perspectives." Current medicinal chemistry **23**(36): 4135-4150.
Mirzaei, H., F. Momeni, et al. (2017). "MicroRNA: Relevance to Stroke Diagnosis, Prognosis and Therapy." J Cell Physiol **9**(10): 25787.
Mirzaei, H., G. Naseri, et al. (2016). "Curcumin: A new candidate for melanoma therapy?" International Journal of Cancer.
Mirzaei, H., A. Sahebkar, et al. (2016). "Diagnostic and Therapeutic Potential of Exosomes in Cancer: The Beginning of a New Tale?" Journal of Cellular Physiology.
Mirzaei, H., A. Sahebkar, et al. (2016). "Circulating microRNAs in hepatocellular carcinoma: potential diagnostic and prognostic biomarkers." Current pharmaceutical design.
Mishra, P. J., B. Song, et al. (2009). "MiR-24 tumor suppressor activity is regulated independent of p53 and through a target site polymorphism." PloS one **4**(12): e8445.
Misiakos, E. P., N. P. Karidis, et al. (2011). "Current treatment for colorectal liver metastases." World J Gastroenterol **17**(36): 4067-4075.
Mohammadi, M., M. Goodarzi, et al. (2016). "Circulating microRNA: a new candidate for diagnostic biomarker in neuroblastoma." Cancer Gene Therapy **23**(11): 371-372.
Molina-Pinelo, S., A. Carnero, et al. (2014). "MiR-107 and miR-99a-3p predict chemotherapy response in patients with advanced colorectal cancer." BMC cancer **14**(1): 1.
Montagnana, M., M. Benati, et al. (2016). "Plasma Expression Levels of Circulating miR-21 are not Useful for Diagnosing and Monitoring Colorectal Cancer." Clinical laboratory **62**(5): 967-970.
Nishida, N., S. Yamashita, et al. (2012). "MicroRNA-10b is a prognostic indicator in colorectal cancer and confers resistance to the chemotherapeutic agent 5-fluorouracil in colorectal cancer cells." Annals of surgical oncology **19**(9): 3065-3071.
Nishimura, J., R. Handa, et al. (2012). "microRNA-181a is associated with poor prognosis of colorectal cancer." Oncology reports **28**(6): 2221-2226.
Ogata-Kawata, H., M. Izumiya, et al. (2014). "Circulating exosomal microRNAs as biomarkers of colon cancer." PloS one **9**(4): e92921.
Ohira, T., S. Naohiro, et al. (2015). "miR-19b regulates hTERT mRNA expression through targeting PITX1 mRNA in melanoma cells." Scientific reports **5**.
Orang, A. V. and A. Barzegari (2014). "MicroRNAs in colorectal cancer: from diagnosis to targeted therapy." Asian Pac J Cancer Prev **15**(17): 6989-6999.
ÖzATA, D. M., H. Xie, et al. (2011). "miR-185 and miR-133b deregulation is associated with overall survival and metastasis in colorectal cancer." Int J Oncol **39**: 311-318.
Peters, U., S. Jiao, et al. (2013). "Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis." Gastroenterology **144**(4): 799-807. e724.
Pu, X. x., G. l. Huang, et al. (2010). "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 **25**(10): 1674-1680.
Qased, A. B., H. Yi, et al. (2013). "MicroRNA-18a upregulates autophagy and ataxia telangiectasia mutated gene expression in HCT116 colon cancer cells." Molecular medicine reports **7**(2): 559-564.
Qian, J., B. Jiang, et al. (2013). "Prognostic significance of microRNA-16 expression in human colorectal cancer." World journal of surgery **37**(12): 2944-2949.

Qu, Y.-L., H.-F. Wang, et al. (2015). "Up-regulated miR-155-5p promotes cell proliferation, invasion and metastasis in colorectal carcinoma." International journal of clinical and experimental pathology **8**(6): 6988.
Rapti, S.-M., C. K. Kontos, et al. (2016). "High miR-96 levels in colorectal adenocarcinoma predict poor prognosis, particularly in patients without distant metastasis at the time of initial diagnosis." Tumor Biology: 1-10.
Ress, A. L., V. Stiegelbauer, et al. (2015). "MiR-96-5p influences cellular growth and is associated with poor survival in colorectal cancer patients." Molecular carcinogenesis **54**(11): 1442-1450.
Saadatpour, L., E. Fadaee, et al. (2016). "Glioblastoma: exosome and microRNA as novel diagnosis biomarkers." Cancer Gene Therapy **23**(12): 415-418.
Sakaguchi, M., S. Hisamori, et al. (2016). "miR-137 Regulates the Tumorigenicity of Colon Cancer Stem Cells through the Inhibition of DCLK1." Molecular Cancer Research **14**(4): 354-362.
Salarini, R., A. Sahebkar, et al. (2015). "Epi-drugs and Epi-miRs: Moving beyond current cancer therapies." Current cancer drug targets.
Schimanski, C. C., P. R. Galle, et al. (2008). "Citation of This Article." World J Gastroenterol **14**(30): 4721-4724.
Schirripa, M. and H.-J. Lenz (2016). "Biomarker in Colorectal Cancer." The Cancer Journal **22**(3): 156-164.
Schou, J. V., S. Rossi, et al. (2014). "miR-345 in Metastatic Colorectal Cancer: A Non-Invasive Biomarker for Clinical Outcome in Non-KRAS Mutant Patients Treated with 3 rd Line Cetuximab and Irinotecan." PloS one **9**(6): e99886.
Shan, L., Q. Ji, et al. (2015). "Diagnostic value of circulating miR-21 for colorectal cancer: a meta-analysis." Cancer Biomarkers **15**(1): 47-56.
Shen, K., Q. Liang, et al. (2012). "MiR-139 inhibits invasion and metastasis of colorectal cancer by targeting the type I insulin-like growth factor receptor." Biochemical pharmacology **84**(3): 320-330.
Silva, J., V. Garcia, et al. (2012). "Analysis of exosome release and its prognostic value in human colorectal cancer." Genes, Chromosomes and Cancer **51**(4): 409-418.
Simonian, M., M. Mosallayi, et al. (2016). "Circulating miR-21 as novel biomarker in gastric cancer: Diagnostic and prognostic biomarker."
Strillacci, A., C. Griffoni, et al. (2009). "MiR-101 downregulation is involved in cyclooxygenase-2 overexpression in human colon cancer cells." Experimental cell research **315**(8): 1439-1447.
Sun, J., W. Ding, et al. (2015). "MiR-200 suppresses metastases of colorectal cancer through ZEB1." Tumor Biology: 1-7.
Tagscherer, K. E., A. Fassl, et al. (2016). "MicroRNA-210 induces apoptosis in colorectal cancer via induction of reactive oxygen." Cancer Cell International **16**(1): 1.
Takahashi, M., M. Cuatrecasas, et al. (2012). "The clinical significance of MiR-148a as a predictive biomarker in patients with advanced colorectal cancer." PloS one **7**(10): e46684.
Tanaka, T., M. Tanaka, et al. (2010). "Biomarkers for colorectal cancer." International journal of molecular sciences **11**(9): 3209-3225.
Tang, Q., Z. Zou, et al. (2015). "MicroRNA-93 suppress colorectal cancer development via Wnt/β-catenin pathway downregulating." Tumor Biology **36**(3): 1701-1710.
Tang, W., Y. Zhu, et al. (2014). "MicroRNA-29a promotes colorectal cancer metastasis by regulating matrix metalloproteinase 2 and E-cadherin via KLF4." British journal of cancer **110**(2): 450-458.
Toiyama, Y., K. Hur, et al. (2014). "Serum miR-200c is a novel prognostic and metastasis-predictive biomarker in patients with colorectal cancer." Annals of surgery **259**(4): 735.
Tong, Z., N. Liu, et al. (2015). "miR-125a-5p inhibits cell proliferation and induces apoptosis in colon cancer via targeting BCL2, BCL2L12 and MCL1." Biomedicine & Pharmacotherapy **75**: 129-136.
Trang, P., J. B. Weidhaas, et al. (2017). MicroRNAs and Cancer. The Molecular Basis of Human Cancer, Springer**:** 277-286.
Treanor, D. and P. Quirke (2007). "Pathology of colorectal cancer." Clinical oncology **19**(10): 769-776.
Tsang, W. P., E. K. Ng, et al. (2010). "Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer." Carcinogenesis **31**(3): 350-358.
Wang, B., W. Li, et al. (2014). "miR-29b suppresses tumor growth and metastasis in colorectal cancer via downregulating Tiam1 expression and inhibiting epithelial–mesenchymal transition." Cell death & disease **5**(7): e1335.

Wang, J., Y. Du, et al. (2015). "MicroRNAs as regulator of signaling networks in metastatic colon cancer." BioMed research international **2015**.
Wang, J., S.-k. Huang, et al. (2014). "Identification of a circulating microRNA signature for colorectal cancer detection." PloS one **9**(4): e87451.
Wang, Y., W. Yuan, et al. (2016). "Expression of microRNA-152 in colorectal cancer and its relationship with prognosis." Zhonghua zhong liu za zhi [Chinese journal of oncology] **38**(10): 763.
Wei, W., Y. Yang, et al. (2016). "MiR-30a-5p Suppresses Tumor Metastasis of Human Colorectal Cancer by Targeting ITGB3." Cellular Physiology and Biochemistry **39**(3): 1165-1176.
Wu, W., J. Yang, et al. (2013). "MicroRNA-32 (miR-32) regulates phosphatase and tensin homologue (PTEN) expression and promotes growth, migration, and invasion in colorectal carcinoma cells." Molecular cancer **12**(1): 1.
Xiong, B., Y. Cheng, et al. (2013). "MiR-21 regulates biological behavior through the PTEN/PI-3 K/Akt signaling pathway in human colorectal cancer cells." International journal of oncology **42**(1): 219-228.
Xu, K., Z. Chen, et al. (2014). "miR-7 inhibits colorectal cancer cell proliferation and induces apoptosis by targeting XRCC2." OncoTargets & Therapy **7**.
Xu, T., C. Jing, et al. (2015). "microRNA-20a enhances the epithelial-to-mesenchymal transition of colorectal cancer cells by modulating matrix metalloproteinases." Experimental and therapeutic medicine **10**(2): 683-688.
Yamazaki, N., Y. Koga, et al. (2016). "High expression of miR-181c as a predictive marker of recurrence in stage II colorectal cancer." Oncotarget **28**(10): 14344.
Yang, B., Z. Tan, et al. (2014). "Study on the molecular regulatory mechanism of MicroRNA-195 in the invasion and metastasis of colorectal carcinoma." International journal of clinical and experimental medicine **8**(3): 3793-3800.
Yang, X., X. Xu, et al. (2016). "miR-31 affects colorectal cancer cells by inhibiting autophagy in cancer-associated fibroblasts." Oncotarget.
Ye, H., L. Pang, et al. (2015). "A critical role of mir-199a in the cell biological behaviors of colorectal cancer." Diagnostic pathology **10**(1): 1.
Yiu, A. J. and C. Y. Yiu (2016). "Biomarkers in colorectal cancer." Anticancer research **36**(3): 1093-1102.
Yong, F. L., C. W. Wang, et al. (2014). "The involvement of miR-23a/APAF1 regulation axis in colorectal cancer." International journal of molecular sciences **15**(7): 11713-11729.
Yu, L., Y. Lu, et al. (2016). "microRNA -140-5p inhibits colorectal cancer invasion and metastasis by targeting ADAMTS5 and IGFBP5." Stem Cell Res Ther **7**(1): 180.
Yu, Y., P. Nangia-Makker, et al. (2015). "miR-21 and miR-145 cooperation in regulation of colon cancer stem cells." Molecular cancer **14**(1): 1.
Yuan, D., K. Li, et al. (2015). "Plasma miR-183 predicts recurrence and prognosis in patients with colorectal cancer." Cancer biology & therapy **16**(2): 268-275.
Yuan, W., Y.-Q. Guo, et al. (2016). "MicroRNA-126 inhibits colon cancer cell proliferation and invasion by targeting the chemokine (CXC motif) receptor 4 and Ras homolog gene family, member A, signaling pathway." Oncotarget **7**(37): 60230-60244.
Zekri, A.-R. N., A. S. E.-D. Youssef, et al. (2016). "Circulating Serum miRNAs as Diagnostic Markers for Colorectal Cancer." PloS one **11**(5): e0154130.
Zhang, G.-j., J.-s. Li, et al. (2015). "MicroRNA-106b promotes colorectal cancer cell migration and invasion by directly targeting DLC1." Journal of Experimental & Clinical Cancer Research **34**(1): 1.
Zhang, G.-J., H.-X. Xiao, et al. (2013). "Upregulation of microRNA-155 promotes the migration and invasion of colorectal cancer cells through the regulation of claudin-1 expression." International journal of molecular medicine **31**(6): 1375-1380.
Zhang, H., Y. Hao, et al. (2011). "Genome-wide functional screening of miR-23b as a pleiotropic modulator suppressing cancer metastasis." Nature communications **2**: 554.
Zhang, H., W. Li, et al. (2011). "MicroRNA expression profile of colon cancer stem-like cells in HT29 adenocarcinoma cell line." Biochemical and biophysical research communications **404**(1): 273-278.
Zhang, H., Y. Li, et al. (2011). "MiR-148a promotes apoptosis by targeting Bcl-2 in colorectal cancer." Cell Death & Differentiation **18**(11): 1702-1710.

Zhang, J., X. Luo, et al. (2014). "MicroRNA-223 functions as an oncogene in human colorectal cancer cells." Oncology reports **32**(1): 115-120.
Zhang, J., K. Zhang, et al. (2014). "Circulating microRNA expressions in colorectal cancer as predictors of response to chemotherapy." Anti-cancer drugs **25**(3): 346-352.
Zhang, Q., Q. Tang, et al. (2015). "Role of microRNA 30a targeting insulin receptor substrate 2 in colorectal tumorigenesis." Molecular and cellular biology **35**(6): 988-1000.
Zhang, Q., L. Yu, et al. (2015). "Role of microRNA-30c targeting ADAM19 in colorectal cancer." PloS one **10**(3): e0120698.
Zhang, X.-F., K.-k. Li, et al. (2015). "miR-191 promotes tumorigenesis of human colorectal cancer through targeting C/EBPβ." Oncotarget **6**(6): 4144.
Zhang, Z., K. Kim, et al. (2014). "MicroRNA-26b represses colon cancer cell proliferation by inhibiting lymphoid enhancer factor 1 expression." Molecular cancer therapeutics **13**(7): 1942-1951.
Zhao, L., H. Yu, et al. (2016). "The tumor suppressor miR-138-5p targets PD-L1 in colorectal cancer." Oncotarget.
Zheng, Y. B., K. Xiao, et al. (2016). "MicroRNA-103 promotes tumor growth and metastasis in colorectal cancer by directly targeting LATS2." Oncology Letters **12**(3): 2194-2200.
Zu, C., T. Liu, et al. (2016). "MicroRNA-506 Inhibits Malignancy of Colorectal Carcinoma Cells by Targeting LAMC1." Annals of Clinical & Laboratory Science **46**(6): 666-674.

Table 1. Tissue-specific microRNAs up/down regulated in CRC

MicroRNA	Expression in CRC	Biomarker	Detection method	Target gene (s)	Sample (cell line, human)	Ref
let-7	Down regulation	Diagnostic	qRT-PCR	RAS, HMGA2	6	(Akao, Nakagawa et al. 2006)
miR-101b	Down regulation	Diagnostic	qRT-PCR	COX2	8	(Strillacci, Griffoni et al. 2009)
miR-124a	Down regulation	Diagnostic	qRT-PCR	CDK6, Rb	Cell line	(Lin, Xia et al. 2016)
miR-133b	Down regulation	Diagnostic	qRT-PCR	c-Met, K-Ras, TAp63	50	(Lin, Li et al. 2014)
miR-137	Down regulation	Diagnostic	qRT-PCR	Cdc42, LSD-1, TGF2I	Cell line/in vivo	(Sakaguchi, Hisamori et al. 2016)
miR-212	Down regulation	Diagnostic	qRT-PCR	MnSOD	Cell line	(Meng, Wu et al. 2013)
miR-27a	Down regulation	Diagnostic	RT-PCR	SGPP1, Smad2	Cell line	(Gao, Li et al. 2013)
miR-214	Down regulation	Diagnostic	qRT-PCR	TP53, CDKN2b, EGFR, TFAP2C	24	(Long, He et al. 2015)
miR-449b	Down regulation	Diagnostic	qRT-PCR	E2F3, CCND1	Cell line	(Fang, Gu et al. 2013)
miR-497	Down regulation	Diagnostic	qRT-PCR	IGF1R	25	(Jiang, Meng et al. 2015)
miR-103	Up regulation	Diagnostic	qRT-PCR	DAPK, KLF4	38	(Zheng, Xiao et al. 2016)
miR-107	Up regulation	Diagnostic	qRT-PCR	DAPK, KLF4	78	(Molina-Pinelo, Carnero et al. 2014)
miR-122	Up regulation	Diagnostic	qRT-PCR	CAT1, ADAM17, cyclin-G, Bcl-W	Cell line/in vivo	(He, Xie et al. 2014)
miR-155	Up regulation	Diagnostic	qRT-PCR	MSH2, MSH6, MCH1, AKT	Cell line	(Zhang, Xiao et al. 2013)
miR-155-5p	Up regulation	Diagnostic	qRT-PCR	-	372	(Qu, Wang et al. 2015)
miR-182	Up regulation	Diagnostic	qRT-PCR	ENTPD5, IGFR1, FoxF2	80	(Cekaite, Rantala et al. 2012)
miR-210	Up regulation	Diagnostic	qRT-PCR	K-Ras, Bcl-2	Cell line	(Tagscherer, Fassl et al. 2016)
miR-221	Up regulation	Diagnostic	qRT-PCR	c-Kit, Stat5A, ETS1, ENOS	182	(Cai, Shen et al. 2015)
miR-451	Up regulation	Diagnostic	qRT-PCR	MIF, IL6R	46	(Li, Wang et al. 2015)

miR-675	Up regulation	Diagnostic	qRT-PCR	RB	30	(Tsang, Ng et al. 2010)
miR-1	Down regulation	Diagnostic	qRT-PCR	MET	52	(Migliore, Martin et al. 2012)
miR-7	Down regulation	Diagnostic	qRT-PCR	XRCC2, YY1,PAX6	8	(Xu, Chen et al. 2014)
miR-9	Down regulation	Diagnostic	qRT-PCR	α-Catenin	80	(Cekaite, Rantala et al. 2012)
miR-10b	Down regulation	Diagnostic	qRT-PCR		88	(Nishida, Yamashita et al. 2012)
miR-16	Down regulation	Diagnostic	qRT-PCR	Cdx2	143	(Qian, Jiang et al. 2013)
miR-17	Up regulation	Diagnostic	*In situ* hybridisation	THBS1, MYC, CDKN1A,TMBIM1, E2F1	24	(Knudsen, Nielsen et al. 2015)
miR-18a	Up regulation	Diagnostic	qRT-PCR	ATM	Cell line	(Qased, Yi et al. 2013)
miR-19a	Up regulation	Diagnostic	qRT-PCR	TF	311	(Huang, Wang et al. 2015)
miR-19b	Up regulation		qRT-PCR	SFPQ and MYBL	40	(Ohira, Naohiro et al. 2015)
miR-20a	Up regulation	Diagnostic	qRT-PCR	PTEN, TMP1	30	(Xu, Jing et al. 2015)
miR-20-5p	Up regulation	Diagnostic	qRT-PCR		544	(Cheng, Zhao et al. 2016)
miR-21	Up regulation	Diagnostic	qRT-PCR	PTEN, BCL2, PDCD4, CDC25A, TIMP1	Cell line, in vivo/30	(Xiong, Cheng et al. 2013; Yu, Nangia-Makker et al. 2015)
miR-23a	Up regulation	Diagnostic	qRT-PCR	MTSS1	30	(Yong, Wang et al. 2014)
miR-23b	Down regulation	Diagnostic	In *situ* hybridization		4	(Zhang, Hao et al. 2011)
miR-24	Down regulation		qRT-PCR	DHFR	48	(Mishra, Song et al. 2009)
miR-24-3p	Down regulation	Diagnostic	qRT-PCR		95	(Gao, Liu et al. 2015)
miR-25	Up regulation	Diagnostic	qRT-PCR	Smad7		(Li, Zou et al. 2013)
miR-26a	Down regulation	Therapeutic	microarray analysis	hnRNP A1-CDK6	Cell line	(Konishi, Fujiya et al. 2015)
miR-27a	Up regulation	Diagnostic	RT-PCR	KITENIN	42	(Gao, Li et al.

						2013)
miR-27b	Up regulation	Diagnostic	qRT-PCR	ARFGEF1	10	(Matsuyama, Okuzaki et al. 2016)
miR-26b	Down regulation	Diagnostic	qRT-PCR	LEF-1	Cell line, In vivo	(Zhang, Kim et al. 2014)
miR-29a	Up regulation	Diagnostic	luciferase assay	KLF4	Cell line, In vivo	(Tang, Zhu et al. 2014)
miR-29b	Up regulation	Diagnostic	qRT-PCR	MMP-2	24	(Wang, Li et al. 2014)
miR-30a	Down regulation	Diagnostic	qRT-PCR	DTL, PIK3CD	60	(Zhang, Tang et al. 2015)
miR-30a-5p	Down regulation	Therapeutic	qRT-PCR		40	(Wei, Yang et al. 2016)
miR-30c	Down regulation	Therapeutic	qRT-PCR	RASA1, ERG, SEMA6D, SEMA3A	60	(Zhang, Yu et al. 2015)
miR-31	Up regulation	Therapeutic	qRT-PCR	TIAM1, FOXC2, FOXP3, HIF1A, FIH1	3	(Yang, Xu et al. 2016)
miR-32	Up regulation	Therapeutic	qRT-PCR	PTEN	Cell line	(Wu, Yang et al. 2013)
miR-33a	Down regulation	Therapeutic	qRT-PCR	GABRB2	Cell line, in vivo	(Ibrahim, Weirauch et al. 2011)
miR-33b	Down regulation	Diagnostic	qRT-PCR		60	(Liao, Gu et al. 2016)
miR-34a	Down regulation	Diagnostic	qRT-PCR	P53	5	(Bu, Chen et al. 2013)
miR-34b	Up regulation	Diagnostic	qRT-PCR		159	(Hiyoshi, Schetter et al. 2015)
miR-34c	Up regulation	Diagnostic	qRT-PCR		159	(Hiyoshi, Schetter et al. 2015)
miR-34a-5p	Down regulation	Diagnostic	qRT-PCR	P53	267	(Gao, Li et al. 2015)
miR-92a	Up regulation	Diagnostic	qRT-PCR	DKK-3, BCL-2	48	(Ke, Wei et al. 2015)
miR-93	Down regulation	Diagnostic	qRT-PCR	HDAC8, TLE4, ERBB2	45	(Tang, Zou et al. 2015)
miR-95	Up regulation	Diagnostic	qRT-PCR	Nexin1	87	(Huang, Huang et al. 2011)
miR-96	Up regulation	Diagnostic	qRT-PCR		54	(Rapti, Kontos et al. 2016)
miR-96-5p	Regulation	Diagnostic	qRT-PCR		80	(Ress, Stiegelbauer et al. 2015)
miR-106a	Up regulation	Diagnostic	qRT-PCR	PTEN, E2F1, RB1, TGFBR2	110	(Diaz, Silva et al. 2008)

miR-106b	Up regulation	Diagnostic	qRT-PCR	p21/CDKN1A	95	(Zhang, Li et al. 2015)
miR-125a-5p	Down regulation	Diagnostic	qRT-PCR	P53, BCL2, BCL2L12, Mcl-1	Cell line	(Tong, Liu et al. 2015)
miR-126	Down regulation	Therapeutic	Microarray	IRS-1	9	(Yuan, Guo et al. 2016)
miR-138	Down regulation	Diagnostic	qRT-PCR	TWIST2	36	(Long, Huang et al. 2013)
miR-138-5p	Down regulation	Diagnostic	In situ hybridization	PD-L1	188	(Zhao, Yu et al. 2016)
miR-139	Down regulation	Diagnostic	qRT-PCR	IGF-IR, RAP1B	34	(Shen, Liang et al. 2012)
miR-139-5p	Down regulation	Diagnostic	qRT-PCR	BCL2	204	(Li, Liang et al. 2016)
miR-143	Down regulation	Diagnostic	qRT-PCR	KRAS, MAPK7, DNMT3A, ERK5	6	(Bauer and Hummon 2012)
miR-145	Down regulation	Diagnostic	qRT-PCR	TGFBRE, APC, IRS1, STAT1, YES1	6	(Bauer and Hummon 2012)
miR-147	Up regulation	Diagnostic	qRT-PCR	CDH1, ZEB1,2	71	(Lee, McCarthy et al. 2014)
miR-148a	Down regulation	Diagnostic	qRT-PCR	TGIF2, Bcl-2	42/273	(Zhang, Li et al. 2011; Takahashi, Cuatrecasas et al. 2012)
miR-151	Up regulation	Diagnostic	Microarray		Cell line	(Zhang, Li et al. 2011)
miR-152	Up regulation	Therapeutic	qRT-PCR		202/28	(Li, Xie et al. 2016; Wang, Yuan et al. 2016)
miR-181a	Down regulation	Diagnostic	qRT-PCR	WIF-1	162/137	(Nishimura, Handa et al. 2012; Ji, Chen et al. 2014)
miR-181a-5p	Down regulation	Diagnostic	qRT-PCR	MT1-MMP	Cell line	(Li, Kuscu et al. 2015)
miR-183	Up regulation	Diagnostic	qRT-PCR	EGR1	10	(Bi, Yin et al. 2016)
miR-185	Up regulation	Diagnostic	qRT-PCR	RhoA, Cdc42	50	(ÖzATA, Xie et al. 2011)
miR-191	Up regulation	Diagnostic	qRT-PCR	TIMP3	16	(Zhang, Li et al. 2015)
miR-192	Down regulation	Therapeutic	qRT-PCR	CDKN1A, DHFR, Bcl-2,	29	(Geng, Chaudhuri et

				Zeb2, VEGFA		al. 2014)
miR-195	Down regulation	Diagnostic	qRT-PCR	BCL2	12	(Yang, Tan et al. 2014)
miR-196a	Up regulation	Diagnostic	qRT-PCR	HoxA7, HoxB8, HoxC8 and HoxD8	7	(Schimanski, Galle et al. 2008)
miR-199a	Down regulation	Diagnostic	qRT-PCR	AXI	28	(Ye, Pang et al. 2015)
miR-199a-5p	Down regulation	Diagnostic	qRT-PCR	FZD6	8	(Kim, Yoo et al. 2015)
miR-200	Down regulation	Therapeutic	qRT-PCR	SOX2, ZEB1, PTEN, ETS1, FLT1	40	(Sun, Ding et al. 2015)
miR-203	Down regulation	Therapeutic	qRT-PCR	ATM, AKT2	72	(Deng, Wang et al. 2016)
miR-205	Up regulation	Diagnostic	qRT-PCR	STAT3, N-CADHERIN	51	(Eyking, Reis et al. 2016)
miR-215	Down regulation	Diagnostic	qRT-PCR	DTL	34	(Karaayvaz, Pal et al. 2011)
miR-218	Down regulation	Diagnostic	qRT-PCR	BMI1	59	(Ilm, Fuchs et al. 2016)
miR-221	Down regulation	Diagnostic	qRT-PCR	PTEN	182	(Cai, Shen et al. 2015)
miR-222	Up regulation	Diagnostic	qRT-PCR	PTEN, ADAM-17	57	(Liu, Sun et al. 2014)
miR-223	Up regulation	Therapeutic	qRT-PCR	FOXO1, IGF-1R	90	(Zhang, Luo et al. 2014)
miR-224	Up regulation	Diagnostic	qRT-PCR	MBD2	85	(Ling, Pickard et al. 2015)
miR-487b	Down regulation	Diagnostic	Microarray	KRAS	36	(DOKI, MORI et al. 2016)
miR-125b	Down regulation	Diagnostic	qRT-PCR		Cell line	(Fujino, Takeishi et al. 2016)
miR-100	Down regulation	Diagnostic	qRT-PCR	mTOR, IGF1R, Fas, XIAP	Cell line	(Fujino, Takeishi et al. 2016)
miR-506	Down regulation	Therapeutic	qRT-PCR	LAMC1	Cell line	(Zu, Liu et al. 2016)

Table 2. Circulating microRNAs up/down regulated in CRC

MicroRNA	Expression in CRC	Materials	Samples	Stage	Ref
miR-21	Up regulation	Serum	20/579	I – IV	(Shan, Ji et al. 2015; Montagnana, Benati et al. 2016)
let-7g	Up regulation	Serum	30	I – IV	(Wang, Huang et al. 2014)
miR-31	Down regulation	Serum	30	I – IV	(Wang, Huang et al. 2014)
miR-92a	Down regulation	Serum	30	I – IV	(Wang, Huang et al. 2014)
miR-181b	Down regulation	Serum	30	I – IV	(Wang, Huang et al. 2014)
miR-203	Down regulation	Serum	30	I – IV	(Wang, Huang et al. 2014)
miR-26a	Up regulation	Plasma	71	-	(Jinushi, Shibayama et al. 2014)
miR-124-5p	Down regulation	Plasma	71	-	(Jinushi, Shibayama et al. 2014)
miR-141	Up regulation	Plasma	102	IV	(Cheng, Zhang et al. 2011)
miR-155	Up regulation	Serum	146	I – IV	(Lv, Fan et al. 2015)
miR-183	Up regulation	Plasma	118	III – IV	(Yuan, Li et al. 2015)
miR-200c	Up regulation	Serum	12	I – IV	(Toiyama, Hur et al. 2014)
miR-221	Up regulation	Plasma	103	I – IV	(Pu, Huang et al. 2010)
miR-19a	Up regulation	Serum	72	IV	(Chen, Xia et al. 2013)
miR-20a	Up regulation	Serum	253	III – IV	(Zhang, Zhang et al. 2014)
miR-130	Up regulation	Serum	253	III – IV	(Zhang, Zhang et al. 2014)
miR-145	Up regulation	Serum	253	III – IV	(Zhang, Zhang et al. 2014)
miR-216	Up regulation	Serum	253	III – IV	(Zhang, Zhang et al. 2014)
miR-372	Up regulation	Serum	253	III – IV	(Zhang, Zhang et al. 2014)
miR-345	Up regulation	Whole blood	138	IV	(Schou, Rossi et al. 2014)
miR-143	Up regulation	Whole blood	138	IV	(Schou, Rossi et al. 2014)

miR-34*	Up regulation	Whole blood	138	IV	(Schou, Rossi et al. 2014)
miR-628-5p	Up regulation	Whole blood	138	IV	(Schou, Rossi et al. 2014)
miR-886-3p	Up regulation	Whole blood	138	IV	(Schou, Rossi et al. 2014)
miR-324-3p	Up regulation	Whole blood	138	IV	(Schou, Rossi et al. 2014)
miR-126	Up regulation	Plasma	68	IV	(Hansen, Carlsen et al. 2015)
miR-106a	Up regulation	Plasma	24	IV	(Kjersem, Ikdahl et al. 2014)
miR-484	Up regulation	Plasma	24	IV	(Kjersem, Ikdahl et al. 2014)
miR-130b	Up regulation	Plasma	24	IV	(Kjersem, Ikdahl et al. 2014)
miR-27b	Up regulation	Plasma	24	IV	(Kjersem, Ikdahl et al. 2014)
miR-148a	Up regulation	Plasma	24	IV	(Kjersem, Ikdahl et al. 2014)
miR-326	Up regulation	Plasma	24	IV	(Kjersem, Ikdahl et al. 2014)
miR-17	Up regulation	Serum	30	I – IV	(Zekri, Youssef et al. 2016)
miR-223	Up regulation	Serum	30	I – IV	(Zekri, Youssef et al. 2016)
miR-6826	Up regulation	Plasma	13		(Kijima, Hazama et al. 2017)
miR-6875	Up regulation	Plasma	13		(Kijima, Hazama et al. 2017)

Table 3. Exosomal biomarkers in CRC

Biomarker		Detection method	Samples (human , cell line)	Stages	Ref
MicroRNA	miR-17-92a	microarray analysis, qRT-PCR	277	IV	(Matsumura, Sugimachi et al. 2015)
	miR-19a	microarray analysis, qRT-PCR	277	IV	(Matsumura, Sugimachi et al. 2015)
	let-7a	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-1229	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-1246	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-150	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-21	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-223	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-23a	qRT-PCR	88	I, II, IIIa, IIIb, IV	(Ogata-Kawata, Izumiya et al. 2014)
	miR-192	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	miR-221	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	miR-100	qRT-PCR	DKO-1, Dks-8, DLD-1		(Cha, Franklin et al. 2015)
	miR-379	qRT-PCR	HCT-116 and HT-29		(Clancy, Khan et al.

					2016)
	miR-210	qRT-PCR	HCT-8		(Bigagli, Luceri et al. 2016)
lncRNA	CRNDE-h	qRT-PCR	468	-	(Liu, Zhang et al. 2016)
Protein	CD63	SDS- PAGE	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	CD9	SDS- PAGE	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	CD81	SDS- PAGE	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	TSG101	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	Alix	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	MET	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	S100A8	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	S100A9	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	TNC	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	EFNB2	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	JAG1	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	SRC	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	TNIK	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	CAV1	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	FLOT1	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)

	FLOT2	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	PROM1	GeLC-MS/MS	SW480		(Ji, Greening et al. 2013)
	FGFR1,	MS/MS	80	I, II	(Chen, Xie et al. 2017)
	IGF1	MS/MS	80	I, II	(Chen, Xie et al. 2017)
	VTN	MS/MS	80	I, II	(Chen, Xie et al. 2017)
	HSP90	MS/MS	80	I, II	(Chen, Xie et al. 2017)
mRNA	ACTB,	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	GAPDH	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
Natural antisense RNAs	LRRC24	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	MDM2	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)
	CDKN1A	qRT-PCR	HCT-15, SW480 , WiDr		(Chiba, Kimura et al. 2012)

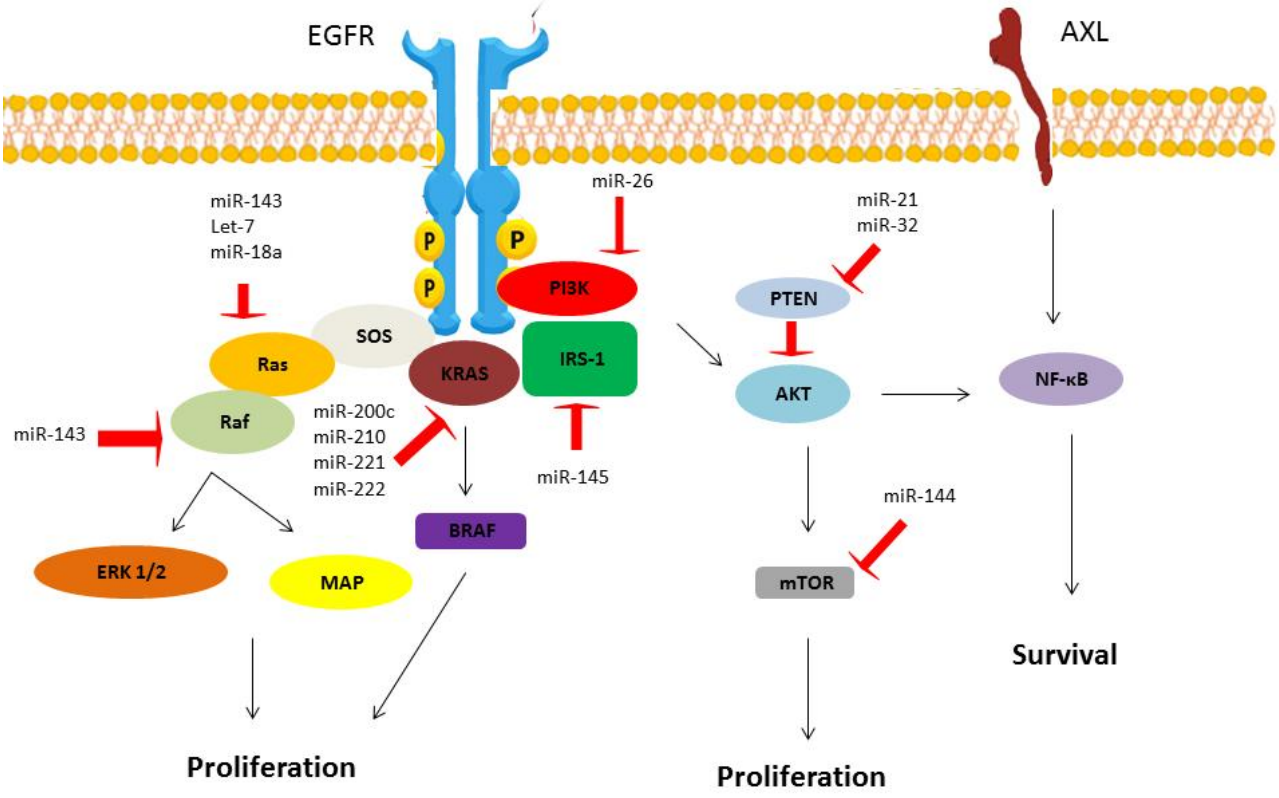

Figure 1: Schematic diagram of various miRNAs network in CRC.