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Review Article

MicroRNA-183 cluster: a promising biomarker and therapeutic target in gastrointestinal malignancies

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Abstract: Small non-coding RNAs (microRNA, miR), powerful epigenetic regulators, were found involved in the regulation of most biological functions via post-translational inhibition of protein expression. Increased expression of pro-oncogenic miRs (known as miR cancer biomarkers) and inhibition of pro-apoptotic miR expression have been demonstrated in different tumors. The recently identified miR-183 was found implicated in gastrointestinal tumor metabolism regulation. Elevated miR-183 expression and cancer-promoting effects were reported in esophageal and colorectal cancers, which was partially contradicted by controversial data observed in gastric cancers. Anti-cancer effect of miR-183 in gastric cancer cells was associated with the Bim-1 and Ezrin genes regulation. Many studies indicated that miR-183 can inhibit tumor suppressor genes in most cell lines, promoting tumor cell proliferation and migration. Increased miR-183 level results in the downregulation of FOXO1, PDCD4, and other tumor suppressor genes in gastrointestinal tumor cells. MiR-183 also influences the signaling of PI3K/AKT/mTOR, Wnt/β-catenin, and Bcl-2/p53 signaling pathways. Mir-183 inhibits apoptosis and autophagy, and promotes epithelial-to-mesenchymal transition, cancer cell proliferation, and migration. Accordingly, gastrointestinal cancer occurrence, development of chemoradiotherapy resistance, recurrence/metastasis, and prognosis were associated with miR-183 expression. The current study assessed reported miR-183 functions and signaling, providing new insights for the diagnosis and treatment of gastrointestinal malignancies.

Keywords: MicroRNA (miR), gastrointestinal malignancy, esophageal cancer, cancer biomarker, miR-183, miR-182, miR-96, epigenetics

Introduction

Prevalent gastrointestinal (GI) malignancies, including colorectal cancer (CRC), gastric cancer (GC) and esophageal cancer (EsC), are the most common GI cancers with high morbidity and mortality rates. Significant progress has been achieved in the diagnostics and treatment of GI tumors, although GI-cancer-related death remains still high, ranking third (GC) and fifth (CRC) positions in cancer epidemiology worldwide [1, 2]. Patients with GC and EsC demonstrate poor survival rates and a high incidence of metastasis [3, 4]. Furthermore, most GI cancers are diagnosed at advanced stages with existing metastasis, high intratumor heterogeneity, and treatment-resistance [5-8]. Late diagnostics of advanced tumors results in poor overall survival rates. For instance, the 5-year survival rate after surgical treatment for stage I GC is between 60% and 80%, while the 5-year survival rate for stage III GC cases is between 18% and 50% [9, 10]. The survival rates of patients with early CRC have been drastically improved (compared to GC). However, the late CRC is considered lethal. Accordingly, the 5-year survival rate of stage I CRC patients is about 93%, while stage IV CRC

patients demonstrated only 8% survival rates during the same period of monitoring [11]. Surgical interventions may offer prolonged survival for CRC patients, although many patients develop metastasis [12]. This data warrants further investigation of molecular mechanisms of GI cancer progression and forces a search for better therapeutic targets for these tumors.

MicroRNAs (miRs) are short single-stranded RNAs (18-24 nucleotide long) that comprise a large class of endogenous, non-coding RNAs with regulatory functions [13]. The expression and function of miRs are directed by many genetic factors and epigenetic networks. It has been reported that miRs are powerful epigenetic regulators which can silence gene activation. Oncogenic miRs (onco-miRs) were shown to promote tumor progression, while anti-oncogenic miRs can inhibit cancer growth and spreading via blockade of oncogenes [14, 15]. MiRs can fully or partially complement the target gene mRNAs through base complementary pairing, guiding the formation of so-called silencing complex (RISC). Formation of RISC helps to degrade the mRNA or impede its translation [16-19]. Activation of miR expression was linked to the regulation of cell proliferation, invasion, differentiation, and apoptosis. Increased expression of oncogenic miRs was observed in different tumors and during stimulation of angiogenesis [20-24].

There are many miRs that were originally associated with normal body functioning, including miR-183 and related miRs (miR cluster). Located at locus 7q31-34 of the human chromosome, miR-183 was suggested to maintain the normal function of visual and sensory organs [25, 26]. It is highly conserved in different organisms [16, 27, 28]. MiR-183 belongs to the miR-183/96/182 cluster (miR-183C) involved in the regulation of immunity, autoimmunity, and cancer-related pathologies [26]. The role of miR-183C in the maturation and functions of various innate and adaptive immune cells have been reviewed recently [26]. Many studies have shown that miR-183 is involved in the regulation of carcinogenesis and is abnormally expressed in various tumors [29], including EsC [30], GC [31], hepatocellular carcinoma (HCC) [32], and CRC [33]. Notably, miR-183-5p expression can vary significantly, producing inconsistent findings [34-37].

All miR-183C members are located within 5 kb of chromosome 7q32 and encoded by the adjacent gene (miR-183C genes). MiR-183C group demonstrated sequence homology. Structural similarities support the possibility that miR-183C members may share common targets and have similar biological functions [38-40]. Interestingly, miRs-183C were found involved in the regulation of cell responses both independently and cooperatively (as a group). Although there is a strong similarity between miR-183C sequences, small differences in their seed coding were associated with overlapping and distinct messenger RNA (mRNA) targets, different target genes, and pathways regulated by each miR-183C member [41, 42]. Therefore, each miR in this cluster may produce specific effects in different tumors.

Previous studies have revealed that miR clusters have regulatory advantages compared to single miR-based effects [43, 44], although this hypothesis warrants further investigation. Nevertheless, Pidikova *et al.* reported that miR-183C expression strongly correlated with the occurrence of metastasis in CRC patients [45]. The expression of miR-183C members is regulated by several oncogenic signaling pathways and growth-promoting transcription factors (TFs). Tang *et al.* reported that glycogen synthase kinase 3 beta (GSK3b), a multifaceted enzyme involved in the development of drug resistance [46], triggers miR-183/96/182 expression in GC cells, employing the β-Catenin/T-cell factor (TCF)/lymphoid enhancer factor (LEF-1) pathway [47]. β-Catenin interacts with bases within miR-183C core promoter gene which contains complimentary sequences for various TFs, supporting a diversity of regulation of this miR cluster. For instance, in prostate cancer cells, miR-183 was found to activate cell growth and motility which were mediated by induction of Dkk-3 (dickkopf homolog-3) and SMAD4 (Mothers against decapentaplegic homolog 4; TF/tumor suppressor) [48]. Several studies reported that carcinogenesis and poor GI cancer prognosis are associated with the activation of miR-183 expression which is coordinated by Wnt/β-Catenin pathway [47, 49, 50] (**Figure 1**). In turn, increased levels of miR-183C were shown to regulate Bcl-2/P53 [51], PI3K/AKT/mTOR [31], and other signaling pathways [52]. The role of various TFs and other upstream epigenetic regulators

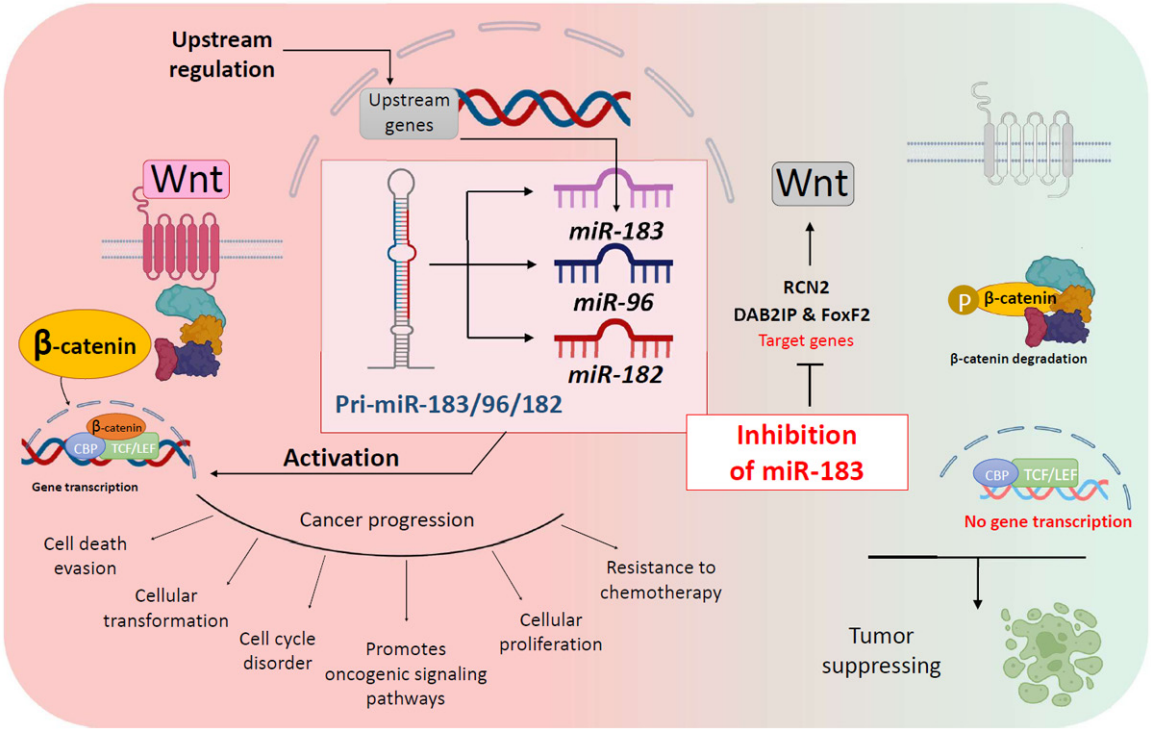

Figure 1. MiR-183/96/182 cluster signaling is activated by Wnt/β-catenin pathway and associated with oncogenic transformation, cell cycle disorders, evasion of cell death, and development of drug resistance in GI cancers. Inhibition of the miR-183 signaling was shown to suppress tumorigenesis. Inhibition of miR-183C signaling was linked to the regulation of FoxF2, RCN2, and DAB2IP (the cluster targets) upstream of Wnt, leading to the and inhibition of cancer progression.

of miR-183C expression will be discussed in this study.

Effects of another miR-183C member, miR-96, were regulated by Forkhead Box O1 (FOXO1) and O3a (FOXO3a), the cell fate directing TFs [53]. MiR-96 stimulated progression of HCC cell growth and colony formation via inhibition of FOXO1/FOXO3 expression [54]. This miR was also identified as a useful biomarker in other solid cancers [55]. The last member of this cluster, miR-182, was also found involved in the stimulation of tumorigenicity and invasiveness [56]. The miR promoted breast cancer cell (BCC) growth via the matrix metalloproteinase inhibitor RECK (Reversion-inducing Cysteine-rich protein with Kazal motifs) [57]. However, controversial expression of miR-182 was reported in GCs [58, 59], suggesting complex role of this miR in carcinogenesis.

This review study is focused on the analysis of the role and expression levels of miR-183C in GI tumors. Confirmed TFs and target genes for this miR cluster are also discussed. To assess the suitability of this miR cluster as a reliable cancer biomarker, we summarized the available information about miR-183C-induced signaling pathways, target genes, and the biological processes involved in the activation of tumor cell proliferation, angiogenesis, metastasis, and development of drug resistance.

Dysregulation of miR-183C expression and their targets in GI malignancies

We summarized the findings reported about the upstream regulation of miR-183 expression and its downstream targets in GI malignancies (**Table 1**). MiR-183 levels varied in different cancer types. MiR-183 is often overexpressed in EsC and CRC, where this miR promotes proliferation and metastasis, while supporting the resistance to apoptosis [30, 60]. However, conflicting data was reported in GCs. We identified at least six studies which reported miR-183 overexpression in GC tissues [51, 61-65], while four studies observed downregulation of miR-183 in GCs [36, 66-68]. Furthermore, the inhi-

Table 1. Proven upstream regulators and downstream target genes of miR-183

Cancer types	Oncogene/Suppressor of miR-183	Position	Downstream target gene/ upstream regulator	Function	Year	Ref.
CC	Oncogene	Downstream regulator	THEM4	Proliferation, invasion and apoptosis	2021	[87]
CC	Oncogene	Downstream regulator	PD-L1	Proliferation and apoptosis	2021	[292]
CC	Oncogene	Downstream regulator	ABCA1	Apoptosis and proliferation	2016	[293]
CC	Oncogene	Downstream regulator	EGR1	Migration	2010	[35]
CRC	Oncogene	Downstream regulator	FOXO1	Proliferation, invasion and angiogenesis	2020	[79]
CRC	Oncogene	Downstream regulator	ATG5	Radioresistance	2019	[60]
CRC	Oncogene	Downstream regulator	FOXO1, FOXO3 and SMAD4	Cellular senescence and apoptosis	2022	[78]
CRC	Oncogene	Downstream regulator	RCN2	Proliferation and invasion	2019	[149]
CRC	Oncogene	Downstream regulator	UVRAG	Autophagy and apoptosis	2016	[85]
EsC	Oncogene	Downstream regulator	FOXO1	Apoptosis	2020	[76]
EsC	Oncogene	Downstream regulator	ABI3BP	Proliferation, migration, and invasion	2020	[294]
ESCC	Oncogene	Downstream regulator	Smad4	Invasion and metastasis	2020	[112]
ESCC	Oncogene	Downstream regulator	PDCD4	Apoptosis, proliferation	2014	[101]
ESCC	Oncogene	Downstream regulator	PDCD4	Promotes proliferation and invasion	2014	[30]
GC	Suppressor	Downstream regulator	EEF2	Proliferation and migration	2019	[66]
GC	Oncogene	Downstream regulator	TPM1	Migration and invasion	2019	[51]
GC	Oncogene	Downstream regulator	UVRAG	Autophagy and apoptosis	2018	[61]
GC	Oncogene	Downstream regulator	PDCD4	Migration, invasion, adhesion, proliferation, colony formation	2016	[62]
GC	Suppressor	Downstream regulator	Ezrin	Invasion	2014	[279]
GC	Suppressor	Downstream regulator	Bmi-1	Proliferation and invasion	2014	[36]
GC	Suppressor	Downstream regulator	Ezrin	Differentiation, metastasis, and prognosis	2012	[68]
CRC	Oncogene	Upstream regulator	Circ_0026344	Metastasis	2019	[190]
CRC	Oncogene	Upstream regulator	AKAP12	Proliferation, migration and invasion	2019	[295]
CRC	Oncogene	Upstream regulator	RANBP1	Proliferation, invasion and apoptosis	2022	[296]
EC	Oncogene	Upstream regulator	LncRNA ELFN1-AS1	Proliferation, migration, and invasion	2020	[297]
GC	Oncogene	Upstream regulator	Lnc BX357664	Proliferation, migration, invasion, and apoptosis	2021	[63]
GC	Oncogene	Upstream regulator	LINC00163	Invasion and metastasis	2020	[64]
GC	Oncogene	Upstream regulator	hsa_circ_0000291	Migration and proliferation	2019	[65]

Abbreviations: CC: colon cancer; CRC: colorectal cancer; EsC: esophageal cancer; ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; THEM4: the profiles of thioesterase superfamily member 4; PD-L1: programmed cell death receptor - Ligand 1; ABCA1: ATP-binding cassette transporter A1; FOXO1: the Forkhead box class O proteins 1; ATG5: Autophagy related gene 5; RANBP1: RAN binding protein 1; RCN2: reticulocalbin-2; UVRAG: Ultraviolet radiation Resistant-associated gene; ABI3BP: ABI family member 3 binding protein; PDCD4: programmed cell death 4; EEF2: eukaryotic elongation factor 2; TPM1: tropomyosin 1; AKAP12: A kinase anchor protein 12.

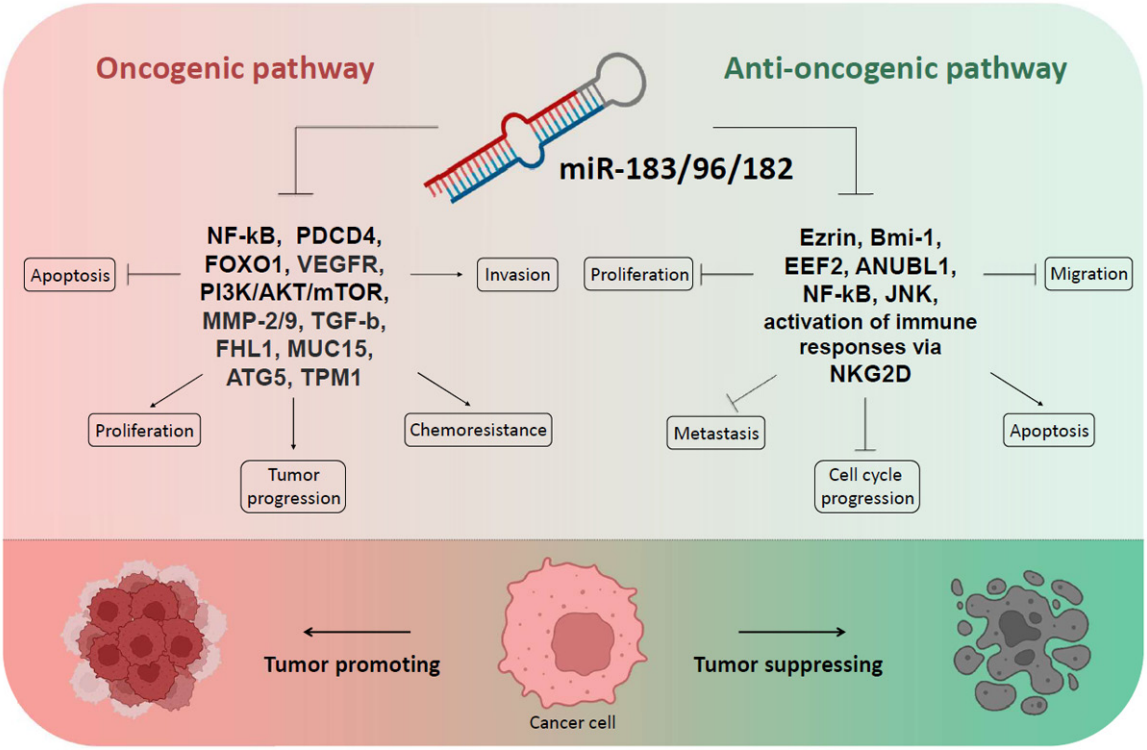

Figure 2. Dual role of miR-183 signaling in GCs. Various targets, including NF-κB, PDCD4, FOXO1, VEGFR, PI3K/AKT/mTOR, MMP-2/9, TGF-β, FHL1, MUC15, ATG5, and TPM1 were associated with the tumor promoting effects of miR-183. Anti-oncogenic and tumor suppressive roles of miR-183 were correlated with the inhibition of Ezrin (actin-binding scaffold protein), Bmi-1, EEF2, ANUBL1, NF-κB, JNK, and activation of immune responses (NKG2D signaling).

bition of proliferation and invasion of GC cells by miR-183 was mediated by downstream targets Bim-1 and Ezrin (**Figure 2**) [36, 67]. Accordingly, the controversy of this observation is associated with the heterogeneity of downstream targets of miR-183 which include oncogenes, tumor suppressor genes, signal transduction molecules, regulators of cell cycle, invasion and metastasis [69].

Multiple studies have shown that FOXO1 mediates miR-183C effects in GI tumors. The FOXOs family members (FOXO1, FOXO3, FOXO4 and FOXO6) are important physiological regulators and versatile TFs. The family controls cell proliferation, apoptosis, differentiation, oxidative stress, DNA damage and recovery, and many others [70-72]. Many normal physiological processes are regulated by miR-183C. It has been reported that miR-183C targeted FOXO1 in the ovary during the follicular-luteal phase, promoting the progesterone production and survival of luteal cells [73]. FOXO1 was indicated as a potential target for miR-182 and miR-183 in endometrial cancers [74]. Higher expression of miR-183 inhibits FOXO1 and promotes the growth of non-small cell lung cancers (NSCLC) in vitro and in vivo [75] (**Figure 2**). Similar effects were reported in EsC cells [76]. Notably, inhibition of miR-183 increased the expression of FOXO1 and pro-apoptotic regulators, including Bim-1 and Noxa proteins [76]. Bim-1 and Noxa proteins control mitochondrial outer membrane permeability and promote apoptosis by binding to and regulating anti-apoptotic Bcl-2 proteins [77]. Consequently, inhibition of miR-183 enhanced cisplatin-induced apoptosis in EsC cells via up-regulation of FOXO1 [76].

A couple of independent investigations found that miR-183 is overexpressed and FOXO1 is downregulated in CRCs [78, 79]. Notably, higher levels of FOXO1 can reverse miR-183-induced tumor angiogenesis. Accordingly, avenanthramide-C (a potent natural antioxidant) was demonstrated to protect from degradation miR-183C common targets, such as FOXO1/FOXO3 and SMAD4, and inhibit tumor growth

[78]. The antioxidant also promoted the expression of p21 and p16 senescence-regulating proteins, which can cause cell cycle arrest and induce cell senescence [78]. Shang *et al.* extracted miR-183-containing exosomes from HT29 CRC cells and co-cultured the exosomes with HMEC-1 cells [79]. Using dual-luciferase reporter, quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and Western blot assays, the study demonstrated that exosomes-linked miR-183-5p decreased FOXO1 expression [79].

Exosomes are small nanovesicles which can be commonly released by tumor cells in vivo [80]. Exosomes enable the transfer of biological information between cells and support antigen presentation in immunity [81]. Often defined as extracellular vesicles, exosomes can participate in the regulation cancer progression, metastasis, and drug resistance [80]. The cancer cell secreted vesicles are used to support communications between tumor cells and tumor microenvironment (TME) [82, 83]. MiR-183-5p was found to be pro-oncogenic in CRC [84-86] and highly expressed in exosomes secreted by CRC cells [87]. Various angiopoietin-related proteins, stimulators of angiogenesis, including vascular endothelial growth factor receptor (VEGFR) [88], angiotensin II [89], placental growth factor [90], and metalloproteases 2 and 9 (MMP-2; MMP-9) [91, 92] were also found to be regulated by miR-183.

GI cancers are often promoted by the activation of inflammatory networks, including various substance and exosomes released by immune cells. For instance, the accumulation of macrophages contributes greatly to CRC progression. The level of exosomal miR-183 was found enriched in M2-polarized tumor-associated macrophages (M2-TAM). Thioesterase superfamily member 4 (THEM4) can be targeted in M2-TAM to prevent miR-183 dependent activation of Akt/NF-κB pathway and CRC progression and invasion [87].

One of the most prominent effects of miR-183 is to inhibit expression of programmed cell death 4 (PDCD4; tumor suppressor gene) proteins in malignant cells. Inhibition of PDCD4 expression results in cancer promoting effects. Accordingly, PDCD4 expression is reduced in various tumors [93, 94]. In GI tumors, the expression of PDCD4 was found to be lower in gastric cancer, colon cancer and pancreatic cancer, compared to the surrounding non-tumor tissues [95-97]. Furthermore, PDCD4 levels are lower in medium-to-low differentiated tissues, compared to highly differentiated tissues [98, 99]. PDCD4 was defined as a miR-183 target in CRCs [100]. This observation can be used as a tumor diagnostic tool and therapeutic target. Supporting this data, the nuclear localization of PDCD4 was significantly reduced or lost in esophageal squamous cell carcinoma (ESCC) cells, in which miR-183 was significantly upregulated [30, 101]. MiR-183 inhibited the expression of PDCD4 gene by binding to PDCD4 3'UTP in ESCC [30, 101]. Application of miR-183 inhibitors weakened the inhibition of cell apoptosis. The inhibition of PDCD4 was pro-carcinogenic and associated with changes in cell cycle, accelerating the G1/S transformation process, and promoting proliferation [102].

PDCD4 is a reliable biomarker for the detection of early EsC [103], and therefore can be a promising target for miR-183 inhibitors. In GCs, the regulatory role of miR-183 in PDCD4 expression was also confirmed. A significant negative correlation between the level of miR-183 and the expression of PDCD4 was reported [62, 104, 105]. Inhibition of miR-183 expression increased the levels of PDCD4-related mRNA and protein [62, 104, 105]. The up-regulation of miR-183 was found to be associated with GC clinical stage, metastasis, and deep tissue invasion [62]. Analysis of 64 GC patient samples demonstrated higher expression of miR-183 in cancer tissues [62]. The tumor samples with high levels of miR-183 showed deeper local invasion, larger tumor size, later TNM staging, and more lymph node metastasis. Interestingly, another study did not confirm the association of miR-183 with the tumor stage or the occurrence of lymphatic metastasis in ESCC patients [30]. However, Fassan *et al.* [93] showed that the expression of PDCD4 negatively correlated with the clinicopathological features of tumors and perivascular invasion in ESCC cells. Therefore, more research is required to clarify the role of miR-183 in EsCs.

Transcriptional regulation of miR-183C expression and the signaling pathways involved

High cancer heterogeneity, cell/tissue context, and other internal and external (chemotherapy)

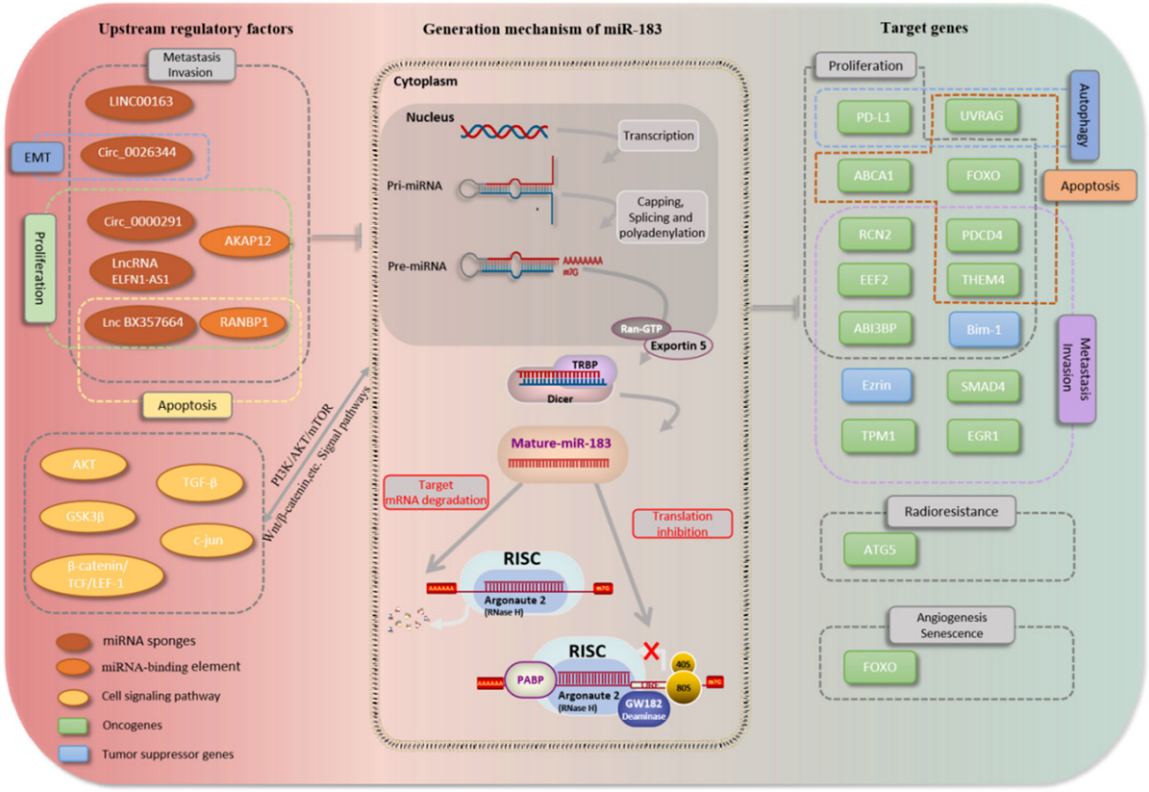

Figure 3. Molecular regulation of miR-183/96/182 cluster in GI malignancies.

factors impact the complexity of transcriptional regulation of the miR-183C [106]. The cluster-based and single miR-targeting regulations of miR-183C expression were reported by different groups, indicating the diversity of transcriptional mechanisms. Transcription of a large primary transcripts (pri-miRs) from a long single hairpin-shaped (hsa)-pri-miR-183C transcript is the first step in the biogenesis of this cluster [107]. Interestingly, overexpression of hsa-miR-183 correlated with poor overall survival for patients with CRC [100], supporting the pro-oncogenic role of miR-183C in GI cancers. The generated pri-miRs are usually cleaved into a precursor miR (pre-miR) which then transformed into the mature miRs [106, 108].

TFs, the upstream regulators of miR-183C expression, can bind miR-183C promoter regions. A large group of TFs triggered pri-miR-183C transcription during activation of oncogenesis in a tissue-specific manner. The generation of miR-183C transcripts in different cells was reported to be regulated by multifunctional TFs, including tumor protein p53 [109], MYC [110, 111], c-Jun [112], ZEB1/ZEB2 [110, 113], β-catenin/T-cell factor (TCF)/lymphoid enhancer factor (LEF) [47], SP1 [114], zinc-finger protein 304 (ZNF304; Krueppel C2H2-type zinc-finger family protein) [115], AVI1 [116], SMAD3 [117], Kruppel-like factor 4 (KLF4) [117], and transforming growth factor β (TGF-β) [30, 112, 118, 119]. For instance, c-Jun binds directly to pre-miR-183 promoter region, leading to the increased expression of miR-183 and decreased levels of SMAD4 in esophageal squamous cell carcinomas [112]. KLF4 was also shown to signal alone and bind miR-183C promoter region in human embryonic stem cells (hESCs) and in melanoma tumors [117].

The implication of β-catenin, a downstream effector of Wnt signaling, was accented previously as oncogenesis-promoting branch in miR-183C network [106]. Wnt signaling pathway is involved in the regulation of many biological functions, including metastasis and apoptosis [120, 121]. The classical signaling pathways Wnt and catenin-β1 were linked to miR-183 expression in several studies [122, 123] (**Figure 3**). The knockdown of Wnt/catenin-β1 decreased miR-183 activity, but increased

expressions of CASP3 and Bax (key pro-apoptotic proteins) in CRC line HCT-116 [49, 50], suggesting that Wnt/catenin-β1 are the upstream regulators of miR-183 in CRC. In GC cells, glycogen synthase kinase 3β (GSK3b) was also associated with the regulation of miR-183C through the Wnt/catenin-β1/TCF/LEF-1 pathway which stimulates cell proliferation [47].

Several of the listed TFs were reported to bind hsa-miR-183 promoter located 1.5-5 kb upstream of the miR sequences. Transcription start site (TSS) of miR-183C promoter has not been confirmed, although the prospective location was suggested at 5207 bases upstream of the precursor of miR-183 [124]. The minimal promoter region, the primary driver of the miR-182C transcription, was described in melanoma cells [117]. The original TSS was predicted to be 139 bp upstream of the miR-183 site [125]. Two secondary TSSs were identified in the miR-96/182 intergenic region (upstream of miR-182) in lung cancer cells [126] and in sarcoma [127].

It has been shown that a couple of TFs can silence miR-183C expression. EVI1 was described as a negative regulator/TF of miR-96 expression in pancreatic cancer [128], although EVI1's role in the regulation of miR-182 and miR-183 transcription remains unclear. Among the identified TFs, ZEB1 (also known as δ-crystallin enhancer binding factor 1 (δEF1) or transcription factor 8 (TCF8)) repressed expression of miR-183 during regulation of epithelial-to-mesenchymal transition (EMT) [129]. However, the controversial data was reported by another group in breast cancer cells [130], accenting the diverse and tissue-specific role of TFs in the regulation of miR-183C expression and its role in cancer progression.

Specific TF was linked to the activation of anti-oncogenic function of miR-183C. E2F1 was shown to trigger the expression of miR-183-5p which demonstrated tumor suppressor role via feed-back loop in breast cancer cells [111]. E2Fs are represented by a family of TFs which are important stimulators of the cell division [131]. The existence of different pre-miR-183C variants with opposite cancer-related functions and their association with specific TFs warrant future investigations. Moreover, a presence of single nucleotide polymorphism (SNP) located near or within the miR-183C regions was associated with the development of different malignancies [132-135], including GI cancers [136]. It remains to understand how SNPs may be associated with the transcriptional regulation of miR-183C expression and regulation of down-stream effectors.

Notably, transcription of miR-183C is generally activated in non-cancerous tissues, including sensory organs. For instance, a key member of the RNA Induced Silencing Complex (RISC), Argonaute 2 (AGO2), was found responsible for the regulation of miR-183C expression in the retina [137]. In non-human (non-cancerous) tissues, transcription of miR-183C was activated by SREBP2 [138] and cMAF [139]. Negative regulation of miR-183 expression by potassium voltage-gated channel subfamily Q member 1 overlapping transcript 1 (KCNQ1OT1) was observed in keratinocytes [140]. miR-183C expression was also downregulated by NF-κB p65 which triggered expression of HDAC2 and increased deacetylation in microglia [141] and neuroblastoma cells [110].

Expression of all three members was increased by hormones during steroidogenesis in adrenal glands. Pretreatment of rats with adrenocorticotropic hormone (ACTH) resulted in the upregulation of miR-183/96/182 expression levels for all three members, although to different degrees [142]. The observed group regulation could be explained by the presence of a common promoter for these three miRs. However, the same study indicated strong upregulation of only miR-182 and miR-96 by 17α-ethinyl estradiol or dexamethasone [142]. It is unclear why the miR-183 was not upregulated, suggesting a presence of powerful post-transcriptional regulation for miR-183 level in this tissue, or generation of different pri-miR-183 with the missing sequences for miR-183 itself. It remains to uncover the exact molecular mechanisms responsible for the observed effects. Using a model cell line of Leydig cells, MLTC-1 cells, the expression of miR-183C members was also increased by Bt2cAMP (an analog of cAMP, a second messenger for the hormonal signaling) by unknown mechanisms. The relevance of these transcriptional regulation to GI cancers remains unclear.

Epigenetic and viral regulation of miR-183C expression

Aside from TFs, epigenetic regulation by methylation of miR-183C CpG islands was shown [143]. Hypermethylation of has-miR-183 was reported in liver cancer cells [144]. Demethylation of CpGs for miR-182 alone was reported in melanomas [145]. Direct binding of a miR to competing endogenous RNA (ceRNA) can also silence miRs [146, 147]. It was reported that several types of ceRNA, including long non-coding RNA (lncRNA) and circular RNA (circRNA), can absorb and isolate miR molecules, acting as miR-targeting sponges, and direct gene expression downstream of miRs [45, 148]. For instance, lncRNA BX357664 binds to miR-183-3p (sponging action) and inhibits downstream PTEN protein expression through PI3K/AKT pathway [63]. Following lncRNA BX357664 treatment, GC cell growth and migration were blocked [63]. LncRNA MALAT1, another spongy ceRNA, was found to decrease miR-183 expression, and block GC cell proliferation, migration, autophagy and chemotherapy resistance to anticancer therapy [149]. LEMD1-AS1 (LEMD1 antisense RNA 1), a recently identified lncRNA, contained complementary sites of miR-183-5p [150] and might act as a miRNA sponge. Notably, LEMD1-AS1 regulated p53 expression by sponging miR-183-5p in ovarian cancer cells [150], although its effect in GI remains to be tested. Another lncRNA NEAT1 also interacted with miR-183-5p, leading to antioncogenic effects in neuroblastoma [151]. The ability of endogenous ceRNAs to inhibit miR-induced target indicated on the existence of internal mechanism to prevent oncogenesis, although they can be also highjacked by cancers.

CircRNAs have no 5' caps and 3' tails and are abundantly expressed in human GI cancers [152-155]. MiR-183 is the target of circ-0000291 in GC cell lines [65]. To estimate the role of circRNAs, circ-0000291 was blocked using silencing vector [65]. The inhibition resulted in upregulated expression of miR-183, suggesting that this circRNA is a natural inhibitor of miR-183 expression in GCs. Notably, the study demonstrated controversial findings to previously observed carcinogenic role of miR-183 [62, 63, 149]. According to the reported data by Cao *et al.* [65], miR-183 plays anti-cancer role in the tested GC cell lines and can inhibit the invasive and metastatic GC phenotypes [65]. Although controversial, this data is compatible with the previously published study which presented activation of apoptosis in endometrial cancer cells with increased expression of miR-183 [156]. Another recent study also indicated a pro-apoptotic role of miR-183-5p in NSCLC [157].

Considering the importance of immune responses and inflammation for cancer progression, it is notable that miR-183C expression can be activated during immune responses to viral infections (an external factor-induced transcriptional activation). Increased expression of all three miR-183C members was observed in cells infected with herpes simplex virus-1 (HSV-1) [158]. All three miR-183C members were upregulated by β-herpesvirus too [159]. The activation was mediated by the viral immediate-early protein ICP0, employing its E3 ubiquitin ligase function. ZEB1/ZEB2 degradation is under control of ICP0 [158]. In turn, reduced levels of ZEB1 are associated with increases in miR-183C expression [158]. Orchestrated effects of ZEB may be mediated by several corepressors, such as C-terminal binding proteins 1 and 2 (CtBP1/CtBP2) and histone deacetylase 2 (HDAC2) in neuroblastoma cells [110]. It remains to confirm whether similar mechanisms are activated in GI cancers.

Regulation of biological processes and prospective clinical applications of miR-183 cluster

MiR-183 regulates autophagy and apoptosis in GI cancers

The crosstalk between autophagy and apoptosis is ultimately associated with the cell fate [160]. While apoptosis (programmed cell death) is a well-established anti-cancer mechanism, autophagy plays dual role in carcinogenesis, and both promote or block cell death in different cells/pathologies. Defined as "self-eating" process, autophagy is marked by the utilization of intracellular resources in case when the external supply is limited or blocked [161, 162]. Autophagy is often activated during cancer hypoxia [163] and may speed up activation of necrosis and apoptosis [164-166]. Autophagy is responsible for processing of damaged

organelles, proteins and pathogens which are enveloped into autophagic vesicles and transported to lysosomes. The degradation of internal resources in lysosomes provides temporary relief for the cell metabolic needs, although may plays negative role in the tumor suppression [167-169]. Accordingly, autophagy-regulating genes are linked to genetic susceptibility to various metabolic dysregulations and GI malignancies, including CRC [170, 171]. In GI cancers, miR-183 controls PDCD4 and FOXO1 target genes [30, 53, 54, 172]. Notably, both genes (PDCD4 and FOXO1) were associated with autophagic responses [173, 174]. Therefore, miR-183 may influence autophagy indirectly, through its effectors (PDCD4 and/or FOXO1), although this requires further testing.

The miR-183-dependent regulation of autophagy and apoptosis in GI tumors was found to be mediated by targeting Ultraviolet Radiation Resistant-Associated gene (UVRAG) [61, 175]. Autophagy resulted in miR-183 downregulation in GC MKN28 cells [176]. Accordingly, overexpressed miR-183 inhibited autophagy and apoptosis in GC and CRC [176]. miR-183 also attenuates hunger-induced autophagy and apoptosis by inhibiting autophagy protein (Lc-3) and apoptosis protein (Bax/Bcl-2). After the endogenous miR-183 expression was inhibited, the expression of mTOR (regulator of autophagy), LC3II protein (autophagosome formation marker), and sequestosome 1 (p62/SQSTMI, a marker of lysosomal degradation) [177, 178] were assessed in HCT116 or HT29 cells [176]. Western blotting analysis confirmed that UVRAG expression enhancement could alleviate miR-183-mediated autophagy and apoptosis reduction in GC and CRC cells [85, 176]. These findings indicate the importance of miR-183 for the regulation of autophagy in cancer tissues.

Metastatic potential and EMT in GC cancers is regulated by miR-183 cluster: mechanisms and main molecular targets

Tumorigenesis is a complex process that employs various biological mechanisms, including EMT. Metastasis and cancer drug resistance are also associated with activation of EMT-related genes [179, 180]. Epigenetic signaling pathways and different miRs were shown to contribute to EMT [181, 182]. A variety of signaling pathways were linked to the regulation of EMT in GI tumors, including Wnt, TGF-β, and Notch signaling pathway [183, 184]. Among the most prominent factors involved into the regulation of EMT, TGF-β network has been shown to control progression of metastasis in GI tumors. Notably, TGF-β1 was suggested to mediate effects of miR-183C in CRC cell lines [34]. The expression levels of all miR-183C members were downregulated in $p21^{-/-}$ cells. Several other miRs were also downregulated (miR-200a/b/c, miR-9, miR-192, and miR-10a), while some other were upregulated (miR-34a, miR-205, and miR-503) in cells with depleted p21, suggesting the activation of orchestrated epigenetic mechanism during oncogenesis [34]. The regulatory role of p21 protein, which can bind different TFs, has been reported previously [185]. The protein has been described as EMT inhibitor, downstream effector of various tumor suppressors, including p53 [186], suggesting that p-21 downstream targets, including miR-183 cluster, can also control EMT.

Expression of miR-200 family members was strongly associated with regulation of Zinc Finger E-Box Binding Homeobox 1 (ZEB1), an established regulator of EMT [187]. The activation of negative feedback loop between miR-183C and ZEB1/ZEB2 was reported and marked by the depletion of ZEB1)/δ-crystallin enhancer binding factor 1 (δEF1) and ZEB2/Smad-interacting protein 1 [158]. It has been found that ZEB1 can inhibit miR-183C transcription in HCT116 CRC cells [34]. Reintroduction of miR-183 repressed ZEB1 expression. ZEB1 binding motif was detected in the 183-S DNA area of hypothetical miR-183 cluster promoter region. The authors of this study also reported that p21 may directly bind ZEB1 (p21-ZEB1 complex) and inhibit its effects on miR-183 transcription. As a result of p21 depletion and inhibition of miR-183, the expression levels of epithelial markers such as E-cadherin and zonula occludens-I (ZO-1) were decreased, while the expression of interstitial markers (vimentin and N-cadherin) were up-regulated. Following these changes, the epithelial-like tumor cells had been transforming due to reorganization of intracellular skeleton. The changes lead to the decline of the cell adhesion and the increase in migration, which may result in metastasis and associated cancer progression [188, 189]. Accordingly, the down-stream tar-

gets of p-21, miR-183C may also inhibit EMT and, therefore represent a reasonable therapeutic target in GI cancers.

Following these findings, miR-183 was declared the anti-metastatic miR in CRC [190]. MiR-183 mediated effects of circ_0026344 which inhibited the synergistic effect of chemokines CCL20 and CXCL8, reduced the expression of E-cadherin, and up-regulated levels of N-cadherin and Vimentin. The anti-EMT function of circ_0026344 and miR-183 were linked to the inhibition of Wnt/β-catenin signaling pathways [190]. However, controversial findings were reported by another group which detected higher expression of miR-183-5p in CRC and indicated its pro-oncogenic role [191]. Targeting genes in different tissues [192, 193], miR-183 was found both to activate or inhibit the Wnt/β-catenin signaling pathway [49, 149], disrupt the balance between pathways, induce tissue cell proliferation, and other biological processes [92, 149] (**Figures 2** and **3**). For instance, inhibition of miR-183-5p led to the blockade of its target gene RCN2 expression and Wnt/β-catenin signaling pathway [149]. The effect also downregulated the growth of CRC cells which was marked by decreased expression of downstream target genes (β-catenin, cyclin D1, c-Myc and MMP-2) [149]. Four and a half LIM protein 1 (FHL1, a tumor suppressor gene) was also targeted by miR-183C. It has been shown that miR-183-5p and miR-96-5p associates with the FHL1-3'-UTR [194] that can lead to the downregulation of this effector [195]. In HCC cells miR-183 also inhibited TGF-β induced apoptosis and stimulated cancer progression [32].

The large variety of controversial data suggests that TGF-β and miR-183 may trigger heterogeneous and cell/tissue-specific effects in different cancers, pre-cancerous pathologies (such as liver fibrosis [196-199]), and immune cells in TME [200, 201]. For instance, in ovarian cancer cells miR-183 promoted cell growth via inhibition of TGF-β/mothers against decapentaplegic homolog 4 (SMAD4) pathway [202]. Similar miR-183 tumor-promoting and TGF-β-inhibiting effects were suggested in breast cancer cell [203], vulvar [204] and lung squamous cell carcinoma [205]. In lung adenocarcinoma miR-183 expression was triggered by TGF-β and helped to promote immune evasion via Natural Killer (NK) cell activating receptors (NKG2D) and the major histocompatibility complex class I chain-related (MIC) proteins MICA/B receptor-ligand system [206]. Further investigation of miR-183C signaling is warranted.

Circulating miR-183 as a biomarker for diagnosis and prognosis of GI cancers

Detection of circulating nucleic acid as cancer biomarkers in the blood/serum of cancer patients represents an attractive method of advanced cancer diagnostics. Accordingly, the presence of high levels of onco-miRs in circulation provides valuable information for the cancer diagnosis and prognosis [34, 207, 208]. Serum miR testing is not only less invasive, simple, accurate and reliable, but also can improve the accuracy of traditional cancer diagnostics, classification, prognosis (recurrency), and overall treatment efficacy [209]. The expression of miRs in peripheral blood varied greatly among different tumor types. In the study of Yuan *et al*., the overall survival of CRC patients with higher expression of miR-183 in plasma was shorter than that of patients with lower expression of this miR [210]. Another study, which aimed to evaluate tumor dynamic before and after surgical intervention, demonstrated that level of miR-183 in plasma decreased after surgery, although 3 patients had increased expression of miR-183 after postoperative recurrence [211]. Therefore, miR-183 levels may reflect the risk of recurrence and poor survival [211].

However, the current data is insufficient and may not deliver clear answers to the role of miR-183 cluster in carcinogenesis and metastasis. For instance, although miR-183 was overexpressed in EsC tissues, the level of miR-183 in plasma was found to be significantly down-regulated in patients with the increased risk of EsC recurrence. The presence of miR-183 in the tumor tissue and blood/plasma may serve different purposes. The correlations between the expression of miR-183 in tumors, blood/serum levels of miR-183, and cancer clinicopathologic characteristics should be assessed in future studies. Preliminary data indicates that miR-183 cluster can be used as a biomarker to predict lymph node metastasis, distant metastasis, pTNM staging, prognosis and aggressiveness of CRC [211-213]. However, large pro-

spective studies are required to assess this hypothesis.

Targeting miR-183 in GI malignancy: a potential which requires verification

Surgery, radio- and chemotherapy have long been the main means of treatment for patients with GI cancer [214, 215]. During last decade, it has been demonstrated that epigenetic regulation and miRs are crucial regulators of cancer sensitivity to chemo/radiotherapy [216-218]. However, the mechanism of miR-induced effects in GI cancers remains largely unclear, although diverse miR downstream targets have been reported [219-222]. Using comprehensive network analysis, it was demonstrated that miR-183 plays a pro-carcinogenic role in synovial sarcoma, rhabdomyosarcoma, and CRC, targeting two tumor suppressor genes, early growth response protein 1 (EGR1) and phosphatase and tensin homolog (PTEN) [86]. Accordingly, anti-miR-183 treatment resulted in decreased cell migration, while EGR1 knockout reversed the anti-migratory effect of this miR inhibition [35]. Another study found that decreases in the proportion of Bax/Bcl-2 and Lc3B-II/Lc3B-I may be caused by miR-183 overexpression. High level of miR-183 also inhibited rapamycin-induced autophagy and apoptosis in GCs [61]. In liver tumor-initiating cells, miR-183-5p directly targeted and downregulated mucin 15 (MUC15) expression, leading to increased tumorigenicity and development of resistance [223]. These studies indicated a high potential of anti-miR-183 therapy.

Cisplatin-based chemotherapy was found to be an effective treatment of EsC. Cisplatin promotes FOXO1-induced up-regulation of pro-apoptotic proteins Bim-1 and Noxa, leading to increased mitochondrial membrane permeability and apoptosis [224]. Inhibition of miR-183 was shown to up-regulate the expression of FOXO1 and enhance cisplatin-induced apoptosis [172, 225-227]. FOXO1 is a context-dependent tumor suppressor, involved in the regulation of cancer chemotherapy resistance [228]. The sensitivity of EsC cells to cisplatin was found to be partially regulated by the level of miR-183 which also regulate levels of FOXO1. Suggestively, targeted manipulations of miR-183/FOXO1 axis may be used to overcome cancer resistance [172, 225-227].

Resistance to radiotherapy in GI malignancies [229] was also linked to miR-183 [60, 227, 230]. The inhibition of miR-183-5p expression improved the sensitivity of HCC to 5-FU and radiotherapy [227]. Alternatively, miR-183 overexpression promoted radiotherapy resistance, mediated by the EGFR/Akt pathway [230]. Zheng *et al.* demonstrated that knockdown of miR-183-5p enhanced autophagy related protein 5 (ATG5) expression and reduces radiation resistance in CRC [60]. This data supports the hypothesis that inhibition of miR-183 expression can also improve the radiosensitivity of some GI tumors, although future investigations are warranted.

Role of miR-182 and miR-96 in GI cancers

Analysis of published data indicates that 26 studies (found on the PubMed on 30 April 2023) which assessed the role and expression of miR-182 in GI cancers. MiR-182 was found to be upregulated in 14 studies with EsC, GC, and CRC tissues (**Table 2**). However, 12 studies reported downregulation of miR-182 in GI malignancies (**Table 2**). MiR-182 was reported to signal both as a tumor suppressor gene or an oncogenic miR. MiR-182 promoted proliferation, migration, and invasion of CRC and EsC cells by targeting FOXO3 [231, 232]. In GC, miR-182-5p directly targeted and downregulated levels of RAB27A, member of RAS oncogene group and the small GTPase Rab family which can enhance the rate of mitosis, migration, and invasion of cancer cells [233]. The dysregulation of RAB27A expression was associated with the occurrence and progression of various cancers, such as CRC [234, 235], pancreatic [236], and lung cancers [237]. Other studies found that miR-182 can silence several tumor suppressor genes, including AT-rich sequence binding protein 2 (SATB2) [238], metastasis suppressor-1 (MTSS1) [239], and 6-sialyltransferase 2 (ST6GALNAC2) [240, 241].

Surprisingly, miR-182 also demonstrated tumor suppressor effects. Knocking down of RBP-J (Recombination Signal Binding Protein For Immunoglobulin Kappa J Region) enhanced the expression of miR-182-5p in CRC, inhibited the Tiam1/Rac1/p38 MAPK signaling pathway, and reduced the volume and weight of CRC tissues [242]. These anti-cancer effects were overturned by the suppression of miR-182-5p [242]. MiR-182 targets and downregulates ANUBL1

Table 2. Upstream regulators and downstream target genes of miR-182 and miR-96

miR	Expression	Disease	Upstream regulator	Downstream target gene	Potential contribution	Year	Ref.
182	Up	CAC		FBXW7	Malignant transformation	2014	[298]
182	Down	CC		VEGF-C	Angiogenesis and lymphangiogenesis	2020	[257]
182	Up	CC	LncRNA XIRP2-AS1		Proliferation and invasion	2019	[282]
182	Down	CRC	AGAP2-AS1	CFL1	Cell growth, migration, invasion, and EMT	2022	[299]
182	Down	CRC	RBP-J	Tiam1	Proliferation, migration and invasion	2021	[242]
182	Up	CRC		FOXO3a	Cell cycle progression	2021	[231]
182	Up	CRC	Lnc-AGER-1		Proliferation, migration and cell apoptosis	2019	[300]
182	Down	CRC		MTDH	Proliferation, metastasis and EMT	2019	[301]
182	Up	CRC		DAB2IP	proliferation, invasion and tumor growth	2019	[302]
182	Up	CRC	lncRNA GAS5		Cell proliferation and cellular apoptosis	2018	[244]
182	Up	CRC		ST6GALNAC2	Tumorigenesis and invasiveness	2017	[240]
182	Up	CRC		ST6GALNAC2	Chemoresistance	2017	[241]
182	Down	CRC	SNHG3		Cellular proliferation	2017	[303]
182	Up	CRC		FOXF2	Cell growth and invasion	2015	[304]
182	Up	CRC		SATB2	Proliferation, metastasis and EMT	2014	[238]
182	Up	EsC	LOC441178	FOXO3a	Proliferation, migration and apoptosis	2020	[232]
182	Down	EsC	Circ-LRP6	Myc	Cell viability, colony formation and invasion	2020	[281]
182	Down	EsC		YWHAG	Metastasis, invasion, proliferation, apoptosis	2018	[305]
182	Down	GAC		CREB1	Cell growth	2012	[58]
182	Up	GC	Circ_0001658	RAB10	Autophagy and apoptosis	2022	[245]
182	Up	GC	Circ_002059	MTSS1	Proliferation and migration	2021	[239]
182	Down	GC	CircNRIP1	ROCK1	Apoptosis, migration and invasion	2020	[283]
182	Down	GC	CircFN1		Viability and apoptosis	2019	[267]
182	Down	GC	Circ-sFMBT2		Proliferation	2018	[306]
182	Up	GC		RAB27A	Viability, mitosis, migration, and invasion	2017	[233]
182	Up	GC	RUNX3		Proliferation and metastasis	2017	[307]
182	Down	GC		ANUBL1	Proliferation	2015	[243]
182	Up	GIST		CYLD	Proliferation, apoptosis, colony formation and migration	2018	[308]
96	Up	CRC		MYC	Proliferative and apoptotic	2020	[309]
96	Up	CRC		TPM1	Chemosensitivity	2020	[246]
96	Up	CRC		FOXO1/FOXO3	Proliferation	2015	[56]
96	Up	CRC		RECK	Invasion	2018	[249]
96	Up	EsC		RECK	Chemo- or radioresistance	2014	[250]
96	Up	GAC		ZDHHC5	Apoptosis	2019	[251]
96	Up	GC		MAP4K4	Proliferation	2019	[256]
96	Up	GC		KIF26A	Metastasis and EMT	2021	[255]
96	Up	GC		FOXO3	Proliferation	2020	[247]
96	Up	GC		FOXO1	Chemosensitivity	2018	[248]

Abbreviations: CAC: colon adenocarcinoma; CC: colon cancer; GAC: gastric adenocarcinoma; EsC: esophageal cancer; GIST: Gastrointestinal stromal tumors; FBXW7: substrate recognition component of a ubiquitin ligase complex functioning; VEGF-C: vascular endothelial growth factor; AGAP2-AS1: LncRNA AGAP2 Antisense RNA 1; CFL1: Cofilin 1; RBP-J: transcription factor; Tiam1: T lymphoma invasion and metastasis 1; FOXO3: The Forkhead box class O proteins 3; MTDH: Metadherin; DAB2IP: DOC-2/DAB2 interactive protein; ST6GALNAC2: sialyltransferase; SNHG3: Small nucleolar RNA host gene 3; FOXF2: forkhead box F2; SATB2: AT-rich sequence binding protein 2; circ-LRP6: circRNA derived from LRP6 gene; CREB1: encoding cAMP responsive element binding protein 1; RAB10: Ras-related protein Rab-10; MTSS1: metastasis suppressor-1; CircNRIP1: circRNA nuclear receptor interacting protein 1; ROCK1: rho-associated protein kinase 1; circFN1: originating from exons 10, 11, and 12 of the FN1 gene hsa_circ_0058147; Circ-sFMBT2: hsa_circ_0017639; RAB27A: small GTPase Rab family; RUNX3: transcriptional factors of the Runt family; ANUBL1: ZFAND4 (zinc finger, AN1-type domain 4); CYLD: cylindromatosis; TPM1: tropomyosin 1; RECK: reversion cysteine-rich Kazal motif; KIF26A: kinesin superfamily protein 26A.

(also known as ZFAND4 (zinc finger, AN1-type domain 4), leading to the inhibition of GC proliferation [243]. Long non-coding RNA (Lnc-RNA) and circ-RNA are the most studied upstream regulators of miR-182. Indicating the similarity to miR-183, miR-182 expression can be also suppressed by ceRNA sponges. LncRNA GAS5 has been shown to inhibit the development of CRC employing the miR-182/FOXO3a axis [244]. Hsa_circ_0001658 plays a carcinogenic role by enhancing cell survival and inhibiting apoptosis via miR-182 sponge mechanism [245].

The regulatory role of miR-96 was also assessed in GI cancers. MiR-96 was found to be

upregulated in 11 cancer assessing studies (**Table 2**). Majority of studies reported that miR-96 is an oncogenic miR and promote carcinogenesis in GI tumors. Upregulated miR-96 promoted cell proliferation, migration, invasion, and enhanced resistance to radiotherapy and chemotherapy [56, 246-251]. MiR-96 targets include tropomyosin 1 (TPM1) [246], FOXO1 and FOXO3 [56, 247, 248], RECK [249, 250], and zinc finger DHHC domain 5 (ZDHHC5) [251]. Both miR-182 and miR-96 were shown to activate NF-κB [252], PI3K/AKT (phosphatidylinositol 3 kinase/protein kinase B) [240, 241, 253], TGF-β [254], focal adhesion kinase (FAK) [255], MAPK/JNK (mitogen-activated protein kinase/c-Jun N-terminal kinase) [242, 256], ERK (extracellular regulated protein kinases)/AKT [257], and Wnt/β-catenin [47] pathways. Interestingly, all three members of miR-183C were linked to the regulation of circadian rhythms. For instance, miR-96 targets PERIOD2 (PER2), a core circadian clock gene [258]. PER2 regulates biological clocks, DNA repair system, and oncogenesis [259]. An association of miR-96 expression and the regulation of PER2 in GI cancer cells remains unexplored.

Dysregulation of miR-182 and miR-96 expression was associated with poor prognosis in various GI tumors. High levels of miR-182 and miR-96 expression correlated with advanced tumor stage and poorer survival rates in CRC patients [260-263]. Accordingly, elevated levels of miR-182 and miR-96 in serum have been identified as potential diagnostic GI cancer biomarkers [254, 264, 265]. Several studies reported that inhibition of miR-182/96 levels can suppress tumor cells growth, invasion, and metastasis [241, 248, 249]. Downregulation of miR-182/miR-96 can also sensitize cancer cells to radio- and chemotherapy [216, 241, 266-270].

Conclusions and future perspectives

Oncogenesis and progression are regulated by epigenetic mechanisms which favour pro-oncogenic signaling and/or silence pro-apoptotic effectors [216, 218]. Oncogenic miRs (oncomiRs), powerful epigenetic regulators, inactivate tumor suppressor genes and facilitate tumor progression [52, 271, 272]. The regulation of tumor growth by miR is mediated by complete or incomplete complementary binding of miRs to the target genes which prevents mRNA translation or direct generation of mRNA [216]. Targeted miR binding results in epigenetic (reversible) gene silencing [273], which can promote cancerogenic signaling pathways [274]. Multiple target genes can be affected by one miR, although the same target gene can be regulated by several miRs, thus, complicating the mechanisms of signaling and therapeutic interventions.

MiR-183C was found to be implicated in the occurrence and development of GI cancers [275, 276]. MiR-183 targets and inhibits tumor suppressor genes in most GI cancers and malignant cell lines, promoting malignant cell proliferation and migration. However, some studies indicated anti-cancer role of this miR [36, 66]. Different groups reported increased levels of miR-183 in EsC [277] and CRC [212, 213], suggesting the potential diagnostic role of this marker. Contradictory results were observed in GCs by different groups [36, 66, 278]. Except for the anti-cancer effect of miR-183 associated with activation of Bim-1 and Ezrin genes (**Figures 2** and **3**) [156, 279], most reported GC data indicates on pro-carcinogenic role of miR-183 [106, 280]. Conflicting data about miR-182 expression was reported in EsC, GC, and CRCs [232, 239, 257, 281-283] (**Table 2**). However, no contradictions were found for the expression of miR-96 which was consistently increased in GI tumors (**Table 2**). In CRC, the expression levels of all three miRs (miR-182/96/183) exhibited the same directional transcription with highly conserved "seed sequence" (as a whole), suggesting a potential group-like regulation and signaling [45, 78, 280]. Although this finding requires future experimental confirmations. Differential expression of miR-183 was also observed in breast [284, 285] and cervical cancers [286, 287]. Variations in miR-183 levels may reflect the dual role of this miR in the regulation of cell growth during different stages of carcinogenesis. Further studies may clarify the inconsistencies and uncover the exact mechanism of miR-183 signaling in cancer tissue and TME.

Several cancer suppressor genes, including FOXO1, PDCD4, EGR1 and PTEN were identified as the downstream miR-183 targets [79, 86, 102, 288]. Overexpressed miR-183 downregulates tumor suppressor genes FOXO1 and PDCD4 in GI [30, 79]. MiR-183 was associate

with the regulation of PI3K/AKT/mTOR [30, 31], Wnt/β-catenin [91], Bcl-2/P53 [51]. AKT and c-Jun were also shown to induce activation of miR-183 promoter [30, 112], suggesting the existence of a feed-back loop in this pathway. Increased expression of miR-183 was linked to the inhibition of apoptosis and autophagy [61, 76, 85] and promotion of EMT [112], proliferation and migration [289]. GI cancer patients with increased levels of miR-183 appear to have a later clinical stage of the disease, more metastatic lymph nodes, distant metastases, and poor prognosis [34, 104, 213]. Radio- and chemotherapy resistance were also observed in some GI cancers with increased expression of miR-183 [172, 225-227]. Accordingly, miR-183 inhibition sensitized EsC cells to cisplatin-induced apoptosis [172, 225-227]. Due to the relative stability of miRs in blood and the easiness of detection of miRs in tumor patients, some studies have proved that analysis of circulating miRs content can provide important information for the prediction and diagnosis of cancer [290, 291]. Several studies indicated that the high expression of plasma miR-183 is linked to lymph node metastasis, distant metastasis, pTNM staging, and invasiveness [112, 213]. Interestingly, the expression of miR-183 is decreased after GI cancer surgery and significantly increased in patients with cancer recurrence, suggesting that plasma miR-183 can be regarded as a potential diagnostic biomarker. However, large clinical studies are warranted to confirm the diagnostic potential of miR-183 cluster.

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