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# Research progress on the circRNA-mediated regulation of tumor angiogenesis through ceRNA mechanisms (Review)

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**Abstract.** Tumors are one of the most common fatal diseases worldwide and pose a severe threat to human health. Effective tumor prevention and treatment strategies are persistent challenges in the medical community. Angiogenesis plays a critical role in and is the basis for tumor development and metastasis. Circular RNAs (circRNAs) are novel single-stranded covalently closed RNA molecules that are widely expressed in tumors due to their structural specificity and conservation. circRNAs affect angiogenesis by functioning as microRNA sponges to regulate vascular endothelial growth factor-related pathways, thereby participating in various stages of tumor growth, invasion and proliferation. The present review summarizes the involvement of circRNAs in the regulation of tumor angiogenesis through competing endogenous RNA mechanisms, with a particular focus on the regulatory role of circRNAs in tumor angiogenesis in various systems. It is considered that circRNAs have great potential for use as tumor diagnostic markers and anti-angiogenic therapies, and are thus worthy of further research and exploration.

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*Key words:* circular RNA, microRNA, tumor angiogenesis, competing endogenous RNAs, vascular endothelial growth factor

## 1. Introduction

In 1971, Folkman (1) first proposed that tumor growth and metastasis were dependent on tumor angiogenesis to a certain extent, which is the theory of tumor angiogenesis. Angiogenesis provides necessary oxygen and nutrients for tumor growth, and blocking angiogenesis has become a tumor treatment approach. Recent research has indicated that circular RNAs (circRNAs) are a noel class of RNAs with special covalently closed loop structures without 5' caps and 3' tails that can regulate angiogenesis-related diseases through multiple mechanisms (2). circRNAs are abnormally expressed in almost all tumor types, play a crucial role in cancer pathogenesis as oncogenes or tumor suppressors (3), and can participate in the proliferation, migration, invasion and apoptosis of tumor cells through various mechanisms (4,5). As opposed to traditional RNAs, circRNAs are more stable and conserved *in vivo* due to their structural specificity and can resist exoribonuclease RNase R-mediated degradation (6). Due to these characteristics, circRNAs are potential clinical diagnostic markers.

The present review summarizes and discusses the biological properties and functions of circRNAs and the related mechanisms of tumor angiogenesis, with specific focus on the mechanisms and roles of circRNAs in tumor angiogenesis in various systems. In addition, the present review elaborates on the clinical applications of circRNAs in tumor angiogenesis and their future prospects as novel diagnostic markers and therapeutic targets in clinical tumor angiogenesis.

## 2. Tumor angiogenesis

Angiogenesis is the process through which endothelial cells proliferate, differentiate and migrate to form microvessels from

existing blood vessels (7). Under physiological conditions, a variety of angiogenic factors promote or inhibit angiogenesis to maintain the stability of the body's internal environment. Cell proliferation, migration and vascular endothelial growth factor (VEGF) secretion are critical for angiogenesis, and an imbalance in these processes can lead to the development of diseases (8). The distinguishing features of tumors are active proliferation and metabolism, and both tumor growth and metastasis are dependent on angiogenesis. Angiogenesis is the key to tumor development, as this process stimulates the vascular system to grow new blood vessels by activating the 'angiogenic switch' in tumors (9,10), which provides sufficient oxygen and nutrients to promote tumor growth and proliferation (11).

With the further development of the theory of tumor angiogenesis, studies have reported the significance of angiogenic factors and their roles in early tumor growth, invasion and metastasis (12-14). Angiogenic factors are divided into pro-angiogenic and anti-angiogenic factors. Anti-angiogenic factors include angiostatin, endostatin and thrombospondin. Pro-angiogenic factors mainly include VEGF (15,16), angiopoietin (17), matrix metalloproteinases (MMPs) (18,19) and fibroblast growth factor (FGF) (20), of which VEGF is a key angiogenic mediator that drives continuous tumor growth (21,22). VEGF is a family of homodimeric glycoproteins with a molecular weight of ~45 kDa and primarily includes VEGFA, VEGFB, VEGFC, VEGFD and placental growth factor (PIGF). The central role of VEGF in tumorigenesis and the spread of tumor cells to other parts of the body indicates that the inhibition of tumor angiogenesis may be an effective strategy and target for tumor therapy.

## 3. Biological functions of circRNAs

circRNAs, as a novel type of RNA molecule, have been found to have potential biological functions, which indicates that some circRNAs may be involved in gene expression regulation as transcriptional or splicing regulators (23,24). The biological basis of tumorigenesis is the abnormal expression of genes, and the structural specificity and abundant biological functions of circRNAs is indicative of their critical role in tumorigenesis and tumor progression.

It has been reported (25) that a number of different circRNAs are expressed in eukaryotic cells at levels ~10-fold those of linear RNAs, which suggests that circRNAs may have potential biological functions. The present review discusses the related biological functions of circRNAs. circRNAs can function as microRNA (miRNA/miR) sponges, which was the earliest discovered function of circRNAs (26) and has become a research hotspot. Some circRNAs contain several miRNA-binding sites that can compete with mRNAs and bind to miRNAs to sponge miRNAs and regulate the expression of target genes (27). circRNAs can interact with RNA-binding proteins (RBPs) to indirectly regulate gene transcription. For example, circRNAs can compete with mRNAs to bind to RBPs, and thus, they can affect the translation of mRNAs. circRNAs can function as RBP super sponges to affect RBP expression and they interact with specific proteins and enhance their functions, and they can also regulate target gene translation (28). circRNAs can also function in protein translation. Of note, two mechanisms of translation have been established: One is dependent on the internal ribosome entry site, while the other is dependent on $N^6$-methyladenosine methylation modification. The post-translation products of circRNAs can participate in multiple physiological processes in the body, such as preventing linear translation products from being degraded by ubiquitin proteases (29), regulating the PI3K/AKT pathway (30) and inhibiting the transcriptional elongation of proto-oncogenes (31).

Previous research has found that circRNAs are stable and conserved *in vivo* due to their structural specificity, and consequently, they have the potential to serve as molecular markers (32). circRNAs have been confirmed to be closely related to aging, cancer and other chronic diseases, and can serve as markers for disease diagnosis and detection. Experiments using *Drosophila* have demonstrated that circRNAs are markers of aging and that circRNAs present in human saliva are also potential disease markers (32,33). Numerous circRNAs also exist in exosomes and can be used as molecular diagnostic markers (34). VEGF is a key factor in the process of tumor angiogenesis, and circRNAs can directly or indirectly target VEGF to regulate this process.

## 4. Related mechanisms through which circRNAs regulate tumor angiogenesis

circRNAs are involved in a variety of physiological and pathological processes, including tumor proliferation, invasion and metastasis (35). Previous studies have demonstrated that circRNAs participate in tumor angiogenesis primarily by functioning as targeting sponges for miRNAs, either by binding to miRNAs, which blocks their expression, or with competing endogenous RNAs (ceRNAs) (26,36,37). miRNAs are linear non-coding RNAs that can adsorb mRNAs, promote their degradation and thus regulate tumor angiogenesis (38). Due to their structural specificity and diverse biological functions, circRNAs play a critical role in tumor angiogenesis by directly or indirectly targeting VEGF or other angiogenic factors.

*Involvement of circRNAs in tumor angiogenesis as ceRNAs.* miRNAs can silence gene expression by binding to mRNAs, and circRNAs can regulate gene expression by competitively binding with miRNAs. ceRNAs are closely related to tumor angiogenesis (39) and play a crucial role in this process.

Circ-RanGAP1 can function as a ceRNA to inhibit the activity of miR-877-3p and increase the expression of the target gene, VEGFA (40), while circ0001429 can target miR-205-5p and regulate VEGFA to promote bladder cancer (41). CircSCAF11 regulates the transcription factor, SP1, through miR-421 and activates VEGFA transcription, which accelerates glioma development through the miR-421/SP1/VEGFA axis (42). Circ-ZNF609 downregulates miR-145 expression and upregulates stathmin 1 expression by acting as a ceRNA to promote cell proliferation, migration and angiogenesis in nasopharyngeal carcinoma (43), while circRNA-104718 functions as a ceRNA and directly binds to miR-218-5p and promotes the progression of liver cancer by targeting the miR-218-5p/thioredoxin domain containing 5 signaling pathway (44). CircFOXO1 is upregulated in

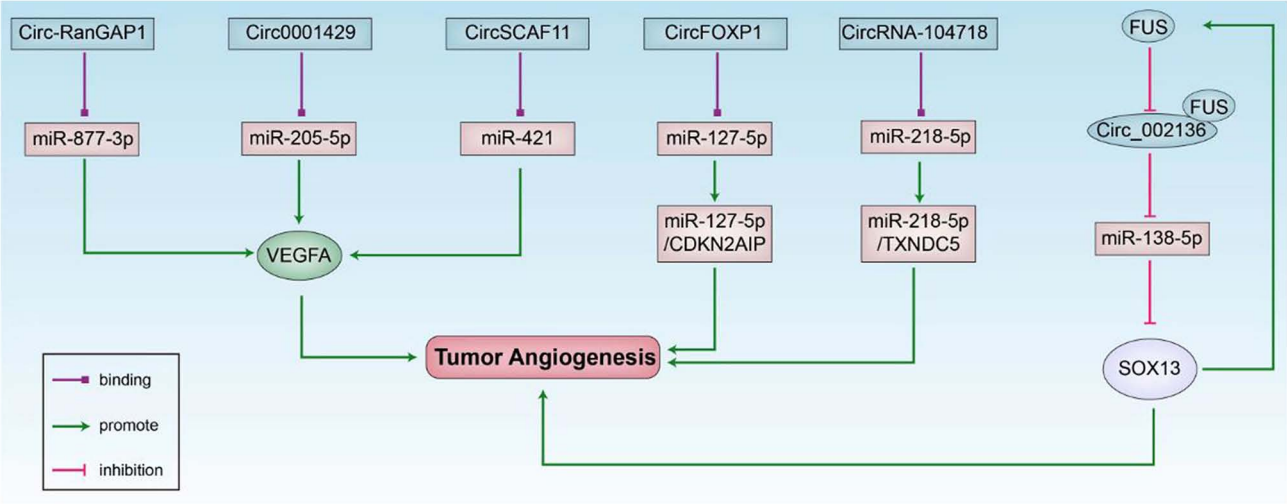


Figure 1. Involvement of circRNAs in tumor angiogenesis through competing endogenous RNAs. circRNA, circular RNA; VEGFA, vascular endothelial growth factor A; FUS, fusion sarcoma.

osteosarcoma to promote the growth of osteosarcoma and can directly combine with miR-127-5p to promote the expression of CDKN2AIP and promote angiogenesis by regulating the miR-127-5p/CDKN2AIP signaling pathway (45). The fusion sarcoma (FUS) gene is a DNA/RNA regulatory protein with a gene regulatory function. The FUS gene is involved in the processes of intracellular RNA transduction, mRNA synthesis, alternative splicing and polyadenylation site selection (46). High FUS gene expression in glioma can work synergistically with Circ_002136. Circ_002136 directly targets miR-138-5P to inhibit the expression of the downstream target gene SOX3 and to promote glioma-exposed endothelial cell (GEC) angiogenesis; the knockout of circ_002136 and the overexpression of miR-138-5P can reduce the angiogenic capacity of gliomas (47). On the whole, the ceRNA mechanism is a typical regulatory mechanism among non-coding RNAs, which supports the further study of circRNAs in tumor angiogenesis (Fig. 1).

*VEGF-dependent regulation of tumor angiogenesis*. VEGF commonly refers to VEGFA, whereas the VEGF family also includes VEGFB, VEGFC, VEGFD and PIGF. The majority of cells in the body can produce VEGFA, which is upregulated under hypoxic conditions (48). VEGF is produced by tumor cells, endothelial cells and tumor-associated macrophages under hypoxic conditions during tumor growth. It has been found that circRNAs can affect tumor angiogenesis by modulating VEGF, which further affects the process of tumor growth, proliferation and metastasis (41).

Circ-RanGAP1 can induce VEGFA expression through miR-877-3p and enhance the invasion and metastasis of gastric cancer (40), while hsa_circ_0023404 directly binds to miR-5047 and regulates the expression of the VEGFA gene (49), which enhances metastasis and chemotherapeutic resistance in cervical cancer. CircFndc3b is downregulated in the mouse heart following myocardial infarction, can interact with fused RNAs in sarcoma and regulate cardiac repair following myocardial infarction through the FUS/VEGFA signaling axis; the regulation of circFndc3b expression has emerged as a potential therapeutic strategy for cardiac functional remodeling following myocardial infarction (50). Circ0001429 increases VEGFA expression via miR-205-5p, accelerates the proliferation, invasion and migration of bladder cancer cells, and promotes bladder cancer progression (41). CircRNA-MYLK is upregulated in bladder cancer and is related to clinical stage; this circRNA can also bind to miR-29a and indirectly regulate the expression of VEGFA, and promote the angiogenesis and metastasis of bladder cancer (51). CircSCAF11 can bind to miR-421 to regulate the transcription factor SP1, activate VEGFA transcription (42), and accelerate glioma development. The expression of hsa_circ_0000096 is downregulated in gastric cancer, and the knockout of hsa_circ_0000096 downregulates VEGFA expression, inhibits cell proliferation and migration and further affects tumor angiogenesis (52) (Fig. 2).

CircRNAs not only function as ceRNAs to regulate VEGFA to affect tumor angiogenesis, but also participate in tumor angiogenesis by influencing the VEGF splicing process. CircSMARCA5 can regulate the splicing and angiogenesis of VEGFA mRNA in glioblastoma multiforme (GBM) by binding to serine and arginine-rich splicing factor 1 (SRSF1) and is therefore a promising therapeutic target in GBM cells (53).

*VEGF-independent regulation of tumor angiogenesis*. In addition to the VEGF family, angiotensin, platelet-derived growth factor (PDGF-β), transforming growth factor (TGF-β) and MMPs (18,19) are also closely associated with tumor angiogenesis (54).

PDGF-β is an effective angiogenic factor involved in GBM that can downregulate the tumor-promoting gene, miR-21, and the tumor suppressor gene, miR-128, to regulate the expression of related factors and promote tumor cell proliferation (55). It has been found that PDGF-β is systemically upregulated in patients with age-related macular degeneration (AMD) and in patients with diabetic macular edema compared with healthy controls; moreover, PDGF-β may be involved in the pathogenesis of neovascular AMD (56). In bladder cancer, circ0001361 interacts with miR-491-5p, which upregulates

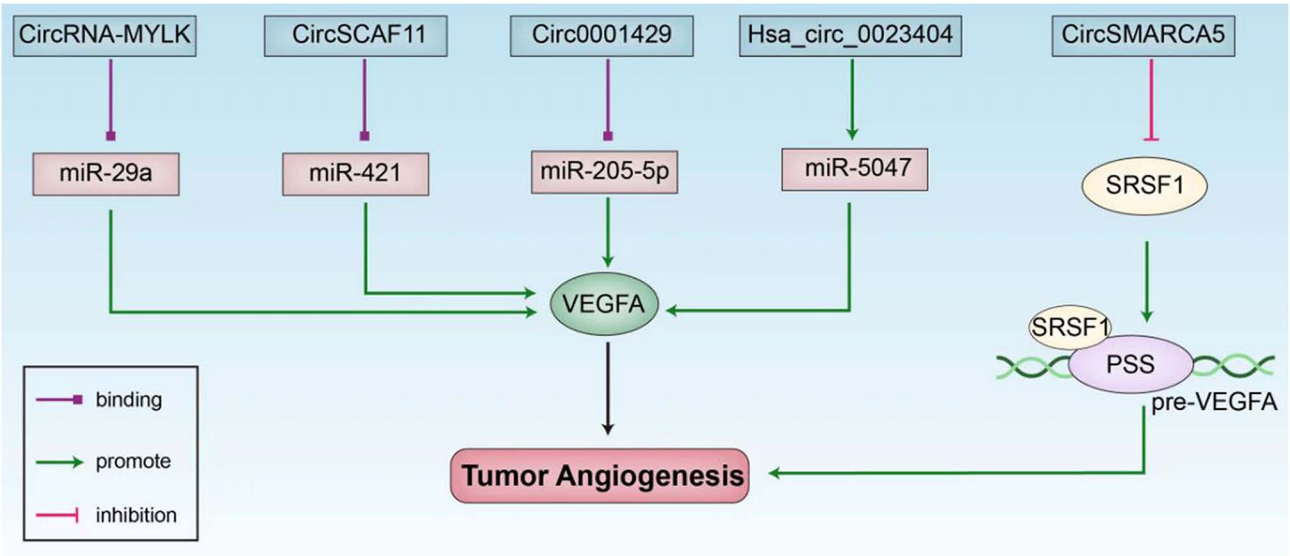


Figure 2. VEGF-dependent regulation of tumor angiogenesis. VEGFA, vascular endothelial growth factor A; SRSF1, serine and arginine-rich splicing factor 1; PSS, proximal splicing site.

MMP9 expression and promotes the migration and invasiveness of bladder cancer cells, and thus, circ0001361 is expected to become a novel therapeutic target for bladder cancer (57). circDLC1 interacts with the RNA-binding protein, HuR, and inhibits MMP1 expression by reducing the stability of MMP1 mRNA, inhibiting the proliferation and metastasis of liver cancer cells and attenuating the progression of liver cancer, which suggests that circDLC1 is a promising diagnostic biomarker and potential therapeutic target for liver cancer (58) (Fig. 3).

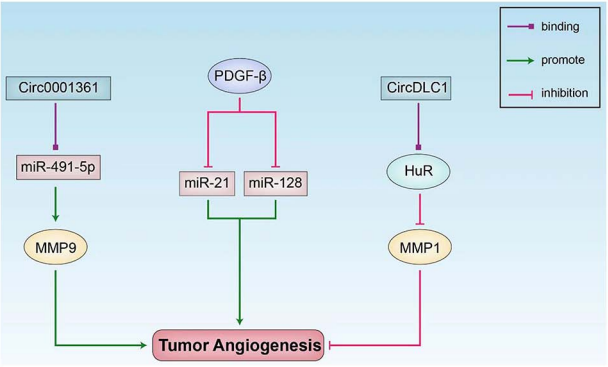


Figure 3. Vascular endothelial growth factor-independent regulation of tumor angiogenesis. MMP, matrix metalloproteinase; PDGF-β, platelet-derived growth factor-β.

## 5. Effects of circRNAs on tumor angiogenesis in various systems

Due to their structural stability and rich biological functions, circRNAs play a criticial role in tumorigenesis by affecting tumor growth, proliferation and metastasis. Studies have found that circRNAs are also widely expressed in the digestive system (40,59), urinary system (51,60), nervous system tumors and other related tumors (61,62), and exert marked effects on tumor angiogenesis and development in various systems.

*circRNAs and gastrointestinal tumor angiogenesis*. circRNAs are widely expressed in gastrointestinal tumors and can affect the progression of these tumors through angiogenesis (Table I). Circ-RanGAP1 is upregulated in the tissues and peripheral blood of patients with gastric cancer, where it promotes the invasion and metastasis of gastric cancer by targeting miR-877-3p to regulate the expression of VEGFA; moreover, the inhibition of circ-RanGAP1 can reduce the invasion and migration of gastric cancer cells (40). Circ29 is upregulated in gastric cancer, binds miR-29a as a ceRNA, and plays a role in gastric cancer angiogenesis by regulating the VEGF pathway (63). In pancreatic ductal adenocarcinoma, circNFIB1 attenuates the carcinogenesis of miR-486-5p and upregulates PIK3R1 expression, which further downregulates VEGFC expression by inhibiting the PI3K/Akt pathway; this in turn inhibits lymphangiogenesis and metastasis in pancreatic ductal adenocarcinoma (64). CircCCT3 functions as a miR-613 sponge to promote the migration and invasiveness of pancreatic cancer (PC) cells by regulating the VEGF/VEGFR2 signaling pathway (59). CircADAM9 promotes PC progression by acting as a sponge of miR-217 to upregulate serine protease 3 expression (65). In colorectal cancer, circ_0056618 binds to miR-206 to upregulate the expression of CXCR4 and VEGFA, which promotes the proliferation, migration and angiogenesis of tumor cells (66). CircRNA UBAP2 is highly expressed in colorectal cancer tissues and cells, and promotes the further development of colorectal cancer via the upregulation of VEGFA expression by promoting the secretion of miR-199a (67). It has been found that the downregulation of circSMARCC1 expression can reduce the survival of colorectal cancer cells and inhibit the protein expression of MMP2, MMP9 and VEGF; moreover, the binding of circSMARCC1 to miR-140-3p can regulate the progression of colorectal cancer (68). Circ-001971 functions as a ceRNA to reduce miR-29c-3p-induced VEGFA upregulation, and promote

Table I. circRNAs and gastrointestinal tumor angiogenesis.

| Origin | circRNA | Mechanism | Functions | (Refs.) |
|---|---|---|---|---|
| Gastric cancer | Circ-RanGAP1 | miR-877-3p/VEGFA | Invasion and metastasis | (40) |
| Gastric cancer | Circ29 | miR-29a/VEGF | Proliferation, migration, tube formation of HUVECs | (63) |
| Pancreatic ductal adenocarcinoma | CircNFIB1 | miR-486-5p/PIK3R1/VEGFC | Inhibits lymphangiogenesis and LN metastasis in pancreatic ductal adenocarcinoma | (64) |
| Pancreatic cancer | CircCCT3 | miR-613/VEGFA/VEGFR2 | Promotes the migration and invasion of pancreatic cancer | (59) |
| Pancreatic cancer | CircADAM9 | miR-217/PRSS3 | Inhibits the proliferation, migration and invasiveness of pancreatic cancer cells | (65) |
| Colorectal cancer | Circ_0056618 | miR-206/CXCR4/VEGFA | Inhibits cell proliferation, migration and angiogenesis | (66) |
| Colorectal cancer | CircRNA UBAP2 | miR-199a/VEGFA | Suppresses cell proliferation, migration and invasion | (67) |
| Colorectal cancer | Circ-SMARCC1 | miR-140-3p/MMPs | Inhibits cell viability, migration, and invasion | (68) |
| Colorectal cancer | Circ-001971 | miR-29c-3p/VEGFA | Suppresses proliferation, invasion and angiogenesis | (69) |
| Colorectal cancer | CircCCT3 | miR-613/VEGFA/Wnt | Promotes migration and invasion, and inhibits cell apoptosis | (70) |
| Esophageal squamous cell carcinoma | Circ_0072088 | miR-377/VEGF | Promotes proliferation, migration, and invasion | (71) |
| Hepatocellular carcinoma | Circ_0001178 | miR-382/VEGFA | Reduces cell viability and suppresses migration and invasion | (72) |

circRNA, circular RNA; VEGF, vascular endothelial growth factor; HUVECs, human umbilical vein endothelial cells; LN, lymph node.

colorectal cancer proliferation, invasion and angiogenesis (69). WNT3 and VEGFA are downstream targets of miR-613 in colorectal cancer cells, and circCCT3 acts as a miR-61 sponge, which regulates the VEGFA and Wnt signaling pathways to enhance colorectal cancer metastasis (70).

In esophageal squamous cell carcinoma (ESCC), circ_0072088 can function as a miRNA-377 sponge to upregulate VEGF gene expression and promote the proliferation, migration and angiogenesis of ESCC cells. Circ_0072088 is expected to become a novel diagnostic biomarker and therapeutic target for ESCC (71). Circ_0001178 is upregulated in hepatocellular carcinoma (HCC) and can directly bind to miR-382. VEGFA is a downstream target of miR-382, and it has been reported that circ_0001178 promotes liver cancer progression by regulating miR-382 and VEGFA; the knockdown of circ_0001178 inhibits HCC growth *in vivo* (72).

*circRNAs and tumor angiogenesis in the urinary system.* Common urinary system cancers include bladder cancer, prostate cancer and renal cell carcinoma; however, research on the role of circRNAs in angiogenesis in urinary system tumors is mostly limited to bladder cancer. CircRNAs targeting oncogenic pathways in urinary system tumors mainly include TGF-β, AKT, VEGF and other pathways. It has been found that circRNAs can target related oncogenic molecules or pathways to regulate tumor angiogenesis in the urinary system (Table II).

The expression of circRNA-MYLK is increased in bladder cancer, and it can directly bind to miR-29a to promote the expression of the target VEGFA by reducing the activity of miR-29a; circRNA-MYLK also promotes the proliferation and epithelial-mesenchymal transition of bladder cancer cells by activating the VEGFA/VEGFR2 signaling pathway. CircRNA-MYLK regulates the expression of VEGFA by binding to miR-29a (51). CircEHBP1 is significantly upregulated in bladder cancer, where it binds to miR-130a-3p and antagonizes the inhibitory effects of miR-130a-3p on the 3'-UTR of TGFBR1. The upregulation of TGFβR1 expression further activates the TGF-β/SMAD3 signaling pathway to induce VEGFD expression, thereby promoting lymphangiogenesis

Table II. circRNAs and tumor angiogenesis in the urinary system.

| Origin | circRNA | Mechanism | Functions | (Refs.) |
|---|---|---|---|---|
| Bladder cancer | CircRNA-MYLK | miR29a/VEGFA/VEGFR2/ Ras/ERK | Suppresses bladder cancer cell proliferation and invasion | (51) |
| Bladder cancer | CircEHBP1 | miR-130a-3p/TGF-β/ SMAD3/VEGFD | Promotes lymphangiogenesis and LN metastasis | (60) |
| Bladder cancer | Circ0001429 | miR-205-5p/VEGFA | Promotes cell proliferation, migration and invasiveness | (41) |

circRNA, circular RNA; VEGF, vascular endothelial growth factor; LN, lymph node.

and lymphatic metastasis in bladder cancer (60). Circ0001429 expression has been found to be upregulated in bladder cancer tissues, and *in vitro* experiments have demonstrated that circ0001429 enhances the proliferation and metastasis of T24 and 5637 cells, and inhibits apoptosis (41). The results of these experiments have revealed that circ0001429 may increase VEGFA expression through miR-205-5p, promote the proliferation and metastasis of cancer cells and thus regulate the progression of bladder cancer (41).

*circRNAs and angiogenesis in gynecological tumors*. Among the gynecological tumors, cervical, ovarian and breast cancer are associated with high morbidity and mortality rates, and pose a substantial threat to the lives and health of women worldwide. circRNAs can bind to miRNAs through miRNA response elements, and can play a crucial role in tumor development and angiogenesis as tumor suppressor genes or proto-oncogenes (26). circRNAs are closely related to the development, metastasis and prognosis of gynecological tumors (Table III).

CircASH2L is highly expressed in ovarian cancer tissues and cell lines, and functions as a ceRNA to regulate the miR-665/VEGFA axis, which promotes VEGFA-mediated angiogenesis and lymphangiogenesis, and enhances the proliferation and invasion of ovarian cancer cells (73). As a highly expressed oncogene in ovarian cancer, circRhoC can not only act function a miR-302e sponge to regulate VEGFA protein expression, but it can also directly bind to and regulate VEGFA, which promotes tumorigenicity and ovarian cancer progression (74). Circ-CSPP1 silencing can lead to the decreased expression of MMP2 and VEGFA, and may promote the proliferation, invasion and migration of ovarian cancer cells by acting as a sponge of miR-1236-3p, which provides insight into the early diagnosis and treatment of ovarian cancer (75). In cervical cancer, hsa_circ_0023404 directly interacts with miR-5047 to regulate VEGFA gene expression and promotes cervical cancer metastasis through the miR-5047/VEGFA and autophagy signaling pathways (49). As a tumor suppressor downregulated in primary breast cancer tissues, miR-140-5p can inhibit the invasiveness and angiogenesis of breast cancer cells *in vitro* and *in vivo* by targeting VEGFA (76).

*circRNAs and tumor angiogenesis in the nervous system*. Central nervous system (CNS) tumors are generally divided into two categories: Primary tumors originating in the CNS and secondary tumors that metastasize from other parts of the body. CNS tumors are associated with a high morbidity and mortality worldwide, and include GBM, medulloblastoma and oligodendroglioma. Among the tumors of the CNS, the regulation of circRNA expression in tumor angiogenesis is mainly observed in glioblastoma and other gliomas.

Circ-RPL15 and VEGFA are upregulated in glioma tissues. Circ-RPL15 can upregulate VEGFA expression by competitively binding to miR-146b-3p, enhancing the proliferation and migration of glioma cells, and promoting glioma progression (77). In gliomas, circITGA7 regulates glioma proliferation and metastasis by acting as a miR-34a-5p sponge that targets VEGFA and regulates the miR-34a-5p/VEGFA pathway, which provides a potential target for the early diagnosis and treatment of gliomas (61). GAUGAA, as an RNA motif, regulates the interaction between circSMARCA5 and SRSF1 and the circSMARCA5-mediated control of GBM cell migration and angiogenic potential (78). CircSMARCA5 is an upstream regulator of the ratio of proangiogenic to anti-angiogenic VEGFA isoforms in GBM cells. This circRNA also regulates VEGFA mRNA splicing and angiogenesis in GBM by binding to SRSF1 and is expected to become an emerging marker and effective therapeutic target for GBM (53).

*circRNAs and other related angiogenic tumors*. Due to their diverse biological functions and specific structures, circRNAs are widely expressed in angiogenic tumors and other related diseases in various systems. In addition to intensive research in the gastrointestinal tract, urinary system, CNS and gynecological tumors, circRNAs are also expressed in diseases, such as osteosarcoma (OS), infantile hemangioma (IH), thyroid cancer and breast cancer (Table IV).

Circ_001621 is an oncogene in OS that regulates VEGF expression through miR-578 sponge activation, and promotes the proliferation and migration of OS cells (62). hsa_circRNA_103801 is involved in VEGF and angiogenesis-related pathways and in OS progression, and is expected to become a biomarker and target for the diagnosis and treatment of late-stage OS (79). In papillary thyroid carcinoma (PTC), circPVT1 acts as a miR-195 sponge to mediate the ceRNA network to regulate VEGFA expression and promote PTC progression (80). Ren *et al* (81) found the abnormal overexpression of circHIPK2 in non-small cell lung cancer

Table III. circRNAs and angiogenesis in gynecological tumors.

| Origin | CircRNA | Mechanism | Functions | (Refs.) |
|---|---|---|---|---|
| Ovarian cancer | CircASH2L | miR-665/VEGFA | Enhances invasion, proliferation, angiogenesis, and lymphangiogenesis | (73) |
| Ovarian cancer | CircRhoC | miR-302e/VEGFA | Enhances migration and invasion | (74) |
| Ovarian cancer | Circ-CSPP1 | miR-1236-3p/MMP-2/VEGFA | Promotes proliferation, invasion and migration | (75) |
| Cervical cancer | hsa_circ_0023404 | miR-5047/VEGFA | Enhances lymphatic vessel formation and promotes metastasis | (49) |
| Breast cancer | MicroRNA-140-5p | miR-140-5p/VEGFA | Suppresses breast cancer metastasis and angiogenesis | (76) |

circRNA, circular RNA; VEGFA, vascular endothelial growth factor A.

Table IV. circRNAs and other related angiogenic tumors.

| Origin | CircRNA | Mechanism | Functions | (Refs.) |
|---|---|---|---|---|
| Osteosarcoma | Circ_001621 | miR-578/VEGF | Promotes proliferation and migration | (62) |
| Thyroid cancer | CircPVT1 | miR-195/Wnt/β-catenin/VEGFA | Inhibits proliferation, migration, and invasion | (80) |
| Non-small cell lung cancer | CircHIPK2 | miR-1249-3p/VEGFA | By competitive absorption of miR-1249-3p mediated VEGFA | (81) |
| Infantile hemangioma | CircAP2A2 | miR-382-5p/VEGFA | Promotes proliferation and invasion | (83) |

circRNA, circular RNA; VEGFA, vascular endothelial growth factor A.

(NSCLC) tissues. The overexpression of circHIPK2 promoted the growth of cisplatin-resistant NSCLC tumors *in vivo*, and the silencing of circHIPK2 inhibited angiogenesis and drug resistance in NSCLC through miR-1249-3p targeting VEGFA. These findings provide new insight into the development of treatment strategies for NSCLC (81). CircFOXP1 can simultaneously target two key miRNAs, hsa-miR-370-3p and hsa-miR-18a-5p, to regulate the VEGF pathway in the processes of proliferation and metastasis and is a novel serum diagnostic marker for NSCLC (82). CircAP2A2 is highly expressed in IH and functions as a ceRNA to promote IH proliferation and invasion by regulating the miR-382-5p/VEGFA axis (83).

## 6. Potential application of circRNAs in tumor angiogenesis

circRNAs are a novel type of RNA whose structural stability contributes to natural advantages that allow these factors to serve as biomarkers; notably, circRNAs in plasma and plasma-derived exosomes are highly reliable tumor diagnostic biomarkers (84,85). Some progress has been made in tumor angiogenesis research. The diversity of the biological functions of circRNAs is represented by their expression in various diseases and their involvement in multiple tumor-related processes. circRNAs are resistant to exonuclease (RNase) activity due to their specific and highly conserved structures, rendering them ideal novel clinical markers.

*Biomarkers*. circRNAs not only play a crucial in the occurrence and development of tumors, but are also likely to serve as markers for the early diagnosis of tumors and targets for tumor therapy (34). miRNA-377 is a tumor suppressor gene that regulates multiple tumor phenotypes (86). Using both *in vitro* and *in vivo* experiments, Fang *et al* (71) found that the expression level of circ_0072088 in esophageal squamous cell carcinoma tissues and cells was directly proportional to the tumor size, depth of invasion and clinical stage of patients with ESCC, and that its mechanism of action may be that circ_072088 functions as a miR-377 sponge to regulate the expression of VEGF, thereby promoting the development of ESCC. This suggests that circ_007 2088 may be a novel molecular marker for the early diagnosis and treatment of ESCC (71). The splicing mechanism is one of the primary mechanisms through which circRNAs are generated (87). It has been demonstrated that circSMARCA5 is expressed at low levels in GBM, and is directly proportional to the overall survival and disease-free survival of patients with GBM (53). Further research has found that circSMARCA 5 acts as a sponge for the splicing factor SRSF1 in GBM, and thus, this circRNA regulates the splicing and angiogenesis of VEGFA mRNA in GBM by binding to SRSF1.

CircSMARC5 is therefore a promising prognostic marker in GBM (53).

*Targeted drugs that act on angiogenics pathways*. As a current clinical research hotspot, circRNAs can not only be used as molecular markers of disease, but they also provide a basis for the development of targeted drugs. CircFOXP1 is upregulated in OS and promotes angiogenesis in OS by regulating the miR-127-5p/CDKN2AIP signaling pathway, which accelerates OS progression (45), and circRNA-related targeted drugs may be key to future antiangiogenesis strategies in these tumors. VEGF overexpression in tumors has been regarded as a key factor in angiogenesis, and the inhibition of angiogenesis and related pathways is an effective approach for the treatment of cancer (54). Bevacizumab, the only anti-angiogenic drug approved for metastatic colon cancer in the USA, has been shown to effectively improve the progression-free survival of patients with metastatic colorectal cancer who are >65 years of age (88). In addition, it has been demonstrated that anti-VEGFA therapy significantly improves the prognosis of patients with advanced renal cell carcinoma and cervical cancer (89). These studies provide insight into the development of novel targeted drugs that block the signaling pathways related to tumor angiogenesis, and provide targets and strategies for anti-angiogenic therapy for glioma and OS.

## 7. Conclusions and future perspectives

In recent years, some research progress has been made on the biological functions of circRNAs; however, research on the mechanisms of circRNAs remains insufficient. Various circRNAs encode proteins, which provides a basis for the study of circRNA-related mechanisms and therapeutic targets for certain diseases. circRNAs play a key role in the pathogenesis of cardiovascular diseases, such as heart failure, cardiac hypertrophy and atherosclerosis (90). In addition, circRNAs are involved in various angiogenesis-induced pathologies, including tumors, which offers a breakthrough for treatment strategies (3).

According to a database search performed in the present study, it is known that circRNAs do not have a common target in different cancer types. It is considered that the same circRNAs are expressed differently in various tumor tissues, which is possibly due to the complexity and heterogeneity of these tissues. circRNA expression is not the same in different types of cancer, and thus, no common targets for circRNAs in different cancer types have been reported. Therefore, in future research, tumor pathogenesis and tumor tissue heterogeneity should be explored in depth, and common targets of circRNAs in different types of cancer need to be actively determined to achieve further breakthroughs in cancer.

It is worth mentioning that miRNAs can exert a pro-angiogenic or anti-angiogenic effect by modulating endothelial cell migration or the cell cycle. Some of these specific miRNAs play a role in tumor angiogenesis by regulating the response of endothelial cells to blood flow or VEGF. As an oncogene, miR-29a is involved in the onset of a variety of cancer types. Using *in vitro* and *in vivo* experiments, Jia *et al* (91) found that lncRNA H19 expression was upregulated in microvessels of glioma-associated endothelial cells. It was further found that lncRNA H19 functioned as a miR-29a sponge to downregulate miR-29a by targeting the 3'-UTR of vasohibin 2, which promoted angiogenesis; additionally, H19 gene knockout attenuated glioma progression by inhibiting miRNA-29a, which prevented glioma angiogenesis (91). Microvesicles can mediate intercellular signal transduction involved in disease progression. Zhang *et al* (92) used a mouse model of tumor implantation and revealed that microvesicles rich in miR-29a inhibited angiogenesis and reduced the tumor growth rate, downregulated cell-derived microvesicles containing miR-29a to alleviate VEGFA inhibition, and promoted angiogenesis in gastric cancer (92). Therefore, perhaps attention should be paid to the role of specific miRNAs in tumor angiogenesis in order to provide new insight into and targets for the treatment of tumors.

VEGF is a key mediator of tumor angiogenesis that promotes tumor growth, and thus, VEGF is a therapeutic target, and its inhibition has become an important tumor treatment strategy (21). Tumor angiogenesis relies on the coregulation of pro-angiogenic factors and anti-angiogenic factors; in addition to VEGF (15,16), pro-angiogenic factors include angiopoietin (17), MMPs and FGF (18-20). circRNAs can directly or indirectly target VEGF to regulate tumor angiogenesis. Circ-RanGAP1 (40), circ0001429 (41) and circRNA-MYLK (51) function as miRNA sponges that upregulate VEGF expression to promote angiogenesis and accelerate tumor progression. On the contrary, as a sponge for SRSF1, circSMARCA5 (53), can negatively regulate VEGF and angiogenesis in GBM. However, compared with VEGF, the circRNA regulation of angiogenesis through angiopoietin, FGF and MMPs has not been extensively studied and warrants further investigation.

In the process through which circRNAs regulate tumor angiogenesis, the ceRNA mechanism is a classic regulatory mechanism and is relatively well studied. In addition, the specificity of circRNA structure and function allows circRNAs to be regulated by other mechanisms; for example, RBPs directly target circRNAs to regulate tumor angiogenesis (24,53). He *et al* (93) found that the expression of the RBPs, MOV10, circ-DICER1 and ZIC4, in glioma-exposed endothelial cells was upregulated, while that of miR-103a-3p/miR-382-5p expression was downregulated. The mechanism involved the binding of MOV10 to circ-DICER1, which adsorbed miR-103a-3p/miR-382-5p as a sponge and attenuated the negative regulation of ZIC4 by miR-103a-3p/miR-382-5, thereby upregulating ZIC4 expression (93). The aforementioned research not only provides a novel mechanism for angiogenesis in glioma, but also provides a promising target for anti-angiogenic therapy in this type of cancer.

circRNAs are recently discovered members of the RNA family that have potential regulatory functions; they are expressed in various types of cancer and can affect tumor angiogenesis via multiple mechanisms. Recent studies have demonstrated that circRNAs participate in the regulation of tumor angiogenesis via two primary means: They can function as miRNA sponges and participate in tumor angiogenesis by regulating related targets or pathways; and they can also directly target RBPs to regulate tumor angiogenesis (24,53). The present review discussed the biological functions of circRNAs, their roles as ceRNAs in the regulation of tumor

angiogenesis, the effects of circRNAs on tumor angiogenesis in various systems and their potential clinical application value. Although some progress has been made in understanding the regulation of circRNAs involved in tumor angiogenesis, the mechanisms are primarily centered on the sponging effect of circRNAs, while little information is available on other mechanisms. It is therefore necessary to further explore other relevant mechanisms and targets of circRNAs that are involved in tumor angiogenesis. In addition, circRNAs play a role in tumor angiogenesis, although the specific mechanisms involved remain unclear, and few target molecules have been reported for the treatment of related diseases. The mechanisms of circRNAs and tumor angiogenesis thus warrant further investigation.

In conclusion, as bioinformatics continues to develop, it is considered that circRNAs have broad prospects as tumor diagnostic markers and anti-angiogenic therapies, and are worthy of further investigation.

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DM wrote and revised the manuscript. RJ and SY participated in the acquisition and analysis of data from the literature for inclusion in the study, and designed and created the figures. MW, XB and CZ searched the references, drafted the manuscript, and edited and revised the figures. WW and ZL conceived and designed the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

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**Competing interests**

The authors declare that they have no competing interests.

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