

MicroRNAs target the Wnt/ β -catenin signaling pathway to regulate epithelial-mesenchymal transition in cancer (Review)

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Abstract. Epithelial-mesenchymal transition (EMT), during which cancer cells lose the epithelial phenotype and gain the mesenchymal phenotype, has been verified to result in tumor migration and invasion. Numerous studies have shown that dysregulation of the Wnt/ β -catenin signaling pathway gives rise to EMT, which is characterized by nuclear translocation of β -catenin and E-cadherin suppression. Wnt/ β -catenin signaling was confirmed to be affected by microRNAs (miRNAs), several of which are down- or upregulated in metastatic cancer cells, indicating their complex roles in Wnt/ β -catenin signaling. In this review, we demonstrated the targets of various miRNAs in altering Wnt/ β -catenin signaling to promote or inhibit EMT, which may elucidate the underlying mechanism of EMT regulation by miRNAs and provide evidence for potential therapeutic targets in the treatment of invasive tumors.

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1. Introduction

Cancer metastasis has always been a challenge in the clinic, and is largely responsible for treatment failure and high mortality. It is known that invasive tumors undergo the EMT process where cells fail to maintain an epithelial phenotype and acquire a mesenchymal phenotype, thus transmitting from the primary tumor to other locations and forming secondary growths (1). To solve this problem, scientists have dedicated themselves to exploring the molecular mechanisms of this process. After four decades of work, various signaling pathways are known to participate in EMT including the transforming growth factor- β (TGF- β), Wnt/ β -catenin, Hedgehog (Hh), Notch, fibroblast growth factor receptors (FGFRs), and nuclear factor kappa B (NF- κ B) signaling pathways (2). Of these, the connections of cell adhesion, the Wnt/ β -catenin pathway and EMT are more clearly studied.

The formation of adherens junctions needs cell-cell adhesion molecules, such as the cadherin superfamily, and nectins (3). Cadherins and nectins bind to their anchoring proteins, catenins and afadin, respectively, to form functional modules that affect the actin cytoskeleton (4). The nectin family, which is composed of four members, namely, nectin-1, -2, -3, and -4 (5), is involved in cell-cell adhesion in various cell types by forming a nectin-afadin complex (6,7). Previous findings have shown the significant role of the E-cadherin/ β -catenin complex in maintaining stabilized cell-cell junctions (8). E-cadherin is regarded as the key component of the adherens junction complex (9), and invasive tumor is characterized by a marked decrease in E-cadherin expression (10).

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Several transcription factors such as Twist, Snail and zinc finger E-box-binding homeobox 1/2 (ZEB1/2) trigger EMT by directly binding to the E-box sequences of E-cadherin promoter, thus repressing its transcription (11). For example, Snail1 and Snail2 bind to *CDH1* (gene of E-cadherin) promoter-based E-box DNA sequences and summon the polycomb repressive complex 2 (PRC2), resulting in CDH1 histone methylation and acetylation (12). Activation of these transcription factors is attributed to the translocation of β -catenin from the cytoplasm to the nucleus, which is considered to be the central event in EMT (13). β -catenin has demonstrated its crucial role in Wnt signal transduction (14). In the presence of Wnt signals, the phosphorylation of β -catenin by glycogen synthase kinase 3 β (GSK3 β) is inhibited, followed by β -catenin disassembly from the destruction complex and accumulation in the cytoplasm (15). Therefore, current research primarily focuses on the canonical Wnt signaling (β -catenin dependent) pathway in which the mechanisms are more clearly established.

MiRNAs are small noncoding molecules with 19-25 nucleotides, which regulate gene expression at the post-transcriptional level by inhibiting mRNA translation or facilitating mRNA degradation (16). Previous findings suggested that EMT is regulated by miRNAs through alteration of the Wnt/ β -catenin pathway (17). However, the complex role of miRNA as an EMT inhibitor or promoter and its underlying mechanism need further clarification.

In this review, we focused on the interaction between miRNAs and the Wnt signaling pathway. Through literature retrieval, we summarized the distinct effects of miRNAs on Wnt signaling in the regulation of cancer metastasis, aiming to identify the mechanism of EMT regulation by miRNAs and potential therapeutic targets in invasive tumor treatment.

2. EMT and tumor metastasis

EMT comprises an essential biological process during which cells fail to maintain epithelial cell polarity and acquire the mesenchymal phenotype, thus increasing cell motility and invasion (18). EMT was reported to be involved in numerous biological activities such as embryogenesis (19), heart-valve (20) and neural crest formation (21). Scientists categorize EMT into three types including embryonic development and organ formation, wound healing and organ fibrosis, and cancer progression (22). The critical role of EMT in cancer has been extensively studied in recent years. It is generally accepted that EMT facilitates the invasion and metastasis of early stage tumors and contributes to cancer progression (23). The latest studies reveal that EMT-induced tumor progression is not only mediated by phenotypic change but also related to stemness (24), immune evasion (25), metabolic reprogramming (26), and therapeutic resistance (27) of cancer cells.

EMT is characterized by decreased expression of epithelial markers such as E-cadherin, γ -catenin and increased expression of mesenchymal markers such as N-cadherin, vimentin, Snail, Twist and ZEB (28). E-cadherin, a pivotal transmembrane adhesion protein in maintaining cell-cell junctions and polarity, was confirmed to stabilize cell junctions through forming the E-cadherin/ β -catenin complex (8). The loss of E-cadherin, which contributes to the mesenchymal phenotype of cancer cells, is a basic event in tumor metastasis (10). As a

result, the newly transformed mesenchymal cells detach from the primary tumor, invade into the circulation, and reform into epithelial cells through MET (29), thus leading to tumor formation at a distant secondary site (30).

EMT is regulated by various signaling pathways such as the TGF- β , Wnt/ β -catenin, Hedgehog and Notch signaling pathway (18). These pathways trigger EMT by stimulating transcription factors including Snail, Twist, and ZEB1/2, which directly bind to the promoter-based E-box DNA sequences of E-cadherin and repress its transcription. In addition, Snail also facilitates the transcription of mesenchymal markers such as vimentin and N-cadherin (31). Among all the signaling pathways, the Wnt/ β -catenin pathway shows its pivotal role in the regulation of EMT.

3. Wnt/ β -catenin signaling pathway and EMT

Wnt (wingless and Int-1) signals are evolutionarily conserved consisting of secreted Wnt ligands, Frizzled (FZD) receptors and coreceptors, intracellular adaptors, and scaffolding proteins (32). The foremost roles of the Wnt signaling pathway in cell proliferation, differentiation, adhesion, invasion, migration, and stem cell self-renewal have been well established (17). Abnormal Wnt signaling is commonly correlated with multiple types of disease such as neural tube defects (33), rheumatoid arthritis (34), hepatic fibrosis (35), and cardiovascular disease (36). The Wnt signaling pathway is divided into two categories, a canonical pathway (β -catenin-dependent) and noncanonical pathway (β -catenin-independent), both of which are closely related to EMT (37). β -catenin is regarded as a key protein in Wnt signaling, since accumulation of β -catenin in the cytoplasm gives rise to its translocation and activation in the nucleus (15), further initiating the transcription of EMT-related genes (38).

When the Wnt signal is absent, β -catenin forms a destruction complex with Axin, adenomatous polyposis coli (APC), casein kinase I α (CKI α) and GSK3 β (39). In this stage, β -catenin is phosphorylated by GSK3 β and CKI α , forming β -catenin degradation by ubiquitination (40). In addition, Wnt signaling inhibitory factors such as Dickkopf (DKK) family, secreted frizzled-related protein (SFRP) family and Wnt inhibitory factor 1 (WIF1) contribute to the inactive status of β -catenin (41). Dkk, a small family of secreted glycoproteins, is comprised of four members, Dkk1-4. Dkk1 and Dkk2 bring about Wnt signal inhibition by binding to low-density lipoprotein receptor-related protein (LRP) 5/6 with high affinity (42). However, Dkk2 plays a dual role as an inhibitor or activator of the Wnt signaling pathway, depending on the cellular context (43,44). Dkk3 was reported to be different from other members of the DKK family as it does not bind LRP6 and does not affect Wnt signaling (45). In addition, there are some studies demonstrating the inhibitory effects of *Xenopus* Cerberus and Wise proteins on Wnt (46). *Xenopus* Cerberus binds to Wnt proteins via independent sites to inhibit the Wnt signaling pathway (47), whereas Wise may inhibit or activate Wnt signaling in a context-dependent manner (48). In addition to Wnt signaling inhibitory factors, E-cadherin also suppresses β -catenin by forming the E-cadherin/ β -catenin complex to prevent nuclear translocation of β -catenin (49). When receptors receive Wnt ligands such as Wnt1 and Wnt3

binding to the FZD and LRP 5/6, LRP 5/6 and FZD form a complex to affect the stabilization of β -catenin and prevent its degradation, resulting in β -catenin accumulation in cytoplasm (50). As a consequence, β -catenin translocates to the nucleus and forms a complex with the T-cell factor/lymphoid enhancer factor (TCF/LEF), which promotes transcription of Wnt target genes including *Twist*, *Snail* and other oncogenes such as *Cyclin D1*, matrix metalloproteinase-7 (*MMP-7*) and cellular myelocytomatosis oncogene (*c-Myc*) (51), thus facilitating EMT (52).

4. miRNAs target the Wnt/ β -catenin signaling pathway to regulate EMT

MicroRNAs are small noncoding molecules with 19-25 nucleotides that play fundamental roles in almost every cellular process such as cell differentiation and homeostasis (53) by regulating gene expression at the post-transcriptional level (54). MiRNA genes are transcribed into primary miRNA (pri-miRNA) by RNA polymerase II (55). Exportin 5 recognizes the 2-nucleotide overhang of the pre-miRNA and transports it to the cytoplasm, then pre-miRNA undergoes multistep biogenesis to become mature miRNAs (56). MiRNAs bind to the 3'-untranslated region (UTR) of target mRNAs to suppress their translation or accelerate degradation. It is reported that approximately 10-40% of mRNAs are regulated by miRNAs in humans (57) and dysregulation of miRNA may result in tumor metastasis (58). Research has increasingly focused on the interaction between miRNA and EMT as miRNAs affect multiple EMT-related signaling pathways such as Wnt/ β -catenin, Notch, TGF- β pathway and their target genes (59). The role of miRNA as a tumor suppressor or oncogene during EMT has attracted much attention. Elucidating miRNA functions in the regulation of EMT may contribute to the finding of potential therapeutic targets.

MiRNA as an inhibitor of EMT. A large number of miRNAs were found to be downregulated in a wide spectrum of cancers (60,61), indicating their inhibitory effect on tumorigenesis and development. Furthermore, clinicopathological analysis also revealed that tumor migration and invasion was negatively correlated with a number of miRNAs (62). Numerous studies reported that miRNAs may function as EMT inhibitors by targeting the Wnt signaling pathway or its downstream transcription factors (Table I, Fig. 1); thus, overexpression of these miRNAs may be a therapeutic method to reverse EMT.

Targeting Wnt signaling downstream transcription factors. The EMT-induction transcription factors, most of which are downstream of the Wnt signaling pathway, have been studied extensively, including E-cadherin suppressors such as ZEB, Twist and Snail, which are considered to be regulated by miRNAs in various types of cancer (10).

The miR-200 family, comprising of 5 miRNA sequences (miR-200a, miR-200b, miR-200c, miR-141 and miR-429), is believed to play a significant role in EMT (63). The EMT initiated in several types of cancer has been shown to be correlated with the underexpression of the miR-200 family such as bladder cancer (64), breast cancer (65), melanoma (66), ovarian

cancer (67), gastric cancer (68), and prostate cancer (69). Gregory *et al* found the levels of the miR-200 family were significantly reduced following TGF- β -mediated EMT in invasive breast cancer since the low level of miR-200 leads to the absence of E-cadherin, indicating miR-200 as a negative regulator of EMT (70). A mechanism study demonstrated that miR-200 inhibits Wnt signaling by targeting transcription factors ZEB1/2 and binding to β -catenin mRNA to suppress its translation (71). The ZEB family, containing two members ZEB1 and ZEB2, binds to the promoter-based E-box DNA sequences of E-cadherin thus repressing its transcription and facilitating the activation of mesenchymal genes (72). The inhibitory effects of miR-200 on β -catenin and ZEB1/2 were further confirmed in gastric adenocarcinoma (73,74), colonic adenocarcinoma (75), and hepatocellular carcinoma (HCC) (76). Overexpression of miR-200 results in E-cadherin upregulation by targeting ZEB1 and ZEB2, thereby inhibiting EMT and restoring the epithelial phenotype of cancer cells (77). However, components of Wnt signaling can inversely affect the miR-200 family. Tian *et al* reported that a downstream target of Wnt signaling, Achaete scute-like 2 (*Ascl2*) negatively regulates miR-200 family expression, thus inhibition of *Ascl2* obviously restores miR-200 expression and suppresses EMT, making *Ascl2* a promising target to reverse EMT (75). In addition to EMT inhibition, restoring the level of miR-200 can also induce cancer cell apoptosis and increase the sensitivity of cancer cells to chemotherapeutic drugs. For instance, niclosamide potentially induces the apoptosis of colon cancer cells by upregulating the miR-200 family members (78). Another study demonstrated that the overexpression of miR-200b could inhibit cell proliferation and enhance apoptosis and then reverse docetaxel chemoresistance of lung adenocarcinoma (LAD) cells by directly targeting E2F transcription factor 3 (E2F3), which were also verified in tissues of LAD patients (79).

In addition to the miR-200 family, miR-33b binds to 3'-UTR of ZEB1 and inhibits ZEB1 expression in lung adenocarcinoma cells, thus blocking Wnt/ β -catenin signaling and suppressing tumor growth and EMT *in vitro* and *in vivo* (80). Research by Zhang *et al* identified miR-498 which was downregulated in liver cancer, and suppressed the growth and metastasis of liver cancer cells partly by directly targeting ZEB2, making miR-498 a potential biomarker for diagnosis and a promising therapeutic target for liver cancer treatment (81). Snail and Twist are also targeted by miRNAs in the regulation of EMT. Yue *et al* demonstrated that miR-519d directly binds to 3'-UTR of Twist1 to facilitate its degradation in gastric cancer cells, suggesting miR-519d as a potential therapeutic target for gastric cancer treatment (82). Jin *et al* reported that miR-122 inhibits EMT in HCC by targeting Snail1 and Snail2 to suppress the Wnt/ β -catenin signaling pathway (83).

The translocation of β -catenin in the nucleus is followed by the activation of TCF/LEF-Legless-Pygo DNA binding proteins, which triggers transcription of many oncogenes such as extracellular matrix receptor III (*CD44*), *c-Myc*, *MMP-7*, and *cyclin D1* (52). LEF1, a pivotal transcription factor in the Wnt signaling pathway, was reported to be a target of miR-708 and miR-34a by directly binding to 3'-UTR of LEF1, suggesting miR-708 and miR-34a as EMT inhibitors in melanoma and prostate cancer, respectively (84,85). Pygopus2 (Pygo2) is

Table I. Inhibition of EMT by miRNAs.

miRNA	Cancer type	Molecular targets	(Refs.)
miR-125b-5p	Hepatocellular carcinoma	STAT3	(62)
miR-200 family	Gastric adenocarcinoma	ZEB1/2, β -catenin	(73,74)
	Hepatocellular carcinoma	β -catenin	(76)
	Colonic adenocarcinoma	ZEB1/2	(75)
	Hepatocellular carcinoma	Wnt1, Snail1/2	(83,96)
miR-122	Hepatocellular carcinoma	Wnt1, Snail1/2	(83,96)
miR-3127-5p	Non-small-cell lung cancer	FZD4	(100)
miR-136	Melanoma	PMEL	(122)
miR-708	Melanoma	LEF1	(84)
miR-203	Breast cancer	DKK1	(178)
miR-490-3p	Colorectal cancer	FRAT1	(103)
miR-34b/c	Prostate cancer	β -catenin	(93)
miR-148a	Hepatocellular carcinoma	Wnt1	(97)
	Pancreatic cancer	Wnt10b	(98)
miR-34a	Prostate cancer	LEF1	(85)
miR-101	Colon cancer	EZH2	(179)
miR-22	Melanoma	FMNL2	(121)
miR-33b	Lung adenocarcinoma	ZEB1	(80)
miR-145	Lung cancer	Oct4	(92)
miR-194	Hepatocellular carcinoma	PRC1	(118)
miR-300	Pancreatic cancer	CUL4B	(110)
miR-338	Gastric cancer	EphA2	(114)
miR-495	Non-small-cell lung cancer	TCF4	(88)
miR-506	Nasopharyngeal carcinoma	LHX2	(116)
miR-3619-5p	Bladder carcinoma	β -catenin, CDK2, p21	(94)
miR-15a-3p	Prostate cancer	SLC39A7	(104)
miR-29c	Colorectal carcinoma	GNA13, PTP4A	(123)
miR-33a	Pancreatic cancer	β -catenin	(95)
miR-302b	Gastric cancer	EphA2	(113)
miR-340	Ovarian cancer	FHL2	(180)
miR-375	Gastric cancer	YWHAZ	(120)
miR-377	Ovarian cancer	CUL4A	(111)
miR-378	Colon cancer	SDAD1	(60)
miR-498	Liver cancer	ZEB2	(81)
miR-504	Glioblastoma	FZD7	(101)
miR-516a-3p	Breast cancer	Pygo2	(87)
miR-519d	Gastric cancer	Twist1	(82)
miR-770	Non-small-cell lung cancer	JMJD6	(124)
miR-876-5p	Gastric cancer	Wnt5A and MITF	(89)
miR-33a-5p	Hepatocellular carcinoma	PNMA1	(181)
miR-383	Pancreatic carcinoma	ROBO3	(182)
miR-371-5p	Colorectal cancer	SOX2	(183)
miR-370-3p	Bladder cancer	Wnt7a	(99)

STAT3, signal transducer and activator of transcription 3; ZEB, zinc finger E-box-binding homeobox; FZD, Frizzled; PMEL, Premelanosome Protein; LEF1, lymphoid enhancer factor 1; DKK1, Dickkopf 1; FRAT1, frequently rearranged in advanced T-cell lymphomas 1; EZH2, enhancer of zeste homolog 2; FMNL2, formin like 2; Oct4, octamer-binding protein 4; PRC1, protein regulator of cytokinesis 1; CUL4B, cullin 4B; EphA2, EPH receptor A2; TCF4, T-cell factor 4; LHX2, LIM homeobox 2; CDK2, cyclin-dependent kinase 2; PTP4A, protein tyrosine phosphatase 4A2; GNA13, G protein subunit alpha 13; FHL2, four and a half LIM domains 2; CUL4A, Cullin 4A; SDAD1, SDA1 Domain Containing 1; Pygo2, Pygopus2; JMJD6, Jumonji Domain Containing 6; MITF, melanogenesis-associated transcription factor; PNMA1, paraneoplastic antigen 1; ROBO3, roundabout guidance receptor 3; SOX2, SRY-box transcription factor 2.

regarded as a tumor promoter in various types of cancer due to its combination with free β -catenin to cause abnormal activa-

tion of downstream oncogenes (86). A study demonstrated that miR-516a-3p inhibits breast cancer cell growth, metastasis

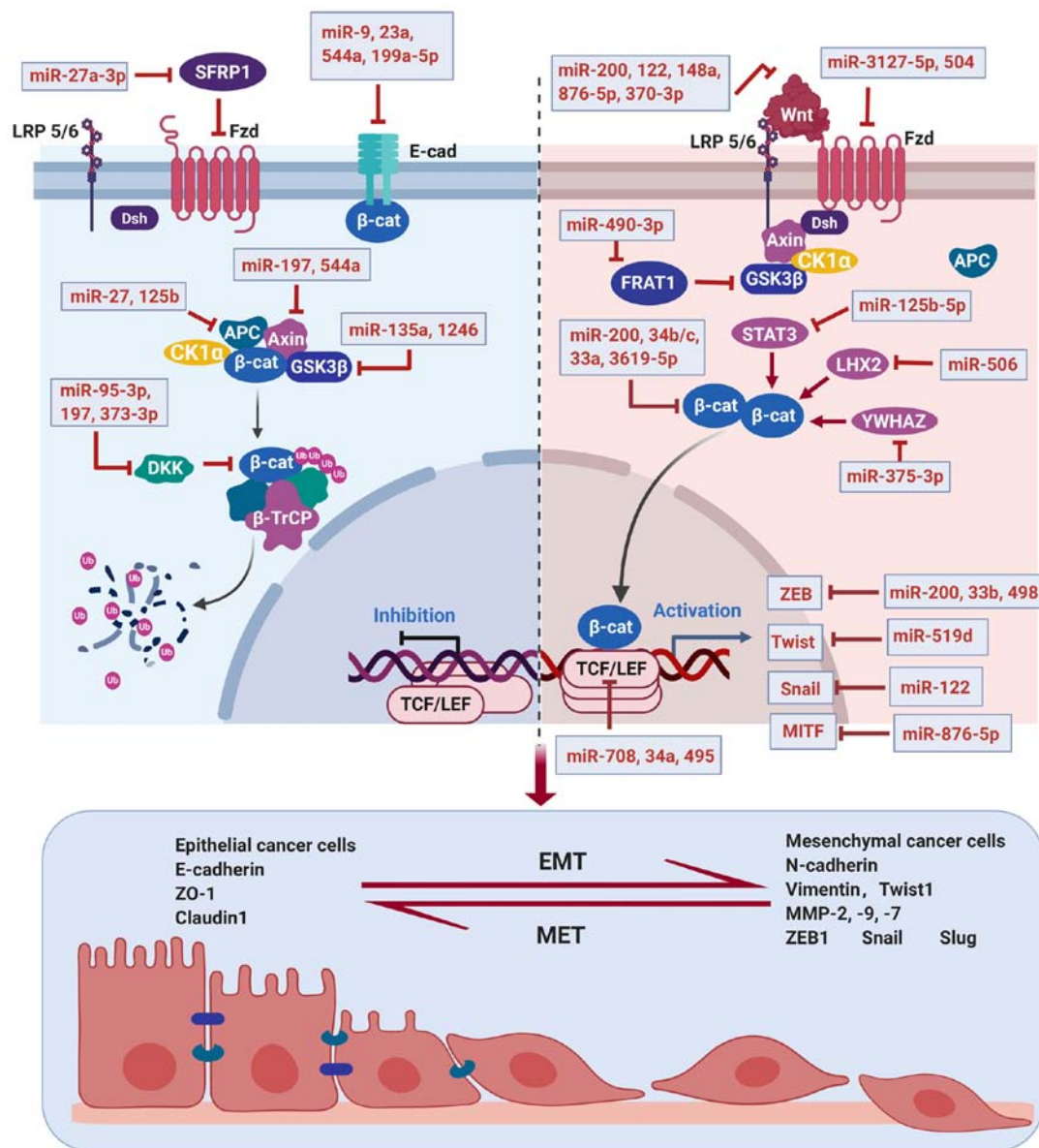


Figure 1. Regulation of Wnt/ β -catenin signaling by miRNAs. Left panel: miRNAs targeting inactive Wnt/ β -catenin signaling to initiate EMT. In the absence of Wnt ligands, β -catenin is phosphorylated by GSK3 β by forming a destruction complex with Axin, APC, CK1 α and GSK3 β , forming β -catenin degradation by ubiquitin. MiRNAs facilitate EMT by targeting Wnt/ β -catenin suppressors. Right panel: miRNAs targeting activated Wnt/ β -catenin signaling to inhibit EMT. When receptors received Wnt ligands, the phosphorylation of β -catenin by GSK3 β was inhibited, followed by β -catenin disassembly from the destruction complex and accumulation in cytoplasm. Then, β -catenin translocated to the nucleus and formed a complex with TCF/LEF, which promoted transcription of Wnt target genes such as *Twist* and *Snail*, thus facilitating EMT. MiRNAs block EMT by targeting various components of the Wnt/ β -catenin signaling pathway.

and EMT by binding to 3'-UTR of Pygo2 mRNA, resulting in blockage of the Pygo2/Wnt pathway (87). In addition, transcription factor 4 (TCF4) has been found to promote the occurrence and development of several cancers by recognizing β -catenin to initiate the transcription of Wnt target genes (38). MiR-495 was reported to bind to the 3'-UTR of TCF4, thereby suppressing the migration, invasion, and proliferation of non-small-cell lung cancer (NSCLC) by inactivating the Wnt/ β -catenin pathway (88).

Some other transcription factors were also reported to be affected by miRNA in the regulation of Wnt/ β -catenin signaling. Melanogenesis-associated transcription factor (MITF), as one of the representative target genes of β -catenin, plays a carcinogenic role in gastric cancer. A study reported that miR-876-5p was able to bind to 3'-UTR of MITF and downregulate its expression, thus suppressing viability and

migration of gastric cancer cells, and inducing cell apoptosis (89). Octamer-binding protein 4 (Oct4), an octamer motif-binding transcription factor, has been confirmed to exhibit an oncogenic effect in several types of cancer (90,91). A study by Ling *et al* demonstrated that miR-145 suppresses EMT in lung cancer cells by targeting Oct4 to inactivate the Wnt/ β -catenin signaling pathway (92).

Targeting key proteins of the Wnt/ β -catenin signaling pathway. Accumulation of β -catenin in cytoplasm is the central event in Wnt signaling activation; thus, miRNAs targeting β -catenin may act as EMT inhibitors. In addition to the miR-200 family mentioned above, miR-34b/c suppress β -catenin mRNA expression by targeting the 3'-UTR of β -catenin in prostate cancer (93). MiR-3619-5p directly

Table II. Promotion of EMT by miRNAs.

MiRNA	Cancer type	Molecular targets	(Refs.)
miR-135	Bladder cancer	GSK3 β	(133)
miR-106b-3p	Esophageal squamous cell carcinoma	ZNRF3	(145)
miR-26b	Colorectal cancer	PTEN, Wnt5A	(150)
miR-27a-3p	Oral squamous carcinoma stem cells	SFRP1	(143)
miR-95-3p	Prostatic cancer	DKK3	(140)
miR-191	Lung cancer	BASP1	(184)
miR-197	Hepatocellular carcinoma	AXIN2, NKD1, DKK2	(126)
miR-373	Endometrial cancer	LATS2	(185)
miR-374a	Breast cancer	WIF1, PTEN, Wnt5A	(15)
miR-9	Synovial sarcoma	E-cadherin	(129)
miR-23a	Epithelial ovarian cancer	ST7L	(186)
	Breast cancer	E-cadherin	(130)
miR-25	Hepatocellular carcinoma	RhoGDI1	(187)
miR-27	Gastric cancer	APC	(132)
miR-93-5p	Lacrimal gland adenoid cystic carcinoma	BRMS1L	(188)
miR-125b	Triple negative breast cancer	APC	(137)
miR-146b-5p	Thyroid cancer	ZNRF3	(146)
miR-373-3p	Tongue squamous cell carcinoma	DKK1	(141)
miR-429	Hepatocellular carcinoma	PTEN	(189)
miR-483-5p	Lung adenocarcinoma	RhoGDI1, ALCAM	(190)
miR-496	Colorectal cancer	RASSF6	(191)
miR-544a	Gastric cancer	E-cadherin, AXIN2	(125)
miR-675	Gastric cancer	PITX1	(192)
miR-1246	Lung cancer	GSK3 β	(134)
miR-192/215	Gastric cancer	SMG-1	(193)
miR-199a-5p	Gastric cancer	E-cadherin	(131)
miR-139	Pancreatic cancer	TOP2A	(194)
miR-150	Colorectal cancer	CREB1, EP300	(195)
miR-421	Non-small cell lung cancer	HOPX	(196)
miR-23a/24	Pancreatic ductal adenocarcinoma	FZD5, TMEM92, HNF1B	(197)
miR-92a	Colorectal cancer	KLF4	(148)

GSK3 β , glycogen synthase kinase 3 β ; ZNRF3, zinc and ring finger 3; PTEN, phosphatase and tensin homologue; SFRP1, secreted frizzled-related protein 1; BASP1, brain abundant membrane attached signal protein 1; LATS2, large tumor suppressor kinase 2; WIF1, Wnt inhibitory factor 1; APC, adenomatous polyposis coli; ALCAM, activated leukocyte cell adhesion molecule; RASSF6, Ras association domain family member 6; PITX1, paired-like homeodomain 1; TOP2A, DNA Topoisomerase II Alpha; CREB1, CAMP responsive element binding protein 1; EP300, E1A binding protein P300; HOPX, homeodomain only protein x; HNF1B, HNF1 homeobox B; KLF4, Kruppel-like factor 4.

binds to 3'-UTR of β -catenin and causes its downregulation in bladder carcinoma (94). Similarly, miR-33a targets the 3'-UTR of β -catenin to block EMT in human pancreatic cancer cells (95).

It is generally recognized that Wnt ligands are regulated by various miRNAs. For example, Wnt1 is a direct target gene of miR-122 in HCC HepG2 and Huh7 cell lines, thus downregulation of miR-122 facilitates EMT in HCC cells by activating Wnt signaling (96). Another study confirmed that Wnt1 is a target gene of miR-148a in HCC cells, suggesting miR-148a acts as an HCC metastasis suppressor by blocking the Wnt signaling pathway (97). In addition, Peng *et al* reported that miR-148a suppresses EMT and invasion of pancreatic cancer cells by targeting Wnt10b and inhibiting

the Wnt signaling pathway, making miR-148a a novel therapeutic target for pancreatic cancer treatment (98). Wnt5A was found to be targeted by miR-876-5p, which suppresses the viability and migration of gastric cancer cells and induces cell apoptosis (89). Moreover, Wnt7a, which activates Wnt signaling to promote EMT of bladder cancer, can be inhibited by miR-370-3p (99).

Wnt ligands transduce signals by binding to several receptors such as FZD and LRP5/6, this process was described to be regulated by miRNAs. When Wnt ligands bind to receptors, FZD and LRP5/6 form a complex on the surface of the cell membrane. Then, Dsh protein is recruited and constitutes a complex with Axin, which binds GSK3 β and CK1 α to release β -catenin, thus forming β -catenin accumulation in the cyto-

plasm (50). MiR-3127-5p was reported to block Wnt/ β -catenin signaling by directly targeting FZD4 in NSCLC (100). Moreover, miR-504 negatively regulates the Wnt/ β -catenin pathway by directly targeting FZD7, thus suppressing the mesenchymal phenotype of glioblastoma (101).

The phosphorylation of β -catenin by GSK3 is necessary for β -catenin degradation when the Wnt signal is absent. Researchers found that proto-oncogene frequently rearranged in advanced T-cell lymphomas 1 (FRAT1) belongs to the GSK3-binding protein family, which inhibits GSK3-mediated phosphorylation of β -catenin and positively regulates the Wnt signaling pathway (102). MiR-490-3p is identified to directly target FRAT1, suggesting its tumor suppressive effects (103). SLC39A7 (ZIP7), a zinc transporter essential for the activation of tyrosine kinase, is considered to be a potential target of Wnt/ β -catenin. A study by Cui *et al* suggested that miR-15a-3p suppresses prostate cancer by targeting SLC39A7 to inhibit the Wnt/ β -catenin signaling pathway (104). In addition, Nimmanon *et al* reported that activation of SLC39A7 drives the PI3K/Akt pathway (105). Thus, targeting SLC39A7 by miR-15a-3p to suppress cancer cell progression may also result from inhibition of the PI3K/Akt pathway.

Targeting other signaling pathways. MiRNAs may regulate Wnt signal transduction by crosstalk with other signaling pathways (106). Signal transducer and activator of transcription 3 (STAT3) has been confirmed to be associated with EMT via regulation of β -catenin (107). Guo *et al* reported that miR-125b-5p targeting STAT3 results in β -catenin phosphorylation and degradation in HCC cells, indicating the inhibitory effect of miR-125b-5p on β -catenin-mediated EMT (62). Cyclin-dependent kinase 2 (CDK2), a member of the Ser/Thr protein kinase family, plays a crucial role in cancer proliferation and metastasis (108). Zhang *et al* found miR-3619-5p directly targets CDK2 and β -catenin to suppress bladder carcinoma progression, while further studies revealed that miR-3619-5p inhibits Wnt signaling partly through the induction of p21 following CDK2 and β -catenin inhibition (94). Cullin 4B (CUL4B), a scaffold protein assembling the cullin-RING-based E3 ubiquitin-protein ligase complexes, plays a critical role in proteolysis and tumorigenesis (109). Zhang *et al* reported that CUL4B is a direct target of miR-300 in pancreatic cancer cells, and downregulation of CUL4B by miR-300 results in inhibition of the Wnt signaling pathway and EMT (110). Similarly, Cullin 4A (CUL4A), also known as a core component of multiple cullin-RING-based E3 ubiquitin-protein ligase complexes, is negatively regulated by miR-377, indicating the inhibitory effect of miR-377 on the Wnt signaling pathway (111). A member of the receptor tyrosine kinases (RTKs) family, EPH receptor A2 (EphA2) is highly expressed in solid tumors, suggesting its important role in tumor initiation, progression, and invasion (112). MiR-302b and miR-338 serve as EphA2 inhibitors to suppress gastric cancer tumorigenesis and metastasis by inactivating the Wnt/ β -catenin pathway (113,114). LIM Homeobox 2 (LHX2), a member of the LIM homeobox family, is involved in elevated β -catenin level and cell proliferation in pancreatic ductal adenocarcinoma (115). Liang *et al* revealed that miR-506 targets LHX2 to repress EMT and lymph node metastasis in nasopharyngeal carcinoma. They also found decreased TCF4 following LHX2

inhibition is responsible for Wnt/ β -catenin signaling inactivation (116). Moreover, protein regulator of cytokinesis 1 (PRC1) was reported to mediate early HCC formation, transfer, stemness and development through Wnt/ β -catenin signaling (117) and miR-194 could target PRC1 to suppress EMT in HCC cells by inactivating the Wnt/ β -catenin signaling pathway (118). Additionally, Chen *et al* found that YWHAZ (14-3-3 ζ) regulates the EMT process by interaction with β -catenin in NSCLC (119). On this basis, Guo *et al* demonstrated miR-375-3p targets YWHAZ to inhibit migration, invasion, and the EMT processes of gastric cancer cells by blocking the Wnt/ β -catenin signaling pathway (120).

Although miRNAs may regulate Wnt signaling by affecting other signaling pathways, the underlying mechanism on how they interact has not been clearly defined. For example, miR-22 targeting formin-like 2 (FMNL2) (121), miR-136 targeting premelanosome protein (PMEL) (122), miR-29c targeting protein tyrosine phosphatase 4A2 (PTP4A2) and G protein subunit alpha 13 (GNA13) (123), and miR-378 targeting SDAD1 (60) all participate in Wnt/ β -catenin signaling inhibition; however, the relationship between these targets and Wnt signaling needs further exploration. Therefore, the study of miRNAs targeting Wnt/ β -catenin signaling, not only reveals the complex process of EMT, but also gives us better understanding of the crosstalk between Wnt signaling and other signaling pathways. For instance, Zhang *et al* found that miR-770 functions as a tumor suppressor by directly targeting the Jumonji domain containing 6 (JMJD6) 3'-UTR and inhibiting the Wnt/ β -catenin pathway in NSCLC, suggesting Wnt/ β -catenin as the downstream signal of JMJD6 in NSCLC cells (124).

miRNA as promoter of EMT. MiRNAs upregulated in various types of cancer display their carcinogenic role in tumor progression, migration, and invasion (125,126). There is a smaller quantity of miRNAs as EMT promoters compared with EMT inhibitors by targeting the Wnt signaling pathway (Table II, Fig. 1), but exploration of these miRNAs as potential therapeutic targets is also meaningful in combating EMT (127).

E-cadherin is an important intercellular adhesion molecule in maintaining cell-cell junctions and polarity. It is known that suppression of E-cadherin may result in cell detachment, invasion, and metastasis (128). Therefore, miRNAs which target E-cadherin are involved in EMT initiation. According to research, miR-9 (129), miR-23a (130), miR-544a (125) and miR-199a-5p (131) suppress E-cadherin to trigger EMT in particular cancer types, indicating these miRNAs are potential targets in cancer therapy.

Axin, APC, and GSK3 β are β -catenin suppressors that act by forming a destructive complex to anchor β -catenin thus making it degrade. Therefore, miRNAs which target Axin, APC, and GSK3 β activate Wnt signaling to trigger EMT by stabilization of β -catenin in the nucleus (132). A study by Mao *et al* demonstrated that miR-135a activates the Wnt/ β -catenin signaling pathway by directly targeting GSK3 β to accelerate the EMT, invasion, and migration of bladder cancer cells (133). In addition, miR-1246 facilitates the Wnt/ β -catenin pathway through targeting GSK3 β , which partly contributes to lung cancer metastasis (134). However, there is another study demonstrating different effects and mechanisms of miRNA on

GSK3 β . GSK3 β modulates the NF- κ B signaling pathway as it facilitates NF- κ B function through post-transcriptional regulation of the NF- κ B complex (135). Liu *et al* found that GSK3 β is a direct target of miR-377-3p and is upregulated by miR-377-3p. Consequently, miR-377-3p promotes cell proliferation and EMT by upregulating GSK3 β expression and activating the NF- κ B pathway in human colorectal cancer (136). In addition, miR-197 was reported to directly target Axin2 in HCC, leading to activation of Wnt/ β -catenin signaling and EMT (126). Similarly, miR-544a plays an oncogenic role by directly targeting Axin2 to trigger EMT of gastric cancer (125). Moreover, APC was identified as the direct and functional target of miR-27 (132) and miR-125b (137) in gastric cancer and breast cancer, respectively, making miR-27 and miR-125b promising therapeutic targets for invasive cancer treatment.

The Wnt/ β -catenin signaling pathway could be negatively regulated by antagonist molecules, therefore miRNAs targeting antagonists of the Wnt signaling have been regarded as EMT drivers. The DKK gene family, composed of DKK1-4 (138), was found to inhibit tumor invasion and migration by negative regulation of β -catenin (139). Some studies focused on the DKK family and found that miR-95-3p targeting DKK3 in prostatic cancer (140), miR-197 targeting DKK2 in HCC (126), and miR-373-3p targeting DKK1 in tongue squamous cell carcinoma (141) are responsible for the activation of Wnt/ β -catenin signaling and EMT. Secreted frizzled-related protein 1 (SFRP1) acts as an antagonist of Wnt signaling by binding to Wnt proteins through its CRD domain against the transmembrane frizzled receptor (142). MiR-27a-3p was confirmed to promote EMT in oral squamous carcinoma stem cells by targeting SFRP1 (143). Zinc and ring finger 3 (ZNRF3) belongs to the E3 ubiquitin ligase family, which negatively regulates Wnt/ β -catenin signaling by promoting the turnover of FZD and LRP6 (144). Qiao *et al* found that miR-106b-3p promotes cell proliferation and invasion by directly targeting ZNRF3, thus triggering EMT of esophageal squamous cell carcinoma (ESCC) (145). In addition, miR-146b-5p induces EMT in thyroid cancer by silencing of ZNRF3 (146). KLF4 (Kruppel-like factor 4), highly expressed in the adult intestine, is another negative regulator of Wnt signaling by interacting with β -catenin (147). Chen *et al* showed that miR-92a acts as an oncogene by directly targeting KLF4, thus affecting Wnt/ β -catenin pathway and participating in colorectal cancer progression (148). A study by Parenti *et al* also demonstrated that Mesalazine treatment suppresses the expression of miR-130a and miR-135b, which target KLF4 mRNA, to mediate β -catenin inhibition in colon cancer (149). Furthermore, it was identified that miR-374a activates Wnt/ β -catenin signaling to promote breast cancer metastasis by targeting multiple negative regulators of Wnt including WIF1, PTEN, and Wnt5A (15). Similarly, downregulation of PTEN and Wnt5A by miR-26b also results in colorectal cancer metastasis (150). However, the effect of the miR-29 family on WIF1 in NSCLC is completely opposite, as miR-29 positively regulates WIF1 expression by inhibiting the methylation of its promoter, thus inhibiting the Wnt signaling pathway (151).

5. Use of miRNAs to regulate EMT

Since miRNAs play important roles in the regulation of EMT by activating or inhibiting the Wnt signaling pathway,

miRNA-based therapies including those inhibiting miRNA function or restoring miRNA expression have been suggested as efficient strategies in cancer treatment (152) (Fig. 2). Delivering miRNA mimics contributes to the restoration of tumor-suppressive miRNA, while miRNA sponges, anti-miRNA oligonucleotides, small molecule inhibitors are useful approaches to block tumor promotive miRNA (153).

The first miRNA-based therapy for cancer is MRX34, which was designed to deliver miR-34 mimic to cancer cells. MiR-34, which exerts a suppressive effect on Wnt signaling and tumor metastasis, is downregulated in various types of cancer including colon cancer, liver cancer, NSCLC, and cervical cancer (154). Several preclinical studies demonstrated that delivery of miR-34 mimic has promising effects against liver cancer (155), lung cancer (156), and prostate cancer (157). MRX34 encapsulated in lipid is under clinical testing (NCT01829971) in several solid and haematological malignancies (158). In addition, miravirsin, a locked nucleic acid (LNA)-based antisense oligonucleotide targeting miR-122, reached phase II trials for treating hepatitis (127). Recently, LNA-modified miR-92a inhibitor MRG-110 and miR-29 mimic MRG-201 are under phase I clinical trials by miRagen Therapeutics, Inc. (159). RGLS5579, which targets miR-10b, demonstrated statistically significant improvements in survival in an orthotopic glioblastoma multiforme animal model, and the addition of a single dose of RGLS5579 combined with temozolomide led to a >2-fold improvement in survival compared to TMZ alone (<https://www.sec.gov/Archives/edgar/data/1505512/000162828020003483/rgls20191231-10k.htm>). Moreover, replenishing tumor-suppressive miRNAs such as miR-200, miR-26a, miR-506, miR-520, miR-15/16 and inhibiting tumor-stimulating miRNAs such as miR-10b, miR-221, miR-155, miR-630 have also been included in preclinical studies (160).

Efforts have been made to explore small molecular compounds targeting EMT-related miRNAs. A natural compound isolated from *Tripterygium wifordii* Hook F, namely, Triptolide (TPL), was reported to exert anti-colorectal cancer properties by downregulating miR-191, thus blocking NF- κ B and Wnt/ β -catenin signaling activation (161). Toosendanin (TSN), a triterpenoid extracted from the bark or fruits of *Melia toosendan* Sieb et Zucc, suppresses gastric cancer proliferation, invasion, and migration by targeting miR-200a to downregulate β -catenin (162). In addition, another study demonstrated that Garcinol exerts antineoplastic effects on aggressive breast cancer due to reversal of the mesenchymal phenotype, which is mediated by miR-200s and let-7s targeting NF- κ B and Wnt signaling (163). Moreover, Du *et al* showed that propofol can inhibit the proliferation and EMT of MCF-7 cells by targeting miR-21 to regulate the PI3K/Akt and Wnt/ β -catenin pathway (164). These findings not only provide promising compounds against EMT but also reveal the mechanism of miRNAs as targets in Wnt signaling regulation.

6. Results and Discussion

As shown in Fig. 1, Wnt/ β -catenin signaling is under solid regulation by miRNAs to prevent EMT prior to tumor metastasis. Dysregulation of miRNAs is involved in multiple types of invasive cancer due to their effects on gene expres-

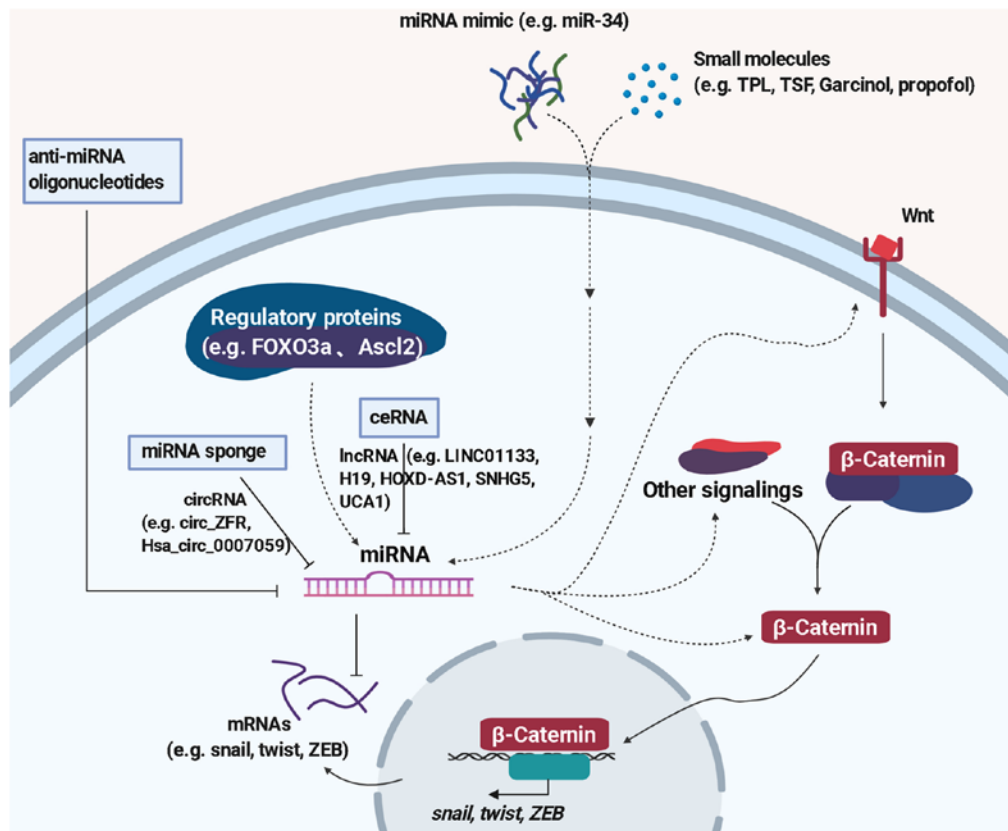


Figure 2. Use of miRNAs to combat EMT. MiRNAs regulate Wnt/ β -catenin signaling by targeting downstream transcription factors and key proteins of Wnt signaling or crosstalk with other signaling pathways. The strategies of using miRNAs to combat EMT include delivering miRNA mimic, anti-miRNA oligonucleotides or small molecule inhibitors. In addition, circRNA as miRNA sponge, lncRNA as ceRNA, and targeting regulatory proteins may constitute new prospective therapeutic strategies for cancer treatment.

sion at the post-transcriptional level (59). A single miRNA can target many genes, similarly a specific gene is regulated by multiple miRNAs, indicating the complex biological effects caused by a small change of miRNA (15,84,85). In this review, we divided miRNAs into two classes including EMT suppressors or stimulators; however, certain miRNAs may play dual roles in different types or different stages of cancer. For example, miR-374a acts as an EMT suppressor in early-stage NSCLC (stages I and II) by targeting cyclin D1 but switches to an EMT promoter in more advanced stages by targeting PTEN (165). Another study demonstrated the paradoxical effects of miR-145 on SW480 and SW620. Ectopic expression of miR-145 suppresses the proliferation, migration and invasion in SW480 but enhances these traits in its metastatic counterpart, SW620, which may be mediated through the downregulation of SIP1 but differential tuning of Wnt signaling and EMT-mediators (166). Interestingly, the dual effects of Wnt/ β -catenin signaling also add to the complexity of EMT regulation. Li *et al* reported miR-630 inhibits EMT of gastric cancer by activating the Wnt/ β -catenin pathway (167). Moreover, there is an exceptional case where a high level of Wnt3A suppresses melanoma growth and metastasis although β -catenin is active (168), indicating the opposite effects of activated Wnt/ β -catenin signaling in response to different Wnt ligands. These results suggest that miRNAs and Wnt signaling may act as double-edged swords, and the level of miRNA affects gene expression in a cell and tissue context-dependent manner (169). Therefore, the dual functions of miRNA and

the strategies of using miRNA targeting Wnt to overcome EMT need further investigation. We should take cancer type, clinical stage, tissue context, and tumor microenvironment into consideration. Additionally, recent studies have elucidated the regulatory effects of miRNAs on EMT-induced cancer drug resistance. For example, Wang *et al* found that miR-200c-3p suppression contributes to the acquired resistance of NSCLC to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors via a mediating EMT process (170). Cochrane *et al* reported that miR-200c could inhibit EMT and reinstate sensitivity to chemotherapeutic drugs in endometrial, breast, and ovarian cancer cells (171). These results indicated that regulation of EMT by miRNAs also plays a role in drug sensitivity, and comprehensive studies of miRNA's effects in all respects are required to combat cancer.

There are numerous studies demonstrating the upstream regulators of miRNA including key proteins, circular RNA (circRNA), and long non-coding RNA (lncRNA) (Fig. 2). For example, Forkhead box-O 3a (FOXO3a) inhibits β -catenin through transactivating miR-34b/c (93). As mentioned above, Ascl2 negatively regulates the miR-200 family which belongs to tumor suppressors, making Ascl2 a potential target to reverse EMT (75). Hsa_circ_0007059 blocks the Wnt/ β -catenin and ERK1/2 pathways by targeting miR-378 in A549 and H1975 cells (172). MiR-106a-3p is a direct target of lncRNA LINC01133 which suppresses gastric cancer metastasis by acting as a competitive endogenous RNA (ceRNA) for miR-106a-3p to regulate APC in Wnt/ β -catenin

signaling (173). Furthermore, lncRNA H19 (174), lncRNA HOXD-AS1 (175), lncRNA SNHG5 (176) and lncRNA UCA1 (177) were confirmed to regulate the Wnt signaling pathway by targeting miRNAs. All the evidence indicate that multiple miRNA-mediated signal transductions participate in the regulation of EMT. Revealing the connections of miRNAs and their upstream regulators may give us new prospective therapeutic strategies for cancer treatment.

Since miRNA has established its role in EMT, the strategy of utilizing miRNA to overcome cancer metastasis has increasingly gained attention. Although the complex mechanism of EMT regulation by miRNA has not been fully defined, miRNAs are still regarded as potential therapeutic implements in cancer (Fig. 2). On the one hand, various methods of directly switching the level of miRNA by miRNA mimics, miRNA sponges, or anti-miRNA oligonucleotides, which are under study for different phases, have been shown to be effective. On the other hand, indirect regulation of miRNAs by affecting upstream regulators (protein, circRNA, lncRNA) or crosstalk with other signaling pathways are also useful approaches to inhibit EMT. Currently, a number of miRNA-based therapies are in clinical trials to treat cancer or other diseases. However, safety concerns regarding miRNA therapy always exist. Off-target side-effects, toxicity, and carcinogenicity of miRNA are important challenges in the development of miRNA therapy. Seeking effective delivery systems for miRNA is also a dilemma, so further research may focus on these issues to improve the utilization value of miRNA therapy.

7. Conclusion

In conclusion, miRNAs regulate Wnt/ β -catenin signaling through targeting transcription factors and key proteins of Wnt signaling or crosstalk with other signaling pathways. However, the complicated role of miRNA as either a tumor suppressor or an oncogene and its underlying mechanism need further exploration. This review, not only provides potential applications of miRNAs as molecular targets in invasive tumor treatment, but also helps us gain a better understanding of the complexity of the EMT process and crosstalk between Wnt/ β -catenin and other signaling pathways.

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Authors' contributions

EXZ and LJD designed the study and revised the manuscript. YHL, LC and GZ searched the literature and drafted the manuscript. AYS, BL, JYS and CFZ were also involved in the conception of the study. JW, XL, CFY and YYC assisted with the critical revision of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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