

Long non-coding RNAs and circular RNAs in tumor angiogenesis: From mechanisms to clinical significance

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Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) execute a wide array of functions in physiological and pathological processes, including tumor progression. Angiogenesis, an elaborate multistep process driving new blood vessel formation, accelerates cancer progression by supplying nutrients and energy. Dysregulated lncRNAs and circRNAs can reportedly impact cancer progression by influencing angiogenesis. However, the expanding landscape of lncRNAs and circRNAs in tumor progression-dependent angiogenesis remains largely unknown. This review summarizes the major functions of angiogenic lncRNAs (Angio-lncRs) and angiogenic circRNAs (termed Angio-CircRs) and their cancer mechanisms. Moreover, we highlight the commonalities of lncRNAs and circRNAs in epigenetic, transcriptional, and post-transcriptional regulation as well as illustrate how Angio-lncRs and Angio-CircRs induce cancer onset and progression. We also discuss their potential clinical applications in diagnosis, prognosis, and anti-angiogenic therapies.

INTRODUCTION

Non-coding RNAs (ncRNAs) are transcribed from the genome but generally lack protein-coding potential. Long ncRNAs (lncRNAs) and circular RNAs (circRNAs) are two major groups of large ncRNAs that play key roles in various pathophysiological processes, especially cancers.^{1–3} lncRNAs are widely defined as a large and heterogeneous class of regulatory transcripts that are at least 200 nt long.^{4,5} circRNAs are also a subtype of endogenous ncRNAs with tissue- and cell-specific expression patterns, whose biogenesis is regulated by a particular form of alternative splicing, termed backsplicing.⁶ With the development of high-throughput technologies and extensive research reports, lncRNAs and circRNAs have gained wide attention for their roles in the development of many human diseases.^{5,7} lncRNAs and circRNAs are generally low in abundance; however, they are significantly differentially expressed in specific cell types, tissues, developmental stages, and disease states.^{8–10} Recently, accumulating independent studies

have shown that the dysregulation of lncRNAs and circRNAs plays multifunctional roles in cancer progression, including tumor angiogenesis.^{11,12} However, the commonalities of their functions and mechanisms in tumor progression-dependent angiogenesis remain largely obscure.

Angiogenesis is a multistep process that involves the formation of new blood vessels from pre-existing vessels, contributing to cancer onset and progression.¹³ Within tumors, the angiogenic switch is activated, thereby inducing the continuous formation of new blood vessels.¹⁴ Targeting angiogenesis is an effective therapeutic strategy against cancer that has been applied in a plethora of cancers.¹⁵ Of note, diverse arrays of molecules play multifaceted roles in the mechanisms underlying tumor angiogenesis.^{16,17} To date, the role of ncRNAs in manipulating cancer phenotypes across various tumor types has been studied, and lncRNAs and circRNAs are emerging as part of a widespread regulatory mechanism that orchestrates gene expression in tumor angiogenesis.

Recent reviews have mainly focused on the respective roles of lncRNAs and circRNAs in angiogenesis;^{18–22} however, their molecular mechanisms and commonalities have not been deeply explored, especially in tumor angiogenesis. This review summarizes the

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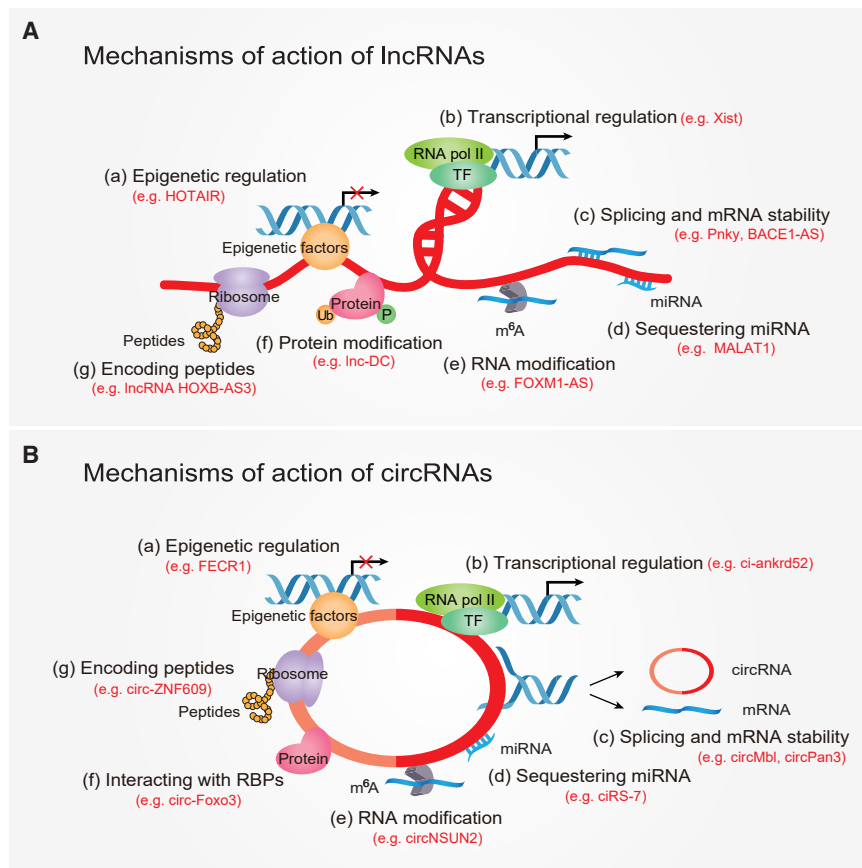


Figure 1. The functional commonalities of lncRNAs and circRNAs

(A and B) Diverse mechanisms have been described for lncRNA regulation (A) and circRNA regulation (B), including (a) epigenetic regulation, (b) transcriptional regulation, (c) splicing and mRNA stability, (d) sequestering miRNA, (e) RNA modification, (f) protein modification or interaction with RBPs, and (g) encoding peptides.

The expanding mechanisms of lncRNAs and circRNAs orchestrating gene expression can be summarized into the following aspects (Figure 1): (1) at the epigenetic layer, lncRNAs and circRNAs recruit diverse epigenetic factors to orchestrate gene transcription and signal transduction;^{28–30} (2) at the transcriptional level, gene transcription is regulated by lncRNAs and circRNAs via interaction with transcriptional factors and co-factors or target gene promoters;^{31–34} (3) at the post-transcriptional level, lncRNAs and circRNAs modulate precursor (pre-)mRNAs and mRNAs of many genes by interacting with microRNAs (miRNAs), splicing factors, and diverse RNA-binding proteins (RBPs);^{35–39} (4) lncRNAs and circRNAs orchestrate a broad repertoire of RNA or protein modifications to affect their activation and stability;^{40–43} and (5) notably, lncRNAs and circRNAs can encode functional peptides that exert crucial roles in distinct biological processes.^{44,45} Taken together, gene regulation by lncRNAs and circRNAs is an extensive and complex process that exists in a plethora of human diseases. The emerging commonalities of lncRNAs and circRNAs show expanding mechanisms that provide hope for new therapeutic interventions in diverse diseases. However, the detailed functions of most lncRNAs and circRNAs are still unclear and require detailed, comprehensive research in preclinical models.

expanding landscape of lncRNAs and circRNAs ranging from epigenetic to transcriptional to post-transcriptional regulation in tumor angiogenesis. This work is the first review on the advance of circRNAs in tumor angiogenesis and the functional commonalities of lncRNAs and circRNAs. Furthermore, we illustrate the roles of angiogenesis-related lncRNAs and circRNAs in multistep tumor development and explore their great potential in tumor angiogenesis as new biomarkers and tumor therapeutic targets.

lncRNAs AND circRNAs: FUNCTIONAL COMMONALITIES IN TUMOR ANGIOGENESIS

Functional commonalities between lncRNAs and circRNAs

Increasing independent research has indicated that lncRNAs and circRNAs can play a broad and diverse spectrum of pathophysiological roles, including tumor angiogenesis.^{23–25} Mechanistically, lncRNAs and circRNAs can directly interact with diverse partners in the form of *cis* or *trans* interactions to regulate gene expression and signal transduction.^{5,26,27} Based on their action mechanism, lncRNAs are generally divided into four functional archetypes: signal, decoy, guide, and scaffold.²⁴ Interestingly, similar complex mechanisms of circRNAs have emerged in a wide variety of cell types and diseases. Moreover, both lncRNAs and circRNAs exhibit common functional features that have not been previously appreciated.

lncRNAs and circRNAs: Novel players in tumor angiogenesis

Angiogenesis is a complicated multistep process stimulated by various pro-angiogenic factors (such as vascular endothelial growth factor [VEGF]). The vascular network's original dynamic balance is compromised, the capillary basement membrane degrades, and endothelial cells begin to migrate and proliferate, forming new primary capillary networks. Capillaries undergo arteriovenous differentiation and remodeling in the form of sprouting and intussusception, and this primitive network expands widely to form a network of vascular systems with complex functions.^{13,46} Generally speaking, angiogenesis occurs in response to physiological and pathological processes, including tumor growth, inflammation, tissue regeneration, and reproduction.¹⁸ During tumor growth, a large number of new vascular systems are needed to provide adequate nutrients and

remove metabolic waste. Therefore, blocking tumor blood vessel formation is equivalent to inhibiting tumor growth and progression; however, tumor-induced blood vessels often present morphological disorders characterized by precocious vascular structure, tortuosity, poor permeability, and dysfunction.⁴⁷ These abnormal vascular networks create a hypoxic microenvironment within the tumor, triggering the expression of multitudinous oncogenes and inducing immunosuppression and metastasis.¹⁹ Therefore, some scholars think that anti-angiogenic therapy may facilitate the metastasis and invasion of cancer cells by activating a cancer cell hypoxic response.^{48–50} However, this is a controversial view and may not occur during clinical therapy.⁵¹ In essence, anti-angiogenesis has always been the focus of anticancer drug development due to the critical role of angiogenesis in tumor growth and progression.¹⁵

VEGF and its receptors are one of the well-documented signaling pathways in tumor angiogenesis.¹⁶ In most solid tumors, hypoxia is one of the key drivers of angiogenesis and induces the expression of angiogenic factors via hypoxia-inducible factors (HIFs).⁵² In tumor hypoxia, HIF-1 α induces the expression of VEGF, which activates VEGF receptor 2 (VEGFR2), thereby stimulating tip cell migration from the arteries to initiate angiogenesis.⁵² Notch regulates the proliferation and migration of the tip cells and stalk cells, and Neuropilin-1 accelerates the separation of arteries and veins,^{53,54} thus continuously promoting the establishment of the vascular system network. Currently, lncRNAs and circRNAs have been identified as novel and versatile players involved in tumor angiogenesis via manipulating angiogenic factors. Specific well-known lncRNAs (such as H19 and MALAT1) have been identified as vital modulators of angiogenic factors.^{55,56} Similarly, circRNA circRhoC enhances ovarian cancer (OC) angiogenesis by regulating the expression of VEGFA.⁵⁷ Increasing evidence indicates that lncRNAs and circRNAs are intricately involved in tumor angiogenesis via diverse mechanisms.

Recently, Yu and Wang¹⁸ named lncRNAs regulating angiogenesis and vascular diseases as *Angio-lncRs*. Herein, we have termed the circRNAs that modulate angiogenesis and vascular disease as *Angio-CircRs*. In reality, *Angio-lncRs* and *Angio-CircRs* play extensive regulatory roles in distinct vascular diseases, such as cancer, atherosclerosis, aneurysm, and diabetic retinopathy, among others.^{18,22} In the field of oncology, the study of ncRNAs has attracted great attention and made rapid progress. Reviewing the current reports of *Angio-lncRs* and *Angio-CircRs* in tumor angiogenesis could help further explore the novel potential targets of ncRNA-related anti-tumor strategies and provide clinical enlightenment for cancer diagnosis and treatment.

ANGIO-lncRs: MECHANISMS OF ACTION IN CANCERS

Current studies have identified that the dysregulation of lncRNAs contributes to tumorigenesis and tumor progression. Generally, lncRNAs exert tumor-promotive and -suppressive roles to regulate gene expression via diverse mechanisms of action. Accumulating evidence shows that lncRNA-modulated cancer progression, especially

tumor angiogenesis, remains to be further explored. In the subsequent sections, we comprehensively summarize the expanding functions and mechanisms of lncRNAs in tumor angiogenesis (Table 1; Figure 2), especially inducing the expression of several key angiogenic mediators, including VEGF and VEGFR.

Angio-lncRs influence chromatin modification

Multiple lines of studies have revealed that many lncRNAs influence epigenetic changes by recruiting or interacting with chromatin remodeling complexes to specific genomic loci, thus leading to epigenetic activation or silencing of gene expression. Enhancer of zeste homolog 2 (EZH2), a catalytic subunit of the polycomb repressive complex 2 (PRC2), can catalyze the methylation of histone H3 lysine-27 for epigenetic regulation.^{92,93} Emerging studies have shown that numerous lncRNAs interact with PRC2 for the epigenetic regulation of tumor angiogenesis. For instance, lncRNA PVT1 is significantly elevated in cholangiocarcinoma (CCA). Mechanistically, by binding to PRC2, PVT1 could mediate the histone methylation of the promoter of angiopoietin-like 4 (ANGPTL4) via reducing the interaction between EZH2 and H3K27 trimethylation sites throughout the promoters of ANGPTL4, resulting in the promotion of cell angiogenesis, cell proliferation, migration, and apoptosis (Figure 2A).⁵⁸ Similarly, H19 is closely related to a plethora of tumor types via manipulating cell proliferation, invasion, and angiogenesis. Silencing of H19 inhibited the capability of EZH2 to recruit methyl groups to the promoter region of the angiogenesis inhibitor vasohibin-1 (*VASH1*), thereby elevating *VASH1* expression and secretion of human amniotic mesenchymal stem cells (HAMSCs) and restraining angiogenesis by interacting with EZH2.⁵⁶ A novel Kaposi's sarcoma-associated herpesvirus (KSHV) reactivation-activated lncRNA, LINC00313, suppresses endothelial cell migration and tube formation via interaction with HIV Tat. Mechanistically, LINC00313 blocks endothelial cell angiogenesis-related properties by binding to PRC2 and decreasing migration-regulating gene expression.⁵⁹ In addition to the interaction with PRC2, certain lncRNAs also bind to other epigenetic factors. Another hypoxia-mediated lncRNA, GATA6-AS, is up-regulated in endothelial cells under hypoxic conditions. Silencing of GATA6-AS inhibits transforming growth factor (TGF)- β -induced epithelial-to-mesenchymal transition (EMT) and tumor angiogenesis. Mechanistically, GATA6-AS interacts with the epigenetic mediator LOXL2 to regulate endothelial gene transcription by inducing histone methylation.⁹⁴ Taken together, increasing evidence shows that dysregulation of lncRNAs contributes to tumor angiogenesis and tumor progression via the recruitment of chromatin-modifying enzymes and their subunits.

In addition to histone methylation, DNA methylation is an important epigenetic modification involved in the expression of many cancer-related genes.⁹⁵ For example, BZRAP1-AS1 suppresses the transcription of thrombospondin-1 (*THBS1*) via interaction with the DNA methyltransferase 3B and induction of methylation of the *THBS1* promoter; this promotes the proliferation, migration, angiogenesis, and tumor growth of hepatocellular carcinoma (HCC) (Figure 2A).⁶⁰ On the contrary, lncRNA AK001058 promotes tumor growth,

Table 1. The expanding roles of Angio-LncRs in various cancers

Mechanism/level	lncRNA	Expression	Function	Molecular mechanism	Cancer type	Refs.
Epigenetic regulation	PVT1	up	pro-angiogenesis	interacts with PRC2 and inhibits transcription of ANGPTL4	CCA	58
	H19	up	pro-angiogenesis	increases VASH1 expression in HAMSCs via binding to EZH2	multiple tumors	56
	LINC00313	down	anti-angiogenesis	binds PRC2 and decreases transcription of cell migration-regulating genes	Kaposi sarcoma	59
	BZRAP1-AS1	up	pro-angiogenesis	inhibits THBS1 transcription by interacting with DNMT3b to induce THBS1 promoter methylation	HCC	60
	AK001058	up	pro-angiogenesis	promotes the methylation level of ADAMTS12 to decrease the expression of ADAMTS12	CRC cell lines	61
	CRNDE	up	pro-angiogenesis	regulates the mTOR signaling pathway through epigenetic mechanisms	hepatoblastoma	62
Transcriptional regulation	RAB11B-AS1	up	pro-angiogenesis	enhances the expression of VEGFA and ANGPTL4 by increasing the recruitment of RNA Pol II	breast cancer cell lines	11
	LINC00312	up	pro-angiogenesis	promotes the expression of VEGFA by binding to YBX1	lung adenocarcinoma	63
	Linc00665	up	pro-angiogenesis	interacts with YB-1 to promote transcription of ANGPT4, ANGPTL3, and VEGFA	lung adenocarcinoma	64
	PVT1	up	pro-angiogenesis	activates transcription of VEGFA and PVT1 by interacting with STAT3	gastric cancer	65
	CPS1-IT1	down	anti-angiogenesis	competitively combines with BRG1 to inhibit the expression of Cyr61 and its downstream targets VEGF and MMP9	melanoma	66
	HOTAIR	up	pro-angiogenesis	activates VEGFA transcription by directly targeting the VEGFA promoter, or upregulates GRP78 expression to mediate VEGFA and Ang2 expression	nasopharyngeal carcinoma	67
	LINC00284	up	pro-angiogenesis	recruits NF- κ B1 and downregulates MEST expression	ovarian cancer	68
	LINC00858	up	pro-angiogenesis	upregulates HNF4 α and downregulates WNK2 expression	colon cancer	69
	HNF1A-AS1	up	pro-angiogenesis	increases the OTX1 expression via interacting with transcription factor PBX3 to activate the ERK/ MAPK pathway	colon cancer	70
	Sequestering miRNAs	MALAT1	up	pro-angiogenesis	sponges miR-126-5p to increase expression of VEGFA, SLUG, and TWIST	CRC
MALAT1		up	pro-angiogenesis	increases VEGFA expression by sponging miR-140, re-directing the M2 polarization of macrophages	HCC	72
MALAT1		up	pro-angiogenesis	promotes VEGF expression via sponging miR-145	breast cancer	73
MALAT1		up	pro-angiogenesis	competitively binds miR145-5p and elevates the NEDD9 protein expression	NSCLC	74
TUG1		up	pro-angiogenesis	sponges miR-143-5p to mediate HIF-1 α expression	osteosarcoma	75
TUG1		up	pro-angiogenesis	sequesters miR-299 to induce VEGF expression	glioblastoma	76
TUG1		up	pro-angiogenesis	sponges miR-34a-5p and increases VEGFA expression	hepatoblastoma	77
ZFAS1		up	pro-angiogenesis	SP1-induced ZFAS1 upregulates VEGFA via competitively binding miR-150-5p, thereby activating the Akt/mTOR signaling pathway	CRC	78
HULC		up	pro-angiogenesis	upregulates the TF E2F1 by sponge miR-107 to increase SPHK1 expression	HCC	79

(Continued on next page)

Table 1. Continued

Mechanism/level	lncRNA	Expression	Function	Molecular mechanism	Cancer type	Refs.
mRNA Stability	lncRNA-APC1	down	anti-angiogenesis	inhibits exosome production via directly interacting with Rab5b mRNA and decreasing its stability	CRC	80
	lncRNA MVIH	up	pro-angiogenesis	interacts with RPS24c mRNA to enhance the stability of each other, inhibiting the secretion of PGK1	CRC	81
	TPT1-AS1	up	pro-angiogenesis	interacts with NF90 and enhances VEGFA mRNA stability	CRC	82
	LINC00346	up	pro-angiogenesis	promotes the degradation of ZNF655 mRNA, further creating an ANKHD1/LINC00346/ZNF655 feedback loop	glioma	83
	HITT	down	anti-angiogenesis	titrates away YB-1 from the 5' UTR of HIF-1 α mRNA via a high-stringency YB-1-binding motif, thereby repressing HIF-1 α expression	colon cancer	84
Protein modification	CamK-A	up	pro-angiogenesis	triggers PNCK to phosphorylate I κ B α and activate NF- κ B	multiple tumors	85
	FLANC	up	pro-angiogenesis	increases the half-life of phosphorylated STAT3 to induce VEGFA expression	CRC	86
	lncRNA-MM2P	up	pro-angiogenesis	regulates M2 polarization of macrophages by increasing phosphorylation on STAT6	osteosarcoma cell lines	87
	lnc-CCDST	down	anti-angiogenesis	facilitates DHX9 degradation through acting as a scaffold to promote the interplay between MDM2 and DHX9	cervical cancer	88
	NBAT1	down	anti-angiogenesis	interacts with Sox9 and reduces its protein stability	gastric cancer	89
Encoding peptides	TNK2-AS1	up	pro-angiogenesis	interacts with STAT3 and elevate VEGFA expression	NSCLC	90
	LINC00908	down	anti-angiogenesis	encodes ASRPS, which interacts with STAT3 and diminishes STAT3 phosphorylation, inhibiting VEGF expression	TNBC	91

Expression is in relation to normal tissue. Cell lines means cell samples, and the rest are human tissue samples. All lncRNAs were measured with qRT-PCR in these studies. CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; RNA Pol II, RNA polymerase II; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer.

accounting for increased cell apoptosis and tumor angiogenesis in colorectal cancer (CRC), which partly depends on the methylation of ADAMTS12, a potential anti-oncogene located on chromosome 5, and resulting in increased expression of VEGFA and angiopoietin II.⁶¹ Additionally, various lncRNAs are also associated with chromatin-modifying complexes to manipulate tumor growth and angiogenesis in distinct signaling pathways, such as the mammalian target of rapamycin (mTOR) signaling pathway.⁶² Collectively, a growing number of studies have shown that lncRNAs epigenetically regulate transcription of tumor angiogenesis-related genes by either directly or indirectly affecting chromatin-modifying factors. This broadens our understanding of angiogenesis and provides a positive direction for the potential application of therapeutic intervention in regulating tumor progression at the epigenetic level.

Angio-lncRNAs in transcriptional regulation

Studies have shown that lncRNAs can manipulate gene transcription by binding specific transcription factors (TFs) to promoters of adjacent or distant genes, thus modulating tumor angiogenesis. For instance, in hypoxic breast cancer cells, RAB11B-AS1 is induced by

HIF-2, promoting tumor angiogenesis and distant metastasis in response to hypoxia. Mechanistically, RAB11B-AS1 facilitates the transcription of VEGFA and ANGPTL4 by promoting RNA polymerase II recruitment (Figure 2B).¹¹ The levels of LINC00312 were high in lung adenocarcinoma (LUAD) patients, which positively correlated with tumor node metastasis. LINC00312 promotes the transcription of VEGFA by directly binding to the TF Y-box binding protein 1 (YB-1, YBX1) and inducing migration and vasculogenic mimicry (VM) (Figure 2B).⁶³ Similarly, in LUAD cells, linc00665 suppresses ubiquitination-dependent proteolysis and induces YB-1 nuclear translocation by directly binding to YB-1. The accumulated nuclear YB-1 promoted transcription of VEGFA, ANGPTL4, and ANGPTL3 by binding to their promoters, thus facilitating tumor angiogenesis.⁶⁴ The lncRNA PVT1 level was elevated and markedly correlated with poor prognosis in gastric cancer (GC). Mechanistically, PVT1 directly interacted with phospho-STAT3 in the nucleus, thereby promoting VEGFA expression by activating the VEGFA promoter to stimulate tumor angiogenesis. Moreover, STAT3 could bind to the PVT1 promoter and facilitate its transcription, which established a positive feedback loop of PVT1 and STAT3 to strengthen

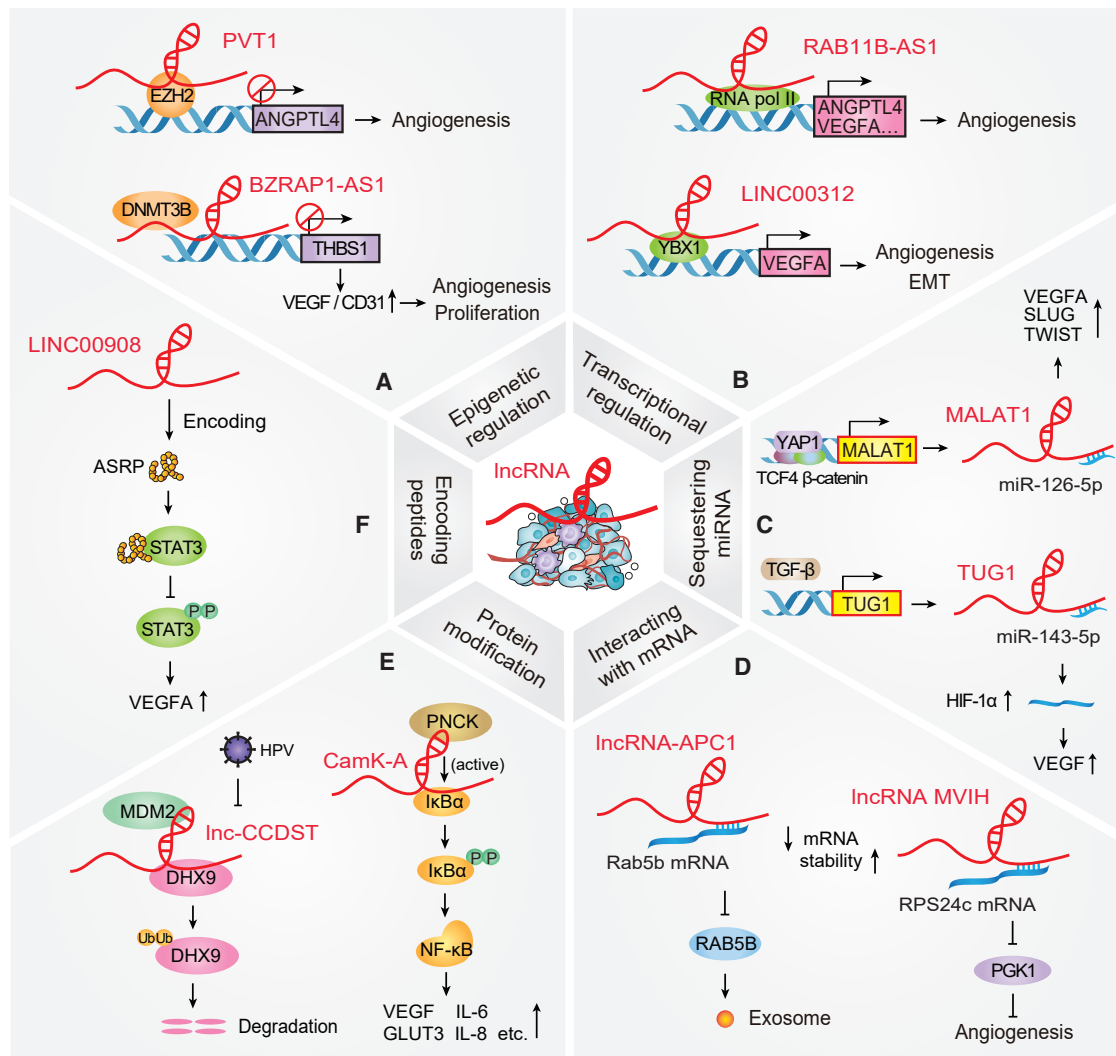


Figure 2. Mechanisms of action of Angio-LncRNAs in cancer progression

(A) lncRNAs epigenetically regulate histone or DNA methylation, e.g., PVT1 and BZRAP1-AS1. (B) lncRNAs mediate transcription of angiogenesis-related genes, e.g., RAB11B-AS1 and LINC00312. (C) lncRNAs act as molecular sponges of miRNAs, e.g., MALAT1 and TUG1. (D) lncRNAs interact with mRNAs to affect the stability of mRNA, e.g., lncRNA-APC1 and lncRNA MVIH. (E) lncRNAs regulate protein modification (phosphorylation and ubiquitination), e.g., CamK-A and lnc-CCDST. (F) lncRNAs also encode bioactive peptides, e.g., LINC00908.

their oncogenic effects.⁶⁵ A well-known lncRNA, HOTAIR, was extremely abundant in nasopharyngeal carcinoma (NPC); it promoted tumor cell growth and angiogenesis by directly activating VEGFA transcription via targeting VEGFA promoter and upregulating the GRP78/VEGFA/Ang2 axis.⁶⁷ lncRNA CPS1-IT1 acts as a tumor suppressor and suppresses EMT, cell migration, and angiogenesis in melanoma. Mechanistic studies uncovered that CPS1-IT1 impedes the transcription of the angiogenic factor cysteine-rich 61 (Cyr61) by blocking the binding of BRG1 to the Cyr61 promoter.⁶⁶

In addition to VEGF/VEGFA, other angiogenic factors are mediated by different lncRNAs to induce cancer angiogenesis and development. For example, Ruan and Zhao⁶⁸ identified that LINC00284 is

associated with angiogenesis during OC development. Silencing LINC00284 inhibits tumor angiogenesis via recruitment of nuclear factor κ B1 (NF- κ B1), thereby upregulating mesoderm-specific transcript (MEST) in OC. Another example, LINC00858, is mainly located in the nucleus and exerts a promotive role in colon cancer growth. Functional assays uncovered that LINC00858 elevates the transcription of HNF4 α , thereby promoting angiogenesis by the HNF4 α /WNK2 axis.⁶⁹ Additionally, lncRNA HNF1A-AS1 is highly expressed in colon cancer. HNF1A-AS1 promotes OTX1 transcription via interacting with the TF PBX3, thereby activating the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway in colon cancer.⁷⁰ Taken together, lncRNAs may act as transcriptional activators or inhibitors, which can directly or

indirectly regulate the transcription of angiogenesis-related genes, thereby affecting the progression of various malignant tumors.

Sequestering miRNAs

lncRNAs can also function as competing endogenous RNAs (ceRNAs) to compete together with miRNAs and dampen the gene expression of miRNA targets, thus participating in post-transcriptional regulation.⁹⁶ This section provides an overview of the direct and indirect mechanisms of lncRNAs by sponging diverse miRNAs to affect tumor angiogenesis. For instance, MALAT1, a widely reported lncRNA, is highly expressed in a variety of tumors. Functional assays indicated that YAP1-mediated MALAT1 could sponge miR-126-5p to facilitate the expression of VEGFA, SLUG, and TWIST, which could promote CRC angiogenesis and EMT (Figure 2C).⁷¹ Similarly, MALAT1 exerts a promotive role in regulating tumorigenesis by sponging miR-140 or miR-145, thereby increasing VEGF and VEGFA expression in HCC and breast cancer.^{72,73} Additionally, estrogen receptor β promotes the progression of lung cancer by upregulating MALAT1 to alter miR-145-5p/NEDD9 signaling, resulting in the facilitation of VM formation and cell invasion.⁷⁴ Similar to MALAT1, the lncRNA TUG1 is also significantly highly expressed in various tumors. Cancer-associated fibroblast (CAF)-derived TGF- β promotes TUG1 expression, and the interplay between CAFs and osteosarcoma (OS) cells induces TUG1 to facilitate OS angiogenesis, proliferation, and metastasis. TUG1 acts as a sponge for miR-143-5p, thereby elevating HIF-1 α levels to promote VEGF expression (Figure 2C).⁷⁵ Similarly, TUG1 knockdown suppresses angiogenesis and tumor growth by decreasing VEGFA expression via upregulation of miR-299 and miR-34a-5p in glioblastoma and hepatoblastoma, respectively.^{76,77} Several groups have shown that many lncRNAs (PVT1, DANCR, LINC01116, linc01105, and SNHG15) contribute to tumor angiogenesis and progression, upregulating VEGF/VEGFA expression by competitively binding to distinct miRNAs in a wide variety of cancers types.⁹⁷⁻¹⁰¹

Recently, lncRNAs were reported to be involved in cellular signaling pathways such as the NF- κ B, phosphatidylinositol 3-kinase (PI3K)/AKT, mTOR, and Wnt/ β -catenin pathways. As relatively upstream regulatory molecules, lncRNAs act by impacting downstream molecules via competitively sponging miRNAs. For example, LINC01410 facilitates GC angiogenesis and metastasis via interaction with miR-532-5p, increasing NCF2 expression and activating the NF- κ B pathway.¹⁰² RP11-79H23.3 inhibits the angiogenesis and pathogenesis of bladder cancer (BCa) by inducing the miR-107/PTEN axis and inactivating the PI3K/Akt signaling pathway.¹⁰³ Similarly, PTENP1, a pseudogene of PTEN, inhibits the oncogenic PI3K/AKT pathway by sponging miR-17, miR-19b, and miR-20a, which results in eliciting pro-death autophagy and dampening angiogenesis.¹⁰⁴ Additionally, MCM3AP-AS1 and HOXA-AS2 regulate the PI3K/AKT pathway and contribute to glioblastoma multiforme (GBM) angiogenesis by influencing miRNA targets.^{105,106} The SP1-induced lncRNA ZFAS1 contributes to CRC progression by elevating VEGFA levels via sequestering miR-150-5p, thereby activating the Akt/mTOR signaling pathway.⁷⁸

Furthermore, lncRNAs indirectly regulate the expression of angiogenesis-related genes through miRNA-mediated TFs. For example, XIST and LINC00339 can act as ceRNAs to sponge miR-137 and miR-539-5p, elevating the expression of the miRNA targets (FOXC1, ZO-2, TWIST1) by increasing promoter activity and downstream gene expression, thereby promoting glioma angiogenesis.^{107,108} lncRNA HULC sequesters miR-107 via a ceRNA model, which increases the transcription of miR-107 target E2F1. As a result, the TF E2F1 binds to the *SPHK1* promoter and enhances *SPHK1* transcription to induce HCC angiogenesis.⁷⁹ In addition, lncRNAs modulate the expression of other angiogenic factors via sequestering different miRNAs to mediate tumor angiogenesis. For example, H19, SNHG16, and MCM3AP-AS were significantly upregulated in diverse cancer types; they regulated the expression of vasohibin 2, ALDH1A1, and KPNA4, respectively, by sponging certain miRNAs to promote tumor growth and angiogenesis.¹⁰⁹⁻¹¹¹ Taken together, current progress indicates that lncRNAs often act as ceRNAs in tumor angiogenesis and may serve as promising targets for cancer therapy.

Angio-lncRs interact with mRNAs

Many studies report that lncRNAs can bind mRNAs to affect their stability and the translation process, thus regulating the expression and secretion of related molecules for tumor progression and tumor angiogenesis. For instance, lncRNA-APC1, as a downstream factor of adenomatous polyposis coli (*APC*) in CRC, suppresses CRC angiogenesis and metastasis by inhibiting exosome production via directly interacting with the *Rab5b* mRNA, which results in decreased *Rab5b* mRNA stability. This study revealed that CRC-derived exosomes regulated the lncRNA-APC1/*Rab5b* axis to inhibit the angiogenesis of CRC, linking APC signaling to the canonical Wnt pathway (Figure 2D).⁸⁰ Another lncRNA, MVIH, activates CRC angiogenesis via interacting with the RPS24c isoform and enhances each other's stability, thereby inhibiting the secretion of PGK1 (Figure 2D).⁸¹ lncRNA TPT1-AS1 directly binds nuclear factor 90 (NF90) and induces the interplay between NF90 and the *VEGFA* mRNA, thus enhancing *VEGFA* mRNA stability and facilitating CRC angiogenesis and metastasis.⁸² Moreover, LINC00346 can bind to the *ZNF655* mRNA by its Alu elements, thereby promoting the degradation of the *ZNF655* mRNA in a Staufen1-mediated mRNA decay manner. Furthermore, ANKHD1 targets LINC00346 and elevates its stability. *ZNF655* targets the promoter region of *ANKHD1* and forms a positive feedback loop that contributes to glioma angiogenesis.⁸³

Hypoxia plays an oncogenic role in angiogenesis, metabolism, tumor invasion, and metastasis. A novel lncRNA termed HIF-1 α inhibitor at translation level (HITT) is downregulated in colon cancer. Mechanistically, HITT inhibits HIF-1 α translation by directly interacting with YB-1 and blocking the interplay between YB-1 and the 5' UTR of HIF-1 α . Furthermore, HITT and HIF-1 α form an autoregulatory feedback loop, where HIF-1 α destabilizes HITT by inducing miR-205, which directly targets HITT for degradation.⁸⁴ In summary, lncRNAs play a diverse spectrum of roles by regulating mRNA

stability; thus, pharmacological targeting to modulate mRNA stability could serve as an antitumor angiogenesis strategy.

Angio-LncRs induce protein modifications

Accumulating studies have revealed that multifaceted functions of lncRNAs are achieved by protein modification to manipulate the activation of proteins. The post-translational protein modifications, such as phosphorylation and ubiquitination, have been modulated by distinct ncRNAs. lncRNAs also manipulate oncogenic and tumor-suppressive protein activation and stability, thereby manipulating tumor phenotypes involved in angiogenesis. For example, the lncRNA CamK-A is highly expressed in many human cancer types and activates the Ca²⁺/calmodulin-dependent kinase PNCK, which phosphorylates IκBα and triggers calcium-dependent NF-κB activation. This results in the active expression of the NF-κB target genes, such as *VEGF*, *GLUT3*, *IL-6*, and *IL-8*, promoting cancer microenvironment remodeling, including macrophage recruitment, angiogenesis, and tumor progression (Figure 2E).⁸⁵ Furthermore, the expression of FLNC was increased and associated with poor survival. Mechanistically, elevated FLNC prolonged the half-life of phosphorylated STAT3, promoting *VEGFA* transcription and inducing CRC angiogenesis. Moreover, pharmacological targeting of FLNC significantly suppressed the metastases of CRC.⁸⁶ lncRNA-MM2P levels are elevated during M2 polarization but decreased in M1 macrophages. Silencing of lncRNA-MM2P significantly inhibited M2 polarization and macrophage-induced tumorigenesis and tumor angiogenesis by regulating STAT6 phosphorylation.⁸⁷

In addition to modulating protein phosphorylation, lncRNAs mediate ubiquitination to regulate the activation and ubiquitination-dependent degradation of distinct proteins. As an example, lnc-CCDST is significantly downregulated in cervical cancer (CC) tissues. Mechanistically, lnc-CCDST interacts with DHX9 and enhances its degradation via the ubiquitin-proteasome pathway by recruiting the E3 ubiquitin ligase MDM2. In HPV-positive cell lines, HPV oncogenes E6 and E7 can abolish the negative effects of lnc-CCDST by increasing DHX9 expression, which facilitates CC cell motility and angiogenesis (Figure 2E).⁸⁸ Another lncRNA, NBAT1, inhibits GC progression and capillary tube formation. Further analysis uncovered that NBAT1 interacted with SRY-related high-mobility-group box 9 (Sox9) and reduced its protein stability by promoting polyubiquitination and proteasome-dependent degradation. Furthermore, Sox9 acts as a TF and interacts with the NBAT1 promoter to diminish its transcription, forming a negative feedback loop of NBAT1 and Sox9.⁸⁹ Similarly, TNK2-AS1 levels were markedly increased in non-small cell lung cancer (NSCLC) and promoted oncogenesis, angiogenesis, and metastasis. Mechanistically, TNK2-AS1 directly binds STAT3 and enhances its protein stability by weakening its proteasome-mediated degradation. In return, STAT3 occupies the *TNK2-AS1* promoter to promote its transcription. The positive feedback loop between TNK2-AS1 and STAT3 enhances STAT3 signaling by elevating *VEGFA* expression.⁹⁰ Taken together, lncRNAs directly or indirectly interact with key proteins through different mechanisms of action and orchestrate tumor angiogenesis

by impacting protein modifications such as phosphorylation and ubiquitination.

Angio-LncRs encode functional peptides

Although lncRNAs are not widely translated by definition, emerging studies have shown that lncRNAs can encode functional peptides to regulate various biological processes, including tumor progression.²⁶ As an example, Huang et al.¹¹² identified that the lncRNA HOXB-AS3 encodes a conserved 53-aa peptide that suppresses aerobic glycolysis and inhibits colon cancer growth. The biological effect of lncRNA-encoded peptides has attracted considerable attention. Moreover, this novel mode of action has been found to regulate tumor angiogenesis and progression. LINC00908, which encodes a 60-aa functional polypeptide termed automatic speech recognition and processing server (ASRPS; a small regulatory peptide of STAT3), is downregulated in triple-negative breast cancer (TNBC). ASRPS directly interacts with STAT3 through the coiled-coil domain and diminishes STAT3 phosphorylation, resulting in VEGF expression inhibition. In a mouse xenograft breast cancer model, silencing of ASRPS promoted tumor growth and angiogenesis, which suggested that LINC00908 and its encoded ASRPS are potential prognostic markers and therapeutic targets for TNBC (Figure 2F).⁹¹ However, circRNAs may be evolutionarily conserved in a wide range of species compared with most peptides encoded by lncRNAs,¹¹³ in which the expression pattern of angiogenesis-mediating circRNAs plays a fundamental role in transcriptional regulation for tumor progression. To date, the functional peptides encoded by lncRNAs have been applied in cancer diagnostics, prognostics, and therapy; this makes them potential new targets for drug development.

ANGIO-CircRs: MECHANISMS OF ACTION IN CANCERS

circRNAs may act as multifunctional regulators to modulate gene expression and signal transduction at multidimensional levels and influence the fate of their targets. Notably, emerging studies disclosed that circRNAs influence cellular functions in tumor progression-dependent angiogenesis. These functions of Angio-CircRs are described in detail below (Table 2; Figure 3).

Angio-CircRs regulate gene transcription

Emerging evidence shows that circRNAs function as epigenetic transcriptional regulators to manipulate distinct gene expression. A few circRNAs recruit specific proteins to certain cellular locations; for example, the circRNA FECR1 recruits TET1 to the promoter region of its host gene *FLII*, thereby demethylating the CpG sites and triggering transcription.⁶ Silencing of the cerebellar degeneration-related protein 1 transcript (CDR1as) promotes IGF2BP3-mediated melanoma invasion and metastasis via epigenetic silencing of LINC00632 in a miR-7-independent manner.¹²⁴ Notably, CCA-associated circRNA 1 (circ-CCAC1) is elevated in cancerous bile-resident extracellular vesicles (EVs) and tissues and epigenetically accelerates CCA tumorigenesis and metastasis. Furthermore, CCA-derived EVs transfer circ-CCAC1 to endothelial monolayer cells and promote angiogenesis by disrupting endothelial barrier integrity. Functional

Table 2. The emerging roles of Angio-CircRns in various cancers

Mechanism/level	circRNA	Expression	Function	Molecular mechanism	Cancer type	Refs.
Epigenetic and transcriptional regulation	circ-CCAC1	up	pro-angiogenesis	Increases SH3GL2 expression by sequestering EZH2 in the cytoplasm	CCA	12
	circSMARCA5	down	anti-angiogenesis	interacts with SRSF1 to regulate VEGFA mRNA Splicing	GBM	114
Splicing and mRNA stability	circPOK	up	pro-angiogenesis	promotes the ILF2/3 complex to bind and stabilize interleukin (IL)-6 and VEGF mRNA	mesenchymal tumor	115
	circRhoC	up	pro-angiogenesis	directly binds and modulates VEGFA expression, sponges miR-302e to regulate VEGFA expression	ovarian cancer	57
Interacting with RBPs	circ-GLI1	up	pro-angiogenesis	interacts with p70S6K2 to upregulate Cyr61 via inducing activation of Hedgehog/GLI1 and Wnt/ β -catenin pathways	melanoma	116
	circ-ATXN1	up	pro-angiogenesis	sponges miR-526b-3p to upregulate the expression of MMP2/VEGFA	glioma	117
Sequestering miRNAs	circSCAF11	up	pro-angiogenesis	sponges miR-421 to promote SP1 expression, which activates the transcription of VEGFA	glioma	118
	circRNA-MYLK	up	pro-angiogenesis	sponges miR-29a to trigger VEGFA/VEGFR2 and the downstream Ras/ERK signaling pathway	bladder carcinoma	119
	circ0001429	up	pro-angiogenesis	sponges miR-205-5p to increase VEGFA expression	bladder cancer	120
	circCCT3	up	pro-angiogenesis	sponges miR-613 to upregulate VEGFA and WNT3 expression	CRC	121
	circ_0056618	up	pro-angiogenesis	sponges miR-206 to upregulate CXCR4 and VEGFA	CRC	122
	circHIPK3	down	anti-angiogenesis	sponges miR-558 to inhibit the expression of HPSE	bladder cancer	123

Expression is in relation to normal tissue. These studies used human tissue samples. All circRNAs were measured with qRT-PCR in these studies. GBM, glioblastoma multiforme; PDAC, pancreatic ductal adenocarcinoma.

assays uncovered that circ-CCAC1 strengthens cell leakiness by sequestering EZH2 in the cytoplasm, thus promoting *SH3GL2* transcription to decrease intercellular junction protein levels. Additionally, circ-CCAC1 facilitates CCA progression via sponging miR-514a-5p to enhance YY1 translation. YY1 acts as a TF to activate *CAMLG* transcription by directly binding to its promoter (Figure 3A).¹² Overall, current studies have shown that circRNAs influence angiogenesis by epigenetically inducing gene transcription, establishing a favorable microenvironment for tumor progression.

Angio-CircRns mediate splicing and mRNA stability

In addition to regulating gene transcription, circRNAs appear to orchestrate tumor angiogenesis by impacting post-transcriptional processes such as alternative splicing and mRNA stability. For example, circSMARCA5 regulates the *VEGFA* mRNA splicing by interacting with the splicing factor serine and arginine-rich splicing factor 1 (SRSF1), resulting in the production of pro-angiogenic (Iso8a) and anti-angiogenic (Iso8b) mRNA isoforms of *VEGFA* in GBM. SRSF1, a proximal splice site of *VEGF*, promotes the expression of pro-angiogenic isoforms (VEGF-Axxxx), contributing to tumor angiogenesis. This study shows that circSMARCA5 is an upstream regulator of the ratio of pro-angiogenic to anti-angiogenic *VEGFA* isoforms within GBM cells, which suggests that circSMARCA5 acts

as a promising prognostic anti-angiogenic biomarker (Figure 3B).¹¹⁴ Another novel circRNA, circPOK, is encoded by the *Zbtb7a* gene in mesenchymal tumor progression. circPOK interacts with the ILF2/3 protein complex and enhances its ability to stabilize the *VEGF* mRNA, thereby inducing pro-angiogenic and pro-proliferative roles in tumor growth. circPOK binds to the promoter of *Il6* as a transcriptional co-activator of ILF2/3, resulting in enhanced *Il6* transcription. These findings indicate that circPOK exerts diverse functions in regulating mRNA transcription and stability (Figure 3B).¹¹⁵ Therefore, targeting angiogenesis-related circRNAs during cancer development and metastasis may be a promising RNA-based therapeutic approach.

Angio-CircRns interacting with RBPs

RBPs exert fundamental roles in orchestrating protein expression, RNA metabolism, and transport and localization of distinct transcripts.¹²⁵ The binding of circRNAs to RBPs has a wide range of functions, such as affecting epigenetic regulation, transcriptional regulation, splicing regulation, and the formation of circRNAs themselves.^{34,39,114} Recent studies have shown that circRNAs directly bind to VEGFs and thus regulate tumor angiogenesis. For example, circRhoC, derived from the *RhoC* mRNA, was significantly highly expressed in advanced-stage OC and contributed to OC angiogenesis and metastasis. Mechanistic analysis indicated that circRhoC

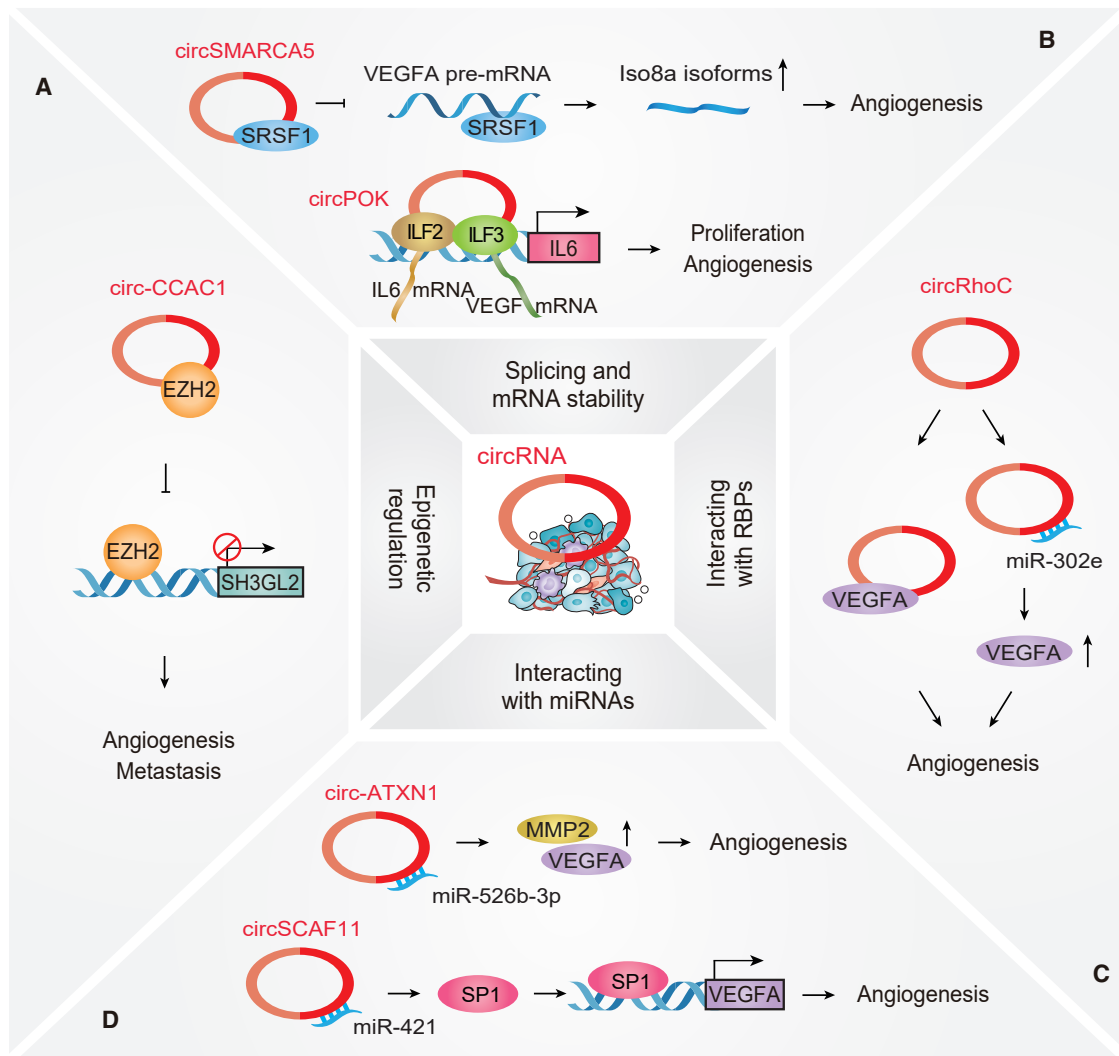


Figure 3. Mechanisms of action of Angio-CircRNAs in cancer progression

(A) circRNAs epigenetically mediate transcriptional regulation, e.g., circ-CCAC1. (B) circRNAs participate in splicing regulation and mRNA stability, e.g., circSMARCA5 and circPOK. (C) circRNAs directly interact with RBPs, e.g., circRhoC. (D) circRNAs act as molecular sponges to sequester miRNAs, e.g., circ-ATXN1 and circSCAF11.

functioned not only as a miR-302e sponge to promote VEGFA translation but also directly bound and regulated VEGFA expression (Figure 3C).⁵⁷ Additionally, circ-GLI1 interacted with p70S6K2 to induce GSK3 β phosphorylation at Ser9, thereby blocking the binding of GSK3 β with GLI1 and β -catenin, elevating their protein expression. This study uncovered that circ-GLI1 facilitates melanoma angiogenesis and metastasis by elevating Cyr61 via p70S6K2-dependent activation of the Hedgehog/GLI1 and Wnt/ β -catenin pathways.¹¹⁶ In summary, the interplay between circRNAs and RBPs could be a common mechanism that is deeply involved in diverse physiological processes.

Angio-CircRNAs act as miRNA sponges

It is well established that circRNAs sponge diverse miRNAs, which is the most extensive mechanism to regulate tumor angiogenesis. Earlier

studies identified many miRNA-binding sites on circRNAs.^{35,36} In tumor cells, circRNAs can also sponge miRNAs and elevate the expression of angiogenic mediators such as VEGF and VEGFA.¹²⁶

A typical example is circ-ATXN1 that can facilitate cell viability, migration, and angiogenesis of glioma-exposed endothelial cells (GECs) by sponging miR-526b-3p to upregulate the expression of MMP2 and VEGFA (Figure 3D).¹¹⁷ Additionally, in gliomas, circSCAF11 activates VEGFA expression by targeting miR-421 to upregulate the TF SP1 (Figure 3D).¹¹⁸ As another example, circRNA-MYLK could sponge miR-29a in BCa, further triggering VEGFA/VEGFR2 and Ras/ERK pathways, thereby promoting EMT, angiogenesis, and metastasis.¹¹⁹ In addition, circRNA-MYLK can sponge miR-513a-5p and upregulate the expression of

VEGFC, thereby promoting cell proliferation, metastasis, and angiogenesis in renal cell carcinoma.¹²⁷ Similarly, in BCa tissues, circ0001429 can increase the expression of VEGFA to promote cell proliferation, migration, and invasion by sponging miR-205-5p.¹²⁰ In CRC, the expression of circ-001971, circCCT3, and circ0056618 was significantly increased, contributing to VEGFA expression. They function as ceRNAs through the adsorption of diverse miRNAs and promote cell proliferation, migration, invasion, and angiogenesis.^{121,122,128}

In addition to VEGF, circRNAs regulate the expression of other angiogenic regulators by modulating miRNAs to control tumor angiogenesis. A study uncovered that circ0020710 acts as a molecular sponge to adsorb miR-370-3p, promoting CXCL12 expression in melanoma. Its downstream CXCL12/CXCR4/CXCR7 axis mediates angiogenesis, tumor development, and recruitment of immunosuppressive cells.¹²⁹ circPRRC2A sponges miR-6776-5p and miR-514a-5p to prevent the degradation of the *TRPM3* mRNA, thereby promoting angiogenesis and metastasis of renal cell carcinoma.¹³⁰ Another circRNA, SHKBP1, upregulates FOXP1 and FOXP2 expression by sponging miR-544a and miR-379, respectively, in glioma, while FOXP1/FOXP2 transcriptionally promote AGGF1 expression to facilitate viability, migration, and tube formation of GECs through the PI3K/AKT/ERK pathway.¹³¹ Similarly, circ-DICER1 and circ002136 promote the tube formation of GECs by the sponging of miRNAs and the resulting upregulation of ZIC4 and SOX13.^{132,133} Additionally, in pancreatic ductal adenocarcinoma (PDAC), hsa_circ_001653 promotes the restoration of cell cycle progression, angiogenesis, and invasiveness, sequestering miR-377 and elevating HOXC6 expression.¹³⁴ circ-ASH2L regulates Notch 1 expression by sequestering miR-34a, promoting tumor invasion, proliferation, and angiogenesis.¹³⁵ hsa_circ_0000092 sponges miR-338-3p to upregulate HN1 in HCC, and hsa_circRNA_002178 sponges miR-338-3p to upregulate COL1A1 in breast cancer, thus promoting angiogenesis.^{136,137} On the contrary, circHIPK3 is decreased in BCa and inversely correlates with cancer grade and lymph node metastasis. Functional assays uncovered that circHIPK3 inhibited the expression of heparanase (HPSE) by sponging miR-558.¹²³ Altogether, these studies indicate that circRNAs extensively modulate miRNAs to regulate angiogenesis, which provides a novel insight to guide tumor therapy through targeting circRNAs.

EMERGING PARADIGMS OF lncRNAs AND circRNAs IN ANGIOGENESIS

Angio-lncRs and Angio-CircRs induce cancer onset and progression

Increasing numbers of studies have shown that lncRNAs and circRNAs orchestrate tumor proliferation, migration, invasion, metastasis, and the local microenvironment for tumor cell colonization.^{138,139} Herein, we provide examples of studies on Angio-lncRs and Angio-CircRs from the perspective of immune escape, EMT and migration, intravasation and extravasation, and the pre-metastasis niche (Figure 4).

Immune escape has always been considered a crucial step in tumor development and progression, including the recruitment of immune cells and macrophage M1/M2 (classically activated/ alternatively activated) polarization.^{140,141} lncRNAs can serve as key regulators of macrophages to impact innate immunity. For example, lncRNA-MM2P and SNHG15 promoted M2 polarization of macrophages, and CamK-A was involved in macrophage recruitment.^{85,87,142} EMT is a cellular process that causes cancer cells to attenuate epithelial characteristics and acquire mesenchymal characteristics, separating them from neighboring cells and allowing them to migrate and invade more efficiently.^{143–145} GATA6-AS increases TGF- β -induced EMT and promotes the formation of blood vessels in mice.⁹⁴ MALAT1 promotes angiogenesis and EMT in CRC by elevating VEGFA, SLUG, and TWIST expression.⁷¹ The circRNA-MYLK contributes to EMT and BCa development by activating VEGFA/VEGFR2 and its downstream Ras/ERK signaling pathways.¹¹⁹ Another circRNA, circ-CSPP1, promotes EMT and OC development by upregulating EMT-related markers.¹⁴⁶ Intravasation and extravasation are the biological processes by which invasive cancer cells pass in and out of circulation through the walls of blood vessels and spread to the site of metastasis.¹⁴⁷ A recent study uncovered that circ-CCAC1 could destroy the endothelial barrier integrity and promote angiogenesis by interacting with EZH2.¹² lncRNA-ATB can mediate TGF- β to promote EMT, invasion, intravasation, and colonization of tumor cells.^{148,149} Furthermore, the pre-metastatic niche is the changed supportive microenvironment of distant organs and tissues before the tumor cells reach the site of metastasis, including the changes in cellular constituents, immune status, blood supply, and extracellular matrix (ECM). In particular, fibroblasts and ECM dynamics are involved in the adhesion, growth, and metastasis of tumor cells.^{150,151} H19 promotes the expression of key ECM-remodeling genes through a variety of mechanisms.¹⁵² Additionally, functional enrichment analysis suggested that CDR1as was associated with angiogenesis, ECM organization, and especially interaction with ECM receptor to modulate the tumor microenvironment.¹⁵³ MALAT1 and the lncRNA XIST can mediate the expression and secretion of fibroblast growth factor (FGF).^{154,155} Current studies indicate that lncRNAs and circRNAs manipulate the progression of diverse cancers via modulating the tumor microenvironment. The new links between Angio-lncRs/Angio-CircRs and multistep tumor progression will open up a new perspective for ncRNA-induced angiogenesis, thus accelerating rational development of antitumor treatment strategies from an anti-angiogenic perspective.

The potential clinical application of lncRNAs and circRNAs

As discussed above, Angio-lncRs and Angio-CircRs contribute to tumor progression by manipulating a plethora of phenotypes, including tumor angiogenesis, cell proliferation, EMT, apoptosis, and metastasis. Therefore, Angio-lncRs and Angio-CircRs could act as promising biomarkers and efficacious therapeutic targets for tumor therapy. To date, only a small portion of lncRNAs and circRNAs have been used as promising tools for diagnostic, prognostic, and therapeutic biomarkers in the clinical application for

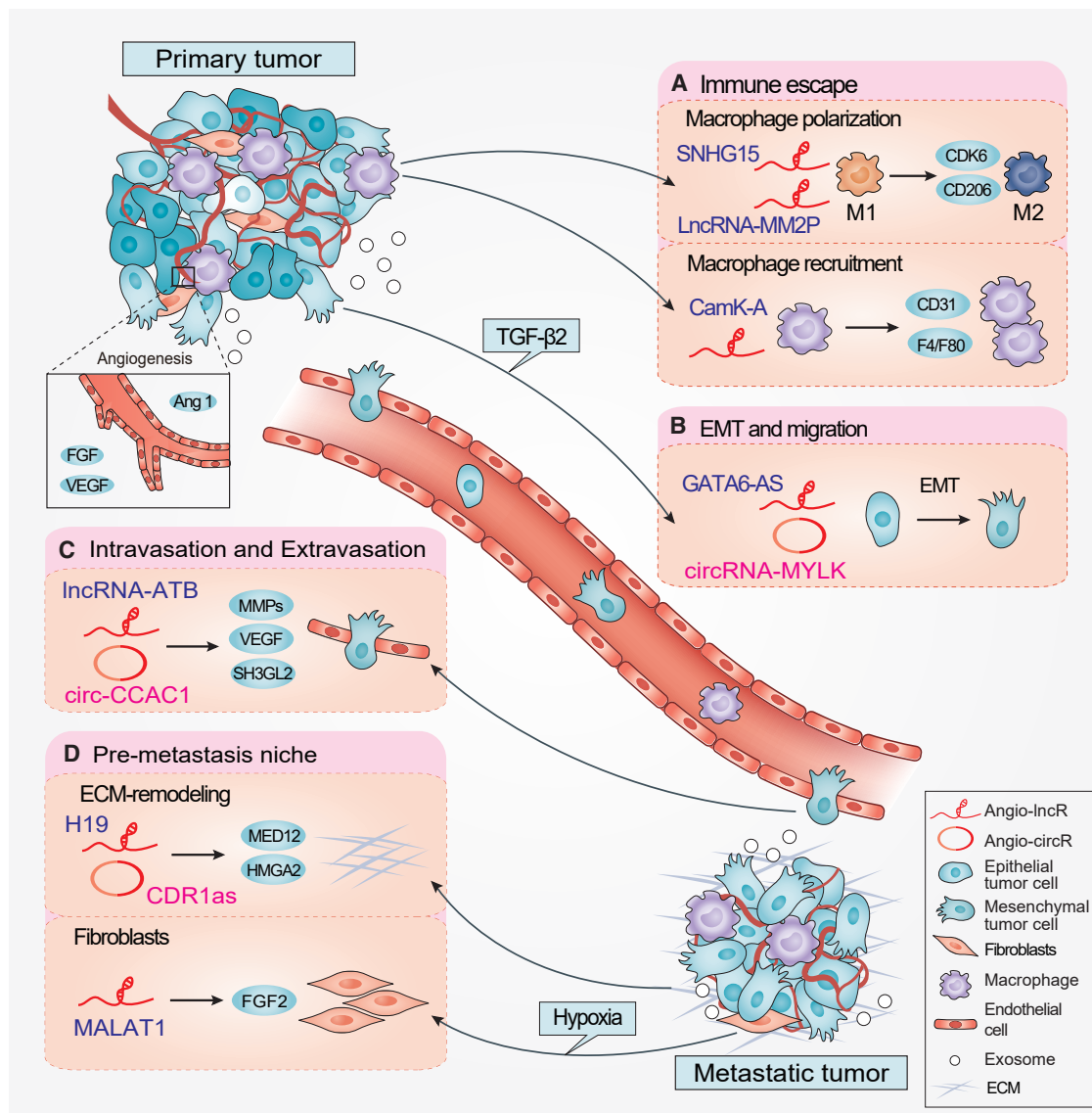


Figure 4. Angio-LncRs and Angio-CircRs in the multistep tumor progression

(A–D) Angio-LncRs and Angio-CircRs exert diverse regulatory roles in tumor progression and metastasis, including (A) immune escape (e.g., SNHG15, LncRNA-MM2P, and CamK-A), (B) EMT and migration (e.g., GATA6-AS and circRNA-MYLK), (C) intravasation and extravasation (e.g., lncRNA-ATB and circ-CCAC1), and (D) the pre-metastatic niche (e.g., H19, CDR1as, and MALAT1).

diverse tumors (Figure 5).^{156,157} A few tumor Angio-LncRs, such as H19, MALAT1 and HULC, can be used as plasma biomarkers in a plethora of cancers.^{158–161} In the case of tumor Angio-CircRs, circHIPK3 can be used as a biomarker for the prognosis of various tumors and new therapies in patients with NPC.¹⁵⁷ hsa-circRNA-002178 could be used as a potential non-invasive biomarker for the early detection of LUAD and could act as a potential target of immune therapy.¹⁶² However, diverse functional identifications need to be explored *in vivo* and *in vitro* to target Angio-LncRs/Angio-CircRs as novel and promising therapeutic options in the clinical setting.

Targeting Angio-LncRs and Angio-CircRs might represent a promising strategy for inhibiting tumor development and progression. Currently, RNA-based therapeutic approaches mainly include RNA interference (RNAi) and antisense oligonucleotides (ASOs), designed to target diverse RNAs and specific regions. The first RNAi-based drug patisiran was approved by the US Food and Drug Administration to treat hereditary transthyretin amyloidosis.¹⁶³ ASOs have also displayed a promising prospect in targeting lncRNAs in a study on patients with Angelman syndrome.¹⁶⁴ Similarly, intravenous treatment with ASOs targeting lncRNAs TUG1 and PVT1 can inhibit tumor proliferation and differentiation by combining with the drug

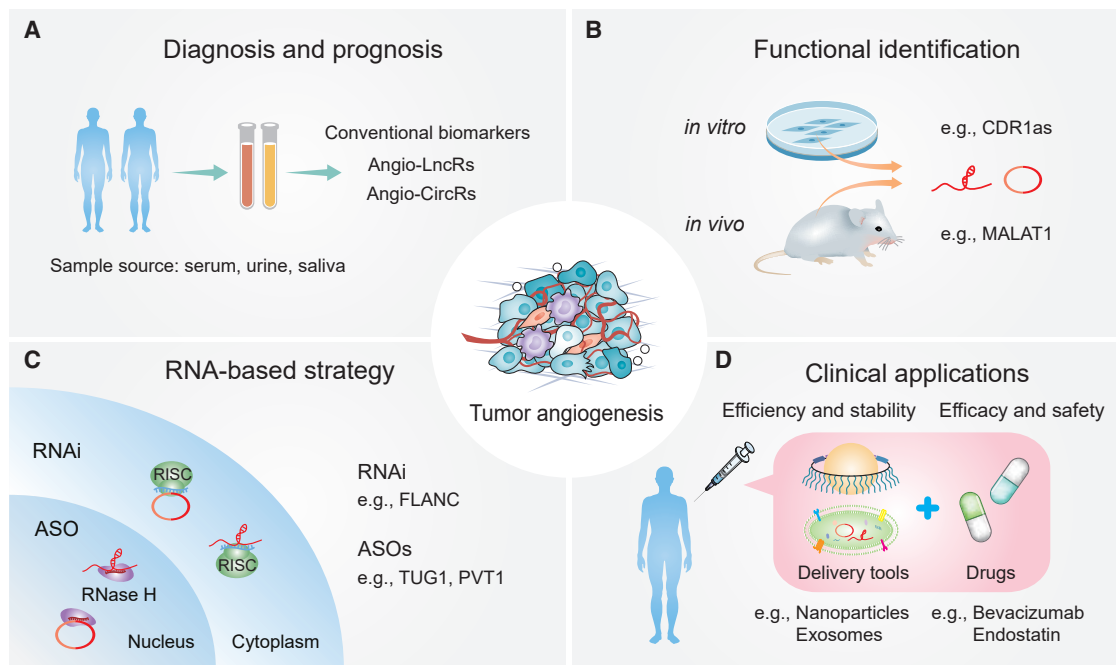


Figure 5. The potential clinical application of Angio-LncRs and Angio-CircRs

(A) These Angio-LncRs and Angio-CircRs can be detected from tumor patient samples and are potential diagnostic and prognostic biomarkers. (B) The functional identifications of Angio-LncRs and Angio-CircRs have been elucidated in preclinical models. (C) RNA-based strategy can effectively target Angio-LncRs and Angio-CircRs in the cytoplasm and nucleus. (D) Combination of targeting ncRNAs and using conventional anti-angiogenic agents enhance therapeutic efficacy through diverse delivery tools *in vivo*.

delivery system.^{165,166} *In vivo* RNAi and pharmacological therapeutic strategy targeting FLANC significantly suppressed tumor angiogenesis and CRC metastasis, while specific small interfering RNAs (siRNAs) significantly suppress the metastases.⁸⁶ Using a double-stranded DNA plasmid, DTA-H19-targeting cancer cells that overexpress H19 induced diphtheria toxin-A expression, thereby reducing the size of multiple tumor types.¹⁶⁷ In addition, emerging research suggests that the peptides encoded by Angio-CircRs have increasing potential for tumor therapy. As in TNBC, the peptide ASRPS encoded by LINC00908 can inhibit tumor angiogenesis, and the peptide CIP2A-BP encoded by LINC00665 can significantly reduce invasion and metastasis, indicating that they are effective anti-TNBC peptides.^{91,168} In the future, the combinatorial application of conventional therapy with targeting Angio-LncRs or Angio-CircRs adds synergy in anti-angiogenic cancer therapy, which broadens our understanding of the progress made in cancer therapy.

Accumulating studies have uncovered that a variety of Angio-LncRs and Angio-CircRs regulate chemotherapy resistance, radiotherapy sensitivity, and immunotherapeutic tolerance. For example, some Angio-LncRs, such as MALAT1, MEG3, and CRNDE, are involved in resistance to 5-fluorouracil, adriamycin, mitomycin, and oxaliplatin in distinct cancers.¹⁶⁹⁻¹⁷¹ Similarly, Angio-CircRs also influence chemotherapy resistance in different cancers. For example, the upregulation of circ-SMARCA5 can enhance the sensitivity of intrahepatic

CCA cells to cisplatin and gemcitabine.¹⁷² hsa_circ_0023404 was up-regulated in cervical tumor cells to promote cisplatin resistance.¹⁷³ In addition, cZNF292 increased the hypoxic tumor cell radiosensitivity of radiotherapy in HCC.¹⁷⁴ hsa-circRNA-002178 can enhance the expression of programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) in tumor cells and T cells and enhance immunotherapy tolerance.¹⁶² To date, several anti-angiogenic drugs such as bevacizumab have been approved in targeting angiogenesis for tumor therapy.¹⁶ However, there are no clinical applications for targeting Angio-LncRs/Angio-CircRs in tumor therapy. Therefore, the detection of lncRNA and circRNA levels in various patients could predict the efficacy and safety of various drugs and suggest implementing different therapeutic doses or methods to promote individualized treatment regimens. Altogether, the development of new biomarkers and treatment strategies for Angio-LncRs and Angio-CircRs could develop potential clinical significance for tumor treatment.

CONCLUSIONS AND FUTURE PERSPECTIVES

This review emphasizes the emerging functions and mechanisms of angiogenic lncRNAs and circRNAs in tumor progression and their potential diagnostic and therapeutic applications. Importantly, Angio-LncRs and Angio-CircRs orchestrate the carcinogenesis and development of diverse cancers via a broad repertoire of molecular mechanisms. We highlight the common dysregulation of

Angio-LncRs and Angio-CircRs in tumor progression to manipulate multiple signaling pathways associated with angiogenesis, cell proliferation, EMT, apoptosis, and metastasis. Additionally, exploring the functional commonalities between lncRNAs and circRNAs may provide a vital hint to understand the biological functions of ncRNAs and suggest clinical values of Angio-LncRs and Angio-CircRs in tumor angiogenesis.

Since the exact mechanisms of action of lncRNAs and circRNAs have not been fully elucidated, their known roles in cancer biology may represent only the tip of the iceberg. Some Angio-LncRs and Angio-CircRs may have multiple levels of mechanical functions in tumor angiogenesis. For instance, PVT1 can not only regulate chromatin remodeling, transcriptional activation, and protein modification, but it also can adsorb a variety of miRNAs regulating downstream target genes.¹⁷⁵ Besides affecting angiogenesis, Angio-LncRs and Angio-CircRs also influence multiple different functional phenotypes. For example, MALAT1 regulates EMT, migration, invasion, metastasis, and ECM remodeling.¹⁷⁶ In that this review focuses on the roles of Angio-LncRs and Angio-CircRs in tumor angiogenesis, we did not elaborate on other functional mechanisms.

Although lncRNAs and circRNAs have shown attractive breakthroughs and prospects, the field is yet to conquer certain challenges and limitations. Utilizing or developing novel technologies, such as CRISPR-mediated gene editing and genome-wide chromatin interrogation, will continue to accelerate advances in preclinical studies for antitumor treatment.¹⁸ The development of RNA sequencing (RNA-seq), global run-on sequencing (GRO-seq), and quantitative RT-PCR (qRT-PCR) techniques has greatly improved the ability to determine the transcription and expression of genes and to elucidate the function of ncRNAs. Moreover, siRNA or short hairpin RNA (shRNA) is often used to silence ncRNAs, and the RNA pull-down assays or immunoprecipitation (RIP) has helped elucidate the interaction between ncRNAs and proteins.^{18,177} Emerging advancements in new technologies and approaches provide exciting opportunities for ncRNA research and its translation to the clinic. However, *in vivo* treatment strategies related to lncRNAs and circRNAs are still limited because of their poor intracellular uptake and stability. Currently, liposomes, lentiviruses, adenoviruses, exosomes, and nanoparticles are commonly used *in vivo* delivery systems for lncRNAs and circRNAs.^{178–181} Future studies, combined with novel technologies, should focus on delivering lncRNAs and circRNAs to target cells in a tissue-specific manner.

Despite current challenges and limitations, significant advances in the field of Angio-LncR and Angio-CircR research are nonetheless being made. Recent advances describing the functions and mechanisms of angiogenic lncRNAs and circRNAs facilitate cancer diagnosis. However, there are a series of key questions to be answered. Are a series of angiogenic ncRNAs more promising as diagnostic markers in angiogenic diseases? Does targeting angiogenic ncRNAs have any impact on the expression of essential genes in normal and tumor tissues? Could the combination of targeting ncRNAs and using conventional

anti-angiogenic agents enhance therapeutic efficacy in heterogeneous tumors? In essence, exploring the functional commonalities between lncRNAs and circRNAs may provide a vital hint to understand the biological functions of ncRNAs. Understanding the mechanism of interaction between lncRNAs or circRNAs and other biomolecules may identify certain lncRNAs and circRNAs that have the potential to be used as biomarkers or therapeutic targets in tumor angiogenesis; this would be a major advance in the beneficial treatment of cancer patients.

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AUTHOR CONTRIBUTIONS

Z.M. conceived the review. Z.M., H.-W.X., and Q.Z. wrote and revised the manuscript. C.-G.L., J.L., and Y.X. drafted the manuscript and prepared the figures. W.L. and S.-X.F. helped to modify the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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