The role of long non-coding RNAs in angiogenesis and anti-angiogenic therapy resistance in cancer

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It is well known that long non-coding RNAs (lncRNAs) play an important role in the regulation of tumor genesis and development. They can modulate gene expression of transcriptional regulation, epigenetic regulation of chromatin modification, and post-transcriptional regulation, thus influencing the biological behavior of tumors, such as cell proliferation, apoptosis, cell cycle, invasion, and migration. Tumor angiogenesis not only provides nutrients and helps excrete metabolites, but it also opens a pathway for tumor metastasis. Anti-angiogenic therapy has become one of the effective treatment methods for tumor. But its drug resistance leads to the limitation of clinical application. Recent studies have shown that lncRNAs are closely related to tumor angiogenesis and anti-angiogenic therapy resistance, which provides a new direction for tumor research. lncRNAs are expected to be new targets for tumor therapy. For the first time to our knowledge, this paper reviews advancement of lncRNAs in tumor angiogenesis and anti-angiogenic therapy resistance and further discusses their potential clinical application.

INTRODUCTION

Currently, cancer is a major public health problem worldwide and results in heavy social and economic burden.[1] The latest Global Cancer Date Report indicates that an estimated 19.3 million new cancer cases and nearly 10 million cancer deaths occurred worldwide in 2020.[2] The occurrence and development of tumors is an intricate process affected by multiple factors and manifested in multiple stages, among which angiogenesis plays an insignificant role.[3] Angiogenesis is a commonality of almost all solid tumors, concerned with tumor grade, malignancy, and poor clinical outcomes.[4,5] Anti-angiogenic therapy has come into being. The combination of anti-angiogenic therapy and other treatment methods has been proven effective.[6–8] Whereas, many studies have shown that anti-angiogenic therapy, like other anti-tumor drugs, inevitably develops drug resistance.[9] It has been discovered that about three-quarters of the human genome can be transcribed, but nearly 98% of the human genome does not encode proteins, and only 2% does.[10] Non-coding RNAs (ncRNAs) without protein-coding function are considered to be non-functional evolutionary junk.[11] As gene sequence technology has developed rapidly, the lncRNA, which is a type of ncRNA with a length of more than 200 nucleotides, has been extensively studied over the past decade.

Examples of lncRNAs regulating tumor and therapeutic resistance are nothing new.[12–16] Our research group found LINC01234 was significantly upregulated in gastric cancer (GC) and non-small cell lung cancer (NSCLC), associated with poor prognosis. LINC01234 upregulated CBFB via sponge miR-204-5p to boost the occurrence and development of GC.[17] A positive feedback loop, c-Myc–LINC01234–HNRNPA2B1–miR-106b-5p–CRY2–c-Myc, was crucial to the progression of NSCLC.[18] It also promoted NSCLC metastasis by activating VAV3 as a miR-27b-3p/miR-340-5p ceRNA or directly inhibiting BTG2.[19] In addition, lncRNA CASC9 promoted NSCLC resistance to gefitinib by recruiting EZH2 to inhibit DUSP1.[20] With the deep-going research, the function of lncRNAs in angiogenesis and anti-angiogenic therapy resistance has been revealed in cancer.[21,22] Here, we first summarize the roles of lncRNAs in tumor angiogenesis and anti-angiogenic therapy resistance.

lncRNAs

The lncRNA is mainly transcribed from the antisense chains and spacers of protein-coding genes. Compared with protein-coding RNAs, lncRNAs are expressed at a lower level but are still characterized by tissue and cell specificity, high interspecific conservation, and high coefficient of variation.[23] lncRNAs are involved in biological processes through adjustment of gene expression, including transcriptional regulation, epigenetic regulation of chromatin modification, and post-transcriptional regulation.[24–29] For instance, lncRNA H19 stimulated osteogenic differentiation of bone marrow mesenchymal stems cells by means of targeting the miR-149/SDF-1 axis.[30] Importantly, lncRNAs are also involved in many pathological processes to influence many diseases,[25] especially tumors.[31] According to their effects, they can be divided into oncogenes and suppressor genes. lncRNA VCAN-AS1 promotes the progression of GC by interacting with eIF4A3 to downregulate p53.[32] On the contrary, lncRNA GAS5 inhibits the metastasis of GC via positively modulating p53.[33] Firstly, lncRNAs are expressed in almost all types of cancers. Secondly, lncRNAs are expressed variously in the same tumor tissue or
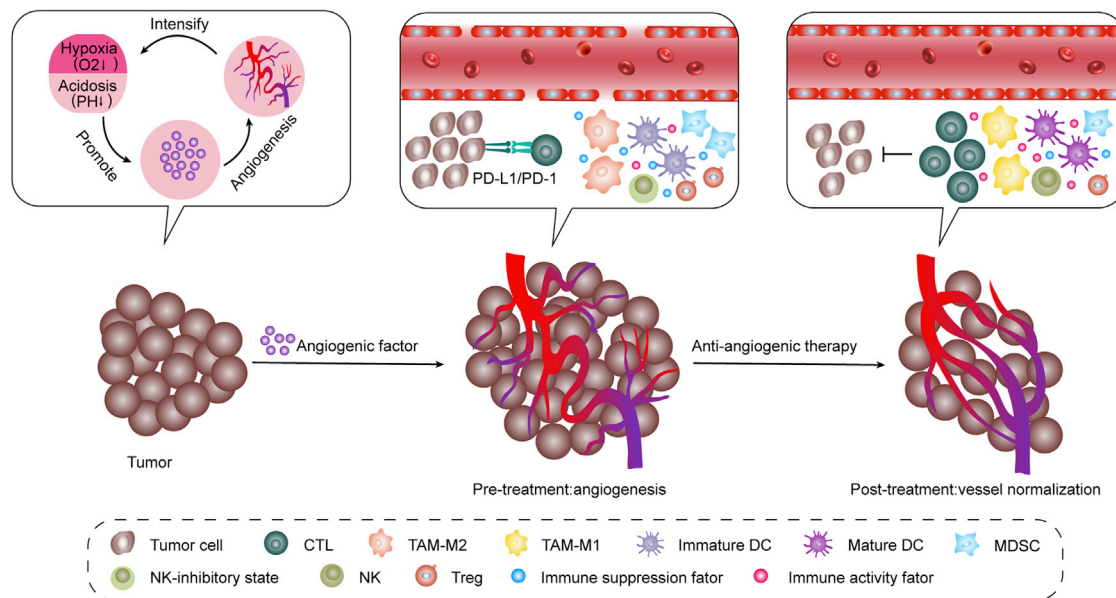
Figure 1. Relationship between tumor angiogenesis and immune microenvironment before and after anti-angiogenic therapy

cell. Using gene chip technology, He et al. found 2,669 upregulated and 3,506 downregulated lncRNAs in GC.[34] And last, the expression levels of the same lncRNA are different in disparate tumors. H19 is upregulated in GC,[35] breast cancer,[36] colorectal cancer (CRC),[37] cholangiocarcinoma,[38] and NSCLC.[39] But it is downregulated in papillary thyroid carcinoma.[40]

ANGIOGENESIS AND ANTI-ANGIOGENIC THERAPY

In 1971, Folkman first proposed the hypothesis that tumor growth and metastasis depended on angiogenesis.[41] Angiogenesis is a highly dynamic, sophisticated process. New blood vessels are generated from existing germinated or ungerminated vascular beds, including degradation of vascular basement membranes; activation, proliferation, and migration of vascular endothelial cells; and reconstruction of new blood vessels and vascular networks.

Tumor micro environment (TME) refers to the local internal environment composed of locally infiltrated immune cells, mesenchymal cells, extracellular matrix, and active mediators, together with tumor cells and tumor stem cells, namely the site of angiogenesis.[42,43] Due to the rapid growth of tumor cells, the blood supply cannot meet the growth needs of tumor cells, leading to hypoxia and acidosis in the TME. Hypoxia induces cells to produce proangiogenic factors, which turn on the switch of tumor angiogenesis.[44] The continuous secretion of proangiogenic factors in the TME leads to abnormal vascular structure with a circuitous leakage state, and ultimately it results in poor blood perfusion of the tumor. This result further aggravates hypoxia and acidosis in the TME. Abnormal tumor blood vessels cause the immunosuppressive state of TME.[45] A large number of immunosuppressive cells and factors are released and collected, including myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs),

M2 phenotype of tumor associated macrophages (TAMs), T regulatory cells (Tregs), IL-10, TGF-β, and so on. The increased expression of PD-L1 in tumor cells inhibited the infiltration of cytotoxic T lymphocyte (CTL) to tumor cells. The cytotoxic effect of NK cells is reduced or even inactivated. The differentiation and maturation of DCs are inhibited, and the antigen presenting ability is decreased. The immunosuppressive state of TME eventually gives rise to immune escape of tumor cells. In addition, hypoxia can induce dedifferentiation of tumor cells and enhance the stem cell phenotype of tumor cells.[46] Anti-angiogenic therapy can inhibit angiogenesis and normalize abnormal tumor blood vessels. Vascular normalization can reprogram the immunosuppressive state into an immune activated state, and the activation of immune cells can in turn promote vascular normalization, thus forming a good positive feedback loop (Figure 1).[47,48] It is the theoretical basis for anti-angiogenic therapy in combination with immune checkpoint inhibitors in the treatment of malignancies.[49]

In February 2004, the US FDA authorized bevacizumab in combination with 5-FU for the first-line treatment of metastatic colorectal cancer.[50] Up to now, angiogenesis theory and inhibitors have gained widespread acceptance. At present, anti-angiogenic drugs are divided into three categories: (1) macromolecular monoclonal antibodies (bevacizumab, ramucirumab), (2) small molecule multi-target anti-angiogenic drugs (sorafenib, sunitinib, and so on), and (3) endostatin (endostar). Anti-angiogenic therapy is more effective in combination with other anti-tumor therapies, especially immunotherapy. Compared with bevacizumab + chemotherapy, atezolizumab + bevacizumab + chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS) of patients with metastatic non-squamous NSCLC, no matter what PD-L1 and EGFR or ALK gene altered status.[51]
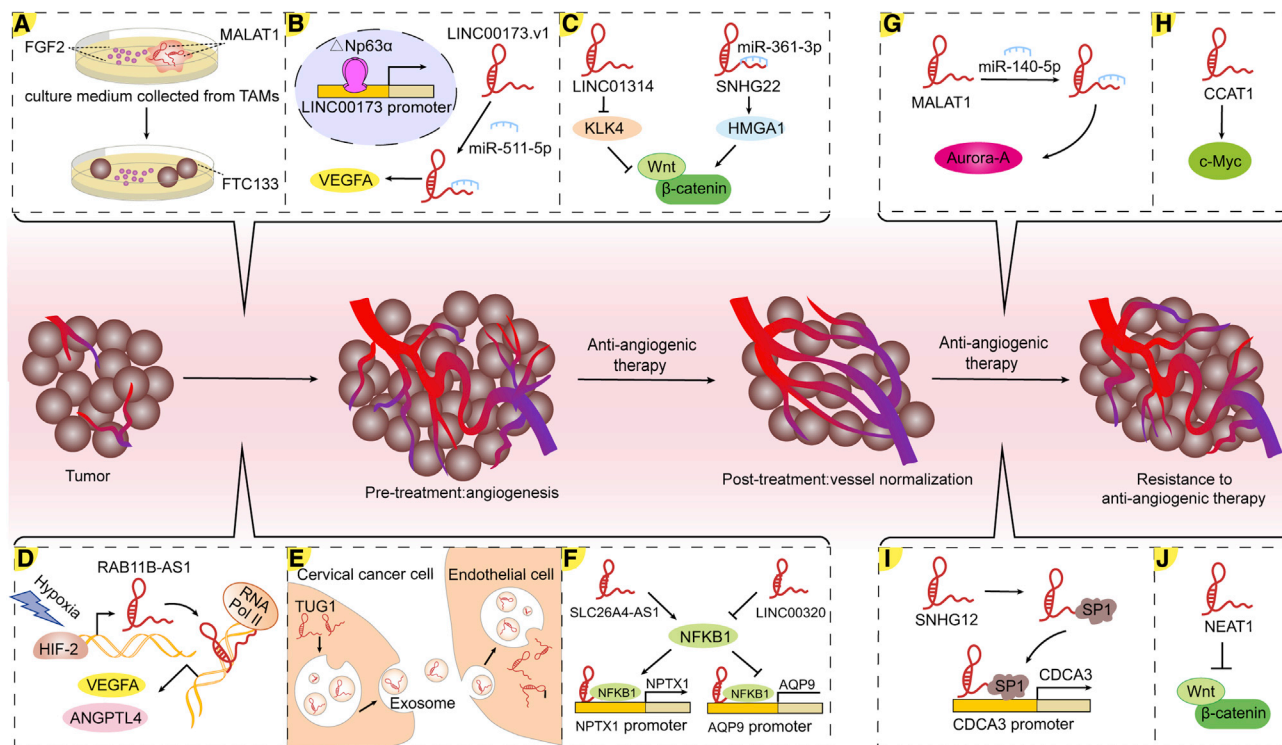
Figure 2. The partial mechanisms of lncRNAs involved in tumor angiogenesis and resistance to anti-angiogenic therapy

Choueiri et al. first reported that avelumab combined with axitinib improved PFS in patients with advanced clear cell renal cancer (RC).[52] However, the resistance of anti-angiogenic therapy critically imposes restrictions on its clinical application.[53,54]

CORRELATION BETWEEN lncRNAs AND ANGIOGENESIS IN CANCER

lncRNAs can regulate angiogenesis in cardiovascular disease,[55,56] diabetes,[57,58] and even tumors. It is common knowledge that the vascular endothelial growth factors (VEGF), Notch, and angiogenin (Ang) signaling pathways are the vital signaling pathways involved in angiogenesis.[59] lncRNAs are closely connected with angiogenesis and may regulate tumor angiogenesis (Figure 2, Table 1).

Head and neck tumors

Nasopharyngeal carcinoma (NPC) with obvious regional aggregation, most frequently occurring in Southeast Asian countries, is a malignant tumor usually occurring in the mucosa and epithelium of the nasopharynx.[76] Chen et al. reported a novel lncRNA SRRM2-AS that is regarded as a potential marker for angiogenesis in NPC. Overexpression of SRRM2-AS was confirmed in NPC tissues. Moreover, further investigations revealed that silencing SRRM2-AS inhibited angiogenesis in NPC by activating MYLK-mediated cGMP/PKG signaling pathway.[66] It was reported that lncRNA MALAT1 might be a new biomarker for thyroid cancer. Fibroblast growth factors 2 (FGF2) is a VEGF-independent angiogenic factor.[77] MALAT1 and FGF2 were dramatically overexpressed in thyroid cancer tissues and

cells (FTC133). It was noteworthy that both of them also presented high expression in TAMs. The culture medium (CM) from TAMs can effectively promote the proliferation, migration, and invasion of FTC133 cells. The CM from M2 macrophages and TAMs effectively increased the angiogenesis of human umbilical vein endothelial cells (HUVECs). After downregulation of MALAT1 in TAMs, the CM could restrain proliferation, migration, and invasion of FTC133 cells and reduce angiogenesis. The same results were observed when FGF2 in TAMs was downregulated. Mechanism studies have found that MALAT1 promoted angiogenesis and enhanced cell proliferation, migration, and invasion by mediating FGF2 protein secretion of TAMs in thyroid cancer (Figure 2A).[74]

Respiratory tumors

Lung cancer remains one of the leading causes of death from malignancies worldwide, despite significant reductions in the death rate from lung cancer after intensive research and standardized treatment.[2] The result of bioinformatics analysis implied LINC00173.v1 was mainly expressed in lung cancer tissues and significantly upregulated in lung squamous cell carcinoma. Overexpression of LINC00173.v1 was a symbol of poorer OS and PFS. This result was confirmed in situ hybridization. Silencing LINC00173.v1 inhibited the proliferation and migration of vascular endothelial cells in vivo and in vitro. The mechanism experiment proved that LINC00173.v1 increased the expression of VEGFA by sponging miR-511-5p to boost the proliferation and migration of vascular endothelial cells in lung squamous cell carcinoma. In a xenograft model of the mice,

Table 1. Correlation between lncRNAs and angiogenesis in tumors

Classification	LncRNA	Cancer	Expression	Mechanism	Biological functions	Ref
CeRNA	LINC00173.v1	lung squamous cell carcinoma	up	ΔNp63α/LINC00173.v1/ miR-511-5p/VEGFA axis	promoting tumorigenesis and angiogenesis	60
	MYLK-AS1	hepatocellular carcinoma	up	miR-424-5p/E2F7/VEGFR-2 axis	promoting proliferation, invasion, migration, and angiogenesis	61
	MALAT1		up	miR-140/VEGFA axis	promoting angiogenesis and changing polarization of macrophage	62
	SNHG17	colorectal carcinoma	up	miR-23a-3p/CXCL12 axis	promoting viability proliferation, migration, and angiogenesis	63
	SNHG22	gastric carcinoma	up	miR-361-3p/HMGA1/Wnt/ β-catenin axis	promoting proliferation, angiogenesis, and transition from G1 phase to S phase; inhibition of apoptosis	64
	TUG1	osteosarcoma	up	miR-143-5p/HIF-1α	promoting invasion and angiogenesis	65
Signaling pathway	SRRM2-AS	nasopharyngeal carcinoma	up	MYLK/cGMP/PKG axis	promoting proliferation, colony formation, angiogenesis; regulating cell cycle; inhibition apoptosis	66
	LINC01314	gastric carcinoma	down	KLK4/Wnt/β-catenin axis	inhibiting migration, invasion, and angiogenesis	67
Angiogenic factors and receptors	EPIC1	non-small cell lung cancer	up	Ang2/Tie2 axis	promoting angiogenesis	68
Recruitment of RNA polymerase	RAB11B-AS1	breast cancer	up	HIF-2/Rab11B-AS1/RNA Pol II/ VEGFA and ANGPTL4	promoting migration, invasion, angiogenesis, and distant metastasis	69
Exosome	TUG1	cervical cancer	up	exosome transfer	promoting angiogenesis	70
Gene transcription	LINC00261	prostate cancer	down	DKK3/GATA6/VEGF and CD31	inhibiting proliferation, migration, invasion, tumorigenicity, and angiogenesis	71
	SLC26A4-AS1	glioma	down	NFKB1/NPTX1	Inhibiting cell viability, proliferation, migration, invasion and angiogenesis	72
	LINC00320		down	NFKB1/AQP9	inhibit proliferation and angiogenesis	73
Tumor associated macrophage	MALAT1	thyroid cancer	up	TAMs FGF2 protein	promoting proliferation, migration, invasion, angiogenesis	74
Cancer stem cells	H19	hepatocellular carcinoma	up	exosome transfer	promoting tube formation and cell-cell adhesion	75

miR-511-5p/VEGFA axis may be the mechanism of LINCC00173.v1 inducing tumorigenesis. Moreover, inhibiting the expression of LINC00173.v1 has therapeutic effect in SQC. ΔNp63α is one of the p53/p63/p73 family transcription factors, which is essential to the occurrence,[78] development, and even drug resistance of a variety of tumors.[79] Further studies demonstrated that ΔNp63α raised the transcription of LINC00173.v1. These events suggested that LINC00173.v1 may be an underlying anti-angiogenic therapeutic target of lung squamous cell carcinoma (Figure 2B).[60] Hou et al. found that lncRNA EPIC1 is upregulated in NSCLC cells and tissues. Mechanistically, EPIC1 enhanced tumor angiogenesis by activating the Ang2/Tie2 axis in NSCLC. Angiogenesis assay in chick chorioallantoic membranes (CAM) showed that overexpression of EPIC1 promoted CAM angiogenesis, while silencing EPIC1 inhibited CAM angiogenesis. A xenograft nude mice model confirmed that EPIC1 overexpression significantly increased tumor angiogenesis, the number of CD31 marked channels, and Ang2 levels. What is more, samples from patients with NSCLC also confirmed the results. EPIC1 might be a biomarker for angiogenesis in NSCLC.[68]

Digestive system tumors

The morbidity and mortality of various digestive system tumors are among the top 10 malignancies in the world.[2] LINC01314 (CTXND1) was low in GC by analyzed GC Chip Data GSE19826. In vivo and in vitro, upregulation of LINC01314 or downregulation of KLK4 reduced the proliferation, migration, invasion, and angiogenesis of GC cells and decreased micro-vessel density. Bioinformatic analysis showed that there was a specific binding site between KLK4 and LINC01314. Dual-luciferase reporter gene assay confirmed the result. The Wnt/β-catenin signaling pathway participated in the adjustment of various pathophysiological procedure.[80–82] Abnormal Wnt/β-catenin signaling pathway can induce many diseases.[83–85] In western blot analysis, the expression levels of KLK4, Wnt-1, β-catenin, Cyclin D1, and N-cadherin were decreased after the upregulation of LINC01314. Animal experiments showed that upregulation of LINC01314 or downregulation of KLK4 can inhibit tumor growth and reduce the micro-vessel density. The preceding results revealed that overexpressed LINC01314 can inhibit the Wnt/β-catenin signaling pathway by downregulating KLK4 to suppress the

angiogenesis in GC.[67] lncRNA SNHG22 can upregulate HMGA1 through sponge miR-361-3p to activate Wnt/β-catenin pathway, thereby promoting GC progression (Figure 2C).[64] 1,081 lncRNAs, 127 microRNAs, and 1,983 differentially expressed mRNAs were screened from RNA-seq data of hepatocellular carcinoma (HCC) patients in the TCGA database. More importantly, lncRNA MYLK-AS1/miR-424-5p/E2F7 axis was the only ceRNA regulatory axis negatively correlated with OS. MiR-424-5p has the dual effects of oncogene and tumor suppressor gene. In LSCC,[86] esophageal cancer,[87] CRC,[88] and thyroid cancer,[89] miR-424-5p mainly intensifies the proliferation, invasion, migration, and drug resistance of tumor cells. However, it has the opposite effect on liver,[90] breast,[91] and nasopharyngeal cancers.[92] Mechanistically, MYLK-AS1 accelerated angiogenesis by regulating the miR-424-5p/E2F7 axis to activate the VEGFR-2 signaling pathway in HCC. This result was further confirmed in xenograft mice tumors.[61] Hou et al. covered that miR-140/VEGFA axis may be the potential mechanism for regulating HCC angiogenesis by MALAT1.[62] In colorectal adenocarcinoma (CRA), SNHG17 boosted CRA angiogenesis through regulating the miR-23a-3p/CXCL12 axis to induce proliferation and migration of CRA cells.[63]

Genitourinary system tumors

According to the latest data, breast cancer overtakes lung cancer as the most common malignancy.[2] Niu et al. established breast cancer cell lines of different oxygen concentrations and found that hypoxia could induce upregulation of lncRNA RAB11B-AS1. HIF, a highly conserved transcription factor, can regulate the expression of multifarious genes responsible for specific physiological responses.[93] ChIP-qPCR analysis showed that HIF-2 induced the overexpression of RAB11B-AS1 in hypoxia. Gain-of-function experiments demonstrated that upregulation of RAB11B-AS1 enhanced invasion and migration of breast cancer cells. The results were opposite in loss-of-function experiment. Animal studies showed that RAB11B-AS1 promoted angiogenesis and metastasis. Mechanistically, RAB11B-AS1 recruited RNA Pol II to enhance hypoxia-induced angiogenic factors, VEGFA, and ANGPTL4, thus motivating angiogenesis in breast cancer (Figure 2D).[69] Lei et al. reported that lncRNA TUG1 was transferred by exosomes to the HUVECs to promote angiogenesis in cervical cancer (CC). TUG1 was meaningly upregulated in HeLa and CaSki cell lines and their exosomes. HUVECs treated with HeLa-Exo and CaSki-Exo significantly enhanced TUG1 levels and angiogenesis. Silencing TUG1 attenuated the angiogenic potential for HeLa-Exo and CaSki-Exo in HUVECs. As a consequence, TUG1 might be a therapeutic target gene for the CC (Figure 2E).[70] In addition, Li et al. obtained 667 prostate cancer-related genes through analysis dataset GSE45016 in the GEO database. LINC00261 had the highest expression differential multiple and was underexpressed in both prostate cancer tissues and cells. Overexpression of LINC00261 inhibited proliferation, migration, invasion, and tube formation of prostate cancer cells. GATA6, a member of the GATA family, is essential for the development of early human organs. Its expression disorders are linked to many human diseases, including cancer.[94] RIP experiment and ChIP assay revealed that

LINC00261 could bind to GATA6, and GATA6 could be combined with DKK3 promoter. The expression of VEGF and CD31 decreased after LINC00261 or DKK3 overexpression. Tumorigenesis in nude mice and immunohistochemical staining supported the results. Altogether, LINC00261 promoted the expression of DKK3 by recruiting GATA6 to refrain proliferation, migration, invasion, and angiogenesis of prostate cancer.[71]

Other tumors

Glioma is the most common primary intracranial tumor with extensive angiogenesis. Neovascularization affords ideal conditions for tumor cells to infiltrate and migrate.[95] It has been reported that lncRNAs are closely correlated with glioma angiogenesis.[96] Analysis of database GSE104291 indicated that there were 91 genes with high expression and 268 genes with low expression.[73] lncRNA SLC26A4-AS1 was meaningly downregulated in glioma tissues and cells. Upregulation of SLC26A4-AS1 in U251 and SHG44 cells inhibited the proliferation, migration, and angiogenesis of U251 and SHG44 cells. RIP and ChIP assays made clear that SLC26A4-AS1 upregulated NPTX1 by recruiting NFKB1 into the NPTX1 promoter. Silencing NPTX1 or NFKB1 partially reversed the invasive and proangiogenic properties of glioma cells induced by overexpression of SLC26A4-AS1. Animal experiment proved that SLC26A4-AS1 inhibited glioma tumor growth and angiogenesis by upregulation of NPTX1. Taken together, SLC26A4-AS1 might be a potential therapeutic target for glioma.[72] However, LINC00320 inhibited AQP9 expression by recruiting NFKB1 to the promoter region of AQP9, thus acting as a tumor suppressor gene in glioma (Figure 2F).[73] Osteosarcoma is a common and highly malignant bone tumor, mostly occurring in adolescents. lncRNA TUG1 was overexpressed in osteosarcoma tissues and is associated with poor prognosis of patients. TGF-β secreted by CAFs motivated the expression of TUG1 in osteosarcoma cells. Bioinformatics analysis showed that miR-143-5p was a potential target binding miRNA of TUG1, and HIF-1α was the target gene of miR-143-5p. Further experiments verified that TUG1 positively regulated HIF-1α through acting ceRNA of miR-143-5p, thereby promoting the invasion and angiogenesis of osteosarcoma cells. The xenografted tumor experiments in nude mice showed that silencing TUG1 refrained tumor growth, peritoneal diffusion, and metastasis in vivo. In short, TUG1 might be a potential therapeutic target and prognostic indicator in osteosarcoma.[65]

Cancer stem cells (CSCs)

CSCs can secrete plenty of VEGF to promote tumor angiogenesis. In the meantime, CSCs depend on vascular niches. CSCs and angiogenesis can form a positive feedback loop to boost the occurrence and development of tumors.[97] CD90 + HCC cells are described as cancer stem-cell-like that exhibit aggressive and metastatic phenotypes. CD90 + cells isolated from Huh7 cell line were found to have mesenchymal phenotype and release exosomes in large quantities in HCC. Exosomes produced by CD90 + Huh7 cells promoted angiogenesis and cell-cell adhesion of HUVECs. Mechanism studies have shown that CD90+ Huh7 cells can overexpress H19 and transfer H19 into HUVECs by secreting exosomes, thus promoting angiogenesis and

Table 2. Correlation between lncRNAs and anti-angiogenic therapy resistance in tumors

Classification	Drugs	Cancer	LncRNA	Role	Mechanism	Ref
CeRNA	sorafenib	hepatocellular carcinoma	MALAT1	up	regulating miR-140-5p/Aurora-A axis	[98]
			TTN-AS1	up	regulating miR-16-5p/cyclin E1/PTEN/AKT axis	[99]
	sunitinib	renal cancer	HOTAIR	up	regulating miR-17-5p/Beclin1 axis	[100]
Gene transcription	sunitinib	renal cancer	SNHG12	up	regulating CDCA3 by stabilizing transcription factor SP1	[101]
			CCAT1	up	regulating c-Myc	[102]
Signal pathway	anlotinib	non-small cell lung cancer	NEAT1	up	regulating Wnt/β-catenin signaling pathway	[103]

adhesion of endothelial monolayer in HUVECs.[75] Due to the difficulty in successfully isolating and identifying CSCs, studies on CSCs are still in infancy. There are few studies on lncRNAs, angiogenesis, and CSCs. Scientific and technological progress will solve the problem of isolation and identification of CSCs in the future. The studies of lncRNAs, angiogenesis, and CSCs will also embrace a qualitative leap by then.

CORRELATION BETWEEN lncRNAs AND ANTI-ANGIOGENIC THERAPY RESISTANCE IN CANCER

Anti-angiogenic therapy, as an important means of tumor therapy, has achieved good efficacy in clinical application. However, the shortcoming of drug resistance has also been highlighted in the long-term clinical application. Many studies have attested that lncRNAs are closely related to anti-angiogenic therapy resistance (Table 2).

Sorafenib

Sorafenib is a multi-kinase inhibitor targeted VEGFR and platelet-derived growth factor receptor (PDGFR) and others.[104] As a first-line treatment for advanced HCC, it has effectively ameliorated the prognosis of patients with HCC.[105] However, patients gradually develop resistance, leading to poor treatment.[106] Fan et al. established HCC cell lines resistant to sorafenib (HepG2-R and SMMC-R). Microarray analysis results displayed that there were 293 upregulated lncRNAs and 207 downregulated lncRNAs in sorafenib-resistant HCC cells, among which MALAT1 was significantly overexpressed. The knockdown of MALAT1 in HepG2-R and SMMC-R cells resulted in the decrease of IC50 value, inhibition of cell proliferation and migration, G2–M cell-cycle arrest, and increase of apoptosis. Aurora-A not only promotes the genesis and progression of tumors, but it also mediates the resistance of chemotherapy and radiotherapy and participates in immunotherapy.[107,108] In clinical trials, its selective inhibitors or siRNA have been demonstrated to have anti-tumor effects.[109,110] Mechanically, MALAT1 upregulated the expression of Aurora-A by sponging miR-140-5p to intensify sorafenib resistance of HCC cells. Clinical patient tissue tests further confirmed these results. Patients with high MALAT1 expression had poor prognosis. More importantly, animal studies indicated that silencing MALAT1 promoted the anti-tumor efficacy of sorafenib in vivo (Figure 2G).[98] In HCC, lncRNA TTN-AS1 was a

potential therapeutic target of HCC. It is common knowledge that cyclin E1 is the tumorigenic factor and biomarker of numerous malignant tumors, such as, breast cancer,[111] osteosarcoma,[112] etc. Research has demonstrated that lncRNA TTN-AS1 can competitively inhibit miR-16-5p to upregulate cyclin E1 and regulate the PTEN/AKT signaling pathway to enhance sorafenib resistance of HCC. In a tumor-forming model in nude mice, knockdown of TTN-AS1 reduced sorafenib resistance in vivo.[99]

Sunitinib

Sunitinib, a multitarget RTK inhibitor with strong anti-angiogenesis, has been approved for imatinib-resistant stromal tumor, renal, and pancreatic neuroendocrine tumors. Sunitinib has been proved to extend PFS and OS of patients with RC, but its efficacy has been overshadowed by drug resistance after the sensitive phase.[113] Li et al. recognized a novel lncRNA, HOTAIR, which was an enhancing factor of sunitinib resistance in RC. HOTAIR promoted sunitinib resistance in RC by negatively regulating miR-17-5p to promote Beclin1-mediated autophagy. Knockdown of HOTAIR partially reversed sunitinib resistance of RC cells in vivo. Thus, miR-17-5p/Beclin1 axis might be the potential mechanism of HOTAIR promoting sunitinib resistance of RC.[100] In renal cell carcinoma (RCC), lncRNA CCAT1 granted resistance to sunitinib in a c-Myc-dependent manner, providing a new target for improving sunitinib therapy (Figure 2H).[102] In addition, Liu et al. first proposed lncRNA SNHG12 could upregulate the expression of CDCA3 by stabilizing transcription factor SP1 to facilitate tumor progressions and resistance to sunitinib in RCC. RNA sequence and bioinformatics analysis demonstrated that SNHG12 was highly expressed in RCC tissues and cells resistant to sunitinib, associating with poor prognoses. Downregulation of SNHG12 meaningly reduced the proliferation, migration, and invasion ability of tumor cells, and partially reversed the resistance to sunitinib. CDCA3, a potential marker for poor prognoses, often acts as an oncogene in digestive system tumors and NSCLC.[114–116] GSEA analysis and rescue assays confirmed that SNHG12 accelerated the progression of RCC by positively regulating CDCA3. RIP and ChIP experiments confirmed that SNHG12 activated CDCA3 transcription by binding and stabilizing SP1. Animal experiments made clear that knockdown SNHG12 inhibited tumor progression and reversed sunitinib resistance. Thus, SNHG12 may be a potential therapeutic target for the reversal of sunitinib resistance in RCC (Figure 2I).[101]

Anlotinib

Anlotinib is a multi-target inhibitor that targets c-kit, PDGFR, fibroblast growth factor receptor, and VEGFR. In 2018, it was approved for patients with NSCLC who progressed after treatment of at least two drugs in China[117] It has been shown to prolong PFS and OS in patients with advanced refractory NSCLC.[118] Previous studies reported that lncRNA NEAT1 played an oncogene role in NSCLC. It promoted the progression of NSCLC by regulating the miR-376b-3p/SULF1 and miR-204/NUAK1 axis, and it even mediated the paclitaxel resistance of NSCLC by activating the AKT/mTOR signaling pathway.[119–121] Gu et al. reported that NEAT1 was involved in regulating anlotinib sensitivity in NSCLC. *In vivo*, the knockdown of NEAT1 in A549 and NCI-H1975 cells enhanced the sensitivity of the cells to anlotinib. Compared with anlotinib alone group, tumor volume and weight were significantly reduced in the NEAT1 knockdown combined anlotinib group *in vivo*. Further studies showed that NEAT1 knockdown promoted the cytotoxicity of anlotinib by inhibiting the Wnt/β-catenin signaling pathway. Downregulation of NEAT1 can enhance the anti-tumor effect of antitinib in mouse xenograft tumor model (Figure 2J).[103]

CONCLUSIONS AND PERSPECTIVES

Cancer poses a serious threat to the global economy and human health. The functions of ncRNAs have been discovered through high-throughput sequence technology. We mainly reviewed lncRNAs that can play ceRNAs of miRNAs, target directly proangiogenic factors and their receptors, or act on some signaling pathways to regulate tumor angiogenesis. The same lncRNA regulates angiogenesis by different mechanisms in different tumors. In addition, we also reviewed most of the lncRNAs regulate the mechanism of anti-angiogenic therapy resistance through sponging miRNA. Ye et al. discovered anisomycin inhibited angiogenesis in ovarian cancer by weakening the molecular sponge effect of lncRNA MEG3/miR-421/PDGFRA axis.[122] Tretinoin can target and inhibit the TR4-mediated expression of lncRNA TASR/AXL axis, thereby reducing sunitinib resistance in RCC.[123] These results further confirmed the feasibility of lncRNAs as potential targets for tumor therapy. Wang et al. reported ASRPS secreted by LINC00908 had anti-tumor angiogenesis effects in triple-negative breast cancer. Mechanically, ASRPS downregulated STAT3 phosphorylation by directly binding to STAT3 to decrease VEGF.[124] Tang et al. prepared an artificial lncRNA (alncRNA) that could target multiple miRNAs to regulate the PTEN/AKT axis. Ad5-alncRNA enhanced the inhibitory effect of sorafenib on HCC cells.[125] These investigations suggested that lncRNAs might even have potential as a therapeutic agent for cancer. In conclusion, lncRNAs, which have great potential for both tumor angiogenesis and anti-angiogenic therapy resistance, may become potential targets or even new medicines for tumor in the future. Antisense oligonucleotide technology and overexpression vector construction technology make it possible to treat diseases by regulating the expression of lncRNAs. Compared with traditional chemotherapy, lncRNA targeted therapy has the following advantages: (1) highly selectivity, (2) high specificity, (3) high affinity, (4) high degree of individualization, and (5) fewer side effects. Liquid biopsy has been gradually used to detect tumor biomarkers.[126] Exosomes can prevent lncRNAs from degradation by nuclease to increase their stability. Researchers have demonstrated that circulating and exosomal lncRNAs are biomarkers for diagnosis and prognosis of malignant tumors.[127–131]Therefore, lncRNAs have great potential for clinical application of tumor diagnosis and treatment. At present, lncRNAs have not been fully identified and mechanisms have not been thoroughly studied. Large amounts of basic experiments and clinical trials will be needed to further explore and verify their clinical application value.

AUTHOR CONTRIBUTIONS

J.L., Q.Z., D.Y., and F.X. wrote and drafted the manuscript and figures. Z.W. designed the manuscript. Z.W. and J.L. revised the manuscript. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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