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Review

# MicroRNAs as novel biomarkers for colorectal cancer: New outlooks

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ABSTRACT

Colorectal cancer is one of the most prevalent cancers with high mortality in the world. MicroRNAs are a class of small non-coding RNAs that regulate gene expression through targeting mRNAs. MicroRNAs involve in many biological and pathological processes such as cell growth, differentiation, apoptosis. etc. Dysregulation of miRNAs expression patterns have been reported in many tumors including Colorectal Cancer. Various studies indicate that miRNAs can be utilized as diagnostic and prognostic biomarkers for evaluation of tumor initiation, development, invasion, metastasis and response to chemotherapeutic drugs. Numerous investigations have also shown dysregulation of miRNAs in tissue samples and body fluids such as serum, plasma and fecal samples from CRC patients. Recently, several studies have demonstrated that miRNAs have regulatory roles in response to anti-cancer drugs and suggested them as predictive factors for successful treatment. In this review, we highlight the facts concerning tumor suppressor miRNAs and oncomiRs in CRC; by emphasizing their importance in different signaling pathways such as the Wnt/β catenin activation, EGFR pathway, (TGF-ß) and the TP53 network and then their potential as biomarker and targets for cancer treatment.

## 1. Introduction

Colorectal Cancer (CRC) is the third most prevalent malignancy after lung and breast cancer all over the world, especially in developed countries [1]. In many areas of the world, incidence rates of CRC are rapidly increasing. Prevalence and mortality rates of CRC have been estimated as high as 1,200,000 and 600,000 cases/year respectively [2]. In spite of diagnosing and treatment of this cancer, patients' survival is vastly correlated with tumor stage at the time of diagnosis and 40–50% of patients die due to distant metastasis [3,4]. Genetic and epigenetic alterations can dysregulate tumor suppressor genes and oncogenes in CRC [5].

MicroRNAs are a class of 21–25 nucleotide non-coding RNAs known to post-transcriptionally regulate gene expression and control different biological mechanisms such as activation of immune system and inflammatory responses, regulation of cholesterol homeostasis, osteogenesis regulation, etc. [6–9]. Affecting oncogenes and/or tumor suppressor genes, Dysregulated miRNAs are implicated in the pathogenesis of CRC [10]. Since, the expression patterns of miRNAs are different in tumor tissues and body fluids such as plasma, serum, urine, saliva, etc. [6]. in comparison with normal controls; thus miRNAs are classified as oncomiR and tumor suppressor miRNA and numerous of them can be used as diagnostic, prognostic and predictive biomarkers of CRC [11,12]. Furthermore, different studies have demonstrated that miRNAs are highly potential molecules to be utilized as therapeutic agents in CRC therapy [10]. Given these, interventions such as inhibition of oncomiRs and restoration of tumor suppressor microRNAs, might be beneficial for CRC treatment [12].

In this review, we summarize new outlooks of miRNAs on the issue of their functioning as oncomiRs or tumor suppressors in CRC through upregulation and downregulation of target genes with accentuating their targets, different molecular mechanisms, and significance of their application as a novel target in CRC diagnosis, prognosis and potential treatment.

## 2. Biogenesis of miRNA

Involving several enzymes and diverse cellular compartments, biogenesis of miRNAs is a complex multipart process with different phases [13]. Primarily, the process starts in the nucleus where miRNA genes are transcripted by RNA Polymerase II and primary miRNAs with variable length (1–3 kb) in the stem-loop form are resulted [14,15]. Through next step in the nucleus, DROSHA and its cofactor DGCR8 cleave the stem-loop structures into short 70 nucleotide precursor-miRNAs (pre-miRNA), which will be transported to the cytoplasm by Exportin 5 [15,16]. In the cytoplasm, pre-miRNAs are further cleaved

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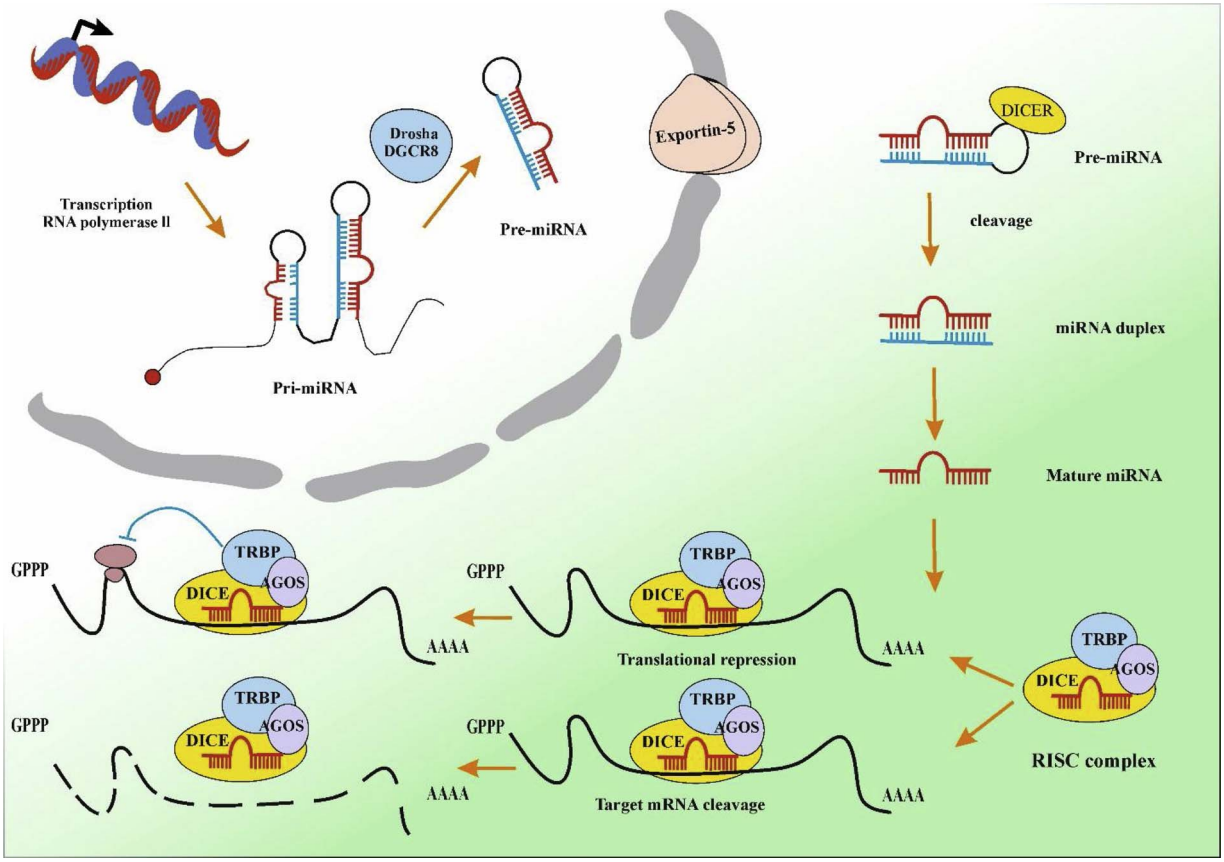


**Fig. 1.** Schematic depiction of miRNA biogenesis and function. There are three steps in the microRNA maturation. In first step, RNA polymerase II transcribes pri-miRNA in the nucleus (1–3 kb). Second, pri-miRNA gets processed by an RNA specific ribonuclease enzyme complex (DROSHA) and its cofactor DGCR8 into short 70 nucleotide precursor-miRNAs (pre-miRNAs). Finally, Pre-miRNA is transported into the cytoplasm by Exportin 5 and cleaved on the loop end by Dicer to form a miRNA-miRNA duplex and two mature microRNAs released by helicase. Then, one strand of this duplex incorporates into the RNA-induced complex (RISC), composed of Transactivation Responsive RNA-Binding Protein (TRBP) and Argonaute. Binding of miRNA/RISC with target mRNA molecules is through the 3' untranslated region (3-UTR) and leads to mRNA degradation and inhibition of translation.

by Dicer endonuclease to generate ~22 nucleotide mature duplex miRNAs with 3′ ends, having two nucleotides overhang [17–19]. Eventually, the mature duplexes join RNA-induced Silencing complex (RISC) with Argonaute family and transactivation responsive RNA-binding protein (TRBP) as the central proteins. One strand of the duplex remains as mature miRNA attached to the complex, while the other strand is released from AGO [20,21] and usually degraded by cellular nucleases [22]. The RISK complex exerts its regulatory effects on the miRNA targets through binding to the 3' untranslated region (3-UTR) of mRNAs (Fig. 1).

This mechanism Results in gens expression regulation through reduction and inhibition of protein production [18].

## 3. General features of miRNA

MicroRNAs (miRNAs) are a family of small, evolutionarily conserved, noncoding RNA molecules (21–25 nucleotides in length) in vertebrates, plants, and protozoa [23] that play an important role in post-transcriptional gene regulation [24]. These molecules exert regulating effects on gene expression by inhibiting translation and causing degradation of target messenger RNA (mRNA) [25].

In 1993, Lee et al. were the first ones to indicate the role of lin-4 in regulation of some biological processes in *C. elegans* [26].

Afterward, in 2000, a major role for miRNAs was identified in nematodes where let-7 was reported to control developmental progression of these organism [27]. After that, numerous miRNAs have been discovered [28].

MiRNAs play important roles in regulation of many cellular biological processes, such as differentiation, proliferation, apoptosis, growth, migration and survival [29,30]. It has been estimated that miRNAs can affect translations of one-third of human genes [31]. Accumulating evidences indicate that aberrant changes in miRNA levels contribute to tumorigenesis and associate with many kinds of human diseases such as various cancers [32].

Some miRNAs can act as oncogenes and/or tumor suppressors during the development and progression of cancers [33]. Cancer initiation, invasion, metastasis and resistance to anticancer drugs occur as the result of miRNA dysregulation [34]. Regarding the knowledge above, it is necessary to identify cancer-specific miRNAs and their biological pathways for diagnosis, prognosis and clinical applications.

## 4. Role of miRNAs in colorectal cancer signaling pathways

According to the literature, there are many miRNAs playing different roles in CRC indisputable upregulation, downregulation or switching off of which can be important in the carcinogenesis of CRC [10,35,36].

MiRNAs are generally classified as tumor suppressor miRNAs and oncomiRs according to their function and status in cancers. OncomiRs are known to downregulate tumor suppressor genes, by contrast, tumor suppressor miRNAs are responsible for downregulation of oncogenes, and are mostly reduced in some cancers [37]. The upregulation of oncomiRs and downregulation of tumor-suppressor miRNAs, have been reported to be causative in development of some cancer [38].

First of all, Michael et al., in 2003, identified association between miRNAs and CRC and reported that levels of miR-143 and miR-145 were decreased in CRC tissue compared to normal tissue [39,40].

Several mechanisms are involved in progression of CRC including