frontiers in Oncology

REVIEW
published: 10 March 2021
doi: 10.3389/fonc.2021.553706

CircRNA-Mediated Regulation of Angiogenesis: A New Chapter in Cancer Biology

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Angiogenesis is necessary for carcinoma progression and is regulated by a variety of pro- and anti-angiogenesis factors. CircRNAs are RNA molecules that do not have a 5'-cap or a 3'-polyA tail and are involved in a variety of biological functions. While circRNA-mediated regulation of tumor angiogenesis has received much attention, the detailed biological regulatory mechanism remains unclear. In this review, we investigated circRNAs in tumor angiogenesis from multiple perspectives, including its upstream and downstream factors. We believe that circRNAs have natural advantages and great potential for the diagnosis and treatment of tumors, which deserves further exploration.

Keywords: circRNA, miRNA, tumor angiogenesis, VEGF, signaling pathways

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Cancer Molecular Targets and Therapeutics, a section of the journal Frontiers in Oncology

Received: *20 April 2020*
Accepted: *07 January 2021*
Published: *10 March 2021*

Citation:
Jiang S, Fu R, Shi J, Wu H, Mai J, Hua X, Chen H, Liu J, Lu M and Li N (2021) CircRNA-Mediated Regulation of Angiogenesis: A New Chapter in Cancer Biology. Front. Oncol. 11:553706. doi: 10.3389/fonc.2021.553706

INTRODUCTION

Angiogenesis is characterized by the proliferation, differentiation and migration of endothelial cells (ECs) on the basis of existing capillaries or venules to generate new blood vessels (1–3). In normal circumstances, blood vessels are regulated by multiple angiogenic factors that promote or inhibit angiogenesis to maintain homeostasis. However, active proliferation and increased energy metabolism are characteristics of a tumor. Primary or metastatic cancer relies on the angiogenesis and formation of a rich network of blood vessels. In response to its own cell necrosis, tumor cells regulate the microenvironment by releasing pro-factors or by blocking the release of anti-angiogenic factors. By activating the "angiogenesis switch" in the tumor, the vascular system is stimulated to sprout new blood vessels (3, 4), so as to obtain more energy and oxygen (5), and to promote the proliferation of the tumor. Meanwhile, tumor cells spread and metastasize in other parts of the body. Therefore, inhibiting angiogenesis has become an important target for cancer therapy and has stimulated the drive to explain the mechanism of tumor angiogenesis.

A number of pro-angiogenic factors have been identified, including VEGF (6, 7), angiopoietin (8), matrix metalloproteinases (MMPs) (9, 10), and fibroblast growth factors (FGF) (11). VEGF specifically promotes vascular endothelial growth by promoting mitosis. Angiopoietins (8) are growth factors secreted by vascular endothelium that regulate vascular maturation and remodeling. Two important angiopoietins are Ang-1 and Ang-2 (12, 13). The balance of Ang-1 and Ang-2 in endothelial cells is key to normal angiogenesis. FGF (11) is a low molecular weight polypeptide

growth factor with a specific structure, most of which can bind to heparin. FGF contains secreted signaling peptides that are secreted into the extracellular matrix (ECM) and can bind to acetylheparin aminoglycan. MMPs are proteases that hydrolyze ECM and remodel angiogenic basement membrane (14).

In contrast to the pro-angiogenic factors, endostatin, arrestin, and angiostatin have been shown to be antiangiogenic factors. Endostatin, a peptide of collagen XVIII, contains a zinc-binding domain and an arginine-binding domain, which allows it to bind to heparin and is important for heparin's antiangiogenic activity (15). Arrestin selectively inhibits endothelial cell proliferation and migration and thus represses angiogenesis (16). Angiostatin (17) is the product of fibrinogen lyolysis. Interestingly, fibrinogen itself has no inhibitory effect on angiogenesis but can directly bind to ATP synthase to trigger apoptosis of endothelial cells, possibly by lowering the pH value in cells (18).

Circular RNAs (CircRNAs) are a type of long non-coding RNA (lncRNA) first identified in plant studies and thought to be a class of viroids (19). Because of low expression in cells, circRNAs were initially thought to be an error in RNA splicing. Next-generation sequencing techniques that do not rely on the 3'-polyA tail have been used to find extensive circRNAs in eukaryotic cells. With the development of deep sequencing, more and more RNA transcripts have been discovered, and the nonstandard pattern of RNA splicing leads to multiple subtypes of circRNAs (20). As the number of identified circRNAs increased, more of them were found to be biologically stable, and many circRNA transcripts were more abundant than their associated mRNA transcripts (21). Hansen and Memczak et al. first demonstrated a function of circRNAs, showing that circRNAs act as a sponge for miR-7 (22, 23). Since then, circRNAs have received extensive attention, and their characteristics and potential applications in clinical diagnosis and treatment have been explored.

It has been previously shown that circRNAs play an important role in tumor growth, angiogenesis, metastasis, recurrence, and antitumor therapy (24). CircRNAs regulate VEGFR-related pathways through adsorption of miRNA to affect tumor angiogenesis. CircRNAs have also been shown to be involved in regulating the tumor microenvironment (25). CircRNAs are highly abundant and stable, conserved in evolutionary species, and widely present in various body fluids. The exploration of tumor angiogenesis-related circRNAs as biomarkers or targets will open new possibilities for anti-tumor treatment strategies. Here, we focus on the biomolecular mechanisms of circRNA in tumor angiogenesis.

CIRCRNA

Biogenesis and Characteristics of circRNAs

After the removal of introns by enzyme-catalyzed precursor mRNA, selective splicing of exons in turn to form mature mRNA is common. Unlike typical mRNA splicing, circRNAs are produced by a back-splicing process, in which the downstream 5' splicing site and the upstream 3' splicing site are connected to form a single-chain covalently closed ring. The spliceosome then removes all or part of the introns and joins the remaining sequences. Three kinds of circRNAs are then produced, including exonic circRNA, intronic circRNA, and exon-intron circRNA (20, 26, 27).

The mechanism of circRNA formation is one of the basic scientific questions underpinning the study of circRNAs. Zhang et al. showed that the formation of circRNAs was determined by rapid transcription, the reverse complementary sequence in RNA, and the effect of long-term accumulation in cells (28). circRNA predictive analysis combined with the technique of long-fragment sequencing revealed that there were many selective splicing modes of circRNA (29). In addition, the formation of circRNAs is closely related to their selective splicing patterns and cell types (30). Besides, RNA binding proteins are involved in the formation of circRNAs. In drosophila, the splicing factor Muscleblind (Mbl) promotes the formation of circMbl from its own precursor mRNA (31). In general, the formation of circRNAs is parallel to the linear RNA transcription, which is related to the transcription speed of corresponding genes. Reverse complementary sequences or RBP binding sequences are important prerequisites for the formation of circRNAs. One gene may correspond to a variety of molecular forms of circRNAs.

Biological Functions of circRNAs

CircRNAs play an important role in tumor growth, angiogenesis, metastasis, recurrence, and antitumor therapy through multiple functions (24). Recent studies suggest that circRNAs act as sponges to bind and block miRNAs, or as competing endogenous RNA (ceRNA) molecules (22, 23, 32). Previously, miRNAs have been shown to bind directly to their target mRNA in the form of base pairing, leading to cleavage of the mRNA transcript or inhibition of mRNA translation (33). Furthermore, RNA binding proteins regulate disease progression by directly targeting circRNAs (34–36). Additionally, circRNAs can compete with linear transcripts for splicing sites during reverse back-splicing (31). On the one hand, when more exons form circRNAs, the mRNA is reduced; on the other hand, circRNAs containing introns directly bind the U1 component in the spliceosome to recruit RNA polymerase II, thereby upregulating expression of the target gene (28). Interestingly, circRNAs have long been considered a non-coding RNA, but that has changed. There is an m6A modification for circRNAs that promotes translation (37). Additionally, the circRNA, circ-FBXW7, directly encodes the protein FBXW7-185aa and cooperates with the FBXW7 protein in linear transcripts to stabilize c-Myc and inhibit the occurrence and progression of malignant glioma (38). Furthermore, Pamudurti et al. found that a large amount of circRNA translated proteins or peptides were found in the *Drosophila* brain (39).

THE INTERACTION BETWEEN MIRNAS AND CIRCRNAS IN TUMOR ANGIOGENESIS

The primary mechanisms by which circRNAs regulate tumor angiogenesis is by functioning as a targeted sponge for miRNAs,

by binding and blocking miRNAs, or by acting as competing endogenous RNA molecules (22, 23, 32). The regulation of miRNAs in tumor angiogenesis has been previously characterized (40). miRNAs directly target the 3'UTR region of the transcripts of pro-angiogenic or anti-angiogenic factors, resulting in the inhibition of mRNA translation and degradation of the mRNA (33). It has been shown that miRNA transcription is downregulated in tumor-related ECs. The reduction of competing miRNAs, which is a target of the 3'UTR region of VEGF-A mRNA, upregulate VEGF-A expression and promotes angiogenesis through VEGF/VEGFR-2 signaling pathways (41). In this study, we reviewed the circRNAs associated with angiogenesis and summarized their expression patterns, mechanism, and functions in tumor cells in **Table 1**.

Pro-angiogenic-Associated circRNAs

CircRNA-MYLK

CircRNA-MYLK is an oncogene in bladder cancer, and it activates the VEGF-A/VEGFR-2 signaling pathway by functioning as a sponge for miR-29a to up-regulate VEGFA expression (42). *In vitro*, overexpression of circRNA-MYLK promotes the ability of HUVECs to form blood vessels and rearrange the cytoskeleton. *In vivo*, upregulation of circRNA-MYLK promotes tumor progression and is a predictor of poor prognosis (**Figure 1**). In addition, studies have also shown that down-regulation of cell-derived microvesicle miR-29a relieves suppression of VEGFA and promotes angiogenesis in gastric cancer (59). The animal model demonstrates that angiogenesis can be inhibited by microvesicles rich with miR-29a. Peng et al. revealed that the lncRNA H19 acts as a miRNA sponge of miR-29a. Downregulating miR-29a promotes angiogenesis by targeting the 3'-UTR region of VASH2 (60). On the contrary, Wang et al. reported that miR-29a serves as an oncogene that activates the AKT pathway by targeting PTEN in endothelial cells and promoting tumor angiogenesis (61). Meanwhile, both miR-29a (62) and miR-362-3P (63) can be modulated by circRNA-MYLK, which up-regulates the expression of downstream Rab23 and promotes the progression of tumors. Therefore, whether circRNA-MYLK promotes tumor angiogenesis remains an open question, and further investigation is required to identify its mechanism in tumors in other than bladder cancer.

Circ-ASH2L

Circ-ASH2L was first identified for promoting tumor angiogenesis in pancreatic ductal adenocarcinoma (44). As an oncogene, it was found in the RIP experiment to be a sponge for miR-34a. miR-34a has been widely reported to inhibit angiogenesis by repressing the Notch1 signaling pathway (64, 65). In the study of Chen et al. (44), circ-ASH2L also promoted angiogenesis by activating the Notch1 signaling pathway. *In vitro*

TABLE 1 | The expression patterns, mechanism, and functions of circRNAs associated with tumor angiogenesis.

CircRNA	Expression	Mechanism	Function	Origin	Ref
circRNA-MYLK	up	miR-29a/VEGFA/VEGFR2/Ras/ERK signaling pathway	proliferation, migration, tube formation of HUVEC and rearranged cytoskeleton	Bladder Cancer	(42)
CircHIPK3 /BCRC-2 /hsa_circ_0000284	down	miR-558/HPSE	migration, invasion, and angiogenesis	bladder cancer	(43)
Circ-ASH2L	up	miR-34a/Notch1	invasion, proliferation and angiogenesis	Pancreatic Ductal Adenocarcinoma	(44)
hsa_circRNA_002178 /hsa_circ_0000519	up	miR-328-3p/COL1A1	cell viability, energy metabolism and tube formation ability	breast cancer	(45)
CircSMARCA5 /hsa_circ_0001445	down	Splicing Factors SRSF1/VEGFA	cells migration and angiogenesis	glioblastoma multiforme	(46, 47)
circ-SHKBP1 /hsa_circ_0000936	up	miR-544a/FOXP1/miR-379/FOXP2/ AGGF1	viability, migration, and tube formation of GEC	GECs	(48)
circ_002136	up	FUS/circ_002136/miR-138-5p/SOX13/ SPON2	viability, migration and tube formation	GECs	(49)
circ-DICER1	up	MOV10/circ-DICER1/miR-103a-3p/miR-382-5p/ZIC4/Hsp90β/PI3K/Akt	cell viability, migration, and tube formation of GECs	GECs	(50)
Exosome has_circRNA_100338	up	VE-Cadherin and ZO-1	cell proliferation, angiogenesis, permeability, and vasculogenic mimicry formation ability of HUVECs	HCC	(51)
hsa_circ_0003575	up	potential circRNA-miRNA-mRNA network	proliferation and angiogenesis ability of HUVECs	HUVECs	(52)
hsa_circ_0010729	up	miR-186/HIF-1α Axis	vascular endothelial cell proliferation and apoptosis	HUVECs	(53)
cZNF609	up	miR-615-5p/MEF2A	retinal vessel loss and suppressed pathological angiogenesis	high glucose and hypoxia stress	(54)
circNfix /hsa_circ_0005660	up	miR-214/Gsk3β/β-catenin/Meis1(TF) Ybx1,Nedd4l cyclin A2,cyclin B1	proliferation angiogenesis and apoptosis	adult heart in humans, rats, and mice	(55)
circHIPK3	up	miR-30a-3p/VEGF-C, FZD4, and WNT2	cell viability, proliferation, migration, and tube formation	diabetic retinas and retinal endothelial cells	(56)
hsa_circ_0074834	down	microRNA-942-5p/ZEB1/VEGF	promote osteogenic differentiation of BMSCs and the repair of bone defects	BMSC	(57)
Circ_0063517	down	miR-31-5p-ETBR	growth, migration, and angiogenesis	placenta tissue of PE	(58)

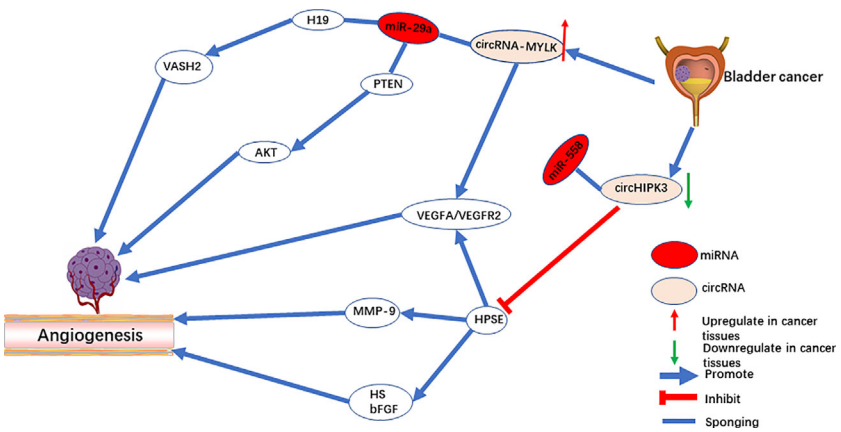

FIGURE 1 | The role of circRNAs in pro-angiogenesis and anti-angiogenesis in bladder cancer.

experiments verified that circ-ASH2L sequesters miR-34a to increase the downstream expression of VEGF through the Notch1 signaling pathway (**Figure 2**). Meanwhile, miR-34a down-regulates VEGF expression through another axis that inhibits the translation and degradation of the E2F3 mRNA in head and neck squamous cell carcinoma (66).

Hsa_circRNA_002178 (hsa_circ_0000519)

Hsa_circ_0000519, a circular transcript of RPPH1, is located on chromosome chr14:20811436-20811534. Hsa_circ_0000519 was upregulated in breast cancer and was suggested as a marker of poor prognosis (45). Knockdown of hsa_circRNA_002178 directly decreased the combination of miR-328-3p, and thus downregulated COL1A1 and impaired breast cancer angiogenesis (**Figure 2**). COL1A1 is upregulated in brain metastases (67) and oral squamous cell carcinomas (68), which are potentially associated with angiogenesis. A previous study showed that miR-328-3p directly targets the 3'UTR of matrix metalloprotease 16 (MMP-16) and suppresses its expression in osteosarcoma cells (69). MMP16 is a member of the matrix metalloproteinase (MMP) family (10) and can hydrolyze ECM proteins. MMPs [such as MMP-9 (70)] can break the ECM and cell connections, promoting tumor angiogenesis and progression. HIF-1 mediates the regulation of VEGF and MMPs at the transcriptional level (71). MMPs (such as MMP-2/-3/-7 and -9) promote angiogenesis by degrading the extracellular protein matrix, releasing VEGF without affecting its activity (9, 72, 73). MMP-16 has a similar structure to MMPs, and the 3'UTR of MMP-16 is targeted by miR-328-3P, while hsa_circ_0000519 can adsorb miR-328-3P. Therefore, further investigation is required to see if hsa_circ_0000519 can promote tumor angiogenesis by sponging miR-328-3p to regulate other MMPs.

GECs Related circRNAs

The method of co-culturing glioblastoma (GBM) cells and endothelial cells was used to explore the cellular

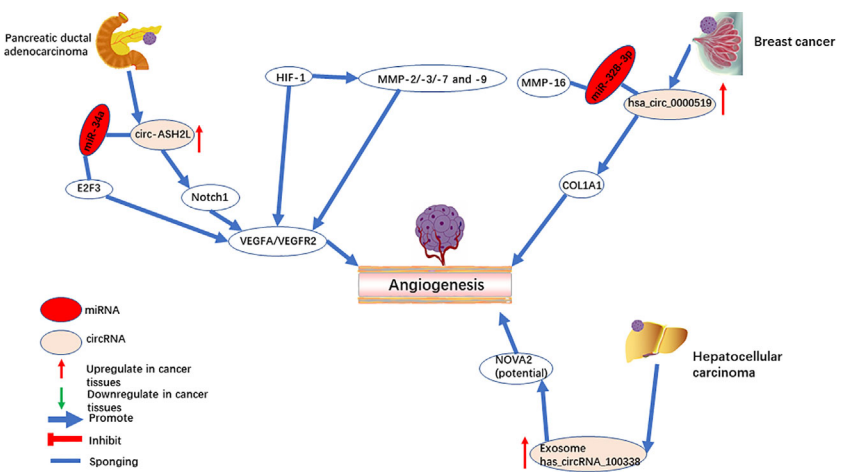

FIGURE 2 | CircRNAs mediate angiogenesis in pancreatic ductal adenocarcinoma, breast cancer, and hepatocellular carcinoma.

communication and molecular adjustment between the two cell types. Three significant upregulated circRNAs [circ-SHKBP1 (48), circ_002136 (49), and circ-DICER1 (50)] were identified (**Figure 3**). Among them, circ-SHKBP1 (circbase ID: hsa_circ_0000936) serves as a sponge for miR-379 and miR-544a, competing with the combination of 3'UTR of FOXP1 and FOXP2. At the same time, FOXP1 and FOXP2 are the angiogenic promoter of AGGF1, which induce tube formation of GECs through the PI3K/AKT and ERK1/2 signaling pathways (**Figure 3**). AGGF1 acts as a angiogenic promoter and has been widely reported in gastric carcinoma (74), hepatocellular carcinoma (75), and medulloblastoma (76). Meanwhile, the activation of the PI3K/AKT and ERK1/2 signaling pathways promoted by AGGF1 has been found when angiogenesis was activated (77–79).

Circ_002136 was found to combine with miR-138-5p, resulting in increased expression of SOX13, which upregulated SPON2 by directly binding the SPON2 promoter region (**Figure 3**). Interestingly, FUS acts as RNA binding protein to upregulate circ_002136, and was upregulated by promotor SPON2, to form a feedback loop. Further research showed that SPON2-knockdown significantly suppresses tumor angiogenesis in GECs. In addition, one of the SPON2 family members inhibited endotheliocyte proliferation, migration, and angiogenesis by inhibiting HIF-1a, VEGFA expression, and the phosphorylation of VEGFR-2 in colon cancer (80). Meanwhile, after IL-1β induced cartilage degradation, overexpressed miR-138-5p was found to be a FOXC1 sponge, and upregulation of MMP-13 was observed (81). Interestingly, SOX13, which was shown to be a target for circ_002136, regulates angiogenesis through a system model of homologous phenotypes (82).

Circ-DICER1 is a target for the RNA binging protein, MOV10, which together regulate angiogenesis (50). circ-DICER1 directly binds the 3'UTR of miR-103a-3p and miR-382-5p and downregulates ZIC4 in GECs (**Figure 3**). Furthermore, ZIC4 promotes tube formation through the PI3K/Akt signaling pathway by upregulating heat shock protein 90β (Hsp90β). In addition, Hsp90β up-regulates the expression of VEGFRs and promotes tumor angiogenesis by VEGFRs promoters in HCC (83, 84). Meanwhile, HSP90β directly targets the BAZF mRNA after activation by the VEGF-A/PRKD2 pathway to promote angiogenesis (85). In another study, miR-103a-3p was also found to target PTEN to promote EPC migration and angiogenesis (86).

Exosome has_circRNA_100338

Exosomes have been used as messengers of intercellular communication, in which circRNA plays an essential role in tumorigenesis and progress (87). circRNA-100338 (51) is upregulated in both HCC cells and their secreted exosomes. Based on RNA pulldown assays, circRNA-100338 potentially targets NOVA2 and promotes angiogenesis in HUVECs (**Figure 2**). Furthermore, a previous study has shown that the downregulation of NOVA2 can disrupt angiogenesis (88). In addition, it was found that exosome-derived ncRNAs promote cell communication in the microenvironment and regulate angiogenesis (89–91). Therefore, as a stable ncRNA in exosomes, a novel therapy has a promising future in the mechanism of tumor angiogenesis and prognosis.

Anti-Angiogenesis Associated circRNA in Tumor

CircHIPK3

CircHIPK3 is located on chromosome chr11:33307958-33309057. In a previous study, circHIPK3 serves as oncogene of multiple tumors. However, in bladder cancer (43, 92) and osteosarcoma (93) tissues, circHIPK3 is significantly downregulated, acting as a tumor suppressor gene. Downregulation of circHIPK3 is associated with angiogenesis (43). CircHIPK3 directly targets miR-558 and suppresses heparinase (HPSE) expression to inhibit angiogenesis in ECs (**Figure 1**). Additionally, studies by Qu et al. (94) and Zheng et al. (95) demonstrated that upregulation of miR-558 in neuroblastoma and gastric cancer cells promoted

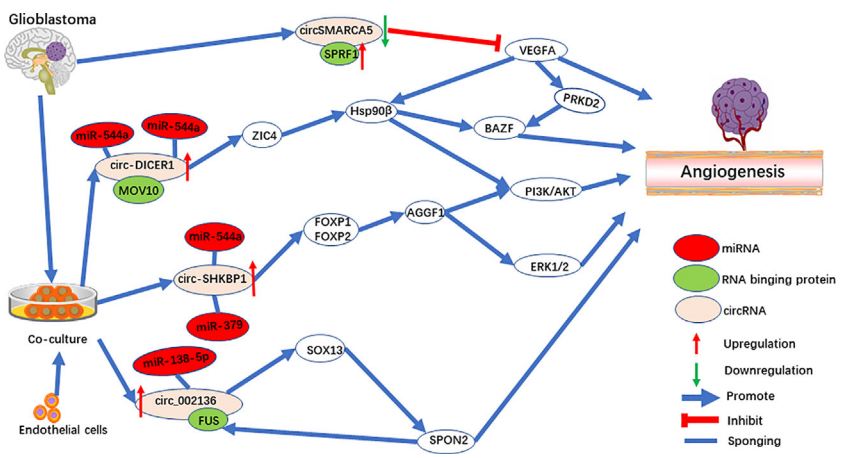

FIGURE 3 | The role of circRNAs in pro-angiogenesis and anti-angiogenesis in glioblastoma.

expression of HPSE by directly activating or weakening the inhibition of HPSE by Smad4. On the one hand, HPSE is highly expressed in cancer tissue but not in mature vascular ECs (96). On the other hand, HPSE significantly cuts off the HS chain in the endothelial cell matrix and stimulates the release of other pro-angiogenic molecules (97). The active bFGF produced by HPSE binds to HS fragments and directly targets endothelial cells to promote angiogenesis (96, 98). Meanwhile, studies have also shown that exogenous HPSE can induce melanoma cells to release VEGF, and this has no correlation with the enzyme activity of HPSE (99).

CircSMARCA5

CircSMARCA5 (circbase ID: hsa_circ_0001445) (46, 47) is downregulated in GBM and is negatively correlated with SRSF1 and VEGFA. SPRF1, a splicing factor, has been shown to bind directly to circSMARCA5 to regulate VEGFA expression (**Figure 3**). Furthermore, circSMARCA5 is significantly correlated with vascular microvessel density, suggesting that circSMARCA5 is a potential biomarker for GBM angiogenesis. In addition, circSMARCA5 is downregulated in gastric cancer (100), cervical cancer (101), non-small cell lung cancer (102), hepatocellular carcinoma (103), multiple myeloma (104), and acts as a biomarker. On the contrary, circSMARCA5 is upregulated in prostate cancer (105).

CircRNA Regulates Angiogenesis in Other Diseases

Upregulation of hsa_circ_0003575 (52) was observed in oxLDL-treated HUVECs to simulate atherosclerosis, and downregulation of hsa_circ_0003575 promoted angiogenesis in HUVECs. In a hypoxia-induced microenvironment, endothelial cells are more prone to angiogenesis, and hsa_circ_0010729 (53) was found to be upregulated and bound miR-186. Knockdown of hsa_circ_0010729 repressed the expression of HIF-1α and inhibited cellular angiogenesis related capacity and promoted apoptosis in HUVECs. Significant upregulation of cZNF609 (54) was observed both *in vivo* and *in vitro* in high glucose-induced microenvironments. Subsequent bio functional experiments demonstrated that cZNF609 inhibited angiogenesis *via* sequestering miR-615-5p and increasing the expression of MEF2A. In an adult mouse model of myocardial infarction, circNfix (55) is regulated by the transcription factor, Meis1-bound superenhancer, thereby promoting angiogenesis and cardiac regeneration. CircHIPK3 (56) is upregulated and served as a sponge for miR-30a-3p, resulting in increased expression of VEGC-C, FZD4 and WNT2, and promoting the formation of new blood vessels in EC. One of the key factors in fracture healing is the recovery of blood flow, and the dysregulation of circRNAs in bone marrow stem cells inhibits angiogenesis. The downregulation of hsa_circ_0074834 (57) releases inhibition of miR-942-5p to upregulate ZEB1 and VEGF, promoting osteogenic differentiation and the repair of bone defects. For patients with preeclampsia, circ_0063517 (58) and ETBR were found downregulated in the placenta tissue; circ_0063517 promotes angiogenesis by sponging miR-31-5p to downregulate ETBR.

The Potential Therapeutic Role of circRNAs

In vivo and *in vitro* experiments have verified that the regulation of the transcriptional patterns of circRNAs is related to the survival and growth of tumor cells. Therefore, there is great potential to use siRNA, ASO, and circRNAs to treat tumors and other diseases. Previous reviews have described a therapeutic role for circRNAs in cardiovascular disease (106). One advantage of circRNAs in its therapeutic role is that it has a stable structure that is not easily degraded compared with other lncRNAs. Additionally, circRNAs have been found in plasma exosomes, which provide a reference model for simulating circRNA as drug targeted delivery *in vivo*. Further, chemical modifications enable gene delivery as a treatment strategy, while minimizing side effects (107).

CircRNAs Associated Bioinformatics Software

With the development of deep sequencing, a large number of transcripts were discovered, and data were formed and developed into databases for further analysis (**Supplementary Table 1**). These databases record the specific ID, sequences, potential functions, and expression patterns of newly discovered circRNAs in different species in different diseases. Different databases may have different results in predicting the function of circRNAs (such as miRNA binding sites, protein binding sites, and coding proteins) due to differences in algorithms and individual heterogeneity. Therefore, the intersection of results from multiple databases may be a potential method to predict the function of circRNA more accurately.

FUTURE PROSPECTIVE AND CONCLUSION

Currently, circRNA plays a significant role in carcinoma angiogenesis through varied biological pathways. Current studies have shown that circRNAs regulate tumor angiogenesis mainly through two pathways. The first is by functioning as a miRNA sponge, thereby upregulating or downregulating downstream genes, and promoting or repressing angiogenesis. Second, RBP directly targets circRNAs to regulate tumor angiogenesis (46, 47, 49, 50). Nevertheless, it has been previously reported that circRNA-encoded proteins regulate GBM malignancy (38). However, current research has not found whether circRNA regulates tumor angiogenesis by encoding proteins. Therefore, there is no doubt that the exploration of circRNAs in tumor angiogenesis is in its infancy, and more detailed analyses is essential.

Tumor angiogenesis is co-regulated by a variety of pro- and anti-angiogenic factors, among which VEGF-related pro-angiogenic factors are the most remarkable (108–110). On the one hand, circRNA-MYLK (42), circHIPK3 (56), and hsa_circ_0074834 (57) act as a miRNA sponge, directly upregulating VEGF expression to promote angiogenesis. On the other hand, circSMARCA5 (46) has

been shown to serve as a sponge for SRSF1, negatively regulating VEGF and anti-angiogenesis in GBM. Thus, whether circRNA regulates angiogenesis through angiogenesis-related factors, such as angiopoietin, FGF, MMPs, and Endostatin, requires further exploration.

As a stable RNA, circRNAs have natural advantages and great potential as a diagnostic biomarker (111). Compared with tumor tissue, circRNA in plasma or plasma exosomes have greater clinical significance as biomarkers for tumor diagnosis (112), because a blood test is less likely to lead to metastasis than a biopsy or surgical removal.

Furthermore, monitoring angiogenesis, the necessary process for oncogenesis and carcinoma progression, to diagnose or evaluate prognosis may be a worthwhile direction to explore. The exosome circRNA, has_circRNA_100338 (51), has been shown to promote angiogenesis and to be a potential biomarker for HCC.

However, circRNA displays heterogeneity as a diagnostic biomarker (113), and circRNAs may be inversely expressed in different types of tumors. circHIPK3 serves as oncogene of a variety of tumor such as CC (114–116) and NSLC (117, 119). However, in bladder cancer (43, 92) and osteosarcoma (93) tissues, circHIPK3 is significantly downregulated, repressing invasion and metastasis of tumor cells and predicting a good prognosis. Additionally, circSMARCA5 is downregulated in gastric cancer (100), cervical cancer (101), NSLC (102), HCC (103), multiple myeloma (104), but upregulated in prostate cancer (105). Therefore, whether such heterogeneity also exists in the regulation of angiogenesis by circRNAs needs further exploration.

In summary, we reviewed the biological characteristics, functions, and molecular mechanisms of circRNAs in tumor angiogenesis. We believe that circRNAs have great potential as a target for antiangiogenic therapy and as a diagnostic biomarker in tumors, which deserves our attention in the future.

AUTHOR CONTRIBUTIONS

SJ: conception and design. SJ, RF, JS, HW, and JM: wrote and critically reviewed the manuscript. SJ, XH, HC, and JL: figure design and elaboration. NL and ML: directed manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by National Natural Science Foundation of China (81400679), Guangdong Natural Science Foundation (2014A030310067), Guangzhou Science and Technology Programs (Grant No. 202002030387; 201704020153), Special fund of Foshan Summit plan[2019D006] and Foundation of Basic and Applied Basic Research of Guangdong Province [2020A1515110073].

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.553706/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.