Novel role of microRNA-126 in digestive system cancers: From bench to bedside (Review)

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Abstract. MicroRNAs (miRNAs) are ubiquitously expressed, small, non-coding RNAs that regulate the expression of approximately 30% of the human genes at the post-transcriptional level. miRNAs have emerged as crucial modulators in the initiation and progression of various diseases, including numerous cancer types. The high incidence rate of cancer and the large number of cancer-associated cases of mortality are mostly due to a lack of effective treatments and biomarkers for early diagnosis. Therefore there is an urgent requirement to further understand the underlying mechanisms of tumorigenesis. MicroRNA-126 (miR-126) is significantly downregulated in a number of tumor types and is commonly identified as a tumor suppressor in digestive system cancers (DSCs). miR-126 downregulates various oncogenes, including disintegrin and metalloproteinase domain-containing protein 9, v-crk sarcoma virus CT10 oncogene homolog and phosphoinositide-3-kinase regulatory subunit 2. These genes are involved in a number of tumor-associated signaling pathways, including angiogenesis, epithelial-mensenchymal transition and metastasis pathways. The aim of the current review was to summarize the role of miR-126 in DSCs, in terms of its dysregulation, target genes and associated signaling pathways. In addition, the current review has discussed the potential clinical application of miR-126 as a biomarker and therapeutic target for DSCs.

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1. Introduction

Cancer is a major global public health problem and a leading cause of mortality. Digestive system cancer types (DSCs) are the most common malignant tumors affecting the organs and glands of the digestive tract. DSCs include esophageal, stomach, colon, rectum, liver, gallbladder and pancreatic carcinomas (1). Colorectal cancer (CRC) is the third most commonly diagnosed cancer type, whilst liver cancer and gastric cancer (GC) were second and third to lung cancer as the most frequent causes of cancer-associated cases of mortality worldwide in 2012 (2). Pancreatic cancer (PC) is usually detected at an advanced stage with extensive invasion and lymphatic metastasis, when the estimated 5-year survival rate is well below 5% (3). Early detection of DSCs is limited by the absence of specific symptoms prior to metastasis, which leads to poor prognosis. Therefore, it is of great importance to identify novel predictive and prognostic biomarkers, including genetic and epigenetic alterations at early stages that can detect and monitor tumor dynamics.

A number of studies have identified that microRNAs (miRNAs) are aberrantly expressed in human cancer types due to genomic or epigenetic alterations (4,5). miRNAs are a class of single-stranded, small RNAs approximately 22 nucleotides in length. miRNAs serve as essential post-transcriptional regulators by binding to the 3'-untranslated region (3'-UTR), 5'-UTR or coding sequences of target mRNAs (6). Notably, miRNAs are thought to modulate almost 30% of human genes (5,7). The extensive regulatory functions of miRNAs are not only associated with developmental timing, cell proliferation and apoptosis, but also play a critical role in oncogenesis and tumor suppression (7). Numerous miRNAs have been demonstrated to interact with their target genes and tumor-associated pathways through subtly regulated networks (7,8). The current review summarizes the latest findings regarding the crucial roles of miR-126 in major DSCs. Furthermore, the potential clinical value of miR-126 as a novel diagnostic and prognostic biomarker

and therapeutic target in DSCs is discussed. The current review aims to improve understanding regarding the significance of the miR-126 regulatory mechanisms in human cancer types.

2. Structure and function of miR-126

miR-126 and its passenger strand, miR-126*, are two endothelial cell-specific miRNAs that mediate angiogenesis (9). Both miR-126 and miR126* are encoded by the epidermal growth factor-like domain 7 (EGFL7) gene (10). miR-126 usually refers to the 3' region of the transcript, also termed miR-126-3p, located within the 7th intron of EGFL7. Whereas, miR-126* refers to the 5' region of the transcript, also termed miR-123 or miR-126-5p, which binds to the main miR-126 transcript at the stem loop structure of the precursor miRNA (10,11) (Fig. 1). EGFL7 is located on chromosome 9 in humans and encodes an endothelial cell-derived factor involved in the repression of smooth muscle cell migration and the regulation of angiogenesis (12,13). EGFL7 is highly expressed in the vasculature during embryonic development and at a relatively lower level in adult blood vessels (13,14). However, an aberrant upregulation of EGFL7 can be observed during pathological angiogenesis in malignant tumors (15).

To the best of our knowledge, miR-126 is the only miRNA with specific expression in the endothelial cell lineage and hematopoietic progenitor cells (11). Targeted deletion of miR-126 results in a loss of vascular integrity, which leads to ruptured vessels and impaired endothelial cell migration (9,10). Functionally, miR-126 is significantly associated with angiogenesis and inflammation. miR-126 suppresses sprouty-related EVH1 domain-containing protein 1 (SPRED1) and phosphoinositide-3-kinase regulatory subunit 2 (PI3KR2), both of which inhibit receptor tyrosine kinase-induced signaling via the mitogen-activated protein kinase (MAPK) and phosphinositide-3-kinase (PI3K) signaling pathways, thereby promoting vascular endothelial growth factor (VEGF) signaling and angiogenesis (9). Although miR-126 expression is usually altered in parallel with the expression of EGFL7 protein, miR-126 can downregulate EGFL7, leading to reduced angiogenesis and cell proliferation via a negative feedback loop mechanism (9,16). In addition, endogenous miR-126 has been revealed to inhibit the expression of vascular cell adhesion molecule 1 (VCAM-1) and prevent leukocyte adhesion and infiltration to further control vascular inflammation (17). Furthermore, miR-126 can suppress inflammation and reactive oxygen species production in endothelial cells under hyperglycemic conditions by post-transcriptionally inhibiting the expression of high-mobility group box 1 (18). The functional properties of miR-126* are less well understood. The significant role of miR-126 as a tumor suppressor involved in various signaling cascades has been demonstrated in previous studies (11,19). Aberrant expression of miR-126 has been identified in numerous human cancer types, including melanoma, osteosarcoma, leukemia and carcinomas of the digestive system, endocrine glands, urogenital system and respiratory system (20).

3. Aberrant expression of miR-126 in DSCs

Numerous miRNAs have been revealed to be abnormally expressed in multiple cancer types (21). Both miR-126 and

miR-126* are highly expressed in endothelial cells *in vivo* (9). In addition, miR-126 is overexpressed in highly vascularized organs, including the heart, liver and lungs (22,23). Table I lists previous studies that have identified that miR-126 expression is significantly decreased in human DSC tissues compared with adjacent non-cancerous tissues (24-58). Notably, miR-126 is involved in angiogenesis and has significantly higher expression levels in hepatocellular carcinoma (HCC) tissues treated with transcatheter arterial chemoembolization (TACE) and surgery, compared with tissues only subjected to surgical resection (53). Another study identified that HCC tissues exhibit an elevated level of miR-126 compared with adjacent non-cancerous tissues, although miR-126 may inhibit tumor angiogenesis and proliferation (16). In addition, miR-126 is aberrantly expressed in certain GC tissues (33,38).

miR-126 expression levels are downregulated in almost all established esophageal cancer (EC), CRC, HCC and PC cell lines and certain GC cell lines (Table I). Restoring or upregulating miR-126 expression can inhibit cancer cell proliferation, migration and invasion *in vitro*, indicating a potential tumor suppressive function or miR-126 in DSCs (19,49,51,56). However, Otsubo *et al* (33) have revealed that five GC cell lines (HSC43, HSC58, NUGC3, NUGC4 and GCIY) exhibit high levels of miR-126. Similarly, miR-126 has also been identified to be significantly upregulated in the AGS, HGC-27, BGC-823, SGC-7901 and MKN-7 cell lines of GC (38), indicating miR-126 may exhibit a potential oncogenic role in GC (33).

Genetic and epigenetic changes lead to alterations in tumor-associated gene expression. Aberrant changes in gene sequence, dicer abundance and epigenetic modifications, including DNA methylation, histone modifications and nucleosome positioning, predominantly account for miR-126 dysregulation in cancer (20). For example, the downregulation of miR-126 in CRC is partly due to promoter methylation of its host gene EGFL7 (45). Pagano *et al* (59) have identified the existence of epigenetic-miRNA loops in hematopoietic cells, which can either modulate or be modulated by epigenetic factors and therefore regulate the gene expression profile. Subsequently, Liu *et al* (26) identified a DNA (cytosine-5)-methyltransferase 1 (DNMT1)-miR-126 epigenetic circuit in esophageal squamous cell carcinoma (ESCC) cells. DNMT1 is aberrantly upregulated in ESCC cells, which leads to the hypermethylation of EGFL7 and downregulation of miR-126, whilst upregulation of miR-126 markedly reduces the expression of DNMT1 (26). In addition, overexpressed HOX antisense intergenic RNA (HOTAIR) in GC serves as a competing endogenous RNA and directly associates with miR-126 to dysregulate the expression of miR-126 (60). Finally, the tumor suppressor nasopharyngeal carcinoma-associated gene 6 has been revealed to upregulate miR-126 in colon cancer (61).

4. Targets of miR-126 in DSCs

miRNAs modulate their target gene expression by binding to the 3'-UTR of the corresponding mRNA. Numerous studies have identified that miR-126 regulates key processes in different cancer types by targeting various genes, including insulin receptor substrate 1, v-crk sarcoma virus CT10 oncogene homolog (CRK), CXC chemokine
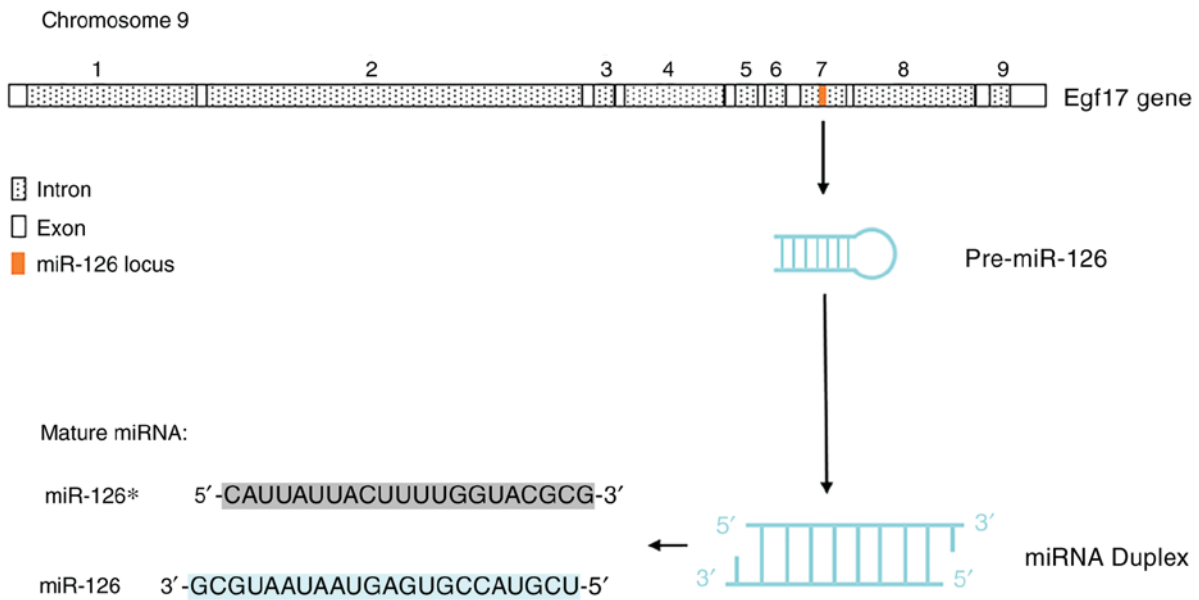
Figure 1. Origin and structure of miR-126/miR-126*. The EGFL7 gene consists of nine introns located on human chromosome 9. A pre-miR structure is located within intron 7 of the EGFL7 gene from which miR-126 and miR-126* originate. miR or miRNA, microRNA; *, passenger strand; EGFL7, epidermal growth factor-like domain 7.

receptor type 4 (CXCR4), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9) and sex-determining region Y-box 2 (SOX2). As presented in Table I, the majority of these target genes are overexpressed in DSCs and function as oncogenes involved in cell proliferation, cell cycle, cell senescence, differentiation, apoptosis and metastasis at both genetic and epigenetic levels. Therefore, miR-126 is an effective regulator of tumorigenesis and progression. VCAM-1 and PI3KR2 are associated with the anti-inflammatory and anti-neoplastic functions of pomegranate polyphenols in colon cancer (42). Golgi phosphoprotein 3 (GOLPH3), the target of miR-126 in ESCC, contributes to tumorigenicity and tumor cell proliferation (27,62). Several studies have demonstrated that miR-126 targets CXCR4 and suppresses its expression, which inhibits tumor cell proliferation, migration, invasion and cell apoptosis, and arrests the cell cycle at the G_0/G_1 transition (46,47). VEGF overexpression and neo-angiogenesis in CRC is associated with miR-126 downregulation (45). The oncogenic targets of miR-126 associated with HCC include the pro-angiogenic PI3KR2 (51) and EGFL7 (16,54), in addition to the pro-metastatic low-density lipoprotein receptor-related protein 6 (LRP6) (51). Abnormally high expression of EGFL7 in HCC is also associated with increased proliferation and decreased apoptosis in HCC cells (54). ADAM9 overexpression in PC (61), regulator of G protein signaling 3 (RGS3) overexpression in GC (41,63) and aberrantly high levels of SOX2 in pancreatic ductal adenocarcinoma (PDAC) (64) are all positively associated with cellular migration, invasion and epithelial-mesenchymal transition (EMT) (56).

The dysregulation of these targets not only promotes the initiation and development of DSCs, but may also be useful as novel markers for diagnosing, monitoring and predicting the prognosis of DSCs. As targets of miR-126 in GC, CRK and CRK-like (CRKL) have been revealed to facilitate adhesion, invasion and migration of cancer cells. Furthermore, overexpression of CRK and CRKL has been associated with

more aggressive clinicopathological features, including a larger tumor size, a higher number of lymph node metastases, deeper local invasion and higher tumor-node-metastasis (TNM) staging (19,34). Overexpression of GOLPH3 may be associated with a poor outcome for patients with ESCC (62). Similarly, the expression level of ADAM9 is a confirmed prognostic factor for HCC (55) and a VEGF polymorphism is associated with higher susceptibility to GC (65). In summary, the aforementioned markers may assist in screening populations at high risk and preventing progression of tumorigenesis.

While the anti-tumor function of miR-126 is well established and is known to depend on targeting and dysregulating the aforementioned oncogenes, there are certain reports that suggest miR-126 serves an oncogenic role in DSCs by targeting certain tumor-suppressor genes. Cell adhesion molecule 1 (CADM1) and SOX2 are suppressed upon miR-126 overexpression in GC cells, leading to carcinogenesis, migration and invasion (33,38). Furthermore, a pro-angiogenic role of miR-126 has been identified in HCC tissues, with SPRED1 inhibition as the underlying mechanism (53). Hansen et al (44) also revealed that a higher expression of miR-126 in CRC tissues is associated with increased expression of VEGFR-2 and a denser microvessel density (MVD).

The targets of miR-126 in DSCs can also be negatively modulated by miR-126 in other tumors. For instance, CRK is targeted by miR-126 in non-small cell lung cancer cells (66) and solute carrier family 7 member 5 has been identified as an miR-126 target in colon cancer and thyroid cancer (50,67). In addition, miR-126 can regulate the same or different targets in DSCs by cooperating with other miRNAs. For instance, miR-145 exerts its role of inhibiting tumor growth in colon cancer by targeting and regulating IRS-1 (68). Additionally, miR-126 and miR-34a can synergistically exert a tumor suppressive effect by targeting VEGF-A, SOX2, cyclin D1, E2F1 and B-cell lymphoma 2 in pancreatic adenocarcinoma (PAC) (58).

Table I. Aberrant expression, target genes and direct functions of miR-126 in various types of digestive system cancer.

A, Esophageal cancer

Expression	Sample(s)	Target gene(s)	Direct function(s)	(Refs.)
Down	Tissues	-	-	(24,25)
Down	Tissues/cell lines	DNMT1 and ADAM9	Forming DNMT1-miR-126 loop and suppressing ADAM9 expression	(26)
Down	Tissues/cell lines	IRS-1 and GOLPH3	Downregulating the expression of IRS-1 and GOLPH3 protein	(27)
Down	Tissues/cell lines	SOX2	Inhibiting SOX2 expression by targeting its mRNA 3'-UTR	(28)
Down	Tissues/cell lines	PI3KR2	Inhibiting PI3K/AKT signaling pathway	(29)
Down	Tissues/cell lines	VEGF-A	Negatively regulating VEGF-A expression	(30)

B, Gastric cancer

Expression	Sample(s)	Target gene(s)	Direct function(s)	(Refs.)
Down	Tissues/cell lines	CRK	Downregulating the expression of CRK	(19,31,32)
Up/down[a]	Cell lines	SOX2	Repressing SOX2 expression by targeting its mRNA 3'-UTR	(33)
Down	Tissues/cell lines	CRKL	Negatively regulating CRKL expression by targeting its mRNA 3'-UTR	(34)
Down	Tissues/cell lines	VEGF-A	Reducing the expression of VEGF-A by binding to its mRNA 3'-UTR	(35)
Down	Tissues/cell lines	PLK2, PI3KR2 and CRK	Synergistically reducing the expression of PLK2, PI3KR2 and CRK	(36)
Down	Tissues/cell lines	LAT-1	Negatively regulating the expression of LAT-1	(37)
Up	Cell lines	CADM1	Downregulating CADM1 expression by targeting its mRNA 3'-UTR	(38)
Down	Cell lines	EZH2	Decreasing EZH2 expression to regulate chemotherapy resistant	(39)
Down	Cell lines	ADAM9	Downregulating ADAM9 expression by binding to its mRNA 3'-UTR	(40)
Down	Tissues/cell lines	RGS3	Post-transcriptionally downregulating the expression of RGS3	(41)

C, Colorectal cancer

Expression	Sample(s)	Target gene(s)	Direct function(s)	(Refs.)
Down	Cell lines	p85β (PI3KR2)	Reducing the level of p85β and phospho-AKT	(42,43)
-	Cell lines	VCAM-1	The expression level of miR-126 inversely correlates with VCAM-1	(42)
Down	Tissues	VEGFR-2	Elevated miR-126 is associated with high VEGFR-2 expression	(44)
Down	Tissues/cell lines	VEGF	Suppressing the expression of VEGF by binding to its mRNA 3'-UTR	(45)

Table I. Continued.

Expression	Sample(s)	Target gene(s)	Direct function(s)	(Refs.)
Down	Tissues/cell lines	CXCR4	Negatively regulating CXCR4 expression	(46,47)
Down	Tissues/cell lines	RhoA/ROCK	Inhibiting RhoA/ROCK signaling pathway	(46,48)
Down	Cell lines	IRS-1	Inhibiting IRS-1 expression by binding to its mRNA 3'-UTR	(49)
Down	Tissues/cell lines	IRS-1, SLC7A5 and TOM1	Reducing the expression of IRS1, SLC7A5 and TOM1	(50)

D, Hepatocellular carcinoma

Expression	Sample(s)	Target gene(s)	Direct function(s)	(Refs.)
Down	Tissues/cell lines	LRP6 and PI3KR2	Negatively regulating LRP6 and PI3KR2/phospho-AKT expression	(51)
Down	Cell lines	SOX2	Inhibiting SOX2 expression by binding to its mRNA 3'-UTR	(52)
Down	Tissues	SPRED1 and VEGF	Inhibiting the expression of SPRED1 and VEGF	(53)
Down	Tissues/cell lines	EGFL7	Suppressing the expression of EGFL7	(54)
Up	Tissues	EGFL7	Downregulating EGFL7 expression to inhibit proliferation and angiogenesis	(16)
Down	Tissues/cell lines	ADAM9	Downregulating the expression of ADAM9	(55)

E, Pancreatic cancer

Expression	Sample(s)	Target gene(s)	Direct function(s)	(Refs.)
Down	Tissues/cell lines	ADAM9	Inhibiting ADAM9 expression by binding to its mRNA 3'-UTR	(56)
Down	Tissues/cell lines	KRAS and CRK	Reducing the expression of KRAS and CRK	(57)
Down	Tissues/cell lines	VEGF-A and SOX2	Downregulating the expression of VEGF-A and SOX2	(58)

[a]In the particular study, it was reported that among the 10 gastric cancer cell lines studied, 4 exhibited high miR-126 expression, whereas 5 exhibited low expression. miR-126, microRNA-126; DNMT1, DNA methyltransferase 1; ADAM9, disintegrin and metalloproteinase domain-containing protein 9; IRS-1, insulin receptor substrate 1; GOLPH3, Golgi phosphoprotein 3; SOX2, sex-determining region Y-box 2; UTR, untranslated region; PI3KR2, phosphoinositide-3-kinase regulatory subunit; PI3K, phosphoinositide-3-kinase; VEGF-A, vascular endothelial growth factor A; CRK, v-crk sarcoma virus CT10 oncogene homolog; CRKL, v-crk avian sarcoma virus CT10 oncogene homolog-like; PLK2, polo-like kinase 2; LAT-1, l-type amino-acid transporter 1; CADM1, cell adhesion molecule 1; EZH2, enhancer of zeste homolog 2; RGS3, regulator of G-protein signaling 3; VCAM-1, vascular cell adhesion molecule 1; VEGFR-2, vascular endothelial growth factor receptor 2; CXCR4, CXC chemokine receptor type 4; RhoA, ras homology gene family, member A; ROCK, Rho-associated protein kinase; SLC7A5, solute carrier family 7 member 5; TOM1, tobamovirus multiplication 1; LRP6, low-density lipoprotein receptor-related protein 6; SPRED1, sprouty-related EVH1 domain-containing protein 1; EGFL7, epidermal growth factor-like domain 7.

Notably, several targets of miR-126 in DSCs are exclusively regulated by miR-126 in specific cancer types. Studies indicate that PI3KR2 and VEGF-A are regulated by miR-126 solely or together in EC (29,30), GC (35,36), CRC (42), HCC (51) and PAC (58). It has also been demonstrated that miR-126 targets IRS-1 only in ESCC (27) and CRC (50). KRAS has been confirmed as a target of miR-126 in PDAC and in contrast to the typical miRNA-target gene interaction, miR-126 binds
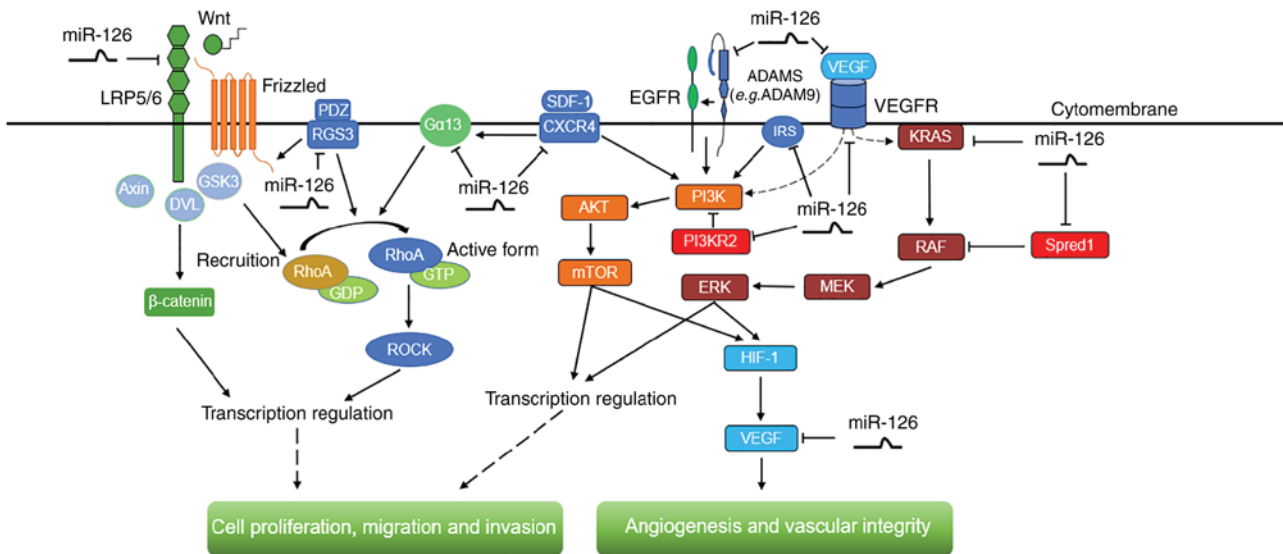
Figure 2. The signaling pathways, including Ras/ERK, PI3K/AKT/mTOR, ADAM9/EGFR/AKT, RhoA/ROCK and Wnt/β-catenin, modulated by miR-126 in digestive system cancer types. These signaling cascades are involved in the regulation of angiogenesis and vascular integrity, as well as cell proliferation, migration and invasion. miR-126, microRNA-126; ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin; ADAM9, disintegrin and metalloproteinase domain-containing protein 9; EGFR, epidermal growth factor receptor; RhoA, ras homology gene family, member A; ROCK, Rho-associated protein kinase; LRP5/6, low density lipoprotein receptor related protein 5/6; GSK3, glycogen synthase kinase 3; DVL, dishevelled; RGS3, regulator of G protein signaling 3; Gα13, G protein α13; GTP, guanosine 5'-triphosphate; GDP, guanosine 5'-diphosphate; SDF-1, stromal cell-derived factor-1; CXCR4, CXC chemokine receptor type 4; PI3KR2, phosphoinositide-3-kinase regulatory subunit 2; IRS-1, insulin receptor substrate 1; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; SPRED1, sprouty-related EVH1 domain-containing protein 1; MEK, mitogen-activated protein kinase; HIF1, hypoxia-inducible factor 1.

to KRAS at an uncommon site in its 3'-UTR (57). However, KRAS expression is not influenced by miR-126 in CRC (69). Furthermore, certain genes that are targeted by miR-126 in several DSCs serve different roles in different cancer types. SOX2, an inhibitor of GC growth (70), promotes tumor cell proliferation and invasion in EC (28). A feedback regulatory loop may also exist between miR-126 and its target genes, as identified with DNMT1 in ESCC, which increases the intricacy of the regulation network of the miRNA (26).

5. Signaling cascades modulated by miR-126 in DSCs

In addition to numerous cancer-associated genes, miR-126 also interacts with the signaling pathways involved in DSCs. Various signaling cascades involved in the regulation of angiogenesis and vascular integrity, as well as cell proliferation, migration and invasion are modulated by miR-126 (Fig. 2).

miR-126 regulates the expression of VEGFR-2 and VEGF in DSCs via the MAPK/ERK and PI3K/AKT pathways (44,45), and can impede the growth of cancer cells by targeting p85β (also termed PI3KR2), leading to decreased levels of phosphorylated AKT, the active form of the kinase (29). AKT phosphorylates a wide range of proteins involved in cell survival, motility and proliferation (71). Myelin transcription factor 1, which is phosphorylated by AKT to modulate the G2/M-phase transition (72), is also upregulated by miR-126 (29). Zhou *et al* (49) identified that miR-126 suppresses the proliferation, migration, invasion and cell cycle progression of cancer cells by targeting IRS-1 via the AKT and ERK1/2 signaling pathways. The anti-angiogenic role of miR-126 in cancer tissues is exerted by targeting VEGF-A, possibly via the MAPK/ERK and AKT/mammalian target of

rapamycin (mTOR) signaling pathways (16,35,53,54), which reduces the MVD in cancer tissues (51). In addition, miR-126 exhibits a suppressive role in the proliferation, apoptosis and angiogenesis of tumor cells and tissues by targeting EGFL7, through the inactivation of the ERK signaling pathway (73). HOTAIR, a long non-coding RNA that is increased in GC and is responsible for drug-resistance, potentially acts by binding to and dysregulating miR-126, leading to the upregulation of miR126-targeted oncogenes, including VEGF-A and PI3KR2, and activation of the PI3K/AKT/multidrug resistance-associated protein 1 pathway (60).

Furthermore, miR-126 inhibits the activity and expression of the Ras homology gene family, member A (RhoA)/Rho-associated protein kinase (ROCK) signaling pathway mediators that are aberrantly upregulated in cancer cells. The expression of these mediators positively correlates with clinical stage and lymph node metastasis but negatively correlates with overall survival of patients with cancer (46). CXCR4 is a putative mediator between miR-126 and the RhoA/ROCK signaling pathway (46,48). It has been identified that miR-126 exerts a tumor suppressive effect by targeting CXCR4 and involving the stromal cell-derived factor 1/CXCR4 axis, which possibly promotes MAPK p42/44 phosphorylation and activates the PI3K/AKT pathway (74,75). Furthermore, miR-126 was revealed to be a tumor suppressor in CRC through the AKT and ERK1/2 signaling pathways, by dysregulating CXCR4 (47). Additionally, Yuan *et al* (46) observed that CXCR4 could prevent the inhibitory action of miR-126 on the RhoA signaling pathway by coupling with Gα13, therefore validating that miR-126 acts as a tumor suppressor by inactivating RhoA signaling via the CXCR4/Gα13/RhoA axis in DSCs.

It has been hypothesized that upregulating miR-126 can weaken the metastatic ability of HCC by suppressing the expression of LRP6, a Wnt co-receptor, and its downstream mediator β-catenin (51). This may be consistent with a study demonstrating that the activation of the Wnt/β-catenin signaling pathway results in spontaneous HCC in farnesoide X receptor-knockout mice (76). In addition, activation of the Wnt/β-catenin signaling pathway is involved in promoting EMT of GC cells (77) and numerous studies have confirmed that various miRNAs, including miR-544a, modulate EMT in GC via Wnt/β-catenin signaling (78). Upregulation of RGS3 can enhance the pro-tumorigenic signals generated by the Wnt/β-catenin pathway and induce EMT (41,63). Therefore, miR-126 directly targeting and downregulating RGS3 is possibly involved in its inhibition of EMT via the Wnt/β-catenin pathway (41). Furthermore, miR-126 functions as a tumor suppressor in ESCC via the ADAM9-EGFR-AKT axis and the downregulation of ADAM9 suppresses the activation of the EGFR-AKT pathway by restricting phosphorylation (26). In addition to the anti-tumor effects of miR-126 through the aforementioned signaling pathways, miR-126 also exhibits a pro-tumorigenic effect in DSCs. A pathway has been proposed in which miR-126 dysregulates SOX2, leading to overexpression of placenta-specific 1, a tumor suppressor for gastric adenocarcinoma; this pathway may serve a positive role in gastric carcinogenesis (33).

It is noteworthy that VEGF, VEGFR, EGFR and CXCR4 are pro-inflammatory factors that are frequently upregulated in the tumor microenvironment, possibly leading to oncogenic events (79). As aforementioned, the interactions between miR-126 and these cytokines or their receptors exert modulatory effects on several dysregulated pathways, including MAPK/ERK, AKT/mTOR and RhoA signaling pathways, which indicates a complicated cross-talk among cytokines, miRNAs and signaling pathways in tumorigenesis and tumor progression. Other miRNAs have also been reported to interact with cytokines in DSCs. For example, Ma *et al* (80) have demonstrated that interleukin (IL)-1β-induced nuclear factor κ-light-chain-enhancer of activated B cells activation results in increased miR-425 transcription, which further facilitates GC cell proliferation by suppressing phosphatase and tensin homolog.

6. miR-126 serves as a useful biomarker in DSCs

miRNAs exhibit several essential features of biomarkers, including an average length of 22 nucleotides, stable expression and ease of detection (81). Due to their ubiquitous and abnormal expression in human cancer types, they exhibit great potential as diagnostic and prognostic factors for cancer (82). As aforementioned, the dysregulation of several target genes due to aberrant expression of miR-126 is involved in DSCs, indicating the potential of miR-126 as a biomarker for this group of cancer types.

Previous studies have revealed that miR-126 is highly expressed in normal tissues compared with cancer tissues and DSC cell lines (Table I). Liu *et al* (25) identified 60 miRNAs, including miR-126, that were expressed differentially between matched EC and paracancerous normal tissues. Lower expression of miR-126 has been observed in both HCC tissues and

liver cancer cells compared with normal controls (16,51). In addition, higher levels of miR-126 can be used to discriminate HCC from metastatic adenocarcinoma in the liver along with other miRNAs (83). Hamada *et al* (56) demonstrated that miR-126 is significantly downregulated in invasive ductal adenocarcinoma (IDA) compared with normal pancreatic tissues, intraductal papillary mucinous adenoma and intraductal papillary mucinous carcinoma tissues. Furthermore, patients with IDA were revealed to exhibit more adverse outcomes compared with patients with intraductal papillary mucinous adenoma or intraductal papillary mucinous carcinoma due to a higher invasive potential (56). Similarly, other studies consider miR-126 as a representative of 21 dysregulated miRNAs when comparing PDAC with serous microcystic adenoma (57). Therefore, detecting the levels of miR-126 in tissues or cells may promote promising new strategies to diagnose DSCs.

Overwhelming evidence has indicated that miR-126 is associated with metastasis, cancer stage, tumor size or other clinicopathological characteristics of DSCs, in which metastasis is a leading cause of cancer-associated cases of mortality (84). Low expression of miR-126 is observed in metastatic CRC cell lines and miR-126 levels are significantly lower in patients with numerous metastatic sites compared with those with only one metastatic location (48,85). Furthermore, the expression of miR-126 is negatively correlated with TNM stage and metastasis in patients with CRC, indicating that lower expression levels of miR-126 may predict a poorer prognosis (46,47). Low levels of miR-126 in tumors are similarly associated with lymph node metastasis, local invasion and TNM stage in GC, ESCC and other DSCs (19,27,29). In addition, miR-126 may serve as an independent prognostic indicator for patients with ESCC (26). Li *et al* (86) established a seven-miRNA signature, with miR-126 designated as protective, to predict the relapse-free survival and overall survival of patients with GC. Similarly, miR-126 was identified as a predictor of venous metastases and survival of patients with HCC in a 20-miRNA prognostic signature (87). Dysregulation of miR-126 is inversely correlated with the clinicopathological parameters of HCC, including tumor size, tumor weight and alpha-fetoprotein (AFP) level, and is involved with tumor angiogenesis, microvascular invasion, tumor metastasis and early recurrence (16,51,55). The gene targets of miR-126 may also exhibit a potential prognostic function. For example, downregulation of miR-126 and upregulation of CRK are synergistically correlated with tumor progression of GC and can therefore be a combined unfavorable prognostic factor for patients with GC (88). Consequently, timely detection of miR-126 and CRK levels may be of great importance in predicting the overall survival of patients with advanced GC (32).

In addition to the tissues, circulating miRNAs are also detected in plasma, which has been demonstrated to be a feasible method for diagnosing human cancer types (89). Previous studies have identified that the serum levels of miR-126 are altered in patients with CRC compared with healthy controls (90), and between patients with CRC with liver metastasis and those with localized CRC (89). Lower levels of miR-126 were also observed in the plasma of patients with PC compared with healthy individuals (91). Since serum

miR-126 levels are significantly different between patients with HCC with hepatitis B virus (HBV-HCC) and their non-HCC counterparts, it is necessary to evaluate the plasma levels of miR-126 and AFP rather than AFP alone for diagnosing HBV-HCC (92).

However, several studies demonstrate ambiguous results regarding the role of miR-126 in DSC diagnosis. miR-126 has been identified as both a benign and an unfavorable prognostic factor. Overexpression of miR-126 accompanied with down-regulation of CADM1 may function as an adverse factor for patients with stage I GC (38). While miR-126 demonstrates no association with the prognosis of patients with EC (24), it can act as an independent predictor of the outcome of ESCC (26).

7. Therapeutic implications of miR-126 in DSCs

miRNAs are promising therapeutic targets for various cancer types on account of their post-transcriptional regulation of numerous cancer-associated target genes (7). Therefore artificially modulating the expression levels of miRNAs and thereby their targets is a rational therapeutic approach. Accordingly, the inhibitory role of miR-126 in tumorigenesis and the development of DSCs could be exploited for treatment of these cancer types. Restoring the expression of miR-126 to influence different targets and pathways could be a novel therapeutic strategy for DSCs. Ectopic expression of miR-126 in CRC (47), GC (19,31), EC (29), HCC (51,52) and PAC (58) attenuates cell-cycle progression, suppresses tumor prolifera-tion, oncogenesis, colony formation, invasion and metastasis, and simultaneously promotes tumor cell apoptosis. Increasing the expression of miR-126 in pancreatic benign cystic tumors prevents them developing into PC (57).

miRNAs have also been implicated in chemoresistance of cancer cells and failed chemotherapy; the miRNAs associated with apoptosis are usually responsible for this phenomenon (93). An association between miR-126 and chemoresistance in DSCs has been reported. A low level of miR-126 in primary CRC tumors is associated with lower sensitivity to oxaliplatin in metastatic CRC (85). In another study, upregulation of miR-126 significantly improved the sensitivity of colon cancer cells to oxaliplatin (50). Multiple studies have revealed lower expression of miR-126 in drug-resistant GC cell lines and re-sensitization to vincristine and adriamycin following ectopic expression of miR-126 (39). miR-126 may also affect the sensitivity of GC cells to cisplatin, which is one of the major chemotherapeutic options in treating patients with advanced GC (60). A previous study identified that miR-126 is downregulated along with a number of other miRNAs in hydroxycamptothecin-resistant GC cells (94). Therefore, another feasible therapeutic strategy is using synthetic miR-126 as a drug-sensitivity mediator in DSCs.

However, there are a number of limitations in the clinical application of miR-126, including delivery of the effector molecule to target sites, which is considered to be the major challenge for miRNA-based treatment (95). Stable nucleic acid lipid particles, polyethylene glycol or virus-like particles have been tested as carriers of miR-126 (95,96). Additionally, another study investigated the possibility of using carci-noma cells targeting oncolytic adenovirus for delivery of miR-126 (58). Despite the generally high efficacy of viral vectors, there are apprehensions regarding their toxicity and immunogenicity, which limit their clinical usage (97).

Recent studies have demonstrated that the dysregulation of miRNAs in cancer is associated with DNA methylation. Therefore, altering the methylation status of tumor-associated genes is a promising epigenetic therapy (98). Zhang *et al* (45) revealed that deficiency of miR-126 in CRC cells may be a result of aberrant DNA methylation, since miR-126 expres-sion was restored following demethylation of CRC cells with 5-aza-2'-deoxycytidine. Similarly, miR-126 expression is regulated by the DNMT1-miR-126 epigenetic circuit in ESCC cells via hypermethylation of the EGFL7 promoter. Therefore, miR-126-associated epigenetic modification exhibits significant therapeutic potential in ESCC (26).

Since miRNAs exert their oncotherapeutic effects by regulating target genes, the direct regulation of target genes should be validated. Suppressing CRKL in GC cells had the same effects as overexpressing miR-126, including inducing cell cycle arrest at G_0/G_1 phase and inhibiting prolifera-tion (34). Similarly, the therapeutic effect of inhibiting ESCC cell proliferation and migration can be acquired not only by the re-introduction of miR-126 but also dysregulation of ADAM9 (26). Furthermore, the miR-126/ADAM9 axis can be a therapeutic target in PC in terms of suppressing migration of tumor cells (56).

The heterogeneity of the miRNA regulation network makes the therapeutic role of miR-126 in DSCs controversial. It has been reported that decreasing but not increasing the expression of miR-126 may inhibit migration and invasion of GC cells (38). Another study hypothesized that a miR-126 inhibitor combined with TACE may achieve an improved therapeutic effect in HCC (53). In addition, the combina-tion of miR-126 with other miRNAs, including miR-34a, targeting different genes could achieve improved results in PAC (58). Notably, overexpression of miR-126 destroyed cell viability, arrested cell cycle, inhibited clonogenicity and blocked tumorigenicity by targeting KRAS-associated genes in multiple KRAS-mutant CRC cells but not in KRAS-WT cancer cells (69).

8. Conclusions

The current review has summarized that miR-126 is a tumor suppressor and its low levels in DSC tissues are associated with tumor development and progression. Therefore, restoring or increasing miR-126 levels is a promising therapeutic strategy for DSCs. However, the difficulty in transporting miR-126 to target sites may be a limitation until safe and effective vectors are developed. In addition, the aberrant serum levels of miR-126 in patients with DSCs may serve as predictive or diagnostic biomarkers.

miR-126 can also act as an oncogene in specific DSCs. Regardless of its function, it exerts its modulatory effects via different target genes and regulatory pathways with associated functions. Considering the significance and complexity of miR-126 and its regulatory network in DSCs, it is essential to further investigate the role of miR-126 in the initiation and progression of different cancer types to identify potential clinical applications.

Availability of data and materials

Not applicable.

Authors' contributions

MH wrote the manuscript. SX made the tables and diagrams. QC, and SZ checked and revised the manuscript; XZ put forward the concept, and was responsible for the organization, revision and submission of this manuscript. All authors 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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