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Mini-Review

# Current Insights of Colorectal Cancer: The Anatomical differences and the miRNA Regulation in Colorectal Cancer -

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## ABSTRACT

Colorectal cancer is one of the leading causes of death in the United States. Recent advances of understandings in anatomical patterns and molecular mechanisms may bring better therapeutical options and treatment plan. This article reviews the different outcomes of colorectal cancer associated with anatomical pattern: left-sided or right-sided; and the recently discoveries of colorectal cancer related miRNA.


## INTRODUCTION

Despite the decline in the age-adjusted cancer incidence rate over the past two decades, cancer is still the second leading cause of death in the United States [1]. Colorectal Cancer (CRC) comprised 8% of all newly diagnosed cancer cases and accounted for an estimated 8% of cancer-related deaths for both sexes in 2016 [1]. Colorectal tissue is under constant threat of carcinogenesis due to sustained exposure to foreign substances that may possess mutagenic properties.

There has been mounting evidence that CRC treatment can be tailored to the anatomical origins of the tumor growth. As a result, CRCs are often classified as either right- or left-sided tumors. This distinction holds prognostic value, as Right-Sided CRC (RCC) and Left-Sided CRC (LCC) have different embryological origins, differing anatomical structures, and are often associated with different symptoms. These symptoms range from general physical discomfort to different sites of metastasis.

Furthermore, signaling pathways are disrupted which leads to the formation of benign growths that may develop into CRC. Such pathways include the Wnt, EGFR, and TGF-® pathways and downstream products of the TP53 and KLK6 genes [2-5]. These pathways are altered in such a way that proliferation, immortalization, and metastasis are favored. Identifying potential biomarkers related to these pathways is of great interest to cancer treatment. One such example are miRNAs and their intervened signaling pathways.

Overall, in treating CRCs it is important to consider both the underlying genetic and anatomical profile of the tumor.

### Right and left-sided colorectal cancer

Most CRC cases share humble origins as a polyp. The size and location of these growth correlate to the stage of cancer development and might entail symptoms associated with either RCC or LCC [6]. However, regardless of the anatomical location of the tumor growth, CRC can be categorized into stages that summarily describe the extent of cancer development. Stage 0 CRC has not grown beyond the intestinal mucosa and are often composed of low grade polyps; stage I CRC has grown into the colon wall, but has yet to spread beyond that point; stage II CRC has grown through the colon wall and potentially into nearby tissue, but has not reached local lymph nodes; stage III CRC will have reached the lymph nodes, but not have spread to distant tissues; and stage IV CRC are the most sever, having spread to other organs and tissues, most often the liver [7,8]. The mortality rate of CRC can be primarily attributed to these metastases [9].

A colonoscopy is the most common screening procedure for CRC [10]. This procedure is typically reserved for older individuals, as age is the most prominent risk factor associated with CRC [11]. This has the unintended consequence of younger patients being diagnosed with CRC at later stages, as initial complaints are not regarded with the same scrutiny reserved for older patients [11]. If a colonoscopy screening returns a positive result for colorectal cancer, then a biopsy is required for definite diagnosis, during which polyps identified during the screening process are removed via polypectomy and examined for signs of cancer [12]. Colonoscopy screenings are more frequently repeated if polyps are identified. Diagnoses should also consider whether the CRC is right-sided or left-sided. This classification is of significant importance to personalized CRC treatment, as the right and left sides of the colon possess several anatomical and embryological differences. The right colon is categorized proximal and is supplied blood via the superior mesenteric artery, whereas the left colon is categorized distal and supplied by the inferior mesenteric artery [13]. Furthermore, the right colon is derived from the midgut and the left colon is derived from the hindgut. These anatomical and embryological distinctions have gathered attention as a point of further study, as such differences might explain discrepancies between the right and left sides of the colon as far as tumor biology and pathophysiology are concerned [14]. For example, patients diagnosed with right-sided CRC are generally older, possess tumors of greater diameter and in a later stage of development, and often have a greater number of positive lymph nodes [15]. Evidence suggests that these are consequences of the larger lumen of the right colon, which affords right-sided colon cancer more time to grow before displaying symptoms. Without proper diagnosis, tailored treatments are rather challenging to manage and prognoses difficult to discern. However, researchers are making strides toward associating certain symptoms and biomarkers with various subtypes of CRC.

Early stage CRCs are largely asymptomatic [12]. Therefore, routine colonoscopies remain an effective method of identifying CRC and is associated with a significant decrease in mortality rate for both right and left colon cancer, though the decrease was slightly greater for left-sided colon cancer [15]. However, there exists several symptoms that may indicate further testing is required, even in patients considered at low risk for developing CRC. These symptoms include anemia, visible blood in the stool, and changes in bowel habits [13]. While not particularly useful in determining the presence of a colorectal tumor without an accompanying colonoscopy and subsequent biopsy, these symptoms may indicate whether the CRC is a right-sided tumor or left-sided tumor. Patients with right-sided CRC exhibit signs of anemia [16], whereas patients with left-sided CRC have visible blood in their stool and changes in bowel habits [15,16]. Furthermore, patients with right-sided tumors tend to present with a more advanced tumor stage than patients with left-sided tumors [13]. These clinical signs are important to consider when developing treatments for CRC.

### miRNA background and affected pathways

miRNA units are small, non-coding RNA strands measuring 18 to 25 bases in length [17]. The majority of genes that encode miRNAs are located in intergenic regions and are transcribed by RNA polymerase II [4]. One of their remarkable functions is that they have the ability

to down-regulate the expression of their target genes [17]. They do so through imperfect pairing to the 3' untranslated region (3'UTR) of the target mRNA which then inhibits translation and destabilizes the mRNA stand [1]. For this interactions to work, complementary base-pairing is essential and it usually involves 6-7 nucleotides, these tend to be nucleotides 2 to 9 of the 5' end miRNA strand, a region known as "seed" [4].

It has been shown that miRNAs are involved in cell differentiation, proliferation and apoptosis [17], processes that are often associated with the development of CRC and many other types of cancer. The ability of miRNAs to impact the progress of such processes has made them promising biomarkers for detection of cancer development [4]. Furthermore, their levels of expression can be potentially used as a method of classification of cancer even for groups of distinct characteristics such as cell type or etiology [4]. There a two types of biomarkers in terms of miRNA, and they are classified according to their effect on gene expression. The first type are those miRNAs that act as oncogenes, often called *oncomirs*, thus stimulating cancer development [4]. On the other hand, the second type are those miRNAs that act as *tumor suppressors* and thus inhibit the development of cancer [18]. In relation to CRC, miRNAs that impact the Wnt pathway, EGFR pathway, TGF-β pathway, the expression of the TP53 gene and the expression of the gene KLK6 will be the main focus of this review.

## miRNAs and the WNT signaling pathway

By affecting the Wnt pathway, miRNAs also affect the proteins synthesized by Wnt signaling and these proteins regulate cell proliferation, doing so in a short-period of action, as well as they regulate self-renewal pathways such those involved in the development of stem cells [3]. Alterations to the WNT signaling that lead to higher activation, oncogenic alterations, will favor cell survival while also inhibit apoptosis or differentiation [4]. An important player in the Wnt pathway is the APC gene, a tumor suppressor gene. It has been shown that higher levels of miR-135a/b act as negative regulators of APC and thus inhibit its tumor suppressor function which then leads to higher activation of the WNT pathway. Another key gene involved in the Wnt pathway is CTNNB1, which encodes a protein know as β-catenin [19]. When APC is functioning, it acts as a negative regulator of CTNNB1 and thus inhibits the production of β-catenin which is a component of the E-Cadherin protein complex [4]. β-catenin is able to bind the promoter of miR-17-92 and activates an oncogenic miRNA cluster that would otherwise be silenced by APC if there were no alterations to this APC gene [20]. More interestingly, up-regulation of β-catenin has been linked with miR-19a in CRC patients [20]. More so, higher levels miR-19a exert an inhibitory effect on processes regulated by APC such as cellular growth, migration, and invasion by targeting the tumor suppressor gene PTEN [20], showing how many genes are interconnected in the Wnt pathway. Another oncomir is miR-574-5p as it activates the Wnt/β-catenin signaling by down-regulation an RNA binding protein know as Quaking 6/7, this protein is involved in regulating cell cycle progression, differentiation and angiogenesis which all relate to metastasis of CRC [20]. Another activator of the Wnt/®-catenin pathway is miR-21 due to its down-regulation of the transforming growth factor beta receptor 2 [20]. More interestingly, miR-224 also acts as an oncomir but it does so by targeting suppressor of the Wnt/β-catenin pathway such as GSK3β which results in higher levels of β-catenin in the cytoplasm which then up-regulate the expression of target genes of the pathway such as c-Myc and cyclinD1 [20].

An interesting case comes about over miR-29a/b, a junction between oncomir and tumor suppressor acting miRNA can be observed. miR-29a acts as an activator of the Wnt/β-catenin pathway through inhibiting antagonist to the pathway such as the sFRP-2 proteins [20]. miR-29b has an opposite effect on the Wnt/β-catenin pathway by down-regulating it and thus exerting a cascade effect that will inhibit processes such as cell growth, tumor angiogenesis and EMT [20]. In fact, there are several miRNAs that exert tumor suppressor activity, another example is miR-23b as it decrease CRC progression by down-regulating a receptor of the Wnt/β-catenin pathway known as frizzled 7 [20]. There are also some miRNAs such as miR-7 that directly target oncogenic transcription factors such as Ying Yang 1 [20]. Different molecules have shown to be targets on tumor suppressor acting miRNAS, such as the case of miR-93 in which a key protein which mediates the nuclear accumulation of β-catenin is targeted and thus the levels of -catenin in the nucleus decrease and this has an inhibitory effect on the Wnt/β-catenin signaling pathway [20]. Furthermore, the loss of mi-R34a has been associated with neoplastic progression in CRC cells thus providing evidence for tumor suppressor function of this miRNA [4]. Interestingly, the epigenetic silencing of mi-R34a due to CpG methylation has been associated with metastatic growth in primary tumors [20].

## miRNAs and the EGFR pathway

Oncogenic mutations to the EGFR pathway have been described in 30-60% of CRC cases [4]. Therefore, there has been an interest to see the role that miRNAs play in mediating this signaling pathway. miR-134 has shown to be down-regulated in CRC and that it has an impact on the expression of the proto-oncogene KRAS [4]. This interaction has been hypothesis to consist of the miRNAs acting as suppressor of cell proliferation [4]. Through a series of *in vivo* experiments, scientists found that increased levels of mi-R143 correlate with decreased levels of the KRAs protein as well as a decrease in cell proliferation [4]. miR-145 has also been associated with tumor suppressor activity in a similar manner to that of mi-R143 [4]. Travelling down the EGFR pathway PIK3/AKT can be found, and there are miRNAs such as miR-30a or miR-126 which under normal colon conditions both act as tumor suppressor miRNAs [4]. Interestingly, the dominant regulator of the PIK3/AKT known as PTEN has also been associated with miRNAs [4]. The PTEN gene codes for the PTEN protein, which acts as a tumor suppressor [21]. The PTEN transcript or mRNA unit of expression of this gene has been shown to be targeted by mi-R19, miR-21, miR-32 and miR-92-1-5p [20]. A recent study by researchers at The Key Laboratory of Living Donor Liver Transplantation in Nanjing, China, have related mi-R545 to tumor suppressor activity [22]. miR-545 negatively regulates cell proliferation as it acts as an inhibitor to the EGFR receptor by affecting its 3'-UTR activity [22].

## miRNAs and the TGF-β signaling pathway

TGF-β controls differentiation, proliferation and apoptosis as well as it acts as a modulator for many parts of the inflammatory response such as adhesion molecule regulation or chemotactic gradients for leukocytes [13]. Although TGF-β is best known as a transforming factor, this review will take a couple steps back onto its unexpressed form of the gene TGFBR2. There have been several miRNAs that are associated with regulating TGFBRR2 such as miR-17-5p, miR-20a, miR-21, miR-23b, miR-106a and miR-301a [4]. Taking a closer look, miR-21 is an interesting candidate to focus on. Interestingly enough it is activated by the Wnt signaling pathway, and it is associated with

regulating stemness through its interaction with TGFBR2 [4]. In the case of the cluster of oncogenic miRNAs composed of miR-17-92, the effect is different in that these miRNAs behave as oncomirs as they perform TGF-β responses through silencing of the protein coding gene TGFBR2 and of the tumor suppressor gene SMAD4 which plays a role further downstream in the TGF-® pathway [4]. This tumor suppressor gene, SMAD4, is responsible for providing instructions to synthesize proteins involved in the transmission of chemical signals from the cell surface to the nucleus thus it plays a key role in cell motility and alterations to its levels of expression tend to happen in the transition of a cancerous tissue to malignancy [23]. It has been shown that a cluster of miRNAs, miR-130a, miR-301a, and miR-454, which are usually up-regulated in CRC tissue are able to target SMAD4 and cause an increase in cell migration and proliferation [4]. Lastly, a decrease in the levels of miR-25 expression has been linked to increases in the Epithelia Mesenchymal Transition (EMT), invasion and metastasis [4].

### miRNAs and TP53

The gene TP53 is referred to as a tumor suppressor gene and encodes tumor protein p53 [4]. Mutations to TP53 occur in the early stages of oncogenesis in CRC [24]. A bioinformatics study proposed that about 46% of the miRNA supposed promoters contain a potential TP53-binding site which speaks to why miRNAs have such an impact on CRC development. One of the miRNAs with the most interesting role in relation to TP53 is miR-34a. This miRNA acts as a tumor suppressor as it down-regulates the transcription factor E2F and it also up-regulates p53 in CRC [4]. E2F is responsible for the synthesis of the transcription factor E2F1, and it is worth of mention that this protein can act as a tumor suppressor by mediating apoptosis in response to cellular stress such as DNA damage but it can also act as an oncogene in response to more aggressive chemoresistant tumors [25]. Other such as miR-339-5p indirectly control TP53 expression by regulating the expression of the MDM2 gene [4]. MDM2 is a proto-oncogene that encodes a E3 ubiquitin ligase in the nucleus, such protein enhances tumor formation as it can target tumor suppressor proteins such as p53 [5]. There are some miRNAs that do not only act as regulators of TP53 but also as effectors that act in response to stimuli, such is the case for miR-192 and miR-215 and they do so by suppressing tumorigenesis through CDKN1A [4]. This later gene, CDKN1A, encodes a cyclin-dependent kinase inhibitor (p21) that plays a key role in regulating the cell cycle progression at the G1 and S phases, and interestingly enough the expression of the CDKN1A gene is controlled by the tumor suppressor protein p53 [2]. Through such interconnectedness we are able to observe a negative feedback loop in which when p53 is up-regulated, transcription of CDKN1A is induced and thus leading to higher levels of p21 which acts as a negative regulator of the cellular levels of p53 [26]. The fact that the body has its own mechanisms for controlling the levels of tumor suppressing agents such as through this negative feedback loop between p53 and p21 is already fascinating, but it is even more fascinating that miRNAs have the ability to impact these mechanisms and drastically alter cell cycle progression.

### miRNAs and the KLK6 gene

The KLK6 gene encodes an active serine protease known as Kallikreins-related peptidase 6 [1]. Kallikreins are known for their ability to chop up extracellular matrix proteins and thus stimulate angiogenesis [1]. It has been shown that KLK6 mRNA expression is high in malignant colorectal tissues, suggesting a possible role in both invasion and metastasis of CRC [1]. Such intriguing suggestion would not be completely resolved without considering the role that miRNAs play in such pathway. The first miRNA of interest is miR-181d and it is in fact down-regulated in KLK6 knockout cells and it acts as a tumor suppressor [1]. More interestingly, the relationship between miR-181d and KLK6 is fundamentally a regulatory feedback loop in which when KLK6 is expressed the levels of miR-181d are higher when compared to a cell line in which the KLK6 gene had been knocked out [1]. Such regulatory feedback loop further proves miR-181d tumor suppressor activity as its expression levels are higher when KLK6 is expressed. In contrast, miR-203 was significantly up-regulated in KLK6 knockout cells when compared to controls [1]. miR-203 has been identified as an miRNA with tumor suppressor functions [27]. Interestingly enough, miR-203 has been associated with the TGF- pathway as it regulates the expression of one of the transcription factors, Snail1, that plays a key role in the Epithelial Mesenchymal Transition (EMT) which is heavily induced by TGF-® signaling [1]. This regulation of Snail1 by miR-203 has been reported to happen through two binding sites located in the 3'UTR region, and such interaction has further been characterized as a double negative feedback loop [1]. Meaning that higher levels of miR-203 expression will decrease the levels of Snail1 expression and vice versa. This negative feedback loop offers more insight into the fascinating mechanisms our bodies have to control the expression of oncogenic and tumor suppressing agents. Another promising finding suggests that miR-203 is able to inhibit KLK6 protein secretion [1]. Furthermore, transfecting with miR-203 resulted in an inhibition of cell migration [1]. Such finding expands the tumor suppressive abilities of miR-203 on to also encompassing its ability to affect cell motility.

## CONCLUSION

Novelties regarding the involvement of miRNAs in the Wnt pathway, EGFR pathway, TGF-β pathway, the expression of the TP53 gene and the expression of the gene KLK6 were discussed to further show the potential of many miRNAs to serve as biomarkers for CRC. Their ways of functioning are distinct as they can act as oncomirs or tumor suppressor miRNAs. Their functions are also unique to their target and thus this makes them specialized targets of small size. Despite their size miRNAs are impactful regulators on many signaling pathways involved in the development of CRC. Their targets are genes or genes products that vary in location from the beginning stages of a pathway to the further downstream stages. Such extended presence of miRNAs throughout these pathways allows to track the progress of CRC from a benign proliferative tumor to malignant tumor masses that are metastasized throughout the body. Furthermore, the location of the tumor mass related to the associated symptoms and prognosis. Evidence suggests that right- and left-sided CRCs exhibit different characteristics as a consequence of the different anatomical structure and embryological origins of the two CRC subtypes. Thus, cancer treatments benefit from making and recognizing these distinctions, as they afford additional prognostic information and inform treatment decisions. This reviewed hopes to further the interest in the role that miRNAs play in CRC and how important is to keep exploring them as potential biomarkers. Approaching CRC treatment from both a molecular and anatomical level may facilitate personalized treatment and is a topic worthy of further study.

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