Gastrointestinal (GI) cancers are among the main reasons for cancer death globally. The deadliest types of GI cancer include colon, stomach, and liver cancers. Multiple lines of evidence have shown that angiogenesis has a key role in the growth and metastasis of all GI tumors. Abnormal angiogenesis also has a critical role in many non-malignant diseases. Therefore, angiogenesis is considered to be an important target for improved cancer treatment. Despite much research, the mechanisms governing angiogenesis are not completely understood. Recently, it has been shown that angiogenesis-related non-coding RNAs (ncRNAs) could affect the development of angiogenesis in cancer cells and tumors. The broad family of ncRNAs, which include long non-coding RNAs, microRNAs, and circular RNAs, are related to the development, promotion, and metastasis of GI cancers, especially in angiogenesis. This review discusses the role of ncRNAs in mediating angiogenesis in various types of GI cancers and looks forward to the introduction of mimetics and antagonists as possible therapeutic agents.

INTRODUCTION

Gastrointestinal (GI) cancers are among the key reasons for cancer mortality worldwide. Colon, liver, and stomach cancer are the most common types of GI cancer, causing the most deaths. Although the worldwide cancer statistics show that pancreatic ductal adenocarcinoma (PDAC) and esophageal cancer are less common than other GI cancers, the incidence of pancreatic and esophageal cancer as compared to liver and stomach cancer depends on the region. Oncogenic mutations are likely to occur in GI tissues (intestines, stomach, and liver) because the epithelial cells are rapidly turned over. Unfortunately, some GI cancers do not show any symptoms in the early stages. This means that diagnosis often occurs at late stages, which reduces the effectiveness of therapy. Therefore, there is a need to generate newer and more efficient therapeutic approaches to increase patients’ survival. In recent years, many attempts to identify the main mutations in GI cancer cells have been carried out, with the aim to design more effective drugs. Despite some successes in newer therapeutic approaches, GI cancers remain life-threatening diseases. Considering its fundamental role in cancer growth and metastasis, angiogenesis has become an attractive target in cancer therapy.

ANGIOGENESIS AND GI CANCERS

The expression of VEGF-A is upregulated in colorectal cancer and is associated with colorectal cancer metastasis and shorter patient survival. VEGF-A, the first VEGF member to be characterized, was the basis for the development of anti-angiogenesis as a therapeutic strategy, including the clinical development of bevacizumab, a humanized monoclonal antibody targeting VEGF-A. In a pivotal clinical trial, the use of bevacizumab in combination with irinotecan, 5-fluorouracil, and leucovorin was shown to improve the survival of patients with metastatic colorectal cancer (mCRC), resulting in its approval as the first antiangiogenic therapy. VEGF-A expression is associated with hematogenous and lymphatic spread, greater microvessel density (MVD), and a poor prognosis in gastric cancer (GC). Higher VEGF-A expression in pancreatic cancer is correlated with cancer progression, higher metastatic risk, and poor prognosis. Fibroblast growth factor (FGF) is a family composed of 20 different molecules, which have various biological functions, including the stimulation of angiogenesis. FGF-1 and FGF-2 are the most studied with regard to angiogenesis. The functioning of FGFs is mediated through tyrosine kinase receptors (FGFR1–FGFR4). Endothelial cells express FGFR-1; however, small amounts of FGFR-2 have also been reported in endothelial cells. Activation of FGFR can induce the migration, growth, and tube formation of endothelial cells. Many cancer cell lines secrete FGF-1 and FGF-2. It has been found that the concentration...
of FGF-2 is increased in the urine of patients with various cancers.\(^{31,32}\) FGFs were upregulated in blood samples of patients with colorectal cancer.\(^{33}\) FGFs can increase invasion and proliferation in colon cancer cells.\(^{34}\) In colorectal cancer patients, higher FGF-2 levels were associated with an elevated risk of metastasis.\(^{35}\) It was reported that there was a positive correlation between levels of FGF expression and stage D of colorectal cancer.\(^{36}\) FGF was upregulated in GC surgical samples.\(^{39}\) It was also reported that FGFs play a role in cancer cell resistance to chemotherapy.\(^{37}\) In addition, serum FGF-2 levels had a predictive value for progression of disease in untreated metastatic colorectal cancer.\(^{38}\) GFR was upregulated in GC surgical samples.\(^{39}\) It was found that there was a positive association between high expression of FGF and invasion of GC cells\(^{40}\) and lymph-node metastasis.\(^{41}\) The expression of FGF-2 in GC could predict recurrence after resection.\(^{42,43}\) FGFs have a role in angiogenesis in pancreatic cancer.\(^{44–46}\) It was found that the level of FGF could be used for prediction of patient survival and risk of metastasis.\(^{47}\) Despite much research, the mechanisms governing dysfunctional angiogenesis are not completely understood. Recently, a number of angiogenesis-related non-coding RNAs (ncRNAs) have been investigated, and they have been found to affect the development of angiogenesis in cancer cells and tumors.\(^{48}\)

### ANGIGENESIS-RELATED ncRNAs AND GI CANCERS

ncRNAs are generated via the transcription of various sections of the genome. MicroRNAs (miRNAs or miRs) are an important group of ncRNAs, estimated to be able to regulate 40%–90% of the human genome.\(^{49}\) miRNAs and long non-coding RNAs (IncRNAs) can modulate gene expression at the transcriptional as well as post-transcriptional levels. They can also act as epigenetic regulators. It has been found that ncRNAs can inhibit the translation of mRNAs. Moreover, ncRNAs can regulate many biological pathways and subsequently alter the cell fate by stimulating or inhibiting the expression of specific genes.\(^{50,51}\)

Recently, many basic research studies have attempted to identify the mechanisms of disease pathogenesis using both living organisms and also \textit{in vitro} and \textit{in silico} systems. These investigations have demonstrated that ncRNAs can play critical functions, for instance in pancreatic cancer development. It has been revealed that miRNAs can affect cancer cell proliferation, migration, invasion, and metastasis.\(^{49,52}\)

### ANGIGENESIS-RELATED microRNAs IN GI CANCER

miRNAs are single-stranded non-coding RNAs, which contain 20–22 nucleotides.\(^{53}\) miRNAs are transcribed from their specific genes by RNA polymerase II and III, to generate pri-miRNAs (primary miRNAs), which are then cleaved by the Drosha enzyme to form pre-miRNAs (precursor miRNAs).\(^{34,55}\) Pre-miRNAs have a hairpin-like structure, which is cleaved when transported from inside the nucleus into the cytoplasm as a miRNA duplex by the Dicer enzyme to form the mature miRNA structure, which is the active form of miRNA.\(^{56,57}\) The less-stable strand of the miRNA duplex is normally incorporated into the RISC (miRNA-induced silencing complex) in order to regulate protein expression (Figure 2). This regulation is often accomplished by hybridization of the miRNA to the 3’ untranslated region (UTR) of the sequence of its target mRNA.\(^{58,59}\)

### Angiogenesis-related microRNAs in colon cancer

miR-145 works in concert with the tumor suppressor p53 and is post-transcriptionally activated by upregulated p53.\(^{60}\) miR-145 was first found to be downregulated in colorectal cancer, and then the deregulation of this miRNA was found in lung, breast, ovarian, bladder, nasopharyngeal, prostate, and GC.\(^{61–63}\) Moreover, miR-145 has a role in smooth muscle cell flexibility and development.\(^{64}\) Xu et al.\(^{55}\) investigated the effects of miR-145 and its targets, p70S6K1, VEGF, and HIF-1, on angiogenesis in colon cancer. They display that miR-145 lowered in ovarian and colon cancer. The expression of p70S6K1 (ribosomal protein S6 kinase beta-1) is post-transcriptionally suppressed by miR-145. HIF-1 and VEGF, which are the downstream mediators of p70S6K1, were decreased by upregulation of miR-145. Exogenous P70S6K1 rescues the miR-145 suppression of VEGF and HIF-1 levels and restores tumor angiogenesis and tumorigenesis. There is therefore an inverse association between the level of miR-145 and p70S6K1 in colon cancer.\(^{65}\)

miRNA-27b is located on chromosome 9\(^{66}\) and has a role in angiogenesis by increasing endothelial sprouting.\(^{57,66}\) miR-27b plays a role as a tumor repressor by targeting PPAR\textgamma (PPAR\gamma) in neuroblastoma, although the function of miR-27b, as well as its target in colon cancer, is not completely clear. In one study, Ye et al.\(^{59}\) assessed the association between miR-27b and VEGF-C in angiogenesis in colorectal cancer. The expression of miR-27b was downregulated in CRC, and the high expression of miR-27b inhibited tumor growth, cell proliferation, and colony formation. They reported that miR-27b could act as a tumor repressor and inhibit angiogenesis by targeting VEGF-C in colorectal cancer. They also found that DNA hyper-methylation of the CpG islands in miR-27b reduced its expression.\(^{69}\)

miR-590-5p is one of the newly identified microRNAs, whose functions are not completely understood. However, some studies have
shown that this miRNA was downregulated in colorectal cancer. It could also act as an oncogene in cervical cancer but as a tumor suppressor in renal cell cancer.\textsuperscript{70,71} It is thought that the direct target of miR-590-5p is the mRNA of the transcription factor family NF90, which is transcribed from the ILF3 gene.\textsuperscript{72} The specific protein isoforms are NF90 and NF110. NF90 is about 90 kDa and is also known as NFA1 or DRBP76. NF110 is about 110 kDa and is also known as NFA2, TCP110, or ILF3.\textsuperscript{72} NF90 and NF110 are different at the C terminus but homologous in the central region and the N terminus.\textsuperscript{72} NF90 was purified as a DNA binding complex that regulated the IL2 promoter.\textsuperscript{73} NF90 has many functions, such as in protein translation from mRNAs, controlling mitosis, RNA processing, and host resistance to infection.\textsuperscript{74} It was also implicated in the occurrence of angiogenesis of breast cancer. Moreover, the NF90/NF45 complex regulated E6 expression in cervical cancer.\textsuperscript{75} Zhou et al.\textsuperscript{76} studied the effects of miR-590-5p, NF90, and VEGF on angiogenesis in colon cancer. The deletion of miR-590-5p in vivo enhanced colorectal cancer progression, while its high expression suppressed tumor growth, angiogenesis, and lung metastasis. NF90 participates in regulating VEGF protein synthesis and is a target of miR-590-5p. High expression of NF90 restored angiogenesis and VEGFA expression. NF90-shRNA reduced tumor development, and the deletion of NF90 decreased the pri-miR-590 and increased miR 590 5p.\textsuperscript{76}

miR-19a and miR-19b are about 96% identical to each other and only differ by one nucleotide at position 11. They have a role in some cellular processes and tumor progression.\textsuperscript{77,78} Chen et al.\textsuperscript{79} investigated the effects of miR-19a and its target, KRAS, on angiogenesis in colon cancer. They generated a KRAS 3’ UTR-Mut by removing the predicted binding site for miR-19a within KRAS. miR-19a inhibited the expression of the gene containing the wild-type KRAS 3’ UTR in HCT116 cells, but the cells with mutant KRAS 3’ UTR were not affected by miR-19a. The high expression of miR-19a decreased the expression of KRAS. In a vascular tube formation assay, the high expression of miR-19a produced anti-angiogenesis effects, which could be rescued via expression of KRAS. They also used a nude mouse xenograft model to study the in vivo function of miR-19a in solid tumors. Findings showed that the density of blood vessels and the size of the xenograft tumors grown from HCT116 cells that overexpressed miR-19a were lower in comparison with the controls. Moreover, the levels of VEGF-A and KRAS were decreased.\textsuperscript{79}

CXCR4 is a constituent of the GPCR family that is expressed in some epithelial cancers, where it increases proliferation, migration, and angiogenesis.\textsuperscript{80–82} Deletion of CXCR4 suppressed CXCL12-induced angiogenesis via downregulating PI3K-AKT, MAPK-ERK, and Wnt-β-catenin signaling pathways.\textsuperscript{83} In a recent study, Fang et al.\textsuperscript{84} assessed the effects of miR-622, CXCR4, and VEGFA on angiogenesis in colorectal cancer. In vitro studies showed that the high expression of miR-622 suppressed angiogenesis in CRC and the proliferation, migration, tube formation, and invasion of human umbilical vein endothelial cells (HUVECs). Moreover, the higher expression of miR-622 inhibited angiogenesis in CRC tumors in vivo, as detected via the quantification of VEGF-A and Ki67 levels and microvessel density. CXCR4 is a target of miR-622, and higher expression of CXCR4 reversed the VEGFA suppression by miR-622 and also restored the angiogenesis that had been inhibited by miR-622.\textsuperscript{84}

Table 1 lists some different angiogenesis-related miRNAs that have been shown to participate in colorectal cancer.

**Angiogenesis-related microRNAs in pancreatic cancer**

It has been shown that miR-139 can suppress proliferation, migration, and metastasis in some types of cancer.\textsuperscript{89} miR-139 was highly expressed in pancreatic cancer endothelial cells (CECs). Li et al.\textsuperscript{100} studied the effects of miR-139 and CXCR4 on angiogenesis in pancreatic cancer. Quantitative polymerase chain reaction (qPCR) analysis was applied to quantify the expression pattern of miR-139. The effects of miRNA expression on CEC proliferation, migration, and tube formation were evaluated after transfecting with a specific miRNA suppressor. The expression of fourteen miRNAs was enhanced more than 20 times in the CECs obtained from pancreatic cancer patients. Among these, miR-200c and miR-139 were most overexpressed in CECs. Transfection with inhibitors of miR-200c or miR-139 decreased migration of CECs (all p < 0.05). The average tube length and proliferation were reduced after miR-200c and miR-139 inhibition in three CEC cultures (all p < 0.05).\textsuperscript{100}

BCL2L1 and BCL-xL are members of the BCL-2 family\textsuperscript{101} that inhibit apoptosis and autophagy in cancer cells. BCL2L1, also known as
Bim, has the opposite function and can stimulate apoptosis by inhibiting BCL2 and BCL-xL. Bim is a pro-apoptotic protein located in the outer mitochondrial membrane, where it promotes the apoptotic cascade. The role of Bim in pancreatic cancer remains somewhat unclear. Liu et al. assessed the effects of the miR-24-Bim pathway on angiogenesis in pancreatic cancer. Expression of miR-24 resulted in lower expression of Bim. miR-24 enhanced tumor development and angiogenesis in vivo by inhibiting Bim expression.

AGTR1 is expressed in several cancers, such as ovarian carcinoma. Suppression of AGTR1 decreased angiogenesis and cell survival via reducing VEGF expression. AGTR1 and angiotensin II have functions in endometrial tumor development by inducing VEGF. Moreover, AGTR1 is upregulated in breast cancer. Inhibition of AGTR1 suppressed proliferation as well as causing G1/S cell cycle arrest. In breast cancer, AGTR1 enhanced invasion, migration, and metastasis and also stimulated angiogenesis by increasing VEGF-A expression. Guo et al. demonstrated the effects of miR-410, AGTR1, and CD31 on angiogenesis in pancreatic cancer. AGTR1 is a target of miR-410, which inhibits its expression, and, conversely, the suppression of miR-410 enhances the AGTR1 expression. Overexpression of miR-410 inhibited cell invasion and growth by reducing AGTR1. In addition, the expression of VEGF and ERK signaling activation were both blocked by miR-410. This was similar to the action of losartan, which acts as an angiotensin II inhibitor. miR-410 blocked the induction of the VEGF and ERK pathways via stimulating angiotensin II. The high expression of miR-410 suppressed angiogenesis in vivo by inhibition of CD31. The deletion of the ERK signaling pathway inhibited angiogenesis, cell invasion, and proliferation in pancreatic cancer. Downregulation of miR-410 was detected in

| microRNA | Expression change in CRC | Target | Inhibit or induce angiogenesis | Model (in vivo, in vitro, human) | Cell line | Reference |
|----------|--------------------------|--------|--------------------------------|-------------------------------|-----------|-----------|
| miR-1    | down                     | VEGF   | inhibit                        | in vitro, human              | HT-29, HCT-116, ClonA1, CL-187, SW-620 | Zhu et al. |
| miR-622  | up                       | CXCR4, VEGFA | inhibit                              | in vitro, in vivo             | Caco-2, HT-29 | Fang et al. |
| miR-19a  | up                       | KRAS   | inhibit                        | in vitro                     | HCT116   | Chen et al. |
| miR-6868-5p | down                | FOXM1  | inhibit                        | in vitro                     | HCT8     | Wang et al. |
| miR-125a-3p | up                     | FUT5, FUT6 | inhibit                              | in vitro, human              | SW480, SW620 | Liang et al. |
| miR-590-5p | down                  | NP90, VEGFA | inhibit                              | in vitro, in vivo, in vivo   | HT29, SW620, LOVO, SW480, HCT116 | Zhou et al. |
| miR-17–92 | up                      | GFRB2, HIF1α, VEGFA | induce                               | in vivo, in vitro             | HCT116   | Ma et al. |
| miR-145-5p | down                  | Cx43   | inhibit                        | in vitro                     | SW480    | Thurmenger et al. |
| miR-126  | down                     | VEGF   | inhibit                        | in vitro, human              | LoVo, HT29, SW480, SW620, NW116, HCT116 | Zhang et al. |
| miR-27b  | down                     | VEGF/PC | inhibit                        | in vitro, human              | SW620, SW480, RKO, HT29, 293T | Ye et al. |
| miR-488-5p | up                     | BMPR1A | inhibit                        | in vitro, in vivo, human      | HCT116, SW620, HCT8, HT29, SW480, DLD-1, FHIC | Chen et al. |
| miR-150-5p | down                  | VEGF   | inhibit                        | human, in vitro, in vivo      | SW1116   | Qian et al. |
| miR-143  | down                     | IGF-1R | inhibit                        | human, in vitro, in vivo      | HeLa, HCT116 | Yamakushi et al. |
| miR-107  | up                       | VEGF, HIF-1b | inhibit                               | human, in vitro, in vivo      | SW1116, SW480 | Xu et al. |
| miR-145  | down                     | p70S6K1, VEGF, HIF-1 | inhibit                              | human, in vitro, in vivo      | SW1116, SW480 | Li et al. |
| miR-318-5p | down                  | MMP-14 | inhibit                        | in vitro, in vivo             | HT-29, LoVo, HCT116, RKO, SW620 | Wei et al. |
| miR-503-5p | down                  | VEGF-A | inhibit                        | in vitro, in vivo, human      | SW620, LoVo, RKO, HT-29, HCT116 | Yan et al. |
| miR-182-5p | down                  | VEGF-C | inhibit                        | in vitro, in vivo, human      | HT-29, COLO205 | Li et al. |

Table 1. Angiogenesis-related miRNAs in colon cancer

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Table 2. Angiogenesis-related miRNAs in pancreatic cancer

| microRNA | Expression in pancreatic cancer | Target (in vivo, in vitro) | Effect on angiogenesis (inhibit/induce) | Model (in vivo, in vitro, human) | Type of cell line | Reference |
|----------|---------------------------------|---------------------------|---------------------------------------|---------------------------------|-------------------|-----------|
| miR-139  | up                              | CXC4                      | inhibit                               | human                           | PANC-1, HUVEC     | Li et al.108 |
| miR290c  | up                              | VEGF                      | inhibit                               | human                           | PANC-1, MIA-PaCa-2 | Li et al.109 |
| miR-24   | up                              | Bim                       | induce                                | in vivo, in vivo                 | PANC-1, MIA-PaCa-2 | Fan et al.117 |
| miR-410  | down                            | AGTR1                     | inhibit                               | in vivo, in vivo, human          | PANC-1, MIA-PaCa-2 | Guo et al.109 |
| miR-454  | up                              | LRP6                      | inhibit                               | in vivo, in vivo                 | PANC-1, MIA-PaCa-2 | Fan et al.117 |
| miR-301a | up                              | SOCS5                     | induce                                | in vivo, in vivo                 | PANC-1, BXPC3     | Hu et al.114 |

miR-454 acts as an oncogene in several cancers, such as uveal melanoma and non-small cell lung cancer. Fan et al.117 investigated the effects of miR-454 and LRP6 on angiogenesis in PDAC. Human pancreatic cancer cell lines (PANC-1 and MiaPaCa-2 cells) were transfected with a miR-454-expressing plasmid and assayed for colony formation, cell proliferation, pro-angiogenic markers, cell cycle, and invasion. The effect of miR-454 overexpression on lung metastasis of PDAC was investigated in vivo. The high expression of miR-454 suppressed colony formation, cell invasion, and proliferation and arrested the cells at the G2/M stage. miR-454-overexpressing PANC-1 cells contained low levels of VEGF and had a lower ability to induce endothelial cell tube-like formation. LRP6 is a target of miR-454, which can suppress the Wnt/β-catenin pathway activation in PDAC. Ectopic expression of LRP6 reversed the inhibitory effects of miR-454 in PDAC.117

Table 2 lists some angiogenesis-related miRNAs involved in pancreatic cancer.

Angiogenesis-related microRNAs in hepatocellular carcinoma (HCC)

miR29a/b/c are members of the miR-29 family. They are broadly similar to each other, but they have some differences in the target sequence they recognize. They are generally downregulated in HCC. Some articles have shown that miR-29 has an inhibitory effect on apoptosis, migration, proliferation, and invasion of non-HCC tumor types.119-121 The miR-29b levels were inversely associated with MMP-2 expression, as well as invasion, metastasis, and angiogenesis. Activation of the MMP-2 enzyme causes degradation of the extracellular matrix (ECM), which then promotes the metastasis and invasion of tumors.122 MMP-2 accelerates ECM remodeling and the secretion of ECM-bound growth factors, which can promote the proliferation and migration of ECs. Generally, the overexpression of MMP-2 is observed in HCC.123,124

Fang et al.125 investigated the effects of miRNA-29b and MMP-2 on angiogenesis in HCC. They studied the effects of miR-29b on tumor invasion, metastasis, and angiogenesis using Transwell assays and capillary tube formation. Human tumor samples, a Matrigel plug assay, and in vivo subcutaneous xenograft tumor growth were used. Loss- and gain-of-function experiments demonstrated that miR-29b inhibited the ability of tumor cells to enhance the formation of endothelial cell capillary tubes and Matrigel invasion. They showed that tumors originating from miR-29b-expressing HCC cells had a lower intrahepatic metastatic capacity and lower microvessel density in mouse models. Experiments showed that MMP-2 was a target of miR-29b. The removal of MMP-2 using a neutralizing antibody or an RNA interference approach duplicated the anti-invasion and anti-angiogenesis properties of miR-29b. They suggested that miR-29b exerted its anti-angiogenic activity by inhibiting the expression of MMP-2 in tumor cells and suppressing VEGFR-2 signaling in endothelial cells.123

Bentwich et al.126 identified miR-503 for the first time, which was confirmed by Sewer et al.127 and cloned by Landgraf et al.128 The miR-503 gene is situated on chromosome Xq26.3, and the targets of miR-503 in ECs were found to be cdc25A (cell division cycle 25 homolog) and CCNE1 (G1/S-specific cyclin-E1). miR-503 inhibits endothelial cell function in diabetes mellitus and could promote reparative angiogenesis following limb ischemia.129 However, the functions of miR-503 in angiogenesis and cancer development are not completely clear.
In 2013, Zhou et al. assessed the effects of miR-503, FGF2, and VEGF on angiogenesis in HCC. miR-503 overexpression lowered angiogenesis in vitro, while in vivo the expression of miR-503 was decreased by HIF1α. VEGF and FGF2 are both targets of miR-503 in cancer; therefore, miR-503 plays an anti-angiogenic role in tumorigenesis. The latter suggested a new mechanism for hypoxia-induced VEGF and FGF2 via HIF1α-induced suppression of miR-503.

Sphingosine kinase 1 (SPHK1) is an enzyme that produces sphingosine-1-phosphate (S1P) and participates in the control of sphingolipid metabolism. SPHK1 can enhance breast cancer tumorigenesis via increasing S1P and inducing angiogenesis. The SPHK1/SIP/SIP-receptor axis was confirmed to participate in the angiogenesis associated with liver fibrosis. Lu et al. investigated the effects of SPHK1 and miR-506 on angiogenesis in HCC. Database analysis demonstrated that miR-506 could target the 3’UTR of SPHK1. Using reverse transcriptase-PCR and western blotting, they revealed that miR-506 decreased the protein and mRNA expression of SPHK1. The overexpression of miR-506 in HepG2 cells decreased the SIP content in the supernatant. This supernatant suppressed HUVEC tube formation and decreased angiogenesis. The supernatant from HepG2 cells with high expression of SPHK1 reversed the suppression of angiogenesis. The use of anti-miR-506 increased the S1P production in the supernatant from HepG2 cells and decreased angiogenesis. The supernatant from HepG2 cells with high expression of SPHK1 reversed the suppression of angiogenesis.

miR-146a has a role in several cancers and can regulate the immune system, such as antiviral activity and inflammatory response. The relatively high expression of miR-146a was observed in papillary thyroid carcinoma and could be related to loss of the KIT transcript and Kit protein. miR-146a could also enhance proliferation in cervical cancer. Zhu et al. studied the effects of miR-146a and PDGFRA on angiogenesis in HCC. They examined the miR-146a expression in HUVECs in the presence or absence of HCC cells. PDGFRA is a miR-146a target, and this miRNA could increase angiogenesis by enhancing PDGFRA in HCC. They also found that miR-146a increased expression of PDGFRA in HUVECs via affecting BRCA1. High expression of PDGFRA in HCC clinical samples was correlated with microvascular invasion and predicted a poor prognosis.

miR-126 has a role in cancers by modulating migration, invasion, and proliferation. miR-126 is known to be a tumor suppressor, preventing proliferation and enhancing apoptosis in HCC cells. Gong et al. investigated the effects of EGFL7 and miR-126 on angiogenesis in HCC. Western blotting and qRT-PCR were used to determine the levels of EGFL7, miR-126, Fas/FasL, ERK, caspase mRNA, and Bcl-2 expression. TUNEL and Cell Counting Kit 8 assays were used to measure apoptosis and proliferation. Flow cytometry was applied to examine cell cycle distribution. A rat model of HCC was established, and the quantity of new blood vessels and tumor weight were measured at 3 weeks post-tumor transplantation. miR-126 was downregulated in HCC, whereas the levels of ERK mRNA and protein and EGFL7 were increased. The high expression of miR-126 inhibited P-ERK, ERK, Bcl-2, and EGFL7 and also enhanced the apoptosis-related proteins caspase-3 and Fas/FasL and suppressed proliferation. Overexpression of miR-126 in nude mice produced fewer blood vessels and reduced the tumor weight. Suppression of miR-126 reduced apoptosis and increased angiogenesis and proliferation.

Table 3 lists some different angiogenesis-associated miRNAs in HCC.

### Angiogenesis-related microRNAs in GC

miR-125a is located in chromosome 19q13, and its expression has been found to be low in several cancers, such as breast, ovarian, and lung cancer and medulloblastoma. In GC, lower expression of miR-125a was correlated to indicators of malignancy, such as tumor invasion and size.

Dai et al. assessed the effects of VEGF-A and miR-125a on angiogenesis in GC and reported that miR-125a could affect VEGF-A expression. Low expression of miR-125a enhanced the release of VEGF-A and also increased Akt phosphorylation in HUVECs, angiogenesis, EC migration, and proliferation. miR-125a expression was reduced in GC and was negatively associated with VEGF-A expression (p < 0.05). miR-125a expression was inversely correlated to the microvessel density in vivo.

VEGF-A has an important function in the regulation of angiogenesis. In addition, levels of VEGF-A are correlated with enhanced tumor aggression and decreased survival in patients.

Xie et al. investigated the effects of miR-1 and VEGF-A on angiogenesis in GC. They evaluated the expression of miR-1 in GC cell lines and the clinicopathological features in 90 paired GC and normal stomach samples. Proliferation and migration assays were used to detect the effects of miR-1 in GC cells. Protein array and bioinformatic analysis was used to identify the miR-1 target. qPCR, ELISA, EC tube formation, and western blotting were used to assess the regulation mechanisms of miR-1. A reporter assay was also used to confirm the presumed binding site of miR-1 on target genes. miR-1 was downregulated in GC specimens. Patients with lower expression of miR-1 had a poor survival compared with those with higher expression of miR-1 (p = 0.0027). miR-1 overexpression in GC suppressed proliferation, EC tube formation, and migration via inhibiting the expression of EDN1 and VEGF-A. Suppression of miR-1 by an antagonist decreased EDN1 and VEGF-A expression in low-malignant GC or non-malignant GC samples.

The PI3K/mTOR signaling pathway is dysregulated in various cancers. Elements of the AKT/PI3K/mTOR signaling pathway can be mutated or dysregulated in cancer, causing hyper-activation of the pathway and affecting chemosensitivity, apoptosis, proliferation, and other biological processes.

Wu et al. assessed the effects of miR-616-3p and the AKT/PI3K/mTOR pathway on angiogenesis in GC. They found that the miR-616-3p was overexpressed in GC and was correlated with a poor prognosis. Also, loss-of-function and gain-of-function studies showed that...
miR-616-3p increased angiogenesis and triggered the epithelial-mesenchymal transition (EMT) in GC.176

The mammalian GI tract secretes members of the trefoil factor family, which are a group of small-molecular-weight polypeptides.177 TFF1 is a member of the trefoil peptide family, which suppresses GI tumorigenesis. The expression of TFF1 is high in the normal human stomach, where it acts to preserve gastric epithelial function and structure.178

Shi et al.179 investigated the effects of miR-632 and TFF1 on angiogenesis in GC using serum samples and GC tissues to measure the expression of miR-632 with real-time PCR. A dual-luciferase reporter assay was performed to examine how miR-632 controlled the TFF1 expression. Endothelial cell recruitment and tube formation assays also were used with or without miR-632 treatment. Moreover, in situ hybridization assays and western blotting were used to determine markers of endothelial migration and angiogenesis. miR-632 expression was high in GC and inversely correlated with its target TFF1. miR-632 stimulated EC recruitment and tube formation, while recombinant TFF1 reversed the miR-632-induced angiogenesis.179

Table 3. Angiogenesis-associated miRNAs in hepatocellular carcinoma

| microRNA | Expression in HCC | Target | Effect on angiogenesis (inhibit/induce) | Model (in vitro, in vivo, human) | Type of cell line | Reference |
|----------|------------------|--------|----------------------------------------|---------------------------------|------------------|-----------|
| miR-1301 | down BCL9        |        | inhibit                                | in vitro, in vivo, human        | Hep3B, HepG2, SMMC-7721, Huh-7 | Yang et al.147 |
| miR-26b-5p| down VE-cadherin, snail, MMP2 |        | inhibit                                | in vitro, in vivo               | BeL402, SMMC7721, HepG2, PLC, LO2 | Wang et al.156 |
| miR-199a-3p| down VEGFA, VEGFR2, VEGFR1, HGF, MMP2 |        | inhibit                                | in vitro, in vivo               | HepG2, SNU449 | Ghosh et al.149 |
| miR-203a | up HOXD3, VEGFR  |        | inhibit                                | in vitro, in vivo               | SMMC-7721, Hep3B | Ghosh et al.149 |
| miR-144-5p| down SGK3        |        | inhibit                                | in vitro, in vivo, human        | PLC/PREF5, SMMC7721, HepG2, Huh7, SK-HEP-1, Hep3B | Wu et al.150 |
| miR-497  | down VEGFA, AEG-1|        | inhibit                                | in vitro, human, in vivo        |                   |           |
| miR-142  | down TGF-β       |        | inhibit                                | in vitro, human                 | HepG2, SMMC-7721 | Yu et al.152 |
| miR-126  | up EGFL7         |        | inhibit                                | in vitro, in vivo, human        | MMC-7721, MHCC-97H, HCCLM3 | Yu et al.152 |
| miR-338-3p| down MACC1, VEGF, β-catenin |        | inhibit                                | in vitro, human                 | Hep3B, Huh7, HepG2, Bel-7402, HEK293T | Zhang et al.153 |
| miR-638  | down VEGF        |        | induce                                 | in vitro, in vivo, human        | Hep3B, SMMC-7721, HepG2, MHCC-97L, MHCC-97H | Cheng et al.154 |
| miR-126  | down EGFL7       |        | inhibit                                | in vitro, in vivo, human        | HepG2, Bel-7402, SMMC-7721 | Gong et al.156 |
| miR-210  | up FGFR1         |        | induce                                 | in vitro, in vivo, human        | SK-HEP-1, HCC-LM3 | Yang et al.157 |
| miR-182  | up RASAI         |        | induce                                 | in vitro, human                 |                     | Du et al.156 |
| miR-126  | down Sprd1       |        | inhibit                                | in vitro, in vivo, human        | HUVECs |                     |
| miR-26a  | down HGF         |        | inhibit                                | in vitro, human, in vivo        | HepG2, SMMC-7721, BEL-7402 | Yang et al.154 |
| miR-126-3p| down LRPI6, PK3R2|        | inhibit                                | in vitro, human                 | MHCC-97L, Huh-7, QGY-7703, MHCC-97H, SMMC-7721 | Wang et al.150 |
| miR-195  | down VEGF, VAV2, CDC42 |        | inhibit                                | in vitro, human, in vivo        | cell line missing | Cao et al.161 |
| miR-302a/b/c| down MACC1     |        | inhibit                                | in vitro, in vivo, human        | HepG2 | Chai et al.162 |
| miR-26a  | down VEGFA       |        | induce                                 | in vitro, in vivo, human        | HCCLM3 | Zhu et al.141 |
| miR-146a | up PDXGFA        |        | induce                                 | in vitro, human                 | HepG2 | Lu et al.128 |
| miR-506  | down SPHK1       |        | inhibit                                | in vitro, human                 | HepG2 |                        |
| miR-98 and miR-214| down VEGF, Ang-1, MMP-2 | | inhibit | in vitro, human | Hep2 | Yabha et al.163 |
| miR-375  | up PDXGFC        |        | inhibit                                | in vitro, human                 | Hep3B, HepG2, Huh1, Huh7 | Li et al.156 |
| miR-503  | down FGFR2, VEGFA|        | inhibit                                | human, in vitro, in vivo        | HepG2, LO2 | Zhou et al.150 |
| miR-29b  | down MMP-2       |        | inhibit                                | human, in vitro, in vivo        | Hep3B | Fang et al.125 |
| miR-200b | down ERG         |        | induce                                 | in vitro, human                 |                   | Moh-Moh-Aung et al.165 |

miR-616-3p increased angiogenesis and triggered the epithelial-mesenchymal transition (EMT) in GC.176

The mammalian GI tract secretes members of the trefoil factor family, which are a group of small-molecular-weight polypeptides.177 TFF1 is a member of the trefoil peptide family, which suppresses GI tumorigenesis. The expression of TFF1 is high in the normal human stomach, where it acts to preserve gastric epithelial function and structure.178

Shi et al.179 investigated the effects of miR-632 and TFF1 on angiogenesis in GC using serum samples and GC tissues to measure the expression of miR-632 with real-time PCR. A dual-luciferase reporter assay was performed to examine how miR-632 controlled the TFF1 expression. Endothelial cell recruitment and tube formation assays also were used with or without miR-632 treatment. Moreover, in situ hybridization assays and western blotting were used to determine markers of endothelial migration and angiogenesis. miR-632 expression was high in GC and inversely correlated with its target TFF1. miR-632 stimulated EC recruitment and tube formation, while recombinant TFF1 reversed the miR-632-induced angiogenesis.179

RUNX1, RUNX2, and RUNX3 are members of the Runt family of transcription factors, with key roles in both normal tissue and
Cancers. RUNX3 has a role in T cell differentiation, neurogenesis within the dorsal root ganglia, and GC tumorigenesis. Lee et al. studied the effects of miR-495, miR-130a, and RUNX3 on angiogenesis in GC and employed bioinformatic and microarray analysis to measure the miR-130a and miR-495 expression. MiR-495 and miR-130a were both highly expressed in GC under hypoxic conditions. MiR-495 and miR-130a both suppressed the expression of RUNX3 at the protein level but not at the mRNA level. MiR-495 and miR-130a suppressed luciferase activity in a reporter assay for RUNX3-3′ UTR binding. MiR-130a and miR-495 reduced apoptosis as shown by annexin V-fluorescein isothiocyanate (FITC)/propidium iodide staining as well as flow cytometry. In SNU484 GC cells, the expression of miR-130a and miR-495 was associated with lower levels of RUNX3, p21, and Bim. Antagonistic miRs for miR-495 and miR-130a decreased angiogenesis, as shown by a Matrigel plug assay.

Table 4 lists some angiogenesis-related miRNAs reported to be involved in GC.

### Table 4. Angiogenesis-related miRNAs in gastric cancer

| microRNA     | Expression in gastric cancer | Target                  | Effect on angiogenesis (inhibit/induce) | Model (in vitro, in vivo, human) | Type of cell line                  | Reference                                      |
|--------------|------------------------------|-------------------------|-----------------------------------------|---------------------------------|------------------------------------|------------------------------------------------|
| miR-632      | up                           | TFF1                    | induce                                  | in vitro                        | BGC823, MGC803, EAhy926, MKN45    | Shi et al.                                    |
| miR-612      | down                         | FOXM1                   | inhibit                                 | in vitro, in vivo               | MKN-45, MKN-28, AGS, SGC-7901    | Wang et al.                                   |
| miR-616-3p   | up                           | PTEN/akt/mTOR pathway   | induce                                  | in vitro                        | KN-28, MGC-80, GES-1, HEK293 T, AGS, SGC-7901 | Wu et al.                                    |
| miR-532-5p   | down                         | LINC01410               | inhibit                                 | in vitro, in vivo               | MKN-45, SGC-7901, AGS, HGc-27, BGC-23, GES-1 | Zhang et al.                                 |
| miR-26a/b    | down                         | HGF VEGF                | inhibit                                 | in vitro, in vivo               | MKN-28, GES-1, AGS, HEK293 T, SGC-7901, MGC-80 | Si et al.                                    |
| miR-1        | down                         | EDN1 VEGF-A             | inhibit                                 | in vitro, in vivo               | SGC7901, MKN28, NCI-N87, BGC823, AGS, HGc-27 | Xie et al.                                   |
| miR-1228     | down                         | CK2A2                   | inhibit                                 | in vitro, in vivo               | AGS, SGC-7901, HEK293 T           | Jia et al.                                   |
| miR-218      | down                         | ROBO1                   | inhibit                                 | in vitro, in vivo               | BGC-823, HUVEC-2C, HMVEC         | Zhang et al.                                 |
| miR-520b/e   | down                         | EGFR                    | inhibit                                 | in vitro                        | SGC-7901, MGC-803                 | Li et al.                                    |
| miR-101, miR-27b, miR-128 | down                     | VEGF-C                  | inhibit                                 | in vitro, in vivo               | MKN-45, SGC-7901, BGC-823        | Liu et al.                                   |
| miR-125a     | down                         | VEGF-A                  | inhibit                                 | in vitro, human                | GES-1, AGS, SGC-7901, BGC-823, HUVEC | Dai et al.                                   |
| miR-130a, miR-495 | up                          | RUNX3                   | induce                                  | in vitro                        | SNU5, SNU16, SNU484, MKN45, MKN1 | Lee et al.                                   |
| miR-506      | down                         | ETS1                    | inhibit                                 | in vitro, human                | AGS, SGC-7901, Kato-III, MKN45, BGC-823, HGc-27, MGC-803 | Li et al.                                   |
| miR-874      | down                         | 3′ UTR of STAT3         | inhibit                                 | in vitro, human                | AGS, BGC823, MKN28, SGC-7901, GES-1 | Zhang et al.                                 |
| miR-126      | down                         | VEGF-A                  | inhibit                                 | in vitro, in vivo, human        | SGC-7901, MKN-28, MKN-45          | Chen et al.                                  |
| miR-29a/c    | down                         | VEGF                    | inhibit                                 | in vitro, human                | HUVE, SGC790, HEK293T            | Zhang et al.                                 |
| miR-135a     | down                         | focal adhesion kinase (FAK) | inhibit                               | in vitro, in vivo, human        | MGC-803, MKN45, SGC-7901, BGC-823, MKN1, GES-1 | Cheng et al.                                |
| miRNA-145    | down                         | 3′ UTR of Ets1          | inhibit                                 | in vitro, in vivo, human        | SGC-7901, GES-1, MKN45, HUVEC, AGS | Zheng et al.                                 |
| miR-616-3p   | up                           | PTEN                    | induce                                  | in vitro, human                | MGC-803, MKN-28, AGS, SGC-7901   | Wu et al.                                    |
| miR-506      | up                           | ETS1                    | inhibit                                 | in vitro, human                | Kato-III, SGC-7901, BGC-823, HGc-27, MKN45, MGC-803, AGS | Li et al.                                    |

Angiogenesis-related microRNAs in other GI cancers
The expression of miR-377 was low in esophageal squamous cell carcinoma (ESCC) cell lines and also in serum and tumor samples from...
ESCC patients. miR-377 is located in chromosomal region 14q32, which is sometimes obliterated in ESCC. The function of miR-377 in cancer is not yet completely clear. CD133 is a marker of tumor-initiating cells (TICs) or cancer stem cells, but the function of CD133 in ESCC is not completely clear, and it is uncertain whether CD133 is a TIC marker in ESCC. Li et al. investigated the effects of miR-377, CD133, and VEGF on angiogenesis in ESCC. miR-377 expression in ESCC was generally low, while the tumor tissue and serum levels of miR-377 were associated with patient survival. Up-regulation of miR-377 was inversely correlated with pathologic tumor stage, distant metastasis, resistance to radiotherapy and chemotherapy, and the amount of residual tumor. In the laboratory, high expression of miR-377 suppressed angiogenesis, metastasis, and proliferation in ESCC cell lines, while knockdown of miR-377 had the opposite effects. Furthermore, miR-377-targeted both VEGF and CD133 via binding to their 3’ UTRs. Systemic delivery of a formulated miR-377 mimic inhibited ESCC tumor development in nude mice, suppressed angiogenesis, and inhibited lung metastasis without any toxicity.

miR-143-3p plays a role in many cancers, including HCC, prostate cancer, lung cancer, and colorectal cancer. Downregulation of miR-143-3p is correlated with poor clinical outcomes. The VEGF family is composed of VEGFA, VEGFB, VEGFC, VEGFD, VEGGE, and PLGF. PLGF has a key role in several cancers, although its activity is limited in normal physiological processes. PLGF stimulates Flt-1 and also synergizes with VEGF effects. Several small-molecule inhibitors of VEGFR2 and VEGF, including cediranib, sunitinib, and vandetanib, have been approved for cancer therapy. Jin et al. studied the effects of miR-143-3p, ITGA6, and PLGF on angiogenesis in gallbladder carcinoma. They found that miR-143-3p was an inhibitor of tumor angiogenesis and development. ELISA, antibody arrays, and a PLGF rescue analysis showed that PLGF had a key role in the anti-angiogenic effects of miR-143-3p. Dual-luciferase assays and miRNA target-prediction software were used to demonstrate that ITGA6 functioned as a miR-143-3p target. Western blotting and ELISAs showed that PLGF expression was reduced via the ITGA6/AKT/PI3K pathway.

Table 5 lists some angiogenesis-related miRNAs in other GI cancers (ESCC and gallbladder cancer).

### IncRNA BIOGENESIS

IncRNAs are over 200 nt in length and are transcribed by RNA polymerase II (Pol II). More than 10,000 different IncRNAs have been estimated to exist in humans. All mammalian IncRNAs have similar functional, structural, and mechanistic properties. They usually can be spliced and have a poly-A tail. In addition, they can modulate target gene expression at the transcriptional or post-transcriptional levels and thereby affect many biological and cellular processes.

Spurlock et al. categorized IncRNAs according to the structural source (Figure 3). In overlapping IncRNAs, the protein-coding gene sequence is overlapped with the IncRNA intron. In divergent IncRNAs, the adjacent protein coding gene and the IncRNA are transcribed on opposite strands. In intronic IncRNAs, the entire sequence of the IncRNA is the same as the intron of a gene. In intergenic IncRNAs, the sequence of the IncRNA is distributed between two distinct genes. Intergenic IncRNAs can either be sense or antisense types, where the IncRNA sequence is located between the exons of a different transcript on the antisense/sense strand. Finally, enhancer RNAs can be transcribed in one sense (1D-eRNAs) or in two senses (2D-eRNAs) as genomic transcriptional enhancers, commonly situated near to protein-coding genes.

Numerous factors can regulate the function of IncRNAs. For example, RNA-binding proteins (RBPs) have been demonstrated as important regulators of IncRNAs. An important regulatory mechanism of IncRNAs is the post-transcriptional regulation by RBPs. Some cancer-associated IncRNAs have been found to be regulated by the interaction with RBPs, such as human antigen R (HuR), ARE/poly(U)-binding/degradation factor 1 (AUF1), insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), or tristetraprolin (TTP). Some IncRNAs can function as scaffolds during formation of subcellular structures, such as nuclear bodies. These nuclear bodies are formed by phase separation of RNA-binding proteins with a prion-like domain, low complexity region, or intrinsic disordered region. The scaffold ncRNAs forming these nuclear bodies are also referred to as architectural RNAs (arcRNAs). They can bind to and assemble RNA-binding proteins and thereby induce liquid-liquid phase separation. Moreover, it has been found that the functions of IncRNAs depend on their subcellular localization. By using RNA fluorescence in situ hybridization in human cell lines, a broad range of subcellular localization patterns, either in the nucleus or the cytoplasm, have been demonstrated. Nonetheless, it is usual to list IncRNAs based on their similar mechanisms of action (Figure 4). Some IncRNAs play a role in the nuclear structure by regulating the structure of nuclear interchromatin granules, paraspeckles, and speckles. Some other roles of nuclear IncRNAs are the regulation of gene expression via epigenetic activities as well as chromatin-
modification factors. In addition, some kinds of stable lncRNAs, as well as circular RNAs (circRNAs) and competing endogenous RNAs (ceRNAs), are located together within the cell, where they act as sponges or decoys to remove their target miRNAs and thereby alter gene expression. The ceRNA hypothesis suggests an intrinsic mechanism to regulate biological processes. However, whether the dynamic changes of ceRNAs can affect miRNA activities remains controversial. The ceRNA hypothesis postulates that RNAs that share miRNA response elements (MREs) in their 3' UTRs can influence the expression of miRNAs and induce gene silencing. Several recent studies have demonstrated that lncRNAs can contain MREs and interact with other RNA transcripts such as ceRNAs. The complex crosstalk involving ceRNAs has been found in many different cancer types, including GC. A more updated concept that builds on this previous idea is the target-directed miRNA decay (TDMD), which involves the direct degradation of the miRNA rather than its dissociation of the miRNA from the AGO PAZ domain. Above all, functional interactions and disequilibrium of ceRNA networks (ceRNETs) may contribute to disease pathogenesis.

IncRNAs have a crucial role in transcription by helping the assembly of transcriptional repressors or activators to modulate transcription. IncRNAs can also regulate gene expression after transcription by modulating RNA-binding proteins, which affect translation and splicing, as well as altering mRNA translation or mRNA stability. Additionally, some IncRNAs can post-transcriptionally regulate protein expression and affect the fate of proteins by increasing ubiquitination.

**IncRNAs and angiogenesis in GI cancer**

The IncRNA SNHG6 is situated on chromosome 8q13.1 and comprises 5 transcripts (SNHG6-201 to SNHG6-205). High expression of SNHG6 has been observed in several different cancers, such as HCC, CRC, lung adenocarcinoma, and breast cancer. Overexpression of SNHG6 was associated with enhanced tumor progression and poor survival in subjects with cholangiocarcinoma (CCA). SNHG6 has a role in cell apoptosis, invasion, proliferation, and migration in vitro, and enhanced tumor growth in vivo, but the role of SNHG6 in CCA remains uncertain. Wang et al. studied the effects of SNHG6 and E2F8 on angiogenesis in CCA. They found that the expression of SNHG6 was generally high in CCA. Moreover, ectopic expression of SNHG6 stimulated cell cycle progression, proliferation, angiogenesis, and migration in CCA, and the deletion of SNHG6 suppressed several cellular processes. Several articles have suggested that SNHG6 could compete with E2F8 to bind to miR-101-3p. The thrombospondin family consists of 5 members, which play a key role in several cellular processes. THBS1 (also known as TSP1) is an endogenous anti-angiogenic factor that inhibits tumor development by suppressing angiogenesis. The high expression of THBS1 on T cells also suppressed angiogenesis and inhibited tumor development. Wang et al. assessed the effects of BZRAP1-AS1 and THBS1 on angiogenesis in HCC. Screening of the IncRNA genes that were expressed in HCC suggested a candidate was BZRAP1-AS1. Microarray-based data analysis and qRT-PCR were employed to measure the expression of THBS1 and BZRAP1-AS1 in HCC. Bisulfite sequencing and methylation-specific PCR were used to measure the gene methylation level. Chromatin immunoprecipitation (ChIP) assays and ribosome-inactivating protein RNA pull-down were performed to assess the interactions between BZRAP1-AS1, DNMT3b, and THBS1. The in vitro role of DNMT3b, THBS1, and BZRAP1-AS1 in angiogenesis and in vivo tumorigenesis were assessed via gain- and loss-of-function tests. BZRAP1-AS1 was found to be overexpressed in HCC. Under-expression of BZRAP1-AS1 in HCC suppressed angiogenesis, proliferation, and migration of HUVECs. Knockdown of BZRAP1-AS1 suppressed angiogenesis and HCC tumor development in vivo, by upregulating THBS1.

The IncRNA OR3A4 was recently discovered to be a regulator of GC and breast cancer. Guo et al. reported that OR3A4 could...
enhance invasion, migration, HUVEC tube formation, and angiogenesis in GC. Because the function of OR3A4 in HCC was unclear, Li et al. studied the effects of OR3A4 and the mTOR/AGGF1/Akt pathway on angiogenesis in HCC. OR3A4 was overexpressed in HCC cell lines and tissues. Loss-of-function assays confirmed OR3A4 as a promoter for HCC development and angiogenesis. They used Kaplan-Meier analysis and qRT-PCR to find a correlation between AGGF1 and OR3A4 expression in tumor samples and poor prognostic outcomes in HCC patients. Spearman’s correlation curve and western blotting demonstrated a positive correlation between OR3A4 and the AGGF1 level. Rescue assays showed that OR3A4 enhanced cancer development and angiogenesis in HCC by affecting AGGF1/Akt/mTOR.

One member of the trypsin-like serine protease family is human kalli-krein-related peptidase 4 (KLK4). The level of KLK4 expression was associated with the development and progression of prostate cancer. Cui et al. showed that KLK4 could control the Wnt/β-catenin pathway to enhance oral squamous cell carcinoma. Tang et al. studied the effects of LINC01314 and KLK4 on angiogenesis in GC. Data analysis and microarrays were used to screen for expression of several lncRNAs in GC, and they detected a binding relationship between KLK4 and LINC01314. The human GC cell line SGC-7901 was modified by overexpression or silencing of LINC01314 or KLK4 to examine how LINC01314 could affect cellular processes in GC. Wnt-1, KLK4 cyclin D1, β-catenin, E-cadherin, and N-cadherin levels were measured, and cell invasion and migration were assessed. Then, microvessel density, tumor weight, and VEGFR-3 and VEGF-C expression in tumors were evaluated. KLK4 was found to be a target gene of LINC01314. Silencing of KLK4 or overexpression of LINC01314 led to less invasion and migration of GC cells and correlated with lower expression of β-catenin, Wnt-1, N-cadherin, and cyclin D1, while E-cadherin was increased. Moreover, the MVD and tumor weight of the transplanted tumors were lower, and angiogenesis was inhibited, accompanied by downregulation of VEGFR-3 and VEGF-C.

Table 6 lists some lncRNAs related to angiogenesis in GI cancers.

**circRNA BIOGENESIS**
circRNAs are non-coding RNAs that can be produced by two possible mechanisms for closed-loop generation. These models were suggested by Jeck et al.: (1) circularization carried out by intron-pairing, and (2) lariat-driven circularization. Both of these have been broadly accepted to occur. The generation of intron-pairing-driven circularization results from the pairing between complementary bases within...
the sequence of various introns. This brings adjacent exons to close proximity, and then the spliceosome cuts away the neighboring exons and the introns combine to form the circRNA configuration. The lariat-driven circularization is based on a covalent binding between the donor and splice acceptor. It results in a circRNA that includes the exon lariat. Another subtype of circRNA is called intron circRNA, which has recently been discovered. The 7-nucleotide G-rich element and 11-nucleotide C-rich element within the parent gene of the intron circRNA are merged to create a circular structure, which is then spliced by the spliceosome. The spliceosome plays a key role in circRNA biogenesis, relying on trans-acting factors and cis-regulatory elements. In one study by Zhang et al., four thiopurines were used to tag newly created RNA to demonstrate that low levels of circRNA could be a byproduct of imperfect pre-RNA splicing. Transcription mediated by RNA polymerase II (pol II) occurred simultaneously with the generation of circRNAs, showing that rapid extension of the strand may improve the reverse splicing of the complementary paired sequences. Moreover, the activity of pol II is rigorously regulated by cis-regulatory elements. Previous research indicated that RNA-binding proteins could also play a role in circRNA generation, as a distinct inhibitory mechanism noted in tumors during the EMT. The RNA helicase DExH-box helicase 9 (DHX9) is specific for the reverse repeat Alu element, which is required for the modulation of RNA post-transcriptional splicing. Alu elements are a group of functional sequences commonly observed in primates and are closely involved with circRNA biogenesis. The levels of DHX9 expression in influences the generation of splicing products, and its deletion was found to promote circRNA biogenesis. Furthermore, exon circularization is a dynamic process that is controlled by adjacent introns. Indeed, flanking and individual introns can regulate circRNA biogenesis via base-pairing. Alterations to the mRNA structure have been found to modulate alternative splicing, transcription, advanced structure, translation, and stability. Moreover, circRNAs and angiogenesis in GI cancers

| Cancer          | lncRNA     | Expression in cancer | Target | Effect on angiogenesis (inhibit/induce) | Model (in vivo, in vitro, human) | Type of cell line | Reference         |
|-----------------|------------|----------------------|--------|----------------------------------------|--------------------------------|------------------|------------------|
| Colon cancer    | HNF1A-AS1  | up                   | OTX1   | induce                                 | in vivo, in vitro              | HCT116, SW620     | Wu et al.        |
|                 | SUMO1P3    | up                   | VEGFA  | induce                                 | in vitro, in vivo, human       | HT29, HCT116, SW480, SW620, LoVo | Zhang et al.     |
| Pancreatic cancer| JHD11D-AS1 | up                   | HGF, FGF1 | induce                             | in vitro, in vivo             | PANC-1           | Kondo et al.     |
| Gastric cancer  | LINC01410  | up                   | NF-kB  | induce                                 | in vitro, in vitro, human      | HGC-27, BGC-23, AGS, MNK-45, SGC-7901 | Zhang et al.     |
|                 | LINC01314  | down                 | KLK4   | inhibit                                | in vitro, in vitro             | SGC-7901          | Tang et al.      |
|                 | PVT1       | up                   | VEGFA  | induce                                 | in vitro, in vivo, human       | BGC-823, MNK-45, GES-1, SGC-7901, HGC-27, HUVEG, AGS, SUN-638 | Zhao et al.      |
|                 | LINC00488  | up                   | TTN1   | inhibit                                | in vitro, in vivo, human       | Huh-7, Hep3B, HCCLM3, MHCC97 | Gao et al.       |
| Hepatocellular carcinoma| lncRNA-OR34A | up | AGGF1 | induce | in vitro, human | Huh7, SMCC-7721, HepG2, Hep3B | Li et al. |  |
|                 | BZR1P1-AS1 | up                   | AS1, BZR1P1 | inhibit | in vivo, in vitro, human | Huh7, BEL-7405, SK-HEp-1, HCCLM3, SGC-7901, BCLC-9 | Wang et al. |  |
|                 | UBE2CP3    | up                   | ERK1/2/HIF-1a/VEGFA | induce | in vitro, in vivo, human | HepG2, SMMC-7721 | Lin et al. |  |
|                 | lncRNA-MVIH | up | PGK1 | induce | human | | Yuan et al. |  |
|                 | MALAT1     | up                   | VEGF-A | induce | in vitro, in vivo, human | | Hou et al. |  |
| Cholangiocarcinoma | SNHG6       | up | E2F8 | induce | human | HCCC-9810, RBE | Wang et al. |  |

Hox genes can regulate cell differentiation and development, receptor signaling, apoptosis, and angiogenesis in cancer. The function of...
Table 7. Angiogenesis-related circRNAs in GI cancers

| Cancer                          | CircRNA             | Expression in gastric cancer | Target       | Effect on angiogenesis (inhibit/induce) | Model (in vivo, in vitro, human) | Type of cell line | Reference         |
|---------------------------------|---------------------|-----------------------------|--------------|----------------------------------------|---------------------------------|------------------|------------------|
| Pancreatic ductal adenocarcinoma| hsa_circ_001653 up  | HOXC6                       | inhibit      | in vitro, in vitro, human              | Capan-2 (ZY-H431), SW1990(ZY-H338), PANC1 (ZL-H147), BXPC3 (ZL-H45) | SK-hep1, HepG2   | Shi et al.287    |
| Hepatocellular carcinoma        | hsa_circ_0000092 up | HN1                         | induce       | in vitro, in vitro, human              | Hep3B, L3M, MHCC97L, SK-hep1, HepG2 | SK-hep1          | Pu et al.291     |
|                                 | ircRNA-100338 up    | MMP2, MMP9                  | induce       | in vitro, in vitro, human              | Hep3B, MHCC97L, MHCC97H, HLE, Huh7, BEL7402, SMCC7721 HCCLM3 and HCCLM6 | SK-hep1          | Huang et al.292  |
|                                 | CircGFRA1 up        | miR-149                     | induce       | in vitro, human                       | SK-HEP-1, Huh6, Huh7, HCCLM3     | SK-hep1          | Yu et al.293     |

HOXC6 in PDAC is not clear, but high expression of HOXC6 in prostate cancer was correlated with disease development. Shi et al.287 assessed the effects of hsa_circ_001653 and the human homeobox on angiogenesis in PDAC. Hsa-circ_001653 expression was evaluated in 83 paired tumor and normal tissue samples. Assays for cell cycle, cell viability, apoptosis, and invasion were used to examine phenotypic changes in PDAC cells. HUVEC tube-like formation was evaluated in the presence of PDAC cells. In addition, crosstalk between miR-377 and hsa_circ_001653 HOXC6 was investigated using Ago2 immunoprecipitation, northern blot analysis, and a dual-luciferase reporter assay. Human PDAC cells were inoculated into nude mice for analysis of in vivo tumor growth. Hsa_circ_001653 expression was high in PDAC samples. Hsa_circ_001653 knock-down in PDAC cells using RNA interference suppressed cell-cycle progression, cell viability, invasion, and in vitro angiogenesis and showed a pro-apoptotic effect. When human PDAC cells were inoculated into nude mice, suppression of hsa_circ_001653 had a therapeutic effect on tumor growth.287

HN1 (hematological and neurological expressed 1) protein was first identified in mouse embryonic tissues288 and has a role in several diseases.289 HN1 was correlated with a poor prognosis in HCC patients.290 Pu et al.291 investigated the hsa_circ_0000092 and HN1 effects on angiogenesis in HCC. The levels of miR-338-3p, HN1, and hsa_circ_0000092 expression in HCC were examined. RNA pulldown, dual-luciferase reporter, and northern blot assays were used to detect the relationship between miR-338-3p, hsa_circ_0000092, and HN1. A group of mimetics, suppressors, or small interfering RNA (siRNA) plasmids were delivered into HCC cells to confirm the ability of HN1, miR-338-3p, and hsa_circ_0000092 to regulate in vitro angiogenesis, cell migration, proliferation, and invasion. The function of hsa_circ_0000092 in HCC tumor development was investigated by silencing hsa_circ_0000092 with siRNA. The expression levels of hsa_circ_0000092 and HN1 in HCC were high, while the expression of miR-338-3p was downregulated. Hsa_circ_0000092 could bind to miR-338-3p in order to increase HN1 expression. Both the downregulation of hsa_circ_0000092 or the upregulation of miR-338-3p were observed to inhibit angiogenesis, cell invasion, proliferation, and migration in HCC cells in vitro, by downregulating HN1. Knock-down of hsa_circ_0000092 inhibited HCC tumor development in vivo.291

Table 7 lists some circRNAs reported to be related to angiogenesis in GI cancers.

FUTURE FOR THERAPEUTIC ncRNAs IN GI CANCER

ncRNAs are involved in the regulation of almost all physiological processes, such as cell development, differentiation, proliferation, and apoptosis. In this context, ncRNAs could have great potential as new biomarkers for diagnosis and prognosis and in therapeutic approaches for cancers, including GI cancer. Recently, new methods and tools have been developed to detect and quantify cancer-regulated ncRNAs. For example, the use of multiplexed qRT-PCR, microarrays, or next-generation sequencing (NGS)-based genome-wide approaches have helped to provide a complete picture of the expression level of many ncRNAs.292 Moreover, bioinformatic approaches and various databases have enabled the discovery of thousands of novel ncRNAs in cancers, including GI cancer. These databases include CRlncRNA, Lnc2Cancer, and LncRNADisease.295–297

The ncRNAs could be an attractive new type of therapeutics, especially against undruggable targets for the treatment of GI cancer.298 Several oncogenic ncRNAs can promote adverse drug reaction resistance in GC. These include miRNAs, such as miR-27a, miR-19a/b, and miR-15a-5p; lncRNAs, such as HOTAIR, CAS9, MRUL, UCA1, D63785, NET1, and HULC; and circRNAs, such as circAKT3 and circFN1.299 Therefore, ncRNAs could provide a new approach for better clinical decision making. For example, miRNAs can mediate potent and specific gene silencing, making them attractive therapeutic tools. To date, the greatest efforts in this setting have been to explore the potential application of ncRNA-based therapeutics for cancer.300

Despite the potential of ncRNAs in cancer therapy, many challenges still remain, including rapid degradation and clearance, poor cellular uptake, off-target effects, and immunogenicity. Rational design, chemical modifications, and improved delivery carriers offer significant opportunities to overcome these challenges.313 Moreover, the
In vivo experiments employing the transfection of ectopic miRNA mimics or inhibitors into cells is a commonly used approach to validate the function of a particular miRNA. However, in some circumstances, the ectopic miRNA mimics or inhibitors in cells are over-expressed to a level that is often much higher than the endogenous level of the miRNA, suggesting the possibility of an exaggerated effect in the study. On the other hand, the concentration of a miRNA may not reach the level that is necessary within an intracellular compartment to allow its function to suppress target genes (in reality, subcellular concentrations of specific miRNAs are very difficult to measure), which could lead to the effect of the miRNA in vitro being underestimated or completely ignored. Furthermore, almost all in vitro studies have demonstrated the direct regulation of drug-metabolizing enzymes and transporters by miRNAs; however, potential indirect regulation cannot be ruled out, since off-target effects of miRNAs may not reach the level that is necessary within an intracellular compartment. In addition to in silico prediction and correlation analysis of the relationship between the expression of a miRNA and the expression of its target mRNA, in vitro experiments are always used before wet-lab validation experiments. However, it is worth noting that the gene expression profiles in the human population (particularly in processes such as angiogenesis) are extremely heterogeneous, due to different genetic backgrounds, environmental exposure, dietary considerations, and overall health status of the tissue donors. A weak association or a non-significant association does not necessarily mean that the expression of a particular ncRNA and an mRNA are not related.

In conclusion, the role of ncRNAs in angiogenesis and GI cancer metastasis remains to be fully determined. Therefore, ncRNA-based therapy is still not available in clinical settings. Even so, with further advances in technology, ncRNA-based therapeutic approaches will likely be applied to combat angiogenesis in GI cancer in the coming years.

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