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REVIEW

The role of miRNAs in the pathogenesis, diagnosis, and treatment of colorectal cancer and colitis-associated cancer

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Abstract

MicroRNAs (miRNAs) are a group of noncoding single-stranded RNA biomolecules that act in posttranscriptional regulation of gene expression. Their role in the development of inflammatory bowel disease (IBD), colitis-associated cancer (CAC), and colorectal cancer (CRC) is currently under investigation. A few miRNAs present promising results in terms of diagnostic or therapeutic use, for example, miR-21 increases in CRC and inflammation, while also being a possible target for cancer therapy; miR-301a increases in inflammation but only in patients with IBD; miR-31 increases in CRC, especially in advanced stages, namely III-IV in TNM scale; miR-200 family plays a role in carcinogenesis of CRC and other tumors; examined as a group, miR-31-5p, miR-223-3p, and let-7f-5p trigger and exacerbate CAC; miR-19a could potentially be used in therapy and prevention of both CRC and CAC. Here, we discuss available studies and outline future directions concerning the validity of using miRNAs in the diagnosis and/or therapy of IBD, CAC, and CRC. Extensive research confirms that miRNAs play an important role in the pathogenesis of CAC and CRC. Since the significantly altered expression of certain miRNAs is an early prognostic marker for the development of these diseases, miRNAs have the potential to serve as diagnostic tools, enabling quick and straightforward disease detection.

Keywords Colorectal cancer · Colitis-associated cancer · Inflammatory bowel disease · microRNA

Abbreviations

AGO	Argonaute
15-PGDH	15-hydroxyprostaglandin dehydrogenase
3′-UTR	3′-untranslated region
5-FU	5-fluorouracil
5-hmC	5-hydroxymethylcytosine
AMER3	PC membrane recruitment protein 3
APC	Adenomatous polyposis coli
AOM	Azoxymethane
BTG1	B cell translocation gene 1
CAC	Colitis-associated cancer
CD	Crohn's disease
CDC42	Cell division cycle 42
CRC	Colorectal cancer
DAPK	Death-associated protein kinase 1
DDX17	DEAD-box helicase 17
DIP1	Disco-interacting protein
DSS	Dextran sodium sulfate
DFS	Disease-free survival
EGFR	Epidermal growth factor signaling
EMT	Epithelial-mesenchymal transition
GM-CSF	Granulocyte–macrophage colony-stimulating factor
HIF-1α	Hypoxia-inducible factor 1 alpha
IBD	Inflammatory bowel disease

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IL	Interleukin
IL17RD	Interleukin-17 receptor D
Keap1	Kelch-like ECH-associated protein 1
KO	Knockout
LATS2	Large tumor suppressor kinase 2
LPS	Lipopolysaccharide
lncRNA	Long noncoding RNA
MAPK/ERK	Mitogen-activated protein kinases/ extracellular signal-regulated kinases
MEG3	Maternally expressed 3
MET	Mesenchymal-epithelial transition
miRNA	MicroRNA
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NR2F2	Nuclear receptor subfamily 2 group F member 2
OS	Overall survival
PDCD4	Programmed cell death protein 4
PDLIM2	PDZ and LIM domain 2
Pgp	P-glycoprotein
Pol II	RNA polymerase II
pri-miRNA	Primary miRNA
pre-miRNA	Precursor miRNA
PTEN	Phosphatase and tensin homolog
qRT-PCR	Quantitative reverse transcription PCR
RASA1	RAS p21 GTPase activating protein 1
RASSF2	Ras association domain-containing protein 2
RhoB	RAS homolog family member B
RISC	RNA-induced silencing complex
RUNX3	Runt-related transcription factor 3
SAV1	Salvador 1 protein
SLC9A9	Solute carrier family 9 subfamily A member 9
SNAIL	Zinc finger protein SNAI1
STAT3	Signal transducer and activator of transcription 3
TET	Ten-eleven translocation
TLR4-COX2-PGI	Toll-like receptor 4-cyclooxygenase 2-prostacyclin
TNFAIP3	Tumor necrosis factor, alpha-induced protein 3
TNF-α	Tumor necrosis factor alpha
TNRC6A	Trinucleotide repeat containing adaptor 6A
UC	Ulcerative colitis
WNT5A	Wingless-type MMTV integration site family member 5A
WT	Wild type
XPO5	Exportin-5

Introduction

The inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a group of inflammatory disorders of the gastrointestinal tract with an unknown etiology. The prevalence of IBD is approximately 0.3% of the European population and has significantly increased in recent years. IBD primarily manifests as diarrhea and abdominal pain; however, over the course of the disease, several serious complications may develop, including colorectal cancer (CRC). IBD-associated CRC, or colitis-associated CRC (CAC), is a form of CRC arising in IBD patients. CAC accounts for approximately 1–2% of all CRC cases and is characterized by distinct clinical features and pathogenesis. The overall incidence of CRC in IBD patients is estimated at 1%, 1.5%, and 2.7% at 10, 20, and 30 years after diagnosis; however, these data vary among studies [1]. Notably, a relatively small fraction of IBD patients develop CAC, but it constitutes approximately 10–15% of deaths among these patients [2]. The exact pathogenesis of CAC remains obscure. Consequently, molecular biomarkers such as albumin levels, DNA, RNA, proteins, and miRNAs have recently been investigated to improve diagnostic modalities, prognostic assessment, and therapy [3–5].

MicroRNAs (miRNAs) are a group of noncoding, single-stranded RNA biomolecules that usually bind to the 3'-untranslated region (3′-UTR) of their specific target mRNAs, thereby suppressing protein synthesis posttranscriptionally (Fig. 1). First discovered in the 1990s and recognized as a class of biological regulators in the 2000s, miRNAs have recently gained popularity as tools for diagnosis and therapy [6]. Multiple studies suggest promising results involving miRNAs in CRC and IBD patients, which could lead to significant changes in clinical practice [5, 6]. miRNAs control the expression of over a thousand transcripts, either directly by binding or indirectly by targeting transcription factors, epigenetic regulators, or effectors of signal transduction pathways. miRNAs are more stable than mRNAs; therefore, they are easily detectable in formalin-fixed, paraffin-embedded tissues and plasma/serum using reliable methods, including quantitative reverse transcription PCR (qRT-PCR) and microarray analysis. For this reason, miRNAs are highlighted as biomarkers that may be sensitive and specific, thus potentially useful for early detection, prognostic classification of CAC, and therapeutic decision-making in its treatment [6, 7].

In this review, we discuss available studies and outline future directions concerning the validity of using miRNAs in diagnosing and treating CAC and CRC, which may interest clinicians, diagnosticians, and scientists involved in developing new diagnostic and therapeutic strategies.

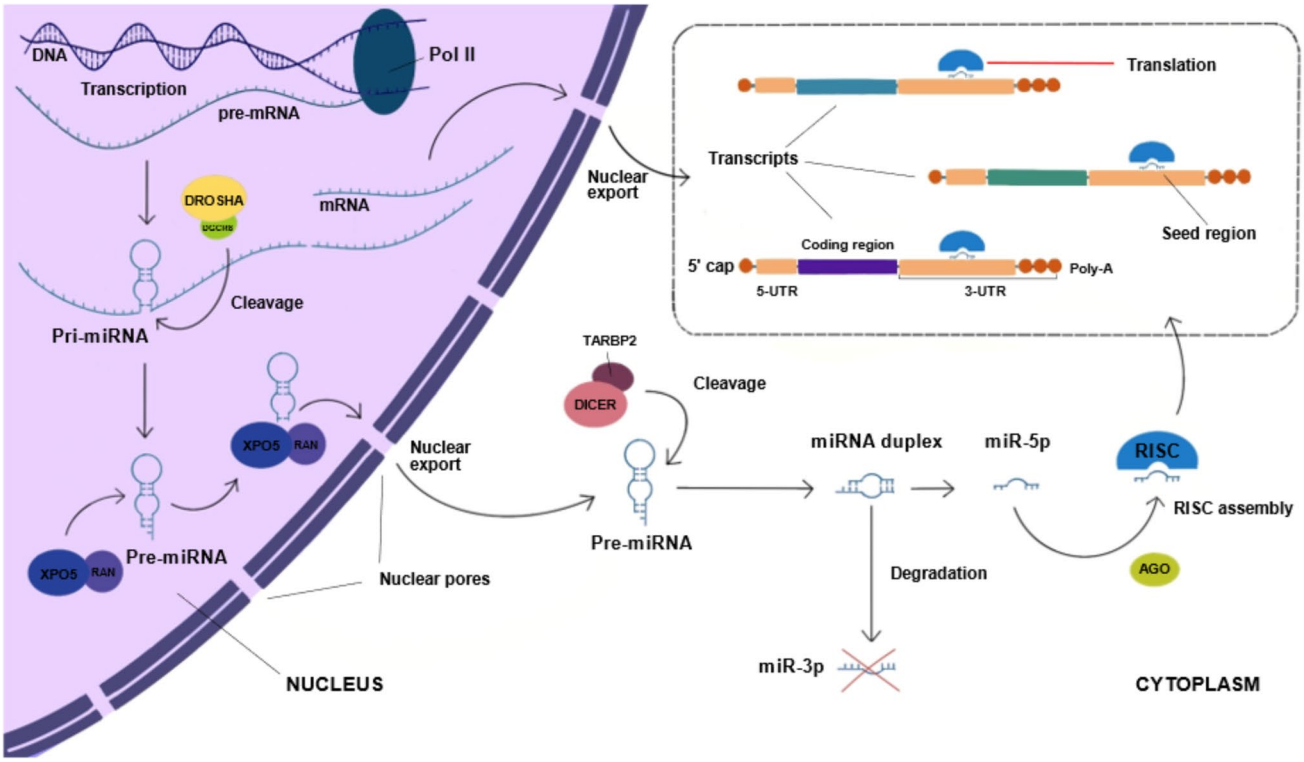

Fig. 1 miRNA biogenesis. miRNAs, similar to mRNA, are transcribed by RNA polymerase II (Pol II) as stem-loop primary miRNA (pri-miRNA). The DGCR8 protein recognizes specific sequences, and the DROSHA endonuclease cleaves them, forming the characteristic hairpin structure of precursor miRNA (pre-miRNA). Pre-miRNA is transported through nuclear pores by exportin-5 (XPO5) in association with the RAN protein. In the cytoplasm, a protein complex containing the DICER nuclease and TARBP protein processes the hairpin structure, generating a miRNA duplex composed of a 5′-miRNA strand and a 3′-miRNA strand. Following unwinding of the duplex, one strand—typically the 3′ strand—is degraded, while the remaining strand forms the mature miRNA. This mature miRNA associates with proteins, including Argonaute (AGO), to form the RNA-induced silencing complex (RISC). miRNAs associated with RISC recognize short complementary sequences (known as the seed region) in the 3′-UTR of target mRNAs. A single miRNA can bind to multiple transcripts, leading to repression of the translation of the target gene

This review comprehensively answers questions about which miRNAs, according to the current state of knowledge, may serve as specific biomarkers of CAC and CRC. It also examines their connections with inflammation and epithelial-mesenchymal transition (EMT), and outlines the possibilities of clinical application of this knowledge in the context of diagnosis and treatment of these diseases.

The overview of the key miRNA in CRC and CAC

It has been confirmed that infiltrating inflammatory cells and proinflammatory mediators in the intestinal microenvironment play a crucial role in colon carcinogenesis among IBD patients [8]. These inflammatory mediators include cytokines, chemokines, transcription factors, reactive oxygen and nitrogen species, prostaglandins, and miRNAs. The expression of miRNAs is altered in various types of human cancer studied to date, including CAC. Specific miRNAs have been shown to have oncogenic or tumor-suppressive properties, highlighting their role as key factors in carcinogenesis [9].

The scientific literature contains a growing number of reports about miRNAs associated with IBD, CD, CAC, and CRC, some of which are listed in Table 1.

However, there are still several miRNAs that have not been evaluated in CAC. Nonetheless, their role has been confirmed in CRC and warrants further investigation among IBD patients. miR-217, miR-144, miR-129, miR-125a, miR-125b, miR-375, miR-328, and miR-194 have been identified as useful prognostic biomarkers of CRC [24, 27, 28, 39–41]. Other miRNAs that are elevated in CRC include miR-21 and miR-31, both of which are linked to advanced cancer stages [42]. Additionally, miR-155 has been shown to increase in CRC and is thought to play a role in tumor development, intestinal barrier dysfunction, and inflammation-related pathways [43]. Moreover, the downregulation of miR-145, miR-192, and miR-375 has been correlated with CRC [44–46]. At the same time, an increase in miR-17-5p leads to a decrease in phosphatase and tensin homolog (PTEN),

Table 1 miRNA level changes in UC, CD, CRC, and CAC

miRNA	Disease	Modification	Sample	Possible targets	References
miR-10a-5p	CD	Downregulated	Feces	IL-12/IL-23p40, NOD2	[10]
miR-10b-5p	CD	Downregulated	Feces	–	[10]
miR-15a	CD	Upregulated	Feces	–	[10]
miR-16	UC CD	Upregulated	Feces	TNF-α, IL-12/IL-23p40, rictor	[10, 11]
miR-18a	CD CAC CRC	Upregulated	Colonic biopsies	PIAS3	[12, 13]
miR-19b	CD	Upregulated	Colon	–	[14]
miR-20a	CD	Upregulated	Colonic biopsies	PHLPP2	[12]
miR-21	UC CD CAC CRC	Upregulated	UC and CD colon tissue fecal matter, saliva	PDCD4, BTG2, TPM1, PTEN	[12, 15–18]
miR-23a	UC, CRC	Upregulated	Ileal/colonic tissue, serum	Lamin-B1, APAF1, SMAD3, STAT3, FAS	[16, 19]
miR-24, miR-24-3p	UC CD	Upregulated	Feces	–	[10]
miR-26b	CAC	Upregulated	Tissues and serum	DIP1, MDM2, CREBBP, BRCA1	[20]
miR-26-5p	CRC	Downregulated	Serum	SMAD4, PTEN, WNT5A	[21]
miR-27a-3p	CD	Upregulated	Feces	Runx1	[10]
miR-29a	UC	Upregulated	Ileal/colonic tissue	–	[16]
miR-30a-5p	CRC	Downregulated	Serum	IRS2l, PIK3CD, TM4SF1, integrin β3, TGFβ pathway	[21]
miR-31	CD CRC CAC	Upregulated	Colonic biopsies	FIH1	[12, 22, 23]
miR-92a	CRC	Upregulated	Serum	KLF4, PTEN, BCL2L11	[24]
miR-99a and miR-99b	CD	Upregulated	Colonic biopsies	–	[12]
miR-99-5p	CRC	Downregulated	Serum	PIK3R2	[21]
miR-100	CD	Upregulated	Colonic biopsies	–	[12]
miR-122	CD	Upregulated	Colonic biopsies	TNF-α	[25]
miR-125 miR-125a	UC CD	Upregulated	Colonic mucosal samples	TRAF6 and A20 (NFκB pathway)	[12, 26]
miR-126	UC CD	Upregulated	Ileal/colonic tissue, fecal matter	–	[12, 16]
miR-129	CRC	Downregulated	CRC tissue	SOX4	[27]
miR-141-3p	CD	Downregulated	Feces	CXCL12β, CXCL2, TGF-β2	[10]
miR-142-5p	CD	Upregulated	Colonic biopsies	–	[12]
miR-144	CRC	Upregulated	CRC tissue	ANO1	[28]
miR-145	CRC	Downregulated	Plasma	KLF5	[17]
miR-146a and miR-146b	UC CD	Upregulated	Colonic biopsies	TNF-α	[14, 25]
miR-150-5p	CRC	Downregulated	Serum	MAP3K12, c-Myb, c-FLIP, VEGFA	[21]
miR-155	UC CD CRC	Upregulated	Colonic biopsies	TNF-α	[25, 29]
miR-181b	CRC	Upregulated	Serum	CREB1, MAP2K1, FGFR1, KPNB, PRKCD	[19]
miR-185	CD	Upregulated	Colonic biopsies	–	[12]
miR-192	UC CD CRC	Downregulated	Ileal/colonic tissue, feces	NOD2, CXCL2	[10, 16, 30]

Table 1 (continued)

miRNA	Disease	Modification	Sample	Possible targets	References
miR-193a	CAC	Downregulated	Tissue	IL17RD	[31]
miR-194	CD	Downregulated	CRC tissues	–	[30]
miR-200	UC	Upregulated	UC dysplastic lesions	INO80D, SHROOM1, HMBOX1, SLC4A4, SMIM5, PLEKHA6, ANK3, KMT2C	[32]
miR-200a-3p	CD	Downregulated	Feces	CXCL2, TGF-β2	[10]
miR-204	CD	Upregulated	Colonic biopsies	–	[12]
miR-204-5p	CRC	Downregulated	Serum	HMGA2, ANGPTL2, CXCL8, RAB22A, TPT1, PCAT6, CREB	[21]
miR-210	UC CD	Upregulated	Colonic biopsies	EFNA3	[12, 33]
miR-214	CAC UC	Upregulated	Colon tissue	PTEN, PDLIM2	[34]
miR-215	CRC	Downregulated	Tissue	–	[30]
miR-221	CD	Upregulated	Colonic biopsies	–	[12]
miR-223	UC CD CAC	Upregulated	Colonic mucosal samples	IKKα	[12, 26, 35]
miR-301a	IBD	Upregulated	PBMC and inflamed mucosa	SNIP1	[36]
miR-375	UC CD CRC	Downregulated	Active UC colon biopsies, feces, serum of CRC patients	CTGF-EGFR, JAK2, PIK3CA, FZD-8, MMP2, vimentin, E-cadherin, N-cadherin, snail, β-catenin	[10, 16, 24, 37]
miR-378a-3p	CD	Downregulated	Feces	–	[10]
miR-422b	UC	Downregulated	Ileal/colonic tissue	–	[16]
miR-423-5p	CRC	Upregulated	Serum	AC007192.1, AKT1, AKT2, BIRC5, BRAF, CASP3, MAPK10, MAPK3, MLH1, MSH2, MSH6, PIK3R2, PIK3R3, RAC1, RAC2, SMAD2, TCF7, TGFBR2	[21]
miR-584	CRC	Upregulated	Serum	STAT1, PTEN, cyclin D	[21]
miR-760	CRC	Downregulated	Serum	CK2, SMAD3	[24]
miR-3074-5p	CD	Upregulated	Feces	–	[10]
miR-3184-5p	CRC	Upregulated	Serum	AC007192.1, AKT1, AKT2, BIRC5, BRAF, CASP3, MAPK10, MAPK3, MLH1, MSH2, MSH6, PIK3R2, PIK3R3, RAC1, RAC2, SMAD2, TCF7, TGFBR2	[21]
let-7a-5p, let-7c-5p	CRC	Upregulated	Serum	AKT2, APC2, BCL2, BRAF, CASP3, MAPK10, MAPK8, MSH2, MSH6, PIK3CA, PIK3R5, SMAD2, TGFBR1, TP53	[21]
let-7d-3p	CRC	Upregulated	Serum	APPL1	[21]
let-7e	UC	Upregulated	Colonic biopsies	p38-α	[38]
let-7f let-7f-5p	UC CRC	Upregulated	Ileal/colonic tissue, CRC patient serum	AKT2, APC2, BCL2, BRAF, CASP3, MAPK10, MAPK8, MSH2, MSH6, PIK3CA, PIK3R5, SMAD2, TGFBR1, TP53	[16, 21]
let-7 g-5p	CD	Downregulated	Feces	THBS1, TGFBR1, SMAD2	[10]

which is associated with resistance to conventional therapy for CRC [47]. Several miRNAs (miR-21, miR-29a, miR-92a, miR-221, and others) are also believed to be related to different stages of CRC, thus opening up the possibility of a new staging technique in patients [48]. Nevertheless, studies suggest that the pathogenesis of CAC differs from that of CRC; therefore, the exact role of CRC-related miRNAs requires further evaluation. The results of our literature search for miRNAs associated with CAC and CRC, including animal and human studies, are described below and summarized in Table 2.

miR-21

miR-21 is one of the first miRNAs for which an increased expression has been associated with cancer development. Extensive research shows that miR-21 is associated with lung cancer, pancreatic cancer, gliomas, breast and prostate cancer, among others [56–58]. miR-21 is also one of the most important miRNAs involved in the progression of CRC [56].

miR-21 levels are higher in CRC and inflammatory disorders, whether the inflammation is due to IBD or acute intestinal obstruction. Evidence suggests that miR-21 impairs intestinal barrier function and increases the secretion of antimicrobial peptides, causing gut dysbiosis and thus acting as a pro-inflammatory agent in IBD [59, 60].

miR-21 is believed to be an archetypal oncogenic factor, found to be upregulated in inflammation, trauma, and CRC patients at advanced stages. By inhibiting nuclear receptor NR2F2 (nuclear receptor subfamily 2 group F member 2) and SMAD7 (Mothers against decapentaplegic homolog 7) expression, miR-21 also promotes TGF-β-induced EMT in CRC, which initiates cancer metastasis and progression [61]. Using miR-21 as a biomarker for CRC has been found effective since its sensitivity was calculated to be 0.77 and specificity to be 0.84; it is also easily detectable [62].

As it is not only present during carcinogenesis but is also actively oncogenetic, miR-21 could potentially be used in therapy. Multiple targets have been identified for miR-21 which show the potential of being modulated to regulate cell proliferation and cancer invasion, such as NR2F2, tumor suppressor PTEN, programmed cell death 4 (PDCD4), Salvador 1 protein (SAV1), RAS homolog family member B (RhoB), cell division cycle 42 (CDC42), and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) [63–65]. In particular, the connection between miR-21, PDCD4, and PTEN appears especially promising [66]. Ke et al. [67] also recently demonstrated that miR-21 promotes UC development via TNF-α (tumor necrosis factor α) and changes in the gut microbiota.

Current data regarding the role of miR-21 in CAC pathogenesis primarily stems from animal studies. Shi et al.

Table 2 Selected miRNA roles and possible use

miRNA	Role	Possible use	References
miR-21	The pro-inflammatory role, active oncogenic factor	Therapy of CAC and CRC	[17, 18]
miR-301a	Apoptosis suppression, cancer proliferation and metastasis promotion, cancer drug resistance progression; pro-inflammatory role; mucosal permeability development in IBD promotion	Therapy of CAC, CRC, and IBD	[36, 49, 50]
miR-31	Promotion of cell proliferation, migration and invasion, regulation of tumor growth, the proliferation of CRC cells through E2F2 inhibition level rise at TNM stage (III-IV)	Therapy of CRC, CAC, and intestinal inflammation cancer invasion and advancement evaluation	[23, 51]
miR-200 family (miR-200a, miR-200b, miR-200c, miR-141, miR-429, miR-200-3p)	Promotion of tumor metastases, the level rise in UC dysplastic lesions, CRC complications	Therapy of CRC and other types of tumor complication evaluation for UC, CRC	[32, 52]
miR-31-5p, miR-223-3p, let-7f-5p	Intestinal dysplasia development miR-223-3p—downregulation of APC protein (a tumor suppressor gene); let-7f-5p—downregulation of SLC9A9 and AMER3, whose levels are correlated with cancer progression	Diagnostic tool for CAC therapy of CAC	[53]
miR-19a	Colitis, CRC, and CAC promotion	Therapy and prevention of CRC and CAC	[54, 55]

CAC *colitis-associated cancer*; CD *Crohn's disease*; CRC *colorectal cancer*, IBD *inflammatory bowel diseases*; miRNAs *microRNAs*; UC *ulcerative colitis*

performed a study on miR-21 knocked-out (KO) mice with AOM/DSS (azoxymethane/ dextran sodium sulfate)-induced CAC, which is 99 accepted experimental model of inflammation-induced CRC. The AOM/DSS mouse model was established by intraperitoneally administering AOS at a dose of 12 mg/kg to 8–10-week-old male mice. Seven days later, the mice were given 2% DSS in their drinking water for five consecutive days. On day 20, a second dose of AOM (12 mg/kg) was given, followed by another 2% DSS treatment for five days, starting seven days after the second AOM injection. Mice were then maintained on plain water and monitored until the end of the experiment, with tumor assessments conducted on days 31 and 81. The study revealed that KO mice, compared with wild-type (WT) mice were characterized by decreased b-catenin levels, increased E-cadherin levels, and reduced expression of Ki67. Furthermore, levels of suppressor protein PDCD4, a potential target of miR-21, were statistically higher in miR-21 KO mice compared with WT mice. Moreover, the authors reported that increased levels of miR-21 were negatively correlated with levels of b-catenin and positively correlated with E-cadherin levels. In summary, miR-21 deficient mice developed less severe neoplastic conditions and appeared resistant to CAC induction [18].

Another study performed by El-Daly et al. [68] revealed that mice with AOM/DSS-induced CAC had higher serum levels of miR-21 compared to the control group. In the same study, higher levels of miR-141, miR-15b, miR-29a, carcinoembryonic antigen, and cancer antigen 19-9 were associated with CAC development. Lai et al. [69] conducted a study on transgenic zebrafish, which revealed that miR-21 is crucial in tumor development in AOM/DSS-induced CAC.

Only a few studies on miR-21 in human CAC are available. Shi et al. demonstrated that UC patients with dysplasia and cancer exhibited significantly higher levels of miR-21 compared to patients with active UC [18]. A similar result was reported by Ludwig K. et al., who analyzed UC patients with and without dysplasia, revealing that miR-21 levels were higher in the former group [15]. Furthermore, Yang et al. [70] revealed that levels of miR-21 increase with the duration of UC. All these studies may help explain the increasing risk of CAC development in the course of IBD.

miR-301a

miR-301a plays a role in multiple biological functions that lead to different types of cancer, such as hepatocellular carcinoma, lung cancer, pancreatic ductal adenocarcinoma, breast cancer, and osteosarcoma; it is also present in the development and progression of both, IBD and CRC [49, 50]. miR-301a is proven to suppress apoptosis; it stimulates the proliferation and metastasis of pancreatic, colon, and gastric cancer; it also plays a role in the progression of drug resistance to cancer. Moreover, miR-301a is suspected to control NF-kB, which plays a crucial role in inflammation-driven carcinogenesis [63].

miR-301a is upregulated in inflamed bowel lesions in IBD, as opposed to no sign of the rise of its levels in mucosa tissue in a healthy patient [49]. Moreover, in lung and colon carcinogenesis miR-301a affects tumor-associated immune cells and through that enhances inflammation [71]. There is also a correlation between miR-301a and IL-1β levels, with IL-1β stimulating the expression of miR-301a in CRC cells and overexpression of miR-301a enhancing the expression of IL-1β, along with IL-6, IL-8, and TNF-α. Different studies show that miR-301a is a factor in mucosal permeability development and regulation of IBD and CAC; therefore, it might play a significant role in the disruption of gastrointestinal immunology [72].

The study conducted by He et al. demonstrated that miR-301a-deficient mice were less susceptible to AOM/DSS-induced CRC and developed fewer tumors compared to the control. Furthermore, miR-301a was proposed to upregulate NF-kB levels in a BTG1 (B cell translocation gene 1)-dependent manner. In the same study, samples from IBD patients were collected and analyzed for miR-301a, BTG1, and NF-kB levels. The analysis revealed that both miR-301a and NF-kB levels were elevated in IBD patients, while BTG1 levels decreased. The authors identified BTG1 as a direct target of miR-301a, a finding confirmed by in vitro studies. Since BTG1 is regarded as a negative regulator of NF-κB, its silencing by miR-301a may contribute to enhanced inflammation driven by the NF-κB pathway (nuclear factor kappa-light-chain-enhancer of activated B cells) [36, 73].

Ma et al. performed a similar study, investigating the role of miR-301a and signal transducer and activator of transcription 3 (STAT3) in developing inflammation-induced lung and CRC. In both cases, carcinogenesis was diminished in miR-301a deficient mice. Nearly 50% of subjects did not develop any tumors and the remaining half developed tumors of smaller sizes and better differentiated architecture. This study suggests that control of NF-kB by miR-301 may occur via STAT3 [49]. In addition, Zhang et al. showed that the level of miR-301a-3p is significantly increased in the HT-29 and SW620 cell lines, as well as in the tissues of CRC patients. miR-301a-3p also contributes to tumor progression by negatively regulating deleted in liver cancer-1 (DLC-1) and runt-related transcription factor 3 (RUNX3), which inhibit migration, proliferation, as well as induce apoptosis in *vitro* models of CRC [74].

Furthermore, a study conducted by Yang et al. [75] revealed that miR-301a was significantly higher in patients with CAC compared with CRC indicating that this miRNA may play a significant role in the pathogenesis of this disease.

miR-31

miR-31 is increased in CRC and is associated with cancers characterized by deeper invasion and advanced TNM stages; the level of miR-31 is higher at TNM stages III-IV than at lower stages. miR-31 plays a role in the promotion of cell proliferation, migration, and invasion, as well as the regulation of tumor growth through HIF-1α (hypoxia-inducible factor 1). Overexpression of miR-31 inhibits the tumor suppressor E2F2, leading to increased proliferation of CRC cells [51].

A connection has also been found between the expression of miR-31 and intestinal barrier dysfunction, which directly influences inflammation and cancer development; it regulates colonic inflammation in IBD by targeting HIF-1a, which, apart from inflammation, also controls cell functions and tumor growth [76]. Thus, miR-31 is linked to the promotion of cell proliferation, invasion, and migration. It is also found to directly target the large tumor suppressor kinase 2 (LATS2), thereby modulating the Hippo pathway, which controls organ size. The downregulation of this pathway is associated with carcinogenesis [77].

A major study about the role of miR-31 in IBD and CAC was performed by Olaru et al. A comparison of IBD patients with healthy individuals revealed that miR-31 levels in tissue are statistically higher in the IBD group. Moreover, IBD patients with neoplastic lesions exhibited 11-fold higher levels of miR-31 than nonneoplastic IBD patients. Intriguingly, the authors reported that miR-31 levels were 20-fold higher in CAC patients compared with sporadic CRC [23].

Another study revealed, that upregulation of miR-31 is associated with dysplastic lesions in patients with UC. However, the authors do not describe the possible target of miR-31 [78].

Similar results are reported by Necela et al. The author revealed, that upregulation of miR-31 is associated with tumorigenesis in the course of bowel inflammation and may be useful in distinguishing specimens with chronic colitis from those with neoplastic progression [79].

In turn, Sun et al. identify RAS p21 GTPase activating protein 1 (RASA1) as a direct target of miR-31, involved in the RAS signaling pathway, the regulation of which by this miRNA significantly accelerates the proliferation of CRC cells in in vitro studies [80]. Moreover, recent studies indicate that factors downregulating miR-31 expression may be a good therapeutic target in CRC. Li et al. reported that long noncoding RNA (lncRNA) MEG3 (maternally expressed 3), a tumor suppressor, can downregulate miR-31 expression, which contributes to the inhibition of CRC cell proliferation and migration [81]. All these data indicate that miR-31 may serve as another significant marker of CAC and CRC, constituting a potential therapeutic target.

miR-200 family

The miR-200 family consists of miR-200a, miR-200b, miR-200c, miR-141, and miR-429. These are the microRNAs that are significant for EMT. The role of the miR-200 family in carcinogenesis through that process refers not only to CRC, but also to other types of tumors [52]. Recent studies confirmed that the levels of miR-200 family increase in UC dysplastic lesions, while miR-200-3p is raised in CRC complications [32].

Different results were reported in a study by Peng S et al., which focused on the role of miR-200a in DSS-induced colitis. The authors performed a study on mice treated with DSS, which revealed that the level of miR-200a was overexpressed for four weeks using an adeno-associated viral (AAV) vector. Furthermore, the authors verified if an overexpression of miR-200a may influence the induction of inflammation. It turned out, that the overexpression of miR-200a resulted in the activation of the Nrf2 antioxidant pathway, thereby alleviating adverse alterations in animal and cellular models1. miR-200a was found to repress Keap1 (Kelch-like ECH-associated protein 1), a protein involved in the regulation of the Nrf2 antioxidant pathway. Given these facts, it seems miR-200a acts as a protective agent against DSS-induced colonic damage through the activation of the Keap1/Nrf2 signaling pathway [82].

The study conducted by Xiao et al. revealed that *Clostridium butyricum*, a human probiotic, alleviates inflammation and cancerogenesis in TNBS/AOM-induced CAC. Moreover, *C. butyricum* decreases cancer cell proliferation and pro-inflammatory cytokine production in cancer cell culture in a miR-200c-dependent way [83].

Olrau et al. [84] reported that miR-200a is increased in the colonic tissue of patients with UC-associated dysplasia; however, potential targets of this miRNA were not evaluated. In addition, Carter et al. proved that the increased expression of the miR-200 family in colon cancer negatively correlated with the level of the tumor suppressor gene RASSF2 (Ras association domain-containing protein 2), associated with the MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) signaling pathway, suggesting that RASSF2 may be a direct target of miR-200 [85]. Given the discrepancies in reports on the involvement of miRNAs from the miR-200 family, further research is necessary to fully elucidate their role in CRC pathogenesis and their links to inflammation.

miR-26b family

miR-26 family, including miR-26a, miR-26b, miR-1297, and miR-4465, is associated with many types of cancer, such as gastric, lung, or prostate cancer. Depending on tumor type,

their levels may be up- or downregulated and act as pro- and anticancerogenic agents [86].

Regarding CRC, data regarding the role of miR-26a are inconclusive; some reports indicate that lower levels of miR-26b were associated with neoplasm progression. Intriguingly, the study performed by Benderska et al. revealed that miR-26b expression is elevated in AOM/DSS-induced CAC. Authors suggest that miR-26b regulates the expression of proteins interacting with the DAPK (death-associated protein kinase 1) signaling pathway; especially the DIP1 protein (disco-interacting protein 1), which contains a putative miR-26b-binding domain. Furthermore, the authors reported that the level of miR-26b is higher in UC patients with neoplastic lesions compared with nonneoplastic patients and patients with the disease in remission. Authors reported that miR-26b was also elevated in celiac disease [20].

Moreover, Zhang et al. reported that transgenic mice overexpressing miR-26a are less vulnerable to AOM/DSS-induced CAC; miR-26a levels were inversely correlated with IL-6, STAT3, and NF-kB levels [87, 88]. In contrast, Fan et al. proposed that miR-26b silences the expression of PTEN and wingless-type MMTV integration site family member 5A (WNT5A), which affect EMT and tumor cell motility. This suggests that elevated miR-26b levels in CRC patients with lymphatic metastases may enhance the invasive potential of cancer cells [89].

Also interesting are the reports of Wang et al. that a higher level of miR-26b expression positively affects 5-fluorouracil (5-FU) treatment in vitro studies using CRC lines. The authors also postulate that this mechanism may be related to targeting P-glycoprotein (Pgp), which activates the intrinsic apoptotic pathway [90].

Due to these discrepancies, further research is required to clarify the role of this miRNA family in CRC development and progression.

Other miRNAs associated with CAC and CRC pathogenesis

miR-19a seems to be one of the factors promoting colitis and the development of CAC through its connection with TNF-α and NF-κB signaling. miR-19a directly targets TNF-α, and the expression of TNF-α, IL-8, and granulocyte–macrophage colony-stimulating factor (GM-CSF) are significantly upregulated by a miR-19a inhibitor. In a study by Huang et al. [55], the role of miR-19a in the connection between metastatic involvements of lymph nodes and TNF-α-induced EMT in CRC was confirmed. It was also observed that the TNF-α stimulation is related to the overexpression of miR-19a in HCT-116 cells. Wang et al. found a relationship between miR-19a, NF-κB, and TNF-α signaling in CAC. They showed that TNF not only led to the overexpression of miR-19a, but the high level of miR-19a induced by TNF may be decreased through inhibition of NF-κB signaling. It was also found that the miR-19a activated the NF-κB signaling pathway via regulating TNFAIP3 (tumor necrosis factor, alpha-induced protein 3) and inducing expression of TNF-α. The upregulation of miR-19a, among other miRNAs (such as miR-17, miR-18a, miR-18b, miR-19b, miR-20a, miR-20b, miR-106), correlates with the risk of CRC relapse [54].

A group consisting of miR-31-5p, miR-223-3p, and let-7f-5p is dysregulated in intestinal dysplasia development. According to a study conducted by Chen et al. [53], the levels of miR-31-5p and miR-223-3p rise in CAC tumor initiation, while the level of let-7f-5p drops; therefore, a connection between the expression of these miRNAs and oncogenesis has been suggested.

Firstly, miR-223-3p is believed to directly regulate the expression of adenomatous polyposis coli (APC) mRNA, thus decreasing the APC level, a protein that controls cell division, adhesion, polarization, and morphogenesis. Secondly, let-7f-5p downregulates the expression of solute carrier family 9 subfamily A member 9 (SLC9A9) and APC membrane recruitment protein 3 (AMER3); SLC9A9 upregulation is linked with cancer progression and poor prognosis in CRC, while AMER3 level is positively correlated with the level of c-Myc, a proto-oncogene expressed in cancer. To sum up, lower levels of let-7f-5p lead to cancer progression [53].

miR-193a-3p is a putative suppressor factor in CAC. Dai et al. reported that miR-193a-3p is upregulated in neoplastic tissue in UC patients compared with nonneoplastic UC patients and the control group. Authors in another study, suggest miR-193a-3p may interfere with epidermal growth factor receptor (EGFR) signaling via regulation of expression of interleukin-17 receptor D (IL17RD). Moreover, there was no significant change in methylation of miR-193a-3p in CAC patients compared with the control group [31, 91].

Analysis of colonic biopsies of UC patients revealed that miR-224 levels exhibit a stepwise increase from healthy tissue to chronic colitis to cancer. miR-224 regulates the expression of p21, which is a protein involved in the control of the G1-S checkpoint [84].

Pekow et al. reported that miR-4728-3p upregulation is associated with dysplastic changes in UC patients. miR-4728-3p controls focal adhesion complexes, which are crucial in epithelial integrity maintenance and tumor invasion [92].

miR-449a is a potential suppressive agent in CAC development. Feng et al. reported that miR-449a is downregulated in patients with UC-associated cancer and mice treated with AOM/ DSS. miR-449a putatively regulates CAC growth by targeting Notch-1 [93].

Interplay between miRNA and cytokine signaling pathways

Chronic inflammation is a key factor predisposing patients with IBD to CRC development; therefore, a thorough analysis of the signaling pathways and factors involved in its progression is crucial for the prevention and more effective treatment of this disease [94]. Studies indicate that miRNAs are strongly involved in cytokine-related signaling pathways in chronic inflammation in CRC. Martínez-Gutierrez et al. demonstrated that 11 different inflammation-related miRNAs are overexpressed in colon cancer (miR-21-5p, miR-304-5p, miR-577, miR-335-5p, miR-21-3p, miR-27b-5p, miR-335-3p, miR-215-5p, miR-30b-5p, miR-192-5p, and miR-3065-5p). The authors identified these miRNAs as important diagnostic markers for colon cancer [95].

One of the key miRNAs associated with inflammatory signaling pathways in CAC is miR-214. A study by C. Polytorchau et al. revealed that miR-214 overexpression is associated with the progression from chronic colitis to cancer development in UC patients. Analysis of human colonic biopsies showed that miR-214 is upregulated in UC patients, but not in those with CD or CRC. Moreover, miR-214 expression was dramatically higher in CAC patients compared with CRC and control individuals. A significant increase in miR-214 levels in UC lasting longer than 10 years was also reported. An experiment on an animal model of CAC revealed that the injection of miR-214 reduced inflammation in colonic tissue. Furthermore, the authors investigated the possible role of miR-214 in Il-6/STAT3 signaling. IL-6 and STAT3 levels were positively correlated with miR-214 upregulation and may regulate its expression. miR-214 putatively suppresses the expression of PTEN and PDLIM2 (PDZ and LIM domain 2), which further downregulates NF-kB-mediated IL-6 expression. These results suggest that the overexpression of miR-214 may contribute to a positive feedback loop in IL-6 signaling, which is a crucial step in inflammation-driven carcinogenesis [34].

miR-29b-5p is another miRNA possibly involved in IL-6/STAT3 signaling. A study conducted by Wang et al. revealed that miR-29a levels are significantly elevated in AOM/DSS-induced CAC. The level of these miRNAs was also upregulated in human cancer cell cultures. The authors suggested that miR-29b may regulate TETs (ten-eleven translocation) activity—an enzyme involved in the synthesis of 5-hmC (5-hydroxymethylcytosine), whose loss is a hallmark of cancer. Furthermore, they revealed that miR-29b expression may be regulated by the Il-6/STAT3 pathway, and along with miR-21, it may participate in a positive feedback loop, leading to carcinogenesis and uncontrolled cell proliferation [96].

IL-6 may also downregulate miR-34b-5p. Yang et al. demonstrated that miR-34b levels are significantly diminished in colonic biopsies of CAC patients compared with those with CRC. Further analysis of colon cancer cell cultures revealed that miR-34b potentially downregulates c-MYC expression, which in turn suppresses CUL4A/4B expression. These three proteins are proto-oncogenes involved in cancer development. Moreover, miR-34b levels were significantly downregulated by IL-6, TNF, and lipopolysaccharide (LPS) in a dose-dependent manner [75].

A study by Zhu et al. revealed that STAT3 may be suppressed by miR-148. miR-148 knockout (KO) mice were more vulnerable to DSS-induced colitis and AOM/DSS-induced CAC. Moreover, KO mice exhibited overexpression of STAT3 and NF-kB. Restoration of miR-148 expression in KO mice alleviated symptoms induced by AOM and DSS. In specimens with restored miR-148 production, lower levels of STAT3 and NF-kB were also reported [97].

These combined studies suggest that miRNAs play a crucial role in cytokine signaling pathways and may serve as a potential link between inflammation and carcinogenesis.

miRNAs involved in epithelial-mesenchymal transition

Switching the phenotype from differentiated epithelial to embryonic mesenchymal cells EMT is crucial in the pathogenesis of many cancers, including CRC and CAC. Recent studies suggest that inflammatory cytokines are essential in EMT development and miRNA may also be involved in this process (Fig. 2) [98–100].

Zheng et al. revealed that miR-200b levels are diminished in experimental mice with CAC compared to controls and that it plays a crucial role in EMT. AOM/DSS-treated mice that received miR-200b injections were characterized by decreased N-cadherin expression and upregulated E-cadherin levels [101]. Similarly, Ranković et al. conducted a study on biopsy samples from CRC patients, showing that miRNAs from this family are involved in modulating EMT. This study analyzed the expression levels of miR-141, miR-200a/b/c, and miR-429, as well as their EMT-related target genes (CDKN1B, ONECUT2, PTPN13, RND3, SOX2, TGFB2, and ZEB2). The expression of miRNAs was significantly decreased, whereas the expression of their target genes was increased. Additionally, a correlation between target gene expression and metastases in patients was demonstrated [102]. Similar research was conducted by Hur et al., who demonstrated an increase in miR-200c expression in liver tissues after CRC metastases and its association with reduced vimentin levels and increased E-cadherin expression [103].

Another miRNA involved in EMT is miR-30a-5p, which is downregulated in both CRC tissues and colon cell lines. As demonstrated by Park et al., its expression level is negatively correlated with the stage of CRC and the severity of

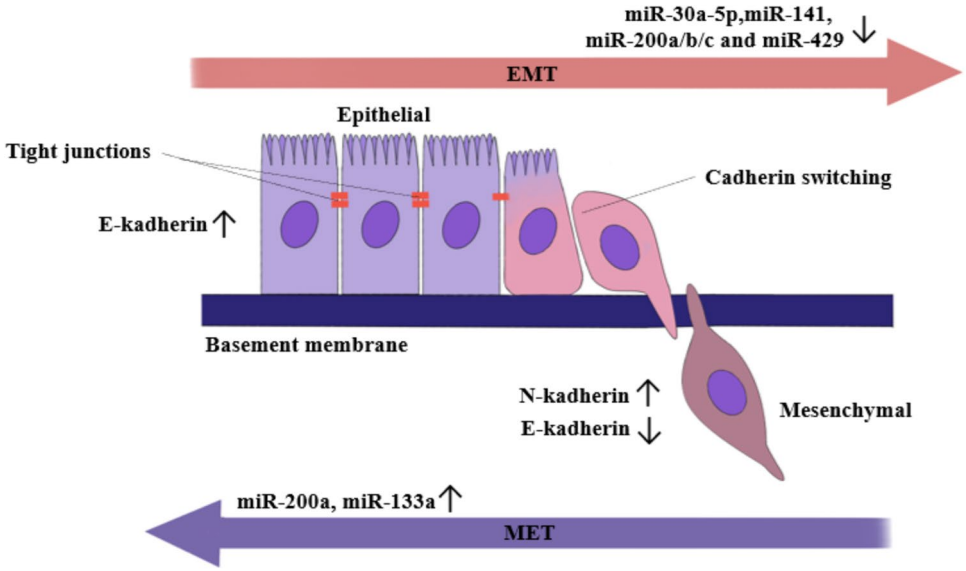

Fig. 2 The role of miRNAs in EMT in CRC and CAC. EMT (epithelial-mesenchymal transition) and MET (mesenchymal-epithelial transition) are cellular processes that involve changes in cell phenotype and adhesion properties, with cadherin switching playing a crucial role. During EMT, epithelial cells lose their adhesive properties, downregulating E-cadherin and upregulating N-cadherin, which facilitates increased motility and invasiveness. Conversely, in MET, mesenchymal cells revert to an epithelial state, with E-cadherin being upregulated and N-cadherin downregulated, promoting stronger cell–cell adhesion and tissue organization. This dynamic cadherin switching is essential for regulating cell migration, tissue remodeling, and processes like wound healing and cancer metastasis. Research shows that these miRNAs play a significant role in the regulation of EMT in both CRC and CAC. miR-200, miR-141, miR-30a, miR-429, and miR-133 are involved in regulating EMT by modulating key targets that affect cell adhesion and migration. miR-200 family members inhibit EMT by decreasing N-cadherin and increasing E-cadherin expression, while miR-30a-5p and miR-133a suppress EMT

lymph node metastases. Furthermore, miR-30a-5p regulates the expression of transmembrane-4-L-six-family protein (TM4SF1), which promotes EMT [104]. In addition, research indicates that the toll-like receptor 4–cyclooxygenase 2–prostacyclin (TLR4-COX2-PGI) axis is involved in EMT and inflammation-induced carcinogenesis. A study conducted by X et al. revealed that increased levels of miR-133a are associated with reduced TLR4-COX2-PGI axis activity, along with diminished EMT. Moreover, the injection of miR-133a alleviates AOM/DSS-induced CAC and EMT development in mice and cell cultures [105, 106].

A study by Rokavec et al. revealed that miR-34a may be a potential link between the Il-6/STAT3 pathway, EMT, and carcinogenesis. Analysis of CRC cell cultures showed reduced levels of miR-34a in cancer cells, and Il-6 repressed miR-34a expression via a STAT3-mediated mechanism. miR-34a potentially suppresses the expression of SNAIL (zinc finger protein SNAI1), which stimulates Il-6 production and EMT. This positive feedback loop is associated with EMT, carcinogenesis, and enhanced cancer cell invasion. Moreover, the authors reported that miR-34a-deficient mice were more sensitive to AOM/DSS [107].

Kim et al. showed that vimentin is a target of miR-17-5p. High expression of miR-17-5p in human colon lines LoVo and Ht-29 was associated with reduced vimentin levels and decreased migration and invasion of the tested cells [108].

The conclusions from the studies mentioned above are promising because, due to the key role of EMT in migration and invasion, the regulation of this process by miRNA opens new therapeutic possibilities for metastasis treatment.

Regulation of miRNAs related to CRC and CAC

As we have shown, in the course of CAC and CRC, numerous miRNAs are deregulated; therefore, other aspects related to the mechanisms of miRNA expression disturbances are critical to fully understanding the importance of these molecules in the pathogenesis, treatment, and diagnosis of these diseases. Studies show that the causes of miRNA deregulation are complex and may be related to miRNA gene mutations, disorders of the transcription machinery, dysfunctions of miRNA biogenesis and processing, and epigenetic modifications such as methylation [109]. Methylation is a particularly important etiological factor in all types of cancer. Hypermethylation of promoter-associated CpG islands in suppressor genes is a crucial step in CRC pathogenesis and occurs in an age-related manner. Some studies suggest that chronic inflammation may accelerate this process, resulting in earlier cancer development. Moreover, recent studies explore the role of hypermethylation in miRNA promoter regions in neoplasms. Patil et al. conducted a global methylation

analysis in CRC, revealing that 25,341 CpG sites are methylated to a different extent in tumors than in healthy tissues and are not limited to promoter sequences. Within miRNA genes, the vast majority of CpG regions are hypermethylated. These findings support the hypothesis that methylation plays an important role in miRNA regulation in CRC [110].

Yang et al. revealed that hypermethylation of the miR-34b promoter region is associated with dysplastic changes in UC patients [75]. Furthermore, CRC cells treated with AZA (azacytidine), a methylation inhibitor, showed increased expression of miR-34b, which resulted in diminished expression of proto-oncogenes c-MYC and CUL4A/4B and decreased cell proliferation. Additionally, hypermethylation in miR-125a and miR-125b promoter sequences has been linked to reduced expression levels of these miRNAs in altered tissues of CRC patients [111].

Some reports also indicate that miR-124a is regulated by methylation in CRC patients [112, 113]. Moreover, Ueda et al. demonstrated that this miRNA is methylated during the carcinogenic process in UC and CAC patients. Therefore, methylation of this miRNA could serve as an early marker of disease development [113]. Balaguer et al. showed that miR-137, located on a CpG island, is regulated by methylation in CRC cell lines [114]. Furthermore, Kashani et al. proved that there is a discrepancy between the methylation level of the miR-137 gene in healthy and affected tissues in CRC patients [115].

Moreover, a study conducted by Wu et al. disclosed that reduced DICER expression, an enzyme essential for miRNA synthesis, is associated with chronic intestinal inflammation, oxidative stress, and colitis-driven carcinogenesis [116]. Vychytilova-Faltejskova et al. analyzed proteins involved in miRNA transcript processing during CRC progression. Their results indicate that the entire biogenesis process is disrupted, as 18 of 19 genes analyzed showed significantly altered expression in CRC patients. Additionally, they assessed the association of miRNA processing gene deregulation with disease-free survival (DFS) and overall survival (OS) finding that high expression of TARBP2 and/or DROSHA is associated with shorter DFS, while overexpression of XPO5 (exportin-5) and/or TNRC6A (trinucleotide repeat containing adaptor 6A) and/or DDX17 (DEAD-box helicase 17) significantly shortens OS [117].

Considering the importance of miRNA synthesis, processing, and epigenetic regulation, these aspects should be prioritized in future CRC and CAC research. This focus is vital because natural mechanisms regulating miRNA expression can be leveraged to design novel therapeutic tools, such as modulating miRNA gene methylation levels or inhibiting nucleases directly involved in miRNA biogenesis.

Current clinical practices based on miRNAs in CAC and CRC

As discussed above, miRNAs may play an important role in developing CAC and CRC and regulate many processes, including immune system function and EMT. Therefore, these molecules can be used as new therapeutic targets or markers for rapid diagnosis of cancers. The current clinical application of miRNAs in CRC is illustrated in Fig. 3.

Three specimens are usually considered for diagnostic purposes: blood, stool, and urine. Blood testing shows promising diagnostic value, while urine samples, though easily collected, appear to be less useful. Due to their ease of detection and often increased expression levels in patients, circulating miRNAs have been proven to constitute noninvasive cancer biomarkers, particularly because their expression levels can change depending on treatment and disease progression. MiRNAs of exosomal origin are especially stable. Studies indicate that the level of exosomal miRNAs detected in the blood may correspond closely to the expression level of a given miRNA in the tumor, significantly facilitating diagnosis and monitoring of disease progression and treatment. Liquid biopsy is easy to perform, minimally invasive, and can be repeated multiple times. Additionally, material obtained from a liquid biopsy is often of better quality than that from a tissue biopsy and enables cancer detection at an early stage [118–120].

It remains uncertain whether detecting miRNAs in fecal samples and quantifying their levels is feasible. Nonetheless, fecal matter contains miRNAs from blood cells released by tumors, and a study by Tung On Yau et al. suggests that it may serve as an accurate diagnostic tool. In this study, miR-21 and miR-92a emerged as the most reliable biomarkers. However, there is insufficient research on the methodologies and clinical applications of these findings, making it challenging to draw definitive conclusions [121].

Colonic biopsies collected during surgeries or invasive procedures are another source of material. Since abnormalities in the colon that precede CAC are well-researched, scaling up this method for broader use could be more straightforward. CAC markers identified in this manner could be analyzed through immunohistochemical staining of formalin-fixed paraffin-embedded tissue; miRNAs, along with other genetic materials like DNA and RNA, can also be isolated. Considering that cancer-associated changes in tissue may also occur in other regions, this method could enable early detection and diagnosis of CAC [44].

An exciting future perspective for miRNA use is their potential as therapeutic targets. For example, miR-135b has been reported as a promising target in CAC treatment, along with other miRNAs such as miR-21, miR-20a, miR-95, and miR-675 [122]. One fundamental therapy involves inhibiting overexpressed miRNAs, which can

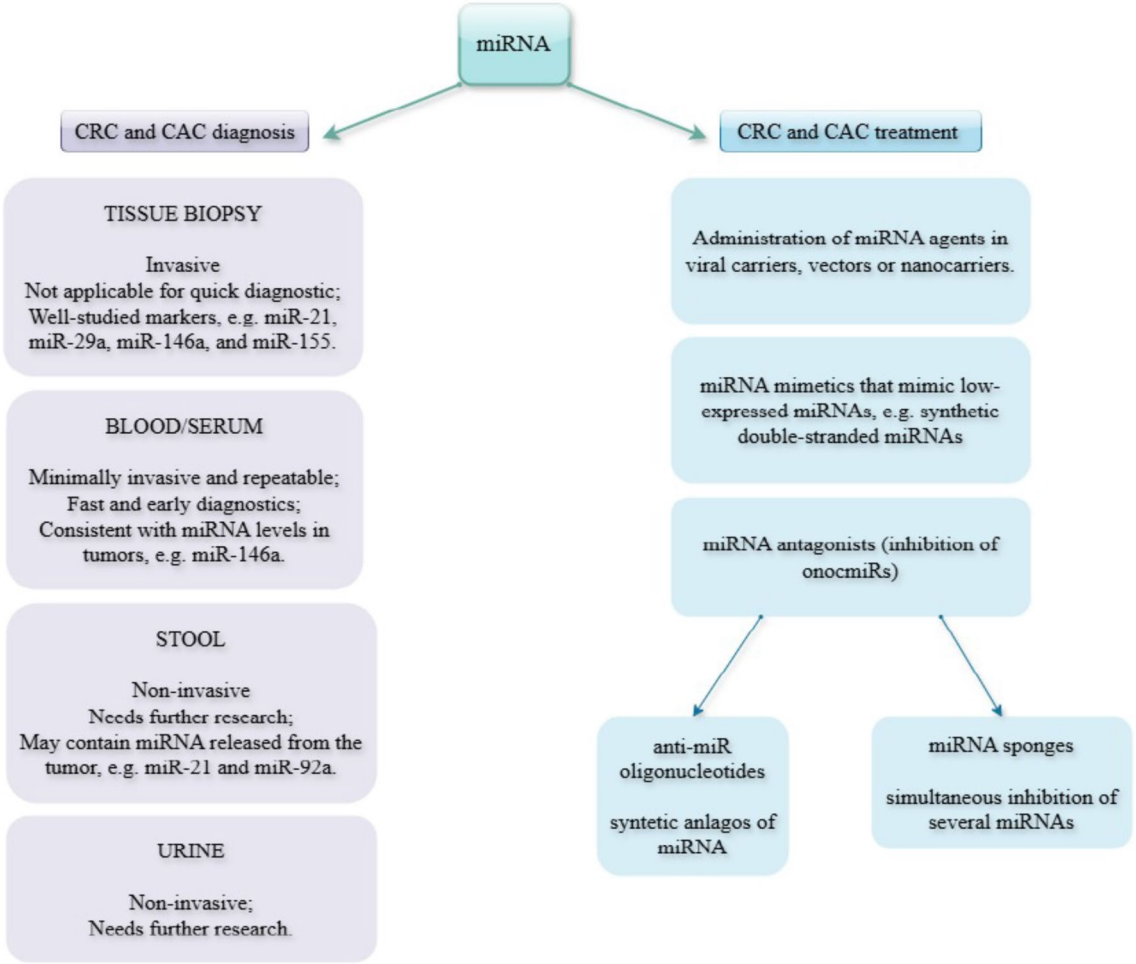

Fig. 3 Current clinical practices based on miRNAs in CAC and CRC. Due to the altered expression patterns in CAC and CRC, miRNAs can act as biomarkers for the diagnosis and prognosis of disease progression. For diagnostic purposes, samples taken from patients during biopsy procedures or obtained from blood, urine, or stool are analyzed to determine the level of marker miRNAs. Deregulated miRNAs may also represent promising therapeutic targets for CAC and CRC. In current practices, the most important miRNA-related treatment strategies include suppressing overexpressed miRNAs and mimicking suppressor miRNAs

be achieved using tools such as short anti-miR oligonucleotides. For suppressor miRNAs, synthetic molecules that mimic the activity of miRNAs, binding to target gene sequences and compensating for the impaired function of downregulated miRNAs, appear effective [119]. Another potential approach involves multipotent miRNA sponges, which have demonstrated effectiveness in breast cancer cell lines. These sponges simultaneously inhibit multiple oncogenic miRNAs, offering greater potential than single-target miRNA sponges [123]. A recent study reported promising outcomes for miRNA-based treatments in CAC animal models: intracolonic administration of anti-miR-18a lentivirus in a mouse CAC model significantly reduced tumor number and size[13]. Additionally, ABX464 (obefazimod), a small-molecule compound that regulates miR-124, has completed a randomized clinical trial in patients with active UC [124].

Challenges associated with miRNAs in the clinical practice of IBD, CAC, and CRC

Although miRNAs hold significant potential for use in diagnostics and as therapeutic tools, their application in clinical settings faces several challenges. The primary obstacle in designing drugs based on miRNAs or their synthetic equivalents, such as anti-miRs and sponges that bind oncogenic miRNAs, lies in achieving adequate molecular stability and determining effective methods of drug administration [119].

The use of natural miRNAs to silence the expression of genes involved in cancer progression signaling pathways is particularly appealing. However, despite the promise of miRNAs as drugs and their relatively higher stability compared to mRNAs, their delivery as therapeutics presents certain difficulties. Due to specific characteristics, such as low stability and pleiotropic effects, miRNA-based treatments

may have side effects and exhibit reduced efficacy. Consequently, it is essential to develop carriers or modifications that enhance the efficiency and safety of direct miRNA administration. One potential approach involves the chemical modification of the sugar backbone to improve RNA stability. Additionally, viral carriers and lipid or peptide vectors can be utilized, though these methods come with limitations such as high costs and low efficiency. A novel alternative is the delivery of miRNAs via nanocarriers, which offer high safety, minimal side effects, and enhanced efficiency (Fig. 4) [125, 126].

Another frequently discussed issue is the multifactorial nature of miRNA interactions, along with their lack of specificity, which may lead to the regulation of off-target signaling pathways and potential side effects. The complex interactions between miRNAs and a wide range of them, and the incomplete understanding of miRNA expression regulation, make it challenging to predict the therapeutic effects of miRNAs accurately. On the other hand, the complexity of the miRNA regulatory network can be an advantage when using these molecules as natural therapeutic agents, as it may result in a more robust response compared to synthetic drugs that target single proteins. In addition, chemical modifications offer several possibilities for enhancing the functionality of miRNAs. The use of mimetics can improve efficiency, functionality, and stability, as well as provide better pharmacokinetic properties [128].

Despite these challenges, continued research and the development of innovative technologies are paving the way for miRNA-based therapies to become a viable option in precision medicine.

Recommendation and future perspective

miRNAs hold great promise as therapeutic agents, but their clinical application faces significant challenges, including low stability, off-target effects, and inefficient delivery. Future strategies should prioritize enhancing miRNA

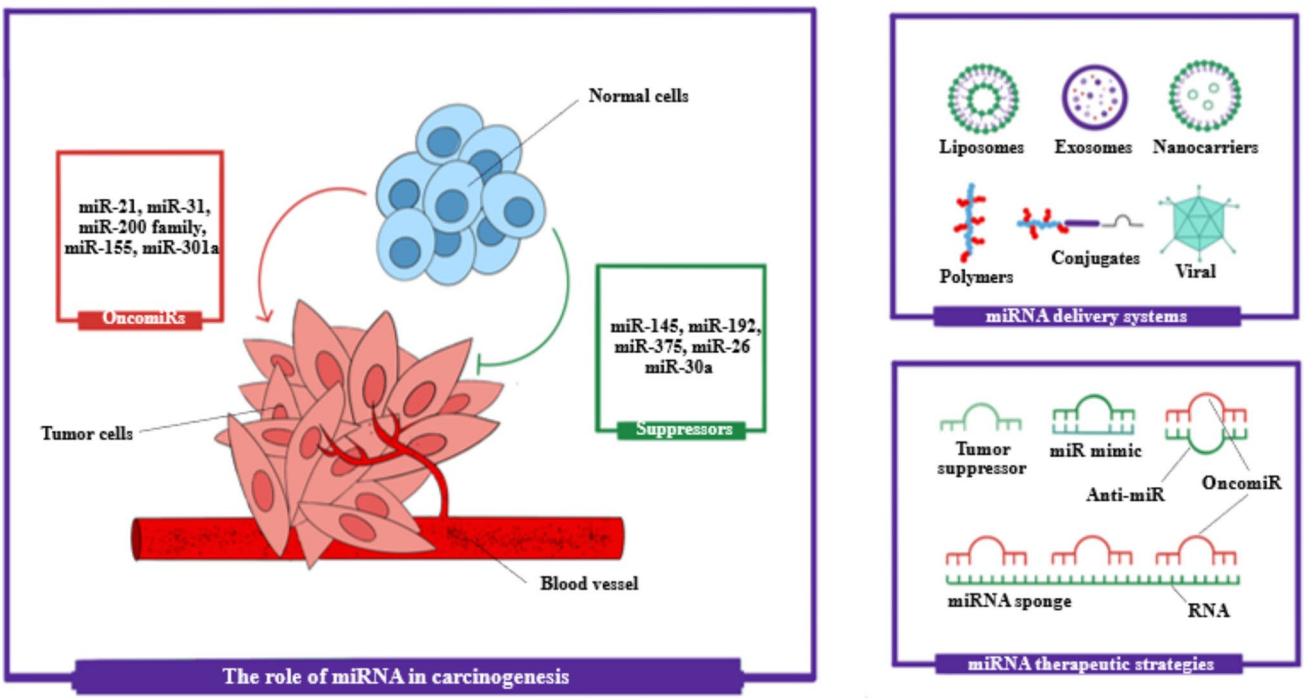

Fig. 4 miRNA therapeutic strategies and delivery systems. miRNAs play diverse roles in the process of carcinogenesis. Some miRNAs act as oncogenes (oncomiRs), and their overexpression promotes cancer cell proliferation, immune evasion, and angiogenesis. Conversely, other miRNAs function as tumor suppressors by silencing oncogene expression. High expression levels of suppressor miRNAs are beneficial, making the direct administration of endogenous miRNAs a potential therapeutic strategy. However, because endogenous miRNAs may lack sufficient specificity, another approach involves designing synthetic molecules that mimic the function of natural suppressor miRNAs. In the case of oncomiRs, two primary therapeutic strategies are employed: inhibition of expression using anti-miRs, or the use of sponges—specially designed RNA molecules with sequences complementary to multiple miRNAs. Anti-miRs and sponges bind oncomiRs, effectively inhibiting their function. Effective delivery systems are essential to ensure the stability, specificity, and efficient uptake of miRNAs in therapeutic applications. Commonly used delivery platforms include liposomes, exosomes, nanoparticles, polymers, conjugates, and viral vectors. Liposomes and exosomes facilitate cellular uptake due to their biocompatibility, while nanoparticles and polymers offer enhanced stability and targeted delivery. Conjugates provide specificity by coupling miRNAs with ligands or peptides, and viral vectors ensure efficient transfection. These systems collectively represent promising tools for the successful administration of miRNA-based therapies [127]

stability through chemical modifications and employing advanced delivery systems such as nanocarriers or lipid vectors to improve safety and targeting precision. A more comprehensive understanding of miRNA interactions with mRNAs is essential to minimize unintended effects and enhance specificity [128].

Personalized medicine approaches, incorporating miRNA profiling and biomarker development, can further optimize treatment strategies. However, the integration of miRNA-based therapies and diagnostics into routine clinical practice remains constrained by a lack of large-scale clinical trials and regulatory challenges. To address these limitations, it is crucial to conduct extensive clinical studies on the miRNAs that demonstrate the highest efficacy in vitro and in animal models. Moreover, overcoming barriers to clinical translation will require the establishment of clear guidelines for evaluating the safety and efficacy of miRNA therapies in clinical trials, as well as the development of cost-effective manufacturing processes for miRNA-based drugs and delivery systems [129].

The successful development and implementation of miRNA-based therapies have the potential to revolutionize the treatment of CRC and CAC, offering innovative solutions rooted in precision and personalized medicine.

Conclusions

Extensive research confirms that miRNAs play a pivotal role in the pathogenesis of CAC and CRC. The significantly impaired expression of certain miRNAs serves as an early prognostic factor for this disease's development, highlighting their potential as diagnostic tools for the quick and easy detection of CAC and CRC. However, it is important to recognize that miRNAs, as key modulators of gene expression capable of targeting multiple genes simultaneously, can have highly complex roles in the progression of CAC and CRC. Therefore, further fundamental research is essential to explore their involvement in signaling pathways, EMT, and inflammatory processes to deepen our understanding of carcinogenesis in IBD patients.

In conclusion, the role of miRNAs in inflammation and carcinogenesis has garnered increasing attention in recent studies. miRNAs have been shown to play a critical role in IBD, positioning them as promising targets for intestinal disease prevention.

Author contributions M. W. wrote the main manuscript text, analyzed the literature data, reviewed drafts of the article, and approved the final draft. K. M. wrote the main manuscript text, analyzed the literature data, reviewed drafts of the article, and approved the final draft. J. B. wrote the manuscript text, prepared tables, and approved the final draft. J. W. wrote the manuscript text, analyzed the literature data, prepared tables reviewed drafts of the article, and approved the final draft. J. B. wrote the manuscript text, prepared figures, reviewed drafts of the article, and approved the final draft. J. F. analyzed the literature data, reviewed drafts of the article, and approved the final draft. I. M. analyzed the literature data, reviewed drafts of the article, and approved the final draft. P. C. analyzed the literature data, reviewed drafts of the article, and approved the final draft. A. S. conceived and designed the concept, reviewed drafts of the article, and approved the final draft. Ł. D. conceived and designed the concept, analyzed the literature data, reviewed drafts of the article, and approved the final draft.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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