

REVIEW

Extracellular vesicle-mediated regulation of tumor angiogenesis— implications for anti-angiogenesis therapy

Shuqiong Zhang  | Junyao Yang | Lisong Shen 

Department of Clinical Laboratory, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence

Lisong Shen and Junyao Yang, Department of Clinical Laboratory, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China. Emails: lisongshen@hotmail.com (LS); yangjunyao@xinhumed.com.cn (JY)

Funding information

National Natural Science Foundation of China, Grant/Award Number: 81802082, 31830039 and 81873863; Shanghai 'Rising Stars of Medical Talent' Youth Development Program-Clinical Laboratory Practitioners Program, Grant/Award Number: 2019016

Abstract

Angiogenesis plays an important role in tumour progression. However, anti-angiogenesis therapy of inhibiting pro-angiogenic factors failed to meet expectations in certain types of tumour in clinical trials. Recent studies reveal that tumour-derived extracellular vesicles (EVs) are essential in tumour angiogenesis and anti-angiogenesis drug resistance. This function has most commonly been attributed to EV contents including proteins and non-coding RNAs. Here, we summarize the recent findings of tumour-derived EV contents associated with regulating angiogenesis and illustrate the underlying mechanisms. In addition, the roles of EVs in tumour microenvironmental cells are also illustrated with a focus on how EVs participate in cell-cell communication, contributing to tumour-mediated angiogenesis. It will help offer new perspectives on developing targets of anti-angiogenesis drugs and improve the efficacy of anti-angiogenesis therapies based on tumour-derived EVs.

KEYWORDS

angiogenesis, drug resistance, endothelial cells, extracellular vesicles, non-coding RNA

1 | INTRODUCTION

Blood vessels are essential to every part of the body including tumours by delivering oxygen and nutrients.¹ Normally, endothelial cells (ECs), which line the inner surface of blood vessels, are involved in tissue growth and repair.² However, tumour vessels are like 'mosaic vessels', which are composed of ECs and tumour cells, displaying abnormal structure and function with the seemingly chaotic organization.³ There is a significant correlation between the degree of angiogenesis and malignancy.⁴ Therefore, the studies about the regulation mechanism of tumour angiogenesis are of great importance to the development of therapeutic strategies against tumour.⁵

Tumour angiogenesis is related to the division, proliferation and migration of vascular ECs. In the process of capillary sprouting, tip cells, which are highly migratory but non-proliferative ECs, guide the new sprout growing in the right direction. Stalk cells, with

high proliferative capacity, elongate the new sprout.⁶ Several pro-angiogenic factors have been found to initiate neovascularization.

Up to date, for the vital importance of VEGF, researchers have focused on developing VEGF and VEGFR inhibitors as anti-angiogenic drugs.⁷ However, clinical trials to anti-angiogenesis therapy by inhibiting pro-angiogenic factors failed to meet expectations. Therefore, studies are required to illuminate the resistance mechanism and develop additional anti-angiogenic drugs according to angiogenesis targets besides VEGF signalling. So far, among the alternative therapeutic strategies and studies, extracellular vesicles (EVs) are reported to have a crucial role in tumour angiogenesis and anti-angiogenesis drug resistance.

According to the EV biogenesis mechanisms, EVs can be classified into two broad categories, referred to here as exosomes and shed microvesicles.⁸ EVs can derive from the endosomal compartment (exosomes) or shed from the plasma membrane (microvesicles,

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. *Journal of Cellular and Molecular Medicine* published by Foundation for Cellular and Molecular Medicine and John Wiley & Sons Ltd.

oncosomes and apoptotic bodies).⁹ EVs mediate intercellular communication between diverse cells and thereby resulting in the impact on normal and pathological conditions.¹⁰ It is due to the abundant molecules that EVs carry such as proteins and peptides, lipids, RNA and DNA, making recipient cells profound phenotypic variations in the tumour microenvironment.^{8,11} EVs have increasingly become the focus of potential targets for novel therapeutic strategies. Moreover, some tumour cell-derived EVs are reported to promote tumour angiogenesis by inducing cancer-associated fibroblast (CAF) differentiation in stromal cells or normal fibroblasts via a complex mixture of small RNAs and proteins. Besides, recent studies revealed that cancer stem cells (CSCs) play a key role in tumour angiogenesis. More importantly, it is observed that treatments with anti-angiogenesis drugs interact with EVs and induce alteration of tumour-derived EVs, which are related to tumour progression and drug resistance. Therefore, anti-angiogenic strategies targeting on tumour cell-derived EVs could represent new approaches for the treatment of tumour development.^{11,12}

Here, we review the currently available data to clarify the mechanisms of intercellular communication these EVs participate in and the consequences of molecular transfer in EVs for tumour angiogenesis and anti-angiogenesis drug resistance. It may help provide the researchers with new perspectives on developing alternative anti-angiogenesis drug and improve the efficacy of anti-angiogenesis therapies.

2 | TUMOUR-DERIVED EVS REGULATING ANGIOGENESIS VIA NON-CODING RNAS AND PROTEINS

Accumulating studies reveal that tumour-derived EVs can transport components including non-coding RNAs such as circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and proteins, thereby offering novel biomarkers and therapeutic targets on tumour angiogenesis.

2.1 | The angiogenic related non-coding RNAs in tumour-derived EVs

Recently, further studies have highlighted the role of non-coding RNAs from tumour-derived EVs in the regulation of tumour angiogenesis.^{5,13}

2.1.1 | circRNAs

circRNAs, formed via back splicing, are single-stranded RNAs with covalent bonding. In eukaryotes, most of the circRNAs are non-coding RNAs acting as microRNA or protein inhibitors, but some encode peptides with tissue-specific and cell-type-specific expression patterns.¹⁴ circRNAs are mostly found in the cytoplasm with a long

half-life.¹⁵ They do not have the typical 5' cap and 3' poly(A) tail-like mRNAs and cannot be degraded easily.¹⁶ Also, it has been shown that circRNAs are enriched and stable in EVs, regulating cellular biological processes, and probably to be biomarkers for different pathological conditions.

Recently, some circRNAs from tumour-derived EVs are found to be related to poor prognosis and advanced tumour node metastasis classification stage, making them potential RNA biomarkers. For example, circ-SHKBP1 and circ-RanGAP1 in gastric cancer (GC) are reported to be up-regulated and effectively delivered from GC-derived EVs into the circulation. circ-SHKBP1 from GC EVs promotes cancer progression by regulating the miR-582-3p/HUR/VEGF axis and suppressing the degradation of HSP90.¹⁷ GC tissues and peripheral blood of patients are found to be rich in circ-RanGAP1. Mechanistically, circ-RanGAP1, acting as a ceRNA, inhibits miR-877-3p, thus making an increased expression of VEGFA.¹⁸ EV circRNA-100,338 is persistently highly expressed in serum of hepatocellular carcinoma (HCC) patients who had the operation of curative hepatectomy may predict lung metastasis and poor survival.¹⁹ What's more, internalized EV circRNA-100,338 in ECs might regulate the angiogenesis by interacting with an RNA-binding protein, NOVA2. These findings reveal a novel mechanism and an alternative therapeutic strategy of circRNAs for tumours (Figure 1).

2.1.2 | lncRNAs

lncRNAs, greater than 200 nucleotides in length, exert essential biological functions by interacting with many molecules in both cytoplasm and nuclei.²⁰ It is extensively reported that lncRNAs are involved in transcriptional regulation. EV lncRNAs that can be found in different types of body fluids are highly stable, thus making them promising biomarkers for tumour liquid biopsy.

Emerging evidence suggests that EV lncRNAs promote the key pro-angiogenesis gene and protein expression, cell proliferation and drug resistance by acting as ceRNA or binding mRNA.²¹ For example, CD90⁺ liver cancer cells' EVs containing lncRNA-H19 induce an obvious increase in the ICAM1 and VEGF expression, leading to increasing ability of ECs to arrange in vitro tubular-like structures and promote heterotypic adhesion between ECs and CSC-like liver cells.²² The lncRNA-APC1 expression is decreased in colorectal carcinoma EVs. lncRNA-APC1 directly binds *Rab5b* mRNA, thereby reducing its stability and ultimately leading to decreased EV production. This action also inhibits the overactivation of the MAPK pathway in ECs and the subsequent suppression of angiogenesis.²³ Epithelial ovarian cancer cells can accelerate angiogenesis through the regulation of EV-mediated transfer of lncRNA-MALAT1 to ECs, regulating well-known pro-angiogenic genes.²⁴ Cervical cancer cells transferred lncRNA-TUG1 to ECs.²⁵ The lncRNA-p21 expression defines prognosis in non-small cell lung cancer and modulates endothelial cell behaviour EVs.²⁶ The lncRNA-GAS5 in the angiogenesis is supposed to be fulfilled by competitively binding miR-29-3p with PTEN.²⁷ In chondrosarcoma, mechanistically, EV

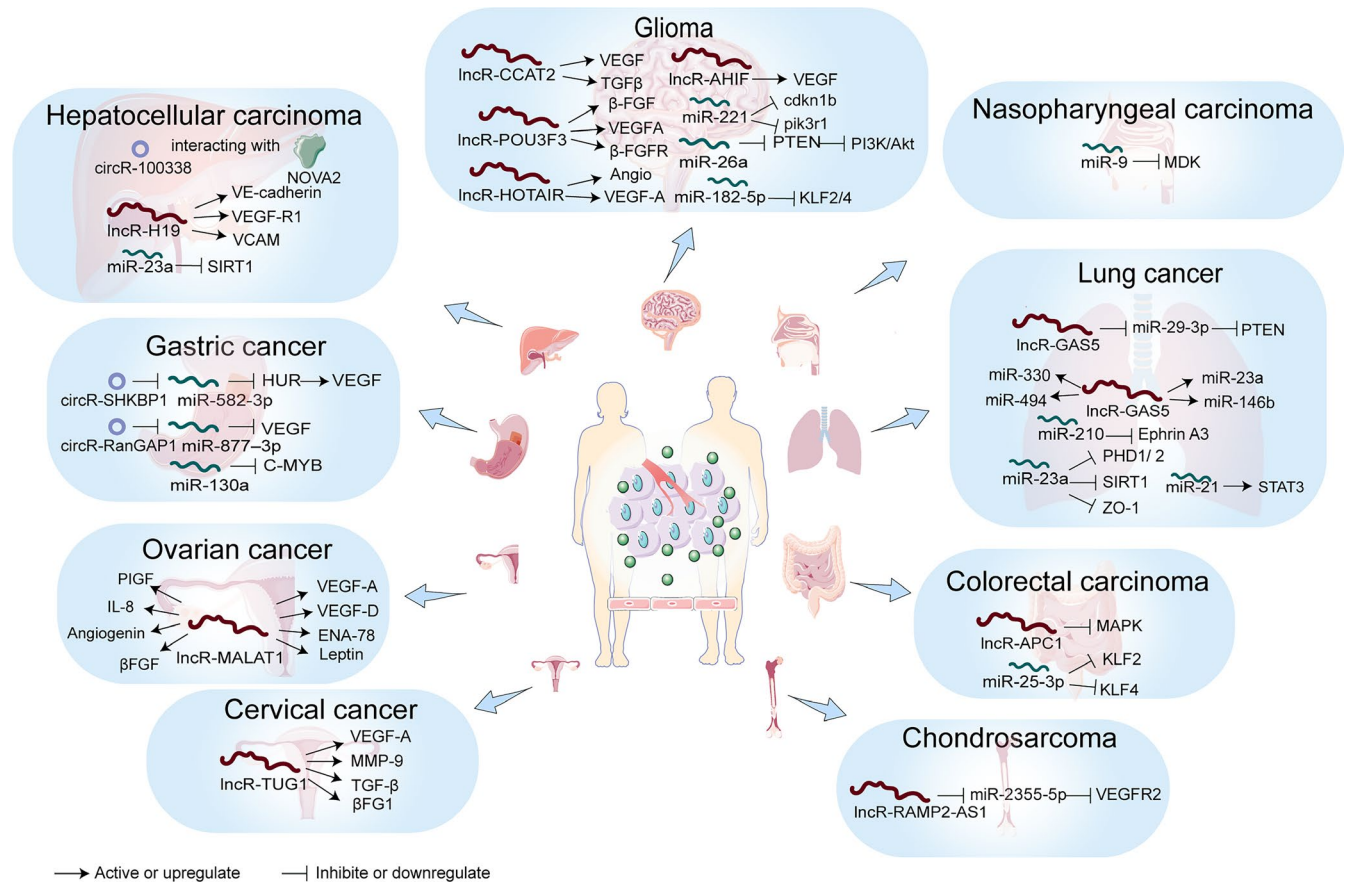


FIGURE 1 Functional mechanisms of the non-coding RNAs in tumour-derived EVs regulating angiogenesis in different types of tumours

lncRNA-RAMP2-AS1 regulates *VEGFR2* expression by acting as a ceRNA of miR-2355-5p.²⁸ In glioma, lncRNA-AHIF is the natural antisense transcript of hypoxia-inducible factor-1 α (HIF-1 α) and is exactly complementary to the 3'-untranslated region of HIF-1 α mRNA.²⁹ Increased lncRNA-AHIF expression has been observed to be in parallel with that of VEGF.³⁰ lncRNA-HOTAIR enhances angiogenesis by induction of *VEGFA* expression.³¹ lncRNA-CCAT2 activates VEGF and TGF- β in ECs.³² lncRNA-POU3F3 increases the expression of FGF2, VEGFA, bFGFR and Angio³³ (Figure 1).

2.1.3 | miRNAs

miRNAs, containing about 23 nucleotides, play an important role in gene regulation by directing protein-coding genes post-transcriptional repression via pairing to the mRNAs.³⁴ So far, it is revealed that miRNAs are important in diverse biological processes of cancer, including tumour growth and drug resistance.³⁵ Extensive studies have revealed that miRNAs are involved in tumour angiogenesis by regulating the activity of ECs.¹³ Importantly, with the development of RNA delivery technology, miRNA-based interventions may become novel therapy to target tumour angiogenesis.⁵

Several miRNAs from tumour-derived EVs have been reported to act as predictive non-invasive biomarkers for anti-angiogenic therapy.^{5,36} For example, miRNA-23a from HCC-derived EVs induces the

process of angiogenesis by targeting SIRT1 in the recipient ECs.³⁷ miR-130a in gastric cancer promotes angiogenesis via targeting C-MYB.³⁸ miR-25-3p from colorectal cancer cell-derived EVs regulates the expression of *VEGFR2*, ZO-1, occludin and Claudin 5 in ECs by targeting KLF2 and KLF4.³⁹ In glioma, miR-26a promotes angiogenesis by targeting PTEN and thereby activates the PI3K/Akt signalling pathway.⁴⁰ miR-221 promotes tip cell behaviour through repression of two targets: *cdkn1b* and *pik3r1*.⁴¹ EV miR-182-5p directly suppressed its targets KLF2 and KLF4, leading to the accumulation of *VEGFR*.⁴² In lung cancer, miR-21 from EVs leads to STAT3 activation, which increases VEGF levels in recipient cells.⁴³ Besides, miR-210 can lead to a down-regulation of ephrin A3, which is miR-210 target protein.⁴⁴ miR-23a activates angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1.⁴⁵ miR-9, which inhibits angiogenesis by targeting MDK and regulating the PDK/AKT pathway, is found to be reduced in EVs derived from cultured NPC cells and plasma samples⁴⁶ (Figure 1).

2.2 | The angiogenic-related proteins in tumour-derived EVs

Up to date, it has been reported that multiple molecules and mechanisms (eg VEGF/ VEGFR2 signalling,⁴⁷ MAPK,⁴⁸ Notch signalling⁴⁹ and Wnt/ β -catenin signalling⁵⁰) are involved in tumour angiogenesis.

TABLE 1 Proteins from tumour-derived EVs regulating angiogenesis

Tumour type	Cargos	Mechanism	Refs
Head and neck squamous cell carcinoma	CEMIP	Up-regulating the cytokines encoded by Ptgs2, Tnf and Ccl/Cxcl	54
Hepatocellular carcinoma	EPHB2	Inducing ephrin-B reverse signalling through STAT3	55
	Ephrin-B2, Dll4	Mediating co-dependence of HCC and EPC intercellular crosstalk	56
Glioma	LOXL4	Activating the FAK/Src pathway	57
	Sema3A	Recruiting myeloid cells in a Sema3A/NRP-1-dependent manner and then secreting pro-angiogenic factors	58
Breast cancer	Proteoglycans glypican-1, syndecan-4	Serve as co-receptors for angiogenic factors	53
	VEGF _{90K}	Activating VEGF receptors and tumour angiogenesis	51
Ovarian cancer	Annexin II	Causing macrophage mediates activation of the p38mapk, NF-κB and STAT3 pathways and increases secretion of IL-6 and TNF-α	59
	Active Notch receptor, ligand, ADAMs and MMPs	Activating Notch signalling pathways	52
	Soluble E-cadherin	Heterodimerizing with VE-cadherin on ECs and transduce a novel sequential activation of β-catenin and NF-κB signalling.	60
Nasopharyngeal carcinoma	ATF2, MTA1, SARS, ROCK1/2	EBNA1 activating AP-1 transcription factor pathway by binding to ATF2 and elevated expression of AP-1 targeting VEGF; SARS and ROCK1/2 are unique regulators in angiogenesis and angiosarcoma tumour progression.	61
	ICAM-1, CD44v5	Regulating several signalling pathways including ERK1/2 kinase, eNOS, MAPK, p38, RhoA/ROCK and Src kinase	62
Bladder cancer	HAX-1	Binding with many cellular and viral proteins	63
	EDIL-3	Activating epidermal growth factor receptor signalling	64

Abbreviations: ADAM, a disintegrin and metalloprotease domain; ATF2, activating transcription factor 2; CD44v5, CD44 variant isoform 5; CEMIP, cell migration-inducing and hyaluronan-binding protein; EDIL-3, EGF-like repeats and discoidin domains 3; eNOS, endothelial nitric oxide synthase; EPCs, endothelial progenitor cells; EPHB2, ephrin type b receptor 2; HAX-1, HCLS1-associated protein X-1; HCC, hepatocellular carcinoma; ICAM-1, intercellular adhesion molecule-1; LOXL4, lysyl oxidase-like 4; MMP, matrix metalloproteinase; MTA1, metastasis-associated 1; Ptgs2, prostaglandin-endoperoxide synthase 2; ROCK1/2, Rho-associated, coiled-coil containing protein kinase 1/2; SARS, seryl-tRNA synthetase; VEGF_{90K}, 90 kD form of vascular endothelial growth factor.

Also, accumulating studies find that tumour-derived EVs contain proteins related to the signalling pathways mentioned above, thus making the EVs a vital role in tumour angiogenesis.

In recent years, the researchers not only identify the proteins from different types of tumour-derived EVs, but also further study

how these proteins are produced, how they exist in the EVs and how they are involved in the angiogenesis. For example, in a recent study, tumour-derived EVs from breast cancer promote VEGF receptors and tumour angiogenesis by VEGF_{90K}.⁵¹ VEGF_{90K} is generated by the cross-linking of VEGF₁₆₅, catalysed by the enzyme

tissue transglutaminase and associated with MVs by the interaction with the Hsp90.⁵¹ And a 3D rotation of EVs displays that Hsp90 and VEGF are located on the surface of the EVs.⁵¹ Furthermore, it is reported recently that the angiogenic effects of tumour EVs are mainly mediated by aspartate β -hydroxylase (ASPH) signalling.⁵² ASPH is found to guide tumour cells to secrete EVs carrying pro-invasive/pro-metastatic components such as active Notch receptor and ligand, and regulators ADAMs and downstream MMPs.⁵² More proteins from different types of tumour-derived EVs and their angiogenesis mechanism are summarized in Table 1.

3 | TUMOUR-DERIVED EVs REGULATING ANGIOGENESIS VIA CAF DIFFERENTIATION

CAFs can release many regulatory molecules and remodel the extracellular matrix, regulating the biological processes of between other stromal cells and tumour cells via intercellular contact.⁶⁵ CAFs are also known to enhance angiogenesis via secretion of factors such as VEGFA, PDGFC, FGF2, osteopontin and frizzled-related protein 2 (SFRP2).⁶⁶ CAFs are revealed to be generated in three major ways: the transformation of residual fibroblasts; endothelial-to-mesenchymal transition (EndMT); and differentiation from mesenchymal stem cells (MSCs).^{67,68} CAFs can derive from multiple resident precursors, such as ECs, smooth muscle cells, myoepithelial cells and MSCs.⁶⁹ Recently, EVs from tumour cells are reported to act on residual fibroblasts or other cells to induce CAF differentiation, then promoting angiogenesis by secreting angiogenic factors, including VEGF, TGF- β , FGF2, MMP9 and MMP2.⁷⁰

Tumour cell-derived EVs have been reported to induce CAF differentiation from stromal cells or normal fibroblasts via a complex mixture of small RNAs and proteins. For example, intercellular contact between MSCs and cancer cells results in MSCs expressing the CAF-like phenotype character such as FSP, α -SMA and CXCL12.^{71,72} Treating with chronic lymphocytic leukaemia (CLL) cells, EVs, the expression of several genes already associated with the CAF gene signature (eg *ICAM1*, *MMP1*), are observed in MSCs and ECs.⁷¹ Besides, it is proposed that increased secretion of NF- κ B signalling, cytokines and chemokines from CLL EVs reprogrammed MSCs to the CAF differentiation.^{71,73} TGF- β 1-dependent fibroblast differentiation can be induced by prostate cancer-derived EVs, which resemble stromal cells isolated from prostate cancer tissue.⁷⁴ Furthermore, colorectal cancer cell-derived EVs facilitate to functional heterogeneity of activated fibroblasts.⁷⁵ What's more, a recent study noted that HCC-derived EV miRNA-21 leads to converting hepatocyte stellate cells to cancer-associated fibroblasts by down-regulated PTEN and activated PDK1/AKT signalling pathway.⁷⁰ Also, clinical data indicated that higher vessel density and greater activation of CAFs are associated with a high level of EV miRNA-21 from HCC patients' serum.⁷⁰

Moreover, further studies have suggested tumour-derived EVs transdifferentiate CAFs by EndMT, initiating angiogenic and metastatic evolution. However, although cancer-derived EVs promoted EndMT, MSC-derived EVs were reported to suppress EndMT,

maintain vascular homeostasis and induce angiogenesis, finally resulting in CAFs back to ECs.⁶⁷

Additionally, it is revealed that EVs derived from different tumour stages can activate fibroblasts displaying various expressions. For example, pro-angiogenic and pro-proliferative proteins are found to be increased in fibroblasts activated by early-stage tumour-derived EVs. In contrast, activated by late-stage tumour-derived EVs, fibroblasts have a greater ability to invade through the extracellular matrix⁷⁵ (Figure 2).

4 | CANCER STEM CELL-DERIVED EVs ACTING AS A KEY ROLE IN ANGIOGENESIS

Cancer stem cells (CSCs), with the ability to self-replicate, differentiation and exist for a long time, are thought to have the potential to develop tumours and in particular, as the tumour metastasis, become the source of new tumour.⁷⁶ It is still not well known how CSCs come, but some studies suggest that they are derived from either oncogenic mutations in normal stem cells or the dedifferentiation of cells to a CSC phenotype.⁷⁷ Specially, CSC-derived EVs also express CSC-specific markers such as CD90, CD105, CD133 and CD44.^{22,78,79} Emerging evidence revealed that CSCs play a crucial part in tumour progression, including tumour angiogenic. For instance, in glioma, a highly angiogenic malignancy, the stem cells with CD44 marker promote phenotypes of cancer stem cell and radiation resistance.⁸⁰ The CD133⁺ stem cells are related to VEGF production and angiogenic phenotype in ECs.^{81,82} Also, it is reported that CSCs might participate in angiogenesis by secreting EVs with pro-angiogenic potential. For example, CSC-like CD90⁺ cells could promote angiogenesis by EVs containing lncRNA-H19, thus influencing the tumour microenvironment.²² Glioma stem cell-derived EVs containing miR-26a induce angiogenesis via activating the PI3K/Akt signalling pathway by targeting PTEN.⁴⁰ In renal cancer, CD105⁺MVs from cancer stem cells contained mRNAs for growth factors such as MMP9, ephrin A3, FGF, MMP2, angiopoietin 1 and VEGF.⁷⁸ It is also reported that mRNAs of genes related to angiogenesis are found only in CD105⁺EVs. Therefore, it suggests the cancer stem cell-derived EVs, rather than the whole tumour cell-derived EVs, promote tumour growth and invasion⁷⁸ (Figure 2).

5 | TUMOUR-DERIVED EVs-RELATED DRUG RESISTANCE

As tumour growth depends on angiogenesis, tumour blood vessels have been recognized as an important target for tumour therapy, and many anti-angiogenesis drugs have been found and tested with good results. Up to date, the US Food and Drug Administration approves the clinical use of the anti-angiogenic drugs targeting VEGF and several VEGF (receptor)-based inhibitors in many types of cancer.² Bevacizumab, aflibercept and ramucirumab targeting the VEGF/VEGFR signalling pathway have been used for certain tumour type

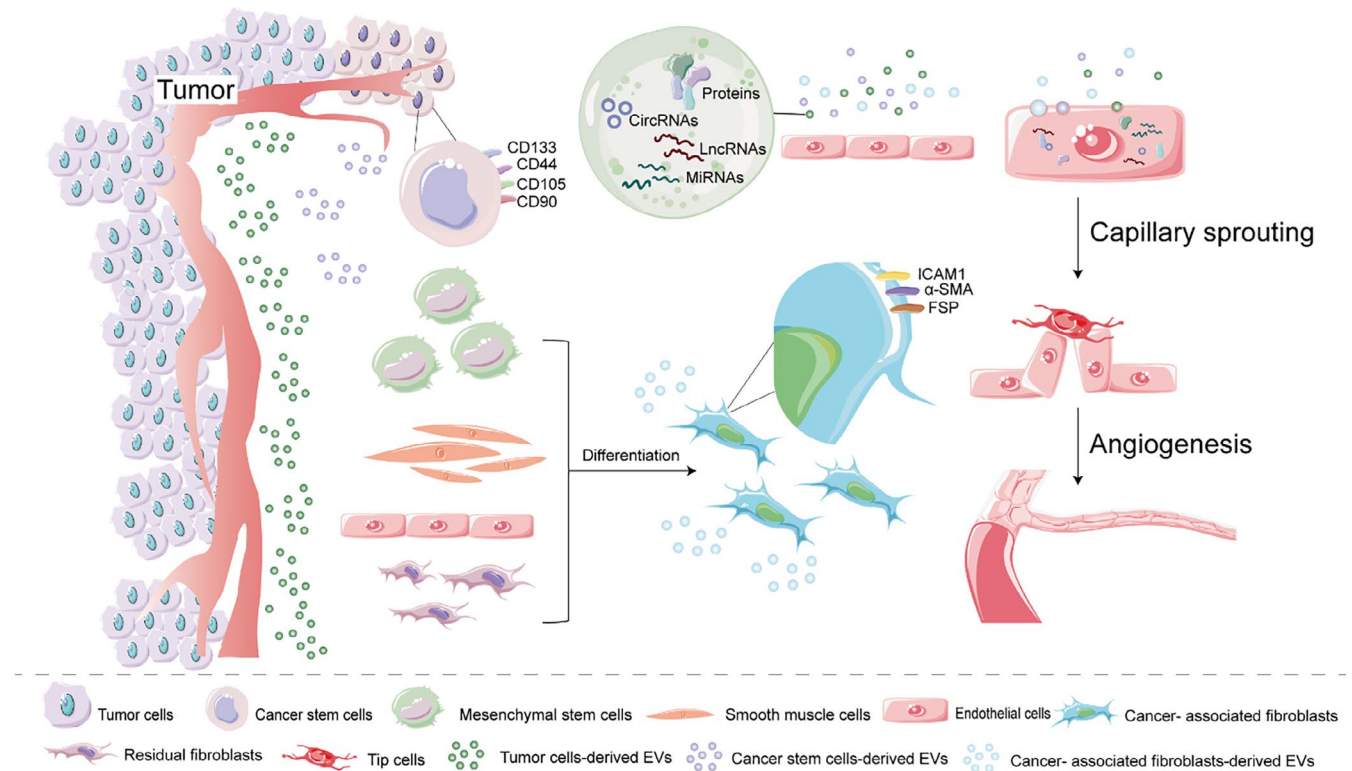


FIGURE 2 Tumour cell-derived EVs promote angiogenesis via being ingested by endothelial cells and inducing CAF differentiation. Tumour cell-derived EVs contain proteins, miRNAs, lncRNAs and circRNAs, which can be absorbed by ECs, promoting angiogenesis. CSCs, with the markers of CD133, CD90, CD44 or CD105, are also found to play an essential part in tumour angiogenic. Besides, tumour cell-derived EVs are reported to induce CAF differentiation in stromal cells, smooth muscle cells, ECs or normal fibroblasts via a complex mixture of small RNAs and proteins

therapy. Multi-targeted tyrosine kinase inhibitors, such as sorafenib and sunitinib, also inhibit angiogenic signals. In recent studies, anti-angiogenesis drugs have been found to alter tumour EV secretion and contents, which result in the suppression of angiogenesis, further supporting its positive effect as an anti-tumour therapy. However, accumulating evidence indicates that monotherapy with VEGF receptor kinase inhibitors fails to take effect and even induce side effects when combined with chemotherapy. Although drug resistance has been intensely researched, the molecular mechanism of tumour resistance remains uncertain. Tumour microenvironment including EVs is revealed to play an essential part in drug resistance. Emerging evidence shows that the mechanisms to induce drug-resistant phenotypes through EVs are the protein transfer and transmission of nucleic acids.²¹ Therefore, blocking tumour angiogenesis signals by controlling of EV secretion or alteration of EV contents may act as a novel strategy to promote the long-term efficacy of anti-angiogenic therapies.⁸³

5.1 | The alterations of tumour-derived EVs under anti-angiogenesis drugs

The contents of tumour-derived EVs can be blocked to suppress tumour angiogenesis and offer new insight into the anti-tumour activity of anti-angiogenesis drugs, thereby supporting its positive use in tumour therapy.⁸⁴ For example, a natural compound, docosahexaenoic

acid with anti-angiogenesis action, alters breast cancer EV secretion and miRNA contents, which results in the suppression of angiogenesis. Among the miRNAs that were altered in EVs, miR-23b and miR-320b in ECs decreased the expression of pro-angiogenic factors and greatly suppressed tube formation.⁸⁴ Additionally, dasatinib, a Src family kinase inhibitor, blocked EC tubular differentiation in response to tumour-derived EVs.⁸⁵ Moreover, both imatinib and dasatinib effectively reduced the release of chronic myeloid leukaemia cell-derived EVs, which induce angiogenesis in Src-dependent signalling, by more than 55%.⁸⁵ Bevacizumab, which neutralizes VEGFA secreted by tumour cells and leads to an increase in Annexin A2 with a decrease in CD44, might suggest alterations in the EVs under bevacizumab treatment.⁸⁶ With the therapy of C6-ceramide (a ceramide pathway activator), the level of miR-29b was increased.⁸⁷ C6 ceramide therapy suppresses the angiogenic activity of multiple myeloma EVs via the miR-29b/Akt pathway. Amla extract down-regulates pro-angiogenic molecules via up-regulation of cellular and EV miR-375 in human ovarian cancer cells⁸⁸ (Figure 3).

5.2 | Tumour-derived EV-related anti-angiogenesis drug resistance

It is also observed that treatment with anti-angiogenesis drugs can interact with EVs, which are associated with therapeutic resistance.

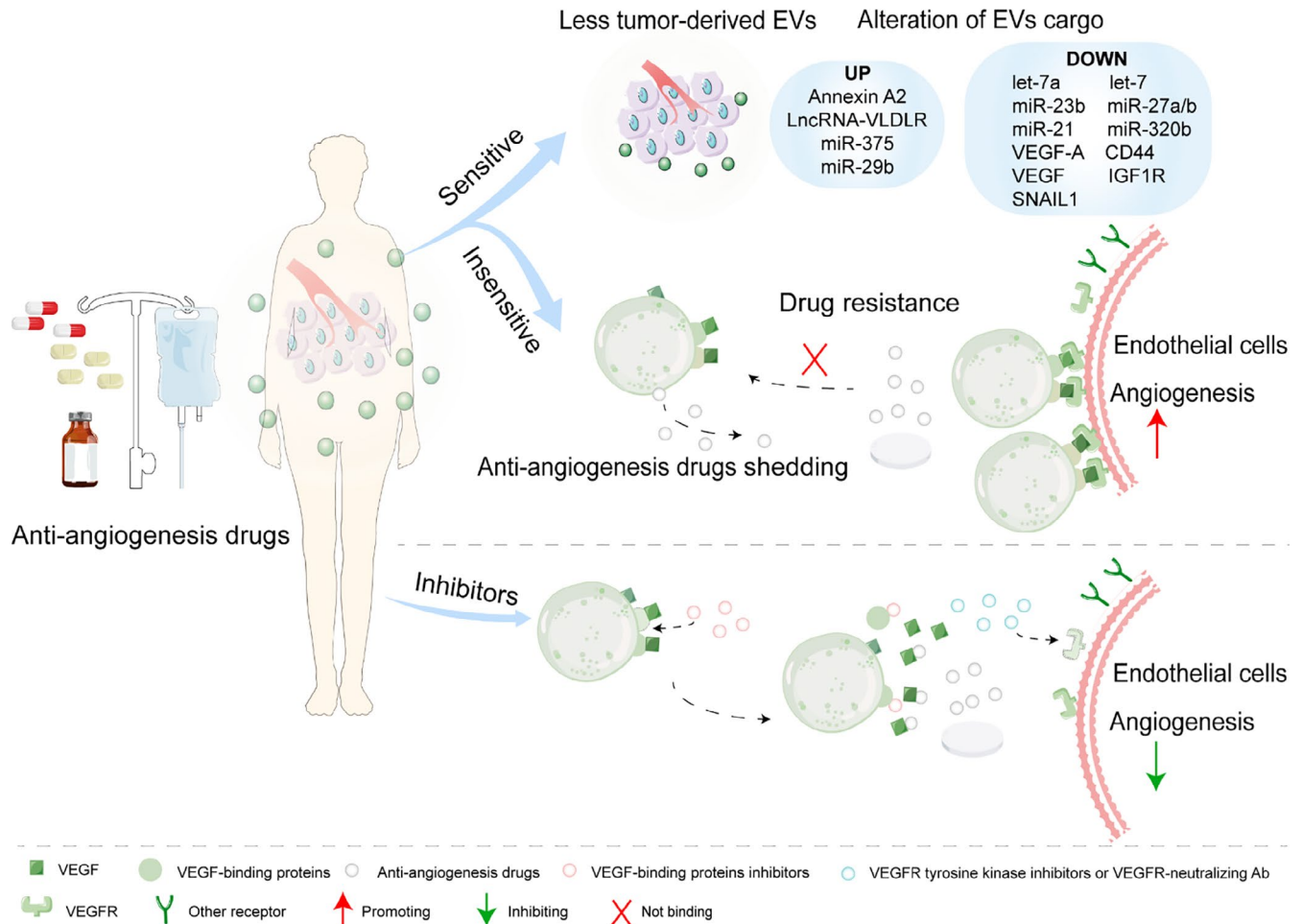


FIGURE 3 The alterations of tumour EVs under anti-angiogenesis drugs and drug resistance. Anti-angiogenesis drugs can reduce tumour-derived EV secretion and alter EV contents. Drugs shedding at the surface of tumour-derived EVs appear as a possible way for cancer cells to shield themselves against treatment. Besides, EV-VEGF is not neutralized by bevacizumab. Treatment with a VEGF-binding protein inhibitors releases VEGF from EVs, promoting the sensitivity of EV-associated VEGF to anti-angiogenesis drugs. The activity of EV-VEGF can be blocked by VEGFR tyrosine kinase inhibitors or VEGFR2-neutralizing antibodies. These inhibitors rather than bevacizumab might be more effective as anti-tumour therapy for patients who have elevated EV-VEGF levels

The emerging studies in EVs are conducive to further understanding the mechanism of anti-angiogenesis drug resistance and improve treatment efficacy in cancer therapy.

Accumulating studies reveal that EVs play an important role in anti-angiogenesis drug resistance. For instance, GBM cells can capture bevacizumab directly and eventually classify bevacizumab at the surface of the GBM cell-derived EVs.⁸⁶ Normally, bevacizumab is located on the surface of EVs and is not internalized in them. However, it is reported that bevacizumab from tumour-derived EVs could not bind to VEGFA, so there is a possibility that tumour cells escape themselves from treatment by bevacizumab shedding at the surface of tumour-derived EVs.⁸⁶ In addition, during incubation with sorafenib (a multikinase inhibitor, has anti-angiogenic effects by inhibiting pro-angiogenesis factor pathways⁸⁹), lncRNA-VLDLR is significantly increased in HCC cells and EVs.⁸⁹ It revealed a novel mechanism about intercellular contact between EVs and recipient cells and regulation of target gene expression leading to acquired drug resistance. Moreover, a recent study suggests that

HCC cell-derived EVs play an important role in sorafenib resistance in liver cancer cells by suppressing sorafenib-induced apoptosis and inducing the HGF/c-Met/Akt signalling pathway. Although the angiogenesis inhibitor, vandetanib, completely inhibits miR-9-induced angiogenesis and promoted autophagy of ECs, it is found to result in the release of VEGF-enriched EVs.⁸³

Besides, recent studies have tried to improve the efficacy of anti-angiogenic therapies by blocking EV drug-resistant molecules. A further study demonstrated that the affinity of EV-associated VEGF_{90K} has a weakened affinity for bevacizumab, leading to the inability of bevacizumab to effectively inhibit EV-dependent VEGF receptor activation. However, VEGF_{90K} is released from EVs with the treatment of an Hsp90 inhibitor, thereby restoring sensitivity to bevacizumab.⁵¹ What's more, the ligand half-life is significantly increased with the interaction of VEGF₁₈₉ and the surface of EVs, and that associated EV-VEGF is hard to be neutralized by bevacizumab. The VEGFR2-neutralizing antibody or VEGFR tyrosine kinase inhibitors can suppress the EV-VEGF action. Therefore, these

inhibitors rather than bevacizumab might be more effective as anti-tumour therapy for patients who have elevated EV-VEGF levels.⁹⁰ These findings suggest that the various levels of EV contents should also be considered as an important factor in anti-angiogenic therapies of selected patients to avoid drug resistance (Figure 3).

6 | CONCLUSIONS

An increasing number of studies have reported the capacity of EVs to actively regulate the tumour-associated angiogenic programmes. It is now well established that EVs can carry and transfer proteins and mRNAs/ncRNAs into target cells, which not only help to reveal the angiogenesis and anti-angiogenesis mechanisms but also created new perspectives on drug targets and drug resistance in anti-angiogenesis. However, the inclusion of different molecules from different tumour-derived EVs may be because of bias in the selection of experimental targets.⁹¹ Studies on EVs are still required to further identify the key EV cargos in angiogenesis and anti-angiogenesis, and develop additional anti-angiogenic drugs targeting EVs. More importantly, their potential should be evaluated in clinical trials, especially the combination therapy with current anti-tumour treatments. Furthermore, for the EVs can be delivered to cells easier with phospholipid bilayer, recent studies are also focusing on using EVs to deliver drugs or synthetic and biological genetic materials to specific target cells,⁹² which also contribute to anti-angiogenesis therapy.

ACKNOWLEDGEMENTS

This study was supported in part by the National Natural Science Foundation of China (81802082 to JY, 31830039 and LS 81873863) and Shanghai 'Rising Stars of Medical Talent' Youth Development Program-Clinical Laboratory Practitioners Program (2019016 to JY).

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

Shuqiong Zhang: Writing-original draft (equal); Writing-review & editing (equal). **Junyao Yang:** Conceptualization (equal); Funding acquisition (equal); Writing-original draft (equal); Writing-review & editing (equal). **Lisong Shen:** Conceptualization (lead); Resources (lead); Writing-original draft (lead); Writing-review & editing (lead).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Shuqiong Zhang  <https://orcid.org/0000-0002-1748-8191>

Lisong Shen  <https://orcid.org/0000-0002-6647-4749>

REFERENCES

- Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature*. 2011;473:298-307.
- Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. *Cell*. 2011;146:873-887.
- Kuczynski EA, Vermeulen PB, Pezzella F, Kerbel RS, Reynolds AR. Vessel co-option in cancer. *Nat Rev Clin Oncol*. 2019;16:469-493.
- Cloughesy TF, Brenner A, de Groot JF, et al. A randomized controlled phase III study of VB-111 combined with bevacizumab vs. bevacizumab monotherapy in patients with recurrent glioblastoma (GLOBE). *Neuro-Oncology*. 2019;22:705-717.
- Wang Y, Wang L, Chen C, Chu X. New insights into the regulatory role of microRNA in tumor angiogenesis and clinical implications. *Mol Cancer*. 2018;17:22.
- Eelen G, de Zeeuw P, Simons M, Carmeliet P. Endothelial cell metabolism in normal and diseased vasculature. *Circ Res*. 2015;116:1231-1244.
- Welti J, Loges S, Dimmeler S, Carmeliet P. Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer. *J Clin Invest*. 2013;123:3190-3200.
- Xu R, Rai A, Chen M, Suwakulsiri W, Greening DW, Simpson RJ. Extracellular vesicles in cancer - implications for future improvements in cancer care. *Nat Rev Clin Oncol*. 2018;15:617-638.
- O'Brien K, Breyne K, Ughetto S, Laurent LC, Breakefield XO. RNA delivery by extracellular vesicles in mammalian cells and its applications. *Nat Rev Mol Cell Biol*. 2020;1-22.
- Colombo M, Raposo G, Thery C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu Rev Cell Dev Bio*. 2014;30:255-289.
- Martinez MC, Andriantsitohaina R. Microparticles in angiogenesis: therapeutic potential. *Circ Res*. 2011;109:110-119.
- Roma-Rodrigues C, Fernandes AR, Baptista PV. Counteracting the effect of leukemia exosomes by antiangiogenic gold nanoparticles. *Int J Nanomed*. 2019;14:6843-6854.
- Wang WF, Zhang ED, Lin CJ. MicroRNAs in tumor angiogenesis. *Life Sci*. 2015;136:28-35.
- Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. *Nat Rev Genet*. 2019;20:675-691.
- Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature*. 2013;495:333-338.
- Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol*. 2020;21(8):475-490.
- Xie M, Yu T, Jing X, et al. Exosomal circSHKBP1 promotes gastric cancer progression via regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation. *Mol Cancer*. 2020;19:112.
- Lu J, Wang Y-H, Yoon C, et al. Circular RNA circ-RanGAP1 regulates VEGFA expression by targeting miR-877-3p to facilitate gastric cancer invasion and metastasis. *Cancer Lett*. 2020;471:38-48.
- Huang XY, Huang ZL, Huang J, et al. Exosomal circRNA-100338 promotes hepatocellular carcinoma metastasis via enhancing invasiveness and angiogenesis. *J Exp Clin Can Res*. 2020;39:20.
- Gutschner T, Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. *RNA Biol*. 2012;9:703-719.
- De Los Santos MC, Dragomir MP, Calin GA. The role of exosomal long non-coding RNAs in cancer drug resistance. *Can Drug Res*. 2019;2:1178-1192.
- Conigliaro A, Costa V, Lo Dico A, et al. CD90+ liver cancer cells modulate endothelial cell phenotype through the release of exosomes containing H19 lncRNA. *Mol Cancer*. 2015;14:155.
- Wang FW, Cao CH, Han K, et al. APC-activated long noncoding RNA inhibits colorectal carcinoma pathogenesis through reduction of exosome production. *J Clin Invest*. 2019;129:727-743.

24. Qiu JJ, Lin XJ, Tang XY, Zheng TT, Lin YY, Hua KQ. Exosomal metastasis-associated lung adenocarcinoma transcript 1 promotes angiogenesis and predicts poor prognosis in epithelial ovarian cancer. *Intern J Biol Sci*. 2018;14:1960-1973.
25. Lei L, Mou Q. Exosomal taurine up-regulated 1 promotes angiogenesis and endothelial cell proliferation in cervical cancer. *Cancer Biol Ther*. 2020;21(8):717-725.
26. Castellano JJ, Marrades RM, Molins L, et al. Extracellular vesicle lincRNA-p21 expression in tumor-draining pulmonary vein defines prognosis in NSCLC and modulates endothelial cell behavior. *Cancers*. 2020;12:734.
27. Cheng Y, Dai X, Yang T, Zhang N, Liu Z, Jiang Y. Low long noncoding RNA growth arrest-specific transcript 5 expression in the exosomes of lung cancer cells promotes tumor angiogenesis. *Journal of oncology*. 2019;2019:2476175.
28. Cheng C, Zhang Z, Cheng F, Shao Z. Exosomal lincRNA RAMP2-AS1 derived from chondrosarcoma cells promotes angiogenesis through miR-2355-5p/VEGFR2 Axis. *Onco Targets Ther*. 2020;13:3291-3301.
29. Dai X, Liao K, Zhuang Z, et al. AHIF promotes glioblastoma progression and radioresistance via exosomes. *Int J Oncol*. 2019;54:261-270.
30. Qiu JJ, Lin XJ, Zheng TT, Tang XY, Zhang Y, Hua KQ. The exosomal long noncoding RNA aHIF is upregulated in serum from patients with endometriosis and promotes angiogenesis in endometriosis. *Repro Sci*. 2019;26:1590-1602.
31. Ma X, Li Z, Li T, Zhu L, Li Z, Tian N. Long non-coding RNA HOTAIR enhances angiogenesis by induction of VEGFA expression in glioma cells and transmission to endothelial cells via glioma cell derived-extracellular vesicles. *Am J Transl Res*. 2017;9:5012-5021.
32. Lang HL, Hu GW, Zhang B, et al. Glioma cells enhance angiogenesis and inhibit endothelial cell apoptosis through the release of exosomes that contain long non-coding RNA CCAT2. *Oncol Rep*. 2017;38:785-798.
33. Lang HL, Hu GW, Chen Y, et al. Glioma cells promote angiogenesis through the release of exosomes containing long non-coding RNA POU3F3. *Eur Rev Med Pharmacol*. 2017;21:959-972.
34. Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell*. 2009;136:215-233.
35. Xie T, Huang MX, Wang Y, Wang LY, Chen C, Chu XY. MicroRNAs as regulators, biomarkers and therapeutic targets in the drug resistance of colorectal cancer. *Cell Physiol Biochem*. 2016;40:62-76.
36. Xu R, Greening DW, Zhu HJ, Takahashi N, Simpson RJ. Extracellular vesicle isolation and characterization: toward clinical application. *Journal of Clinical Investigation*. 2016;126:1152-1162.
37. Sruthi TV, Edatt L, Raji GR, et al. Horizontal transfer of miR-23a from hypoxic tumor cell colonies can induce angiogenesis. *J Cell Physiol*. 2018;233:3498-3514.
38. Yang H, Zhang H, Ge S, et al. Exosome-derived miR-130a activates angiogenesis in gastric cancer by targeting C-MYB in vascular endothelial cells. *Mol Ther*. 2018;26:2466-2475.
39. Zeng Z, Li Y, Pan Y, et al. Cancer-derived exosomal miR-25-3p promotes pre-metastatic niche formation by inducing vascular permeability and angiogenesis. *Nat Commun*. 2018;9:5395.
40. Wang ZF, Liao F, Wu H, Dai J. Glioma stem cells-derived exosomal miR-26a promotes angiogenesis of microvessel endothelial cells in glioma. *J Exp Clin Can Res*. 2019;38:201.
41. Nicoli S, Knyphausen CP, Zhu LHJ, Lakshmanan A, Lawson ND. miR-221 is required for endothelial tip cell behaviors during vascular development. *Dev Cell*. 2012;22:418-429.
42. Li J, Yuan H, Xu H, Zhao H, Xiong N. Hypoxic cancer-secreted exosomal miR-182-5p promotes glioblastoma angiogenesis by targeting kruppel-like factor 2 and 4. *Mol Can Res*. 2020;18:1218-1231.
43. Liu Y, Luo F, Wang BR, et al. STAT3-regulated exosomal miR-21 promotes angiogenesis and is involved in neoplastic processes of transformed human bronchial epithelial cells. *Cancer Lett*. 2016;370:125-135.
44. Cui H, Seubert B, Stahl E, et al. Tissue inhibitor of metalloproteinases-1 induces a pro-tumourigenic increase of miR-210 in lung adenocarcinoma cells and their exosomes. *Oncogene*. 2015;34:3640-3650.
45. Hsu YL, Hung JY, Chang WA, et al. Hypoxic lung cancer-secreted exosomal miR-23a increased angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1. *Oncogene*. 2017;36:4929-4942.
46. Lu J, Liu QH, Wang F, et al. Exosomal miR-9 inhibits angiogenesis by targeting MDK and regulating PDK/AKT pathway in nasopharyngeal carcinoma. *J Exp Clin Can Res*. 2018;37:147.
47. Balaji Rangunathrao VA, Anwar M, Akhter MZ, et al. Sphingosine-1-Phosphate receptor 1 activity promotes tumor growth by amplifying VEGF-VEGFR2 angiogenic signaling. *Cell Rep*. 2019;29(11):3472-3487.
48. Li S, Mai H, Zhu Y, et al. MicroRNA-4500 inhibits migration, invasion, and angiogenesis of breast cancer cells via RRM2-Dependent MAPK signaling pathway. *Mol Ther Nucl Acids*. 2020;21:278-289.
49. Lim R, Sugino T, Nolte H, et al. Deubiquitinase USP10 regulates Notch signaling in the endothelium. *Science*. 2019;364:188-193.
50. Fang Q, Yang A, Dong A, Zhao L. CircPDS1 stimulates the development of colorectal cancer via activating the Wnt/ β -Catenin signaling. *Oncotarget Ther*. 2020;13:6329-6337.
51. Feng Q, Zhang C, Lum D, et al. A class of extracellular vesicles from breast cancer cells activates VEGF receptors and tumour angiogenesis. *Nat Commun*. 2017;8:14450.
52. Lin Q, Chen X, Meng F, et al. ASPH-notch Axis guided Exosomal delivery of Prometastatic Secretome renders breast Cancer multi-organ metastasis. *Mol Cancer*. 2019;18:156.
53. Monteforte A, Lam B, Sherman MB, et al. (*) Glioblastoma exosomes for therapeutic angiogenesis in peripheral ischemia. *Tissue Eng Part A*. 2017;23:1251-1261.
54. Rodrigues G, Hoshino A, Kenific CM, et al. Tumour exosomal CEMIP protein promotes cancer cell colonization in brain metastasis. *Nat Cell Biol*. 2019;21:1403-1412.
55. Sato S, Vasaikar S, Eskaros A, et al. EPHB2 carried on small extracellular vesicles induces tumor angiogenesis via activation of ephrin reverse signaling. *Jci Insight*. 2019;4(23):e132447.
56. Jamshidi-Parsian A, Griffin RJ, Kore RA, Todorova VK, Makhoul I. Tumor-endothelial cell interaction in an experimental model of human hepatocellular carcinoma. *Exp Cell Res*. 2018;372:16-24.
57. Li R, Wang Y, Zhang X, et al. Exosome-mediated secretion of LOXL4 promotes hepatocellular carcinoma cell invasion and metastasis. *Mol Cancer*. 2019;18:18.
58. Treps L, Edmond S, Harford-Wright E, et al. Extracellular vesicle-transported Semaphorin3A promotes vascular permeability in glioblastoma. *Oncogene*. 2016;35:2615-2623.
59. Maji S, Chaudhary P, Akopova I, et al. Exosomal Annexin II promotes angiogenesis and breast cancer metastasis. *Mol Cancer Res*. 2017;15:93-105.
60. Tang MKS, Yue PYK, Ip PP, et al. Soluble E-cadherin promotes tumor angiogenesis and localizes to exosome surface. *Nat Commun*. 2018;9:2270.
61. Yi H, Ye J, Yang XM, Zhang LW, Zhang ZG, Chen YP. High-grade ovarian cancer secreting effective exosomes in tumor angiogenesis. *Inter J Clin Exp Pathol*. 2015;8:5062-5070.
62. Chan YK, Zhang H, Liu P, et al. Proteomic analysis of exosomes from nasopharyngeal carcinoma cell identifies intercellular transfer of angiogenic proteins. *Int J Cancer*. 2015;137:1830-1841.
63. You B, Cao X, Shao X, et al. Clinical and biological significance of HAX-1 overexpression in nasopharyngeal carcinoma. *Oncotarget*. 2016;7:12505-12524.
64. Beckham CJ, Olsen J, Yin PN, et al. Bladder cancer exosomes contain EDIL-3/Del1 and facilitate cancer progression. *J Urology*. 2014;192:583-592.

65. Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. *Nat Rev Drug Discovery*. 2019;18:99-115.
66. de Palma M, Bizziato D, Petrova TV. Microenvironmental regulation of tumour angiogenesis. *Nat Rev Cancer*. 2017;17:457-474.
67. Yeon JH, Jeong HE, Seo H, et al. Cancer-derived exosomes trigger endothelial to mesenchymal transition followed by the induction of cancer-associated fibroblasts. *Acta Biomater*. 2018;76:146-153.
68. De Veirman K, Rao L, De Bruyne E, et al. Cancer associated fibroblasts and tumor growth: focus on multiple myeloma. *Cancers*. 2014;6:1363-1381.
69. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. *J Cell Sci*. 2012;125:5591-5596.
70. Zhou Y, Ren H, Dai B, et al. Hepatocellular carcinoma-derived exosomal miRNA-21 contributes to tumor progression by converting hepatocyte stellate cells to cancer-associated fibroblasts. *J Exp Clin Can Res*. 2018;37:324.
71. Paggetti J, Haderk F, Seiffert M, et al. Exosomes released by chronic lymphocytic leukemia cells induce the transition of stromal cells into cancer-associated fibroblasts. *Blood*. 2015;126:1106-1117.
72. Luga V, Wrana JL. Tumor-stroma interaction: revealing fibroblast-secreted exosomes as potent regulators of Wnt-planar cell polarity signaling in cancer metastasis. *Can Res*. 2013;73:6843-6847.
73. Whiteside TL. Exosome and mesenchymal stem cell cross-talk in the tumor microenvironment. *Semin Immunol*. 2018;35:69-79.
74. Webber JP, Spary LK, Sanders AJ, et al. Differentiation of tumour-promoting stromal myofibroblasts by cancer exosomes. *Oncogene*. 2015;34:290-302.
75. Rai A, Greening DW, Chen M, Xu R, Ji H, Simpson RJ. Exosomes derived from human primary and metastatic colorectal cancer cells contribute to functional heterogeneity of activated fibroblasts by reprogramming their proteome. *Proteomics*. 2019;19:e1800148.
76. Patel P, Chen EI. Cancer stem cells, tumor dormancy, and metastasis. *Front Endocrinol*. 2012;3:125.
77. Visvader JE. Cells of origin in cancer. *Nature*. 2011;469:314-322.
78. Grange C, Tapparo M, Collino F, et al. Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. *Cancer Res*. 2011;71:5346-5356.
79. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nat Rev Cancer*. 2008;8:755-768.
80. Pietras A, Katz AM, Ekstrom EJ, et al. Osteopontin-CD44 signaling in the glioma perivascular niche enhances cancer stem cell phenotypes and promotes aggressive tumor growth. *Cell Stem Cell*. 2014;14:357-369.
81. Kohga K, Tatsumi T, Takehara T, et al. Expression of CD133 confers malignant potential by regulating metalloproteinases in human hepatocellular carcinoma. *J Hepatol*. 2010;52:872-879.
82. Sharma A, Shiras A. Cancer stem cell-vascular endothelial cell interactions in glioblastoma. *Biochem Biophys Res Comm*. 2016;473:688-692.
83. Zeng Y, Yao X, Liu X, et al. Anti-angiogenesis triggers exosomes release from endothelial cells to promote tumor vasculogenesis. *J Extracell Vesicles*. 2019;8:1629865.
84. Hannafon BN, Carpenter KJ, Berry WL, Janknecht R, Dooley WC, Ding WQ. Exosome-mediated microRNA signaling from breast cancer cells is altered by the anti-angiogenesis agent docosahexaenoic acid (DHA). *Mol Cancer*. 2015;14:133.
85. Mineo M, Garfield SH, Taverna S, et al. Exosomes released by K562 chronic myeloid leukemia cells promote angiogenesis in a Src-dependent fashion. *Angiogenesis*. 2012;15:33-45.
86. Simon T, Pinioti S, Schellenberger P, et al. Shedding of bevacizumab in tumour cells-derived extracellular vesicles as a new therapeutic escape mechanism in glioblastoma. *Mol Cancer*. 2018;17:132.
87. Liu L, Ye Q, Liu L, et al. C6-ceramide treatment inhibits the proangiogenic activity of multiple myeloma exosomes via the miR-29b/Akt pathway. *J Transl Med*. 2020;18:298.
88. De A, Powers B, De A, et al. Emblica officinalis extract downregulates pro-angiogenic molecules via upregulation of cellular and exosomal miR-375 in human ovarian cancer cells. *Oncotarget*. 2016;7:31484-31500.
89. Takahashi K, Yan IK, Wood J, Haga H, Patel T. Involvement of extracellular vesicle long noncoding RNA (linc-VLDLR) in tumor cell responses to chemotherapy. *Mol Can Res*. 2014;12:1377-1387.
90. Ko SY, Lee W, Kenny HA, et al. Cancer-derived small extracellular vesicles promote angiogenesis by heparin-bound, bevacizumab-insensitive VEGF, independent of vesicle uptake. *Comm Biol*. 2019;2:386.
91. Ludwig N, Whiteside TL. Potential roles of tumor-derived exosomes in angiogenesis. *Exp Opin Therap Targ*. 2018;22:409-417.
92. Chinnappan M, Srivastava A, Amreddy N, et al. Exosomes as drug delivery vehicle and contributor of resistance to anticancer drugs. *Cancer Lett*. 2020;486:18-28.

How to cite this article: Zhang S, Yang J, Shen L. Extracellular vesicle-mediated regulation of tumor angiogenesis—Implications for anti-angiogenesis therapy. *J Cell Mol Med*. 2021;25:2776-2785. <https://doi.org/10.1111/jcmm.16359>