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Role of vascular endothelium and exosomes in cancer progression and therapy (Review)

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Abstract. Cancer poses a significant global health challenge and its progression is intricately connected to the interplay among various cell types and molecular pathways. In recent years, research has focused on the roles of vascular endothelial cells (VECs) and exosomes within the tumor microenvironment. Anomalies in tumor vascular integrity and function create a conducive milieu for cancer cell proliferation. Despite efforts in clinical anti-angiogenic interventions, the anticipated outcomes remain elusive. VECs have the capability to transition into mesenchymal cells through endothelial-to-mesenchymal transition, thereby affecting cancer advancement. Exosomes are minute membrane-bound vesicles generated by cells, serving as vital extracellular elements that facilitate cell-to-cell communication. They participate in modulating the tumor microenvironment, thereby influencing tumor progression, metastasis, drug resistance and angiogenesis. Additionally, exosomes serve as efficient carriers for drug delivery, as well as targeting and suppressing tumor cells. In summary, understanding the intricate and interconnected mechanisms of VECs and exosomes in cancer, encompassing tumor angiogenesis, microenvironment modulation and immune regulation, is crucial. A comprehensive exploration of these mechanisms may provide insight into cancer treatment and prevention and yield novel therapeutic targets.

Contents

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1. Introduction

Cancer poses a significant global health challenge as the second leading cause of death after cardiovascular disease. Extensive studies have been carried out over the years on cancer remedies, encompassing traditional interventions such as chemotherapy, radiotherapy and surgical procedures (1). Considering the elevated rate of occurrence and distribution, there is a pressing demand for substitute treatment options with improved efficacy and safety profiles compared with the aforementioned interventions (1). Hence, there is a requirement for comprehensive research to improved understand the pathways involved in cancer formation and growth. The tumor microenvironment (TME) is integral to the development of cancer by enabling the spread of information that supports the growth of tumor cells, formation of new blood vessels (angiogenesis) and dissemination to distant sites. Communication between cancer cells and surrounding tissues results in changes to the local environment that support tumor progression, immune evasion and invasion (2). Furthermore, interactions with distally located non-cancerous tissues contribute to the establishment of new habitats for cancer cells to thrive and aid in the spread of the disease (2).

Endothelial cells (ECs) are specialized cells lining both large and small blood vessels throughout the body. They serve an important role in regulating coagulation, inflammation and blood pressure, as well as the development of new blood vessels. This role is indispensable for their function in the supply of oxygen and nutrients, as well as the removal of metabolic wastes from the internal organs. The endothelial lining primarily acts as a barrier between the blood and the surrounding tissue, while permitting limited exchange of cellular and molecular substances. Disruption of this barrier function can lead to the promotion of blood clot formation (3). Therefore, the growth of new blood vessels is vital for the development of embryonic organs, tissue repair and wound healing (3). Angiogenesis, which is the creation of new capillaries, involves numerous physiological and pathological processes. This intricate and well-organized process culminates in the development of fully operational blood vessels (4). Studies have examined the

significance of ECs in the process of angiogenesis, which plays a major role in the advancement of tumors (5,6). In addition to their involvement in angiogenesis through proliferation, migration and adhesion, vascular endothelial cells (VECs) can undergo a process similar to epithelial-to-mesenchymal transition (EMT). VECs have the ability to transition their phenotype to exhibit mesenchymal characteristics, which in turn affects tumor advancement (7). This mechanism is termed endothelial-to-mesenchymal transition (EndoMT), affecting the advancement of tumors in various manners. Moreover, exosomes have the capacity to affect tumor progression by initiating both EMT and EndoMT. Along with the endothelial compartment, cancer-associated fibroblasts (CAFs) are the most prevalent stromal cells in the TME and serve a crucial role in advancing tumors. Tumor cells engage with one another to create a myofibroblastic microenvironment that enhances tumor development and viability and sustains malignancy (8). Consequently, CAFs affect both the arrangement and growth characteristics of tumors. CAFs can originate from normal fibroblasts and epithelial cells (8); they can also originate from VECs through the EndoMT process (9).

Exosomes (diameter: 40-160 nm) function as important vehicles for intercellular communication within both nearby and far-reaching cells. They act as valuable indicators for diagnosing and predicting diseases (10). Exosomes are notably involved in the spread of tumors, are present in high quantities in bodily fluids and help maintain the stability of the biomarkers they transport. As a result, they enhance the accuracy of cancer detection, monitoring of treatments and forecasting of cancer outcomes (10). They are secreted into the extracellular space by ECs and various other cells, such as platelets, immune cells, smooth muscle cells and cancer cells (10-12). The continuous exchange of bioactive molecules within exosomes takes place extracellularly, enabling intercellular communication in both healthy and diseased conditions (13). The interaction between tumors and exosomes results in alteration of the TME, thereby promoting tumor proliferation, resilience, evasion of the immune system and infiltration (14). Exosomes, an important element of the TME, have been extensively studied in recent decades and have demonstrated distinct roles in tumor development, advancement, spread, vascularization and resistance to drugs (15). Furthermore, distinctive genetic characteristics passed down from the initial tumor cells provide tumor-derived exosomes (TEXs) with the capacity to anticipate tumor advancement and outlook. They can be modified as therapeutic carriers to transport a range of small compounds; mRNAs, non-coding RNAs (ncRNAs), DNAs, proteins, or anticancer drugs and convey them to target cells. Exosomes exhibit considerable promise in cancer treatment (16,17). They serve as potential preclinical biomarkers for a variety of types of cancer (such as lung, hepatocellular, pancreatic, colorectal, melanoma, breast, prostate, ovarian, glioblastoma and nasopharyngeal) (18-24). Studies have demonstrated that disrupting the production, release, or absorption of exosomes originating from tumors shows great potential for advancing the field of cancer treatment (25,26).

The aim of the present review was to elucidate the cross-talk between vascular endothelium and exosomes in tumor progression, focusing on the roles of EndoMT and exosomes in tumorigenesis, metastasis, tumor drug resistance and the TME as well as their applications in tumor therapy and diagnostic prognosis. These advances will help to realize clinical applications based on vascular endothelium and exosomes in cancer.

2. Role of VECs in the TME

The TME is a critical area of study in cancer research. Cancer cells reside alongside stromal cells in a complex environment, relying on interactions with various components of the TME for their growth and spread. In tumor tissues, ECs are mainly divided into lymphatic endothelial cells (LECs) and VECs, including arterial endothelial cells (ArtECs), venous endothelial cells (VenECs) and capillary-like endothelial cells (CapECs). LECs exhibit two different differentiation lineages: One is responsible for lymphangiogenesis and the other is involved in antigen presentation (27). VECs serve an essential role in tumor angiogenesis and the provision of blood supply, which are vital processes for the progression of solid tumors. As a result, targeting angiogenic factors and their receptors through anti-angiogenic therapy has become a significant approach in the treatment of tumors (27-30).

To support the rapid growth of tumors, cancer cells induce the development of new lymphatic and blood vessels from existing ones to satisfy their high oxygen and nutrient requirements. Previous research has shown that blood and lymphatic vessels associated with tumors serve a crucial role in aiding immune evasion and disrupting immune surveillance by T cells. The tumor vasculature contributes to the TME by promoting conditions favorable to cancer cell survival, such as hypoxia, acidity and high interstitial pressure, while also acting as a physical barrier to T cell penetration (31). The ECs that compose the tumor vasculature actively impede the recruitment, attachment and function of T cells (31). Previous research has recognized diverse elements of the TME that affect malignant behavior and advancement (32). Alongside malignant cells, the TME is comprised of adipocytes, fibroblasts, immune cells, dendritic cells, CAFs and ECs of the blood and lymphatic vessels. Each of these cellular categories possesses a distinct immune capability, which can dictate the survival of the tumor and its effect on surrounding cells (32,33).

In the TME, cancer cells engage in constant interactions with various elements through the secretion of soluble factors (such as cytokines, chemokines, growth factors and enzymes for matrix remodeling) or by direct communication with stromal cells. This leads to chronic inflammation, immune suppression and a microenvironment that supports angiogenesis, facilitating cancer cell metastasis and hindering the effectiveness of treatments, such as immunotherapy. Of note, this interaction is bidirectional, with TME matrix components effectively influencing cancer cell behavior throughout all stages of cancer progression. For instance, research indicates that the immune system can eliminate early-stage tumors through immunosurveillance (34). Nevertheless, cancer cells can later evade immune detection and even exploit the immune system to support tumor growth (34). The development of an immune escape cancer cell phenotype involves various mechanisms, which include reduced immunogenicity from the loss of tumor-associated antigens or major histocompatibility complex class I molecules, changes in DNA copy numbers and oncogenic signaling, along with heightened expression of immune

checkpoint proteins, such as programmed death-ligand 1 (PD-L1), indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase (TDO), as well as shifts in metabolism leading to lowered pH levels and increased immunogenicity of TDO. This results in alterations in the immune response, promoting immune evasion in cancer cells (35). Furthermore, cancer cells manipulate the polarization, activity and expansion of different immune cell subpopulations by enhancing the production of immunosuppressive and pro-tumorigenic cytokines (31). They also interact with ECs, causing changes in their structural integrity and functional properties, ultimately dampening antitumor immune responses (31).

Tumor-associated vascular system promotes immunosuppressive TME. Small solid tumors trigger tumor angiogenesis to meet the high demands for energy and essential nutrients (such as oxygen and glucose) required for growth. This process involves the creation of new blood vessels within an existing vascular network (36). A recent study has shown that angiogenesis can occur at any stage of tumor progression and it involves the development of neovascularization from established vascular beds, with tumor tissue infiltrating more CapECs than VenECs and ArtECs compared with adjacent non-tumor tissue. The tumor angiogenic trajectory is a differential trajectory from VenECs to ArtECs passing through CapECs; tumor angiogenesis starts from VenECs (27).

Pathological angiogenesis results mainly from an imbalance in pro- and anti-angiogenic signaling within the TME. Primary factors promoting angiogenesis include vascular endothelial growth factor-A (VEGF-A), basic fibroblast growth factor and interleukin-8 (IL-8), among others. These cytokines are prevalent in the TME and counteract vaso-suppressive signals, promoting the activation of pro-angiogenic pathways by inhibiting vasopressor and endothelial suppressor effects (37). Furthermore, hypoxia plays a key role in tumor angiogenesis (27). Cancer cells are able to release significant quantities of VEGF, leading to the stimulation of VEGF-independent blood vessel formation. This is achieved through the secretion of various pro-angiogenic molecules, such as placental growth factor (PGF), VEGF-C, VEGF-D and platelet-derived growth factor-C (PDGF-C). Additionally, cancer cells exhibit a response to survival-promoting and metastasis-promoting VEGF cues in an autocrine or paracrine manner. This response is triggered by pro-survival and pro-metastatic VEGF signaling (36). Controversially, placental growth factor (PlGF) is a member of the VEGF family and has been reported to have both pro- and anti-angiogenic properties. In preclinical tumor models, the efficacy of anti-PlGF therapy in inhibiting angiogenesis and stopping tumor growth remains a conflicting result (38).

The present study presents the process of angiogenesis stimulated by the critical pro-angiogenic factor VEGF. Despite its involvement in sustaining the blood supply in tumors, tumor angiogenesis results in an unstable, disordered and underdeveloped vascular structure, characterized by poor circulation. This significantly atypical angiogenesis plays a role in upholding the tumor's tumorigenic and immune-suppressing TME and has a profound effect on the cancer cells' evasion of immune monitoring, metastasis and response to immunotherapy (39). The disorderly vascular arrangement leads to inconsistent and reduced blood flow, linked to the immature, unstable, leaking and curved nature of the blood vessels. Moreover, the high interstitial fluid pressure (IFP) within the tumor, caused by vascular leakage, renders these vessels prone to collapse, thereby narrowing the perfused tumor region (Fig. 1) (39).

The hypoxic and acidic TME resulting from elevated anaerobic glycolysis in cancer cells enhances the development of genetically and epigenetically altered tumor cells, thus increasing their invasive properties. Importantly, hypoxia and acidosis facilitate the attraction and attachment of immune-suppressing cells, diminish the antitumor effectiveness of infiltrating T cells and hinder the distribution of therapeutic drugs and immune-based treatments, thereby impeding the elimination of cancer cells through radiotherapy, chemotherapy and immunotherapy (40).

Anti-angiogenic therapy. Targeting the VEGF/vascular endothelial growth factor receptor (VEGF/VEGFR) pathway has been the most commonly used combination strategy in studies related to immunotherapy. Initially, treatment with anti-angiogenic drugs, such as the anti-VEGF antibody bevacizumab, was employed to prolong patient survival by obstructing VEGF/VEGFR-driven blood vessel formation, thereby halting tumor advancement (41). Despite encouraging preliminary findings in preclinical trials, this vascular-directed therapy, referred to as vascular obstruction, did not produce the expected outcomes in patients with cancer. Subsequent preclinical investigations indicated that blocking angiogenesis resulted in an augmentation of hypoxic regions within tumors, ultimately promoting tumor expansion and metastatic spread (42). Certainly, hypoxia induced by anti-VEGF/VEGFR therapy could contribute to the angiogenic relapse and drug resistance observed following vascular blockade approaches. This could potentially involve various immunosuppressive cell types, such as $Gr1^+CD11b^+$ myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (43). The cancer cell-derived vasopressor chemokine C-X-C motif chemokine ligand 14 recruits myeloid cells and subsequently stimulates phosphoinositide-3-kinase (PI3K) signaling in these cells. Therefore, blocking this pathway is essential for the sustained benefits of anti-angiogenic treatment (44).

Enhancing the function of blood vessels through vascular normalization enhances tumor blood flow and optimizes the delivery of medication (including small amounts of chemotherapy drugs and monoclonal antibodies), ultimately boosting the effectiveness of treatment (45,46). This increase in vascular transport capability is heavily reliant on sufficient blood circulation within the tumor (47). Other approaches, aside from blocking the VEGF/VEGFR pathway, have demonstrated the ability to promote vascular normalization (48,49). For instance, chloroquine (CQ), a first-generation autophagy inhibitor, induces vascular normalization *in vivo* through activation of the Notch signaling pathway in ECs within the blood (50). CQ decreases tumor growth and enhances the TME (51). CQ normalizes the vascular structure and function of tumors, leading to improved blood flow. This normalization results in reduced hypoxia, decreased cancer cell invasion and metastasis and enhanced delivery and effectiveness of chemotherapy (51). Research conducted

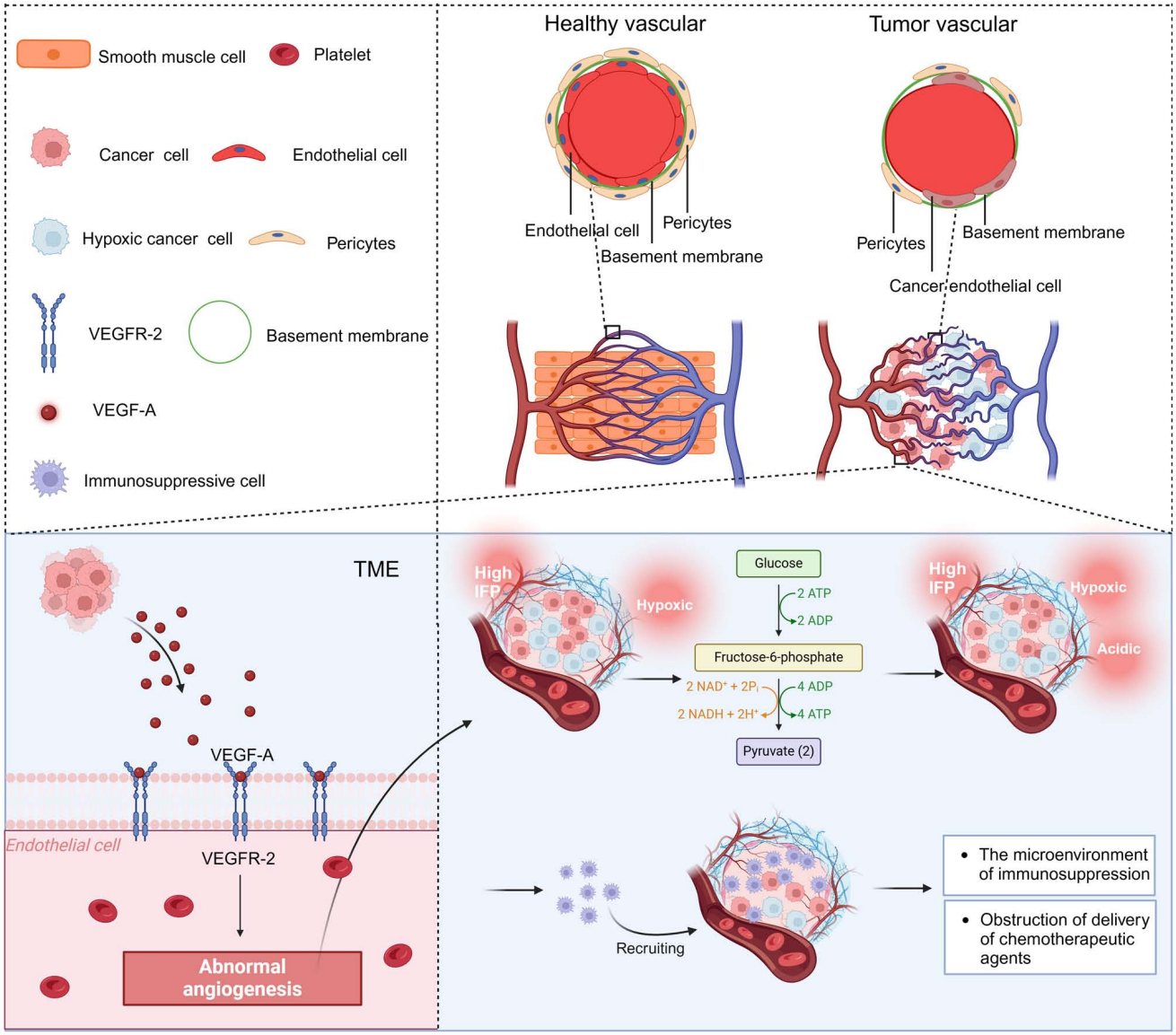

Figure 1. The tumor-associated vascular system induced by the key pro-angiogenic factor VEGF has an important effect on the tumor microenvironment. A well-organized vascular network ensures a comprehensive nutrient supply. Mature blood vessels have a layer of endothelial cells surrounded by basement membrane and pericytes (such as smooth muscle cells) with tight connections between endothelial cells. In contrast, tumor-associated vascular networks are disorganized, with low pericyte coverage and loose connections between endothelial cells. This leads to vascular leakage and increased IFP. Damaged or collapsed vessels create a hypoxic TME (hypoxic cells are indicated in green). In addition, the glycolytic properties of (hypoxic) tumor cells acidify the pH of the TME. This aberrant angiogenesis promotes an immunosuppressive microenvironment. IFP, interstitial fluid pressure; TME, tumor microenvironment; VEGF-A, vascular endothelial growth factor-A; VEGFR-2, vascular endothelial growth factor receptor 2. Created with BioRender.com.

on animals indicates that even with its minimal impact on the immune system, CQ does not hinder the ability of the body to fight against tumors and may enhance the effectiveness of immunotherapy (52).

Angiogenesis inhibitors are used in cancer therapy to affect the formation of new blood vessels in tumors, which opens up new frontiers for the treatment of a wide range of solid tumors. However, due to the complexity of tumor angiogenesis and limited research, anti-angiogenic therapy still has some limitations (53). Examples include lack of therapeutic efficacy, drug resistance and prevalence of treatment modalities (53).

It is important to note that excessive restriction of angiogenesis affects drug transport and exacerbates the pathological manifestations of TME. This induces a stronger hypoxic response and tumor aggressiveness, which ultimately leads to drug resistance and even cancer metastasis (54).

Drug resistance has been limiting the clinical outcomes of targeted antiangiogenic therapy (55). This can involve a high degree of heterogeneity of the TME, endothelial heterogeneity, tumor cell autophagy, cancer stem cell (CSC) differentiation, stromal cell infiltration, tumor type, genetic mutations in the tumor or target, stage of tumor progression, the patient's medication history and other factors, all of which can affect a patient's response to, and tolerance of, antitumor therapy (56-58).

In addition, there is a lack of effective biomarkers characterizing changes in the vasculature and TME to prevent tumor escape and monitor patient response to drugs and treatment progression (59,60). Exploration of effective cancer-specific

biomarkers responsive to the angiogenic system to enhance anti-angiogenic efficacy is a pressing concern. Indeed, the development of biomarkers will be a great challenge due to a number of factors such as the complexity of tumor angiogenesis, tumor heterogeneity and variability and limitations of preclinical and clinical trials.

Emerging approaches to improving anti-angiogenic therapy. Combination therapies based on antiangiogenic drugs have been used in the antitumor field since the approval of the first angiogenesis inhibitor, bevacizumab, for the treatment (61). In recent years, combination therapy with angiogenesis inhibitors and immune checkpoint inhibitors has attracted considerable research attention. Treatment of patients with hepatocellular carcinoma (HCC) and patients with renal carcinoma using a combination of programmed cell death 1 (PD1) and VEGFR2 inhibitors yielded improved results compared with monotherapy (62-64). If immunotherapy is accompanied by anti-angiogenic drugs targeting the VEGF pathway, it can neutralize excess VEGF while reversing VEGF-induced immunosuppression and enhancing the immune function of patients, rebuild the vascular system of the tumor tissue, normalize the vascular network, inhibit excessive angiogenesis and limit tumor growth, invasion and metastasis (65). However, the effectiveness and toxicity of this combination therapy need to be optimized by further studies on the dose, duration and sequence of treatment in different patients (66,67).

In tumor angiogenesis, various angiogenic tyrosine kinases act synergistically to induce a series of intracellular signaling cascades rather than working individually (68). The development of novel selective multi-targeted kinase inhibitors can effectively avoid the adverse events of broad-spectrum inhibitors, exert multiple anti-angiogenic effects, avoid drug-drug interactions and develop a more stable pharmacokinetic profile (69).

Hyperactivation of pro-angiogenic factors and over-inhibition of anti-angiogenic mediators contribute to abnormal angiogenesis in tumor tissues (53). Therefore, endogenous anti-angiogenic components or their derivatives may be beneficial for vascular normalization and therapeutic efficacy. For example, endostatin can compete with fibroblast growth factor to limit VEC proliferation and tumor development. Recombinant human endostatin is a non-cytotoxic angiogenesis inhibitor approved by the Chinese Food and Drug Administration for the treatment of various cancers, including non-small cell lung cancer (70,71).

Moreover, studies have demonstrated the significant effect of small ncRNAs termed micro-RNAs (miRNAs) on the process of angiogenesis. These molecules serve a crucial role in modulating gene expression via RNA interference mechanisms (72,73). For example, hypoxia induces pro-angiogenic miRNAs (including miR-210 and miR-494) (74). Specific miRNAs such as miR-16, which also disrupts the transforming growth factor-beta (TGF-β) pathway, affect the pathway of VEGF and VEGFR and manage the process of angiogenesis (75). miR-494 enhances the migration of VECs and stimulates angiogenesis by inhibiting phosphatase and tensin homolog (PTEN), leading to activation of the protein kinase B (AKT)/endothelial nitric oxide synthase pathway (76).

The present study also discussed the mechanisms through which TEXs, including but not limited to miRNAs, can alter the state of VECs and, thus, affect tumor growth. Since tumor-associated conditions can promote miRNA expression to support a highly angiogenic TME, miRNAs can be considered potential targets for anti-angiogenic/vascular normalization approaches. However, further studies are needed to improve understanding of the mechanism by which specific targeting of miRNAs can enhance the efficacy of immunotherapy. Further research is warranted to investigate whether exosomes can be used as carriers of miRNAs and good drug delivery vehicles for exosome-mediated targeting of vascular endothelial-specific molecules to improve tumor therapeutic responses. Moreover, it is important to determine whether tumor vascular normalization strategies are the optimal therapeutic options for improving T-cell function and immunotherapy. Such research advances will broaden our knowledge on the role of endothelial function and dysfunction, increase understanding and control of the TME and facilitate the optimization of anti-angiogenic and vascular modification therapies for cancer and other diseases.

3. Role of EndoMT in cancer

EndoMT is a dynamic process in which VECs transition, thereby abolishing their distinctive characteristics and gaining mesenchymal properties (77). Typical characteristics include morphological transformation of VECs, altered gene expression and functional changes. Morphological transformation refers to the change from an ovoid cell shape to an elongated, spindle-shape. Changes in gene expression involve a decrease in specific protein markers, such as von Willebrand factor, platelet endothelial cell adhesion molecule-1, vascular endothelial cadherin, VEGFR2, Tie2 and zonula occludens-1. There is also an increase in the expression of mesenchymal proteins, such as alpha-smooth muscle actin, fibroblast activation protein, vimentin, fibronectin, N-cadherin, fibroblast-specific protein 1 and collagen type I. Functional changes include the loss of intercellular connections, heightened vascular permeability, decrease in vasculature formation and the acquisition of migratory, invasive and contractile qualities (78). Some of these protein markers are consistent with EMT (Table I) (79).

Occurrence of EndoMT. Research studies show that TGF-β is significantly involved in the development and advancement of EndoMT (80,81). The Smad2/3-mediated pathways are considered classic and powerful pathways in cellular signaling. In this process, homodimers of activated TGF-β bind to heterodimeric TGF-β receptor complexes on the cell surface, initiating the activation of the TGF-β pathway. Interaction between activated TGF-β molecules and their respective cell surface receptors induces a series of intricate molecular reactions. Smad proteins, which belong to a diverse family of intracellular proteins, serve a crucial role in mediating this cascade of events in conventional TGF-β signaling (82). They transduce signals triggered by TGF-β cell surface binding from the cell membrane to the nucleus (Fig. 2) (83). The TGF-β receptor initiates a signaling pathway involving two transmembrane serine threonine kinases; TGF-β receptor types I and II. Upon binding of TGF-β, the receptor complex undergoes

Table I. Similarities and differences between EMT and EndoMT.

Similarity/difference	EMT	EndoMT	(Refs)
Cell type	Epithelial cells	Endothelial cells	-
Induction mediator	TGF-β	TGF-β	(78,79)
	Wnt/β-catenin	Hypoxia	
	Notch	Oxidative stress	
		Notch	
		Wnt/β-catenin	
Epithelial/endothelial marker	E-cadherin	VE-cadherin	
	N-cadherin	CD31/PECAM-1	
		vWF	(79)
Mesenchymal marker	α-SMA, FSP1, vimentin		(79)
Transcription factor	Slug, Snail-1 and -2, Twist		

EMT, epithelial-to-mesenchymal transition; EndoMT, endothelial-to-mesenchymal transition; TGF-β, transforming growth factor-beta; PECAM-1, platelet endothelial cell adhesion molecule-1; VE-cadherin, vascular endothelial-cadherin; vWF, von Willebrand factor; α-SMA, alpha-smooth muscle actin; FSP1, fibroblast-specific protein 1.

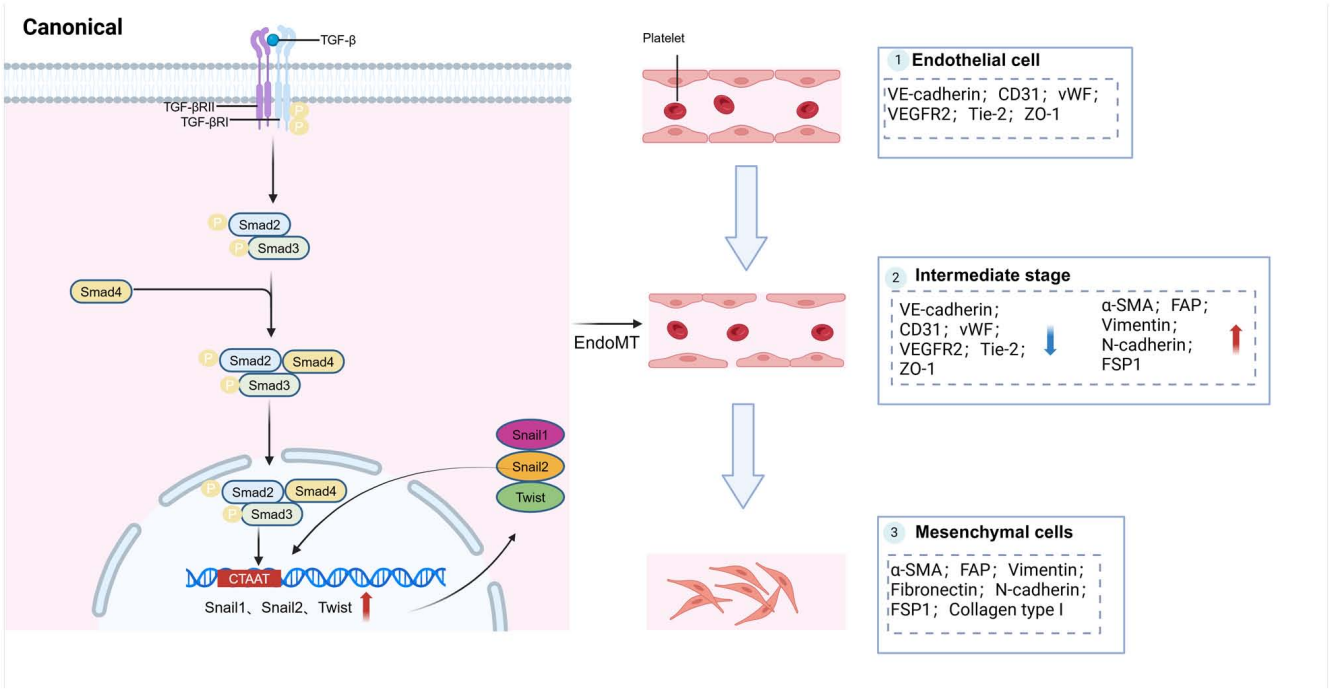

Figure 2. Typical pathway of EndoMT and characterization of endothelial-to-mesenchymal cell transformation. Binding of TGF-β to the cell surface transmembrane heterodimeric TGF-β I/II receptor complex leads to phosphorylation-mediated activation. The activated TGF-β I/II receptor complex phosphorylates cytoplasmic Smad2 and Smad3 proteins, leading to their activation. Activated Smad2 and Smad3 form a complex with Smad4 and translocate to the nucleus. In the nucleus, the Smad2/Smad3/Smad4 complex interacts with and stimulates the transcription of Smad-binding elements of TGF-β-responsive genes, including genes encoding pro-fibrotic ECM macromolecules and the transcription factors Snail1, 2 and Twist. The morphology of the endothelial cells during EndoMT, as well as some protein markers, are altered. EndoMT, endothelial-to-mesenchymal transition; TGF-β, transforming growth factor-beta; ECM, extracellular matrix; α-SMA, alpha-smooth muscle actin; FAP, fibroblast activation protein; FSP1, fibroblast-specific protein 1; VE-cadherin, vascular endothelial-cadherin; VEGFR2, vascular endothelial growth factor receptor 2; vWF, von Willebrand factor; ZO-1, zonula occludens-1. Created with BioRender.com.

autophosphorylation of TGF-β receptor type II, followed by transphosphorylation of specific residues in TGF-β receptor I to form an active complex. This leads to phosphorylation of serine residues in Smad2 and Smad3 proteins, resulting in their activation. Thereafter, the phosphorylated Smad2/Smad3 complex interacts with Smad4 and translocates to the nucleus. Within the nucleus, the Smad2/Smad3/Smad4 complex binds to Smad binding elements of TGF-β response genes, thereby promoting their transcription. This mechanism involves the binding of Smad proteins to specific sites in the promoter regions of target genes, facilitating gene expression in response to TGF-β signaling (78).

Of note, tumor cells release extracellular vesicles (EVs) that also serve a role in regulating EndoMT. Yeon *et al* (84) reported that exosomes derived from both breast cancer cells and mouse melanoma cells triggered EndoMT in VECs. Moreover, Yamada *et al* (85) demonstrate that colon cancer cell-derived conditioned medium contains EVs capable of inducing EndoMT in human umbilical vein endothelial cells (HUVECs). This process may be facilitated by miR-92a-3p. In addition, EVs may regulate the EndoMT process in pre-metastatic ecological niches (86). Additional clarification concerning the effector molecules found in EVs that trigger EndoMT is imperative to enhance our comprehension of the biological activities of EVs in the advancement of tumors. Moreover, this knowledge will be useful in addressing illnesses facilitated by the interaction between EVs and vascular VECs.

The high occurrence rate of EndoMT across various types of cancer in humans and the wide array of tumor-related factors that trigger EndoMT imply that EndoMT could be a major event in the advancement of tumors and have a significant function in disease progression. VECs that undergo EndoMT hasten tumor growth through the enhancement of tumor cell growth, viability and vascularization. Furthermore, this process may facilitate tumor spread by affecting numerous essential processes, such as the transition from epithelial to mesenchymal states, movement, infiltration, internalization and externalization of tumor cells. Moreover, EndoMT may facilitate tumor evasion from the immune system and resistance to treatments (87).

EndoMT mediates the formation of CAFs. CAFs are important stromal cells in the TME, controlling tumor development, spread, immune system suppression and resistance to medication (88-90). They originate from a range of cell types, primarily pericytes, cells of the blood vessel walls, VECs undergoing EndoMT, cancer cells undergoing EMT, fibroblasts remaining in tissues (such as hepatic stellate cells) and cells derived from the bone marrow [such as mesenchymal stromal cells (MSCs)] (91). EndoMT is involved in various processes, making significant contributions. For instance, >50 and 40% of CAFs stem from EndoMT in gliomas and melanomas, respectively (9,92). Improved insight into the heterogeneity of CAFs can be achieved by investigating the involvement of EndoMT in promoting CAF differentiation and its influence on tumor advancement.

EndoMT affects angiogenesis. Continuous angiogenesis is a common characteristic of cancerous growth and a focal point of studies on therapies targeting tumors. The mesenchymal transition of VECs can lead to partial loss of their blood vessel-forming capabilities, while they retain or acquire the capacity to produce and release VEGF, stimulating angiogenesis through signaling pathways (93). This process affects the efficacy of anti-angiogenic therapy (94).

EndoMT promotes tumor cell proliferation, survival, metastasis and treatment resistance. Identification of the factors that support tumor cell growth and targeted interventions could hinder tumor development. EndoMT can enhance tumor cell proliferation, thus hastening tumor growth in HCC and breast cancer (95,96). The exact molecular mechanism underlying this facilitation process needs to be further elucidated.

Tumor cells exhibit increased resistance to hypoxia, starvation and other severe conditions caused by tumor expansion and medical treatments. Importantly, EndoMT may be a critical factor in this mechanism. Breast cancer cells cultured alongside VECs undergoing EndoMT demonstrated improved resilience to starvation and higher rates of survival (96). This suggests that inhibition of EndoMT reduces tumor cell survival and may provide new avenues for tumor therapy.

The process of tumor metastasis is complex and consists of multiple steps, starting with the invasion and migration of cancer cells from the original tumor location. This is followed by infiltration in the living system, exit from the circulation and vascular network and ultimately establishment and expansion at the secondary site of metastasis (97). EndoMT affects tumor metastasis at the original location and exerts a significant effect on the secondary site. This enhances the EMT, as well as the migration and infiltration of tumor cells at the primary tumor location. The enhancement of vascular permeability may also benefit tumor cell internalization. Similarly, EndoMT at the metastatic site aids in the extrication of tumor cells and can potentially contribute to the establishment of a pre-metastatic microenvironment.

EndoMT promotes breast cancer cell invasion and migration (96,98). Notably, the invasive and migratory capacity of tumor cells is mainly acquired through the EMT process (99). VECs undergoing EndoMT also trigger the process of EMT in oral squamous cell carcinoma cells through the secretion of TGF-β (98). Enhanced permeability of blood vessels triggered by EndoMT at the primary tumor location is an additional potential mechanism that boosts the spread of cancer and could aid in the internalization of tumor cells during metastasis.

Nevertheless, there has been limited research on EndoMT occurring at the metastatic site. The presence of EndoMT has not been identified in metastatic tumor tissues of human origin. Using a live mouse model of breast cancer, Smeda *et al* (100) demonstrate that EndoMT within the lung endothelium coincides with a rise in vascular permeability at the onset of metastasis. According to research findings, human melanoma cells that have metastasized to the brain triggered EndoMT in brain VECs. This process results in the disruption of the monolayer's integrity, which is confirmed by a decrease in transendothelial electrical resistance. Additionally, there is an increase in metastatic cell adhesion to the endothelial layer, along with a heightened melanoma cell transendothelial migration (101). Notably, Kim *et al* (86) reveal that EVs discharged by breast carcinoma cells prompted EndoMT in VECs of the liver sinusoids. The results indicate that cancer cells have a tendency to trigger EndoMT at the location of metastasis. This may contribute to the creation of pre-metastatic microenvironments aiding in cancer cell extravasation and, therefore, supporting tumor spread. Detecting EndoMT in metastatic human tumor samples and investigating whether this process precedes or follows tumor spread can enhance our comprehension of the involvement of EndoMT in tumor metastasis.

Chemotherapy, radiotherapy and targeted therapy have shown effectiveness in treating advanced tumors. Nonetheless, the process of EndoMT can lead to tumor cell resistance to these treatments. Recent research conducted by Huang *et al* (92) demonstrated that suppressing EndoMT

markedly increases the responsiveness of glioma cells to treatment with temozolomide. According to Choi *et al* (102), the use of radiotherapy triggers EndoMT in VECs, leading to a decrease in the effectiveness of this treatment. Furthermore, the expression of VEGFR2 was diminished in VECs that underwent EndoMT, rendering them impervious to anti-VEGF treatment in cases of glioblastoma (94). Focusing on tumor treatment-related EndoMT and implementing targeted interventions can improve treatment outcomes.

EndoMT mediates tumor immune escape. The immune surveillance function of the immune system is critical for identifying and removing abnormal elements in the body, such as tumor cells resulting from genetic mutations. Failure of immune surveillance can result in the growth and advancement of tumors. Previous studies have identified numerous factors contributing to the induction of tumor immunosuppression (103-107). Notably, EndoMT can promote tumor immune escape by inducing macrophage M2 polarization (108). In the TME, tumor-infiltrating lymphocytes (TILs) serve a vital role as stromal cells and are significantly linked to tumor immunomodulation (109). EndoMT-induced irregularities in the development, blood vessel formation, blood flow and openness of CAFs can directly or indirectly impact the entry and performance of TILs (110,111) (Fig. 3). Additional research focusing on the interactions between EndoMT and TILs might broaden the scientific knowledge in this area.

To summarize, the vascular endothelium plays a major role within the TME. Throughout tumor growth and metastasis, VECs are responsible for forming the structural framework of the tumor vascular network and for regulating both the normal and abnormal processes within the TME. Initially, VECs affect the blood flow to tumors by controlling the permeability and hemodynamic characteristics of blood vessels. Within tumor tissues, these cells are able to control the permeability of blood vessel walls, thus facilitating the transportation of necessary nutrients and oxygen to fuel tumor growth. Additionally, VECs are involved in modulating the immune response in the TME. By secreting cell adhesion molecules, they attract immune and inflammation-related cells to the tumor, influencing tumor growth and metastasis.

Furthermore, these cells are involved in managing tumor neovascularization and angiogenesis. As tumors develop, they release various factors that stimulate the proliferation and movement of nearby VECs, leading to the creation of a new vascular network to sustain tumor growth. The diverse population of VECs that undergo EndoMT promotes tumor progression, metastasis, immune suppression and treatment resistance through various mechanisms. Understanding the precise molecular pathways involved in these processes will guide targeted therapies for EndoMT (87).

In the TME, the vascular endothelium plays a complex and diverse role. This role is intricately linked to tumor growth, metastasis and drug resistance, as well as various aspects of tumor blood supply and angiogenesis. Further investigation into the mechanisms underlying the function of the vascular endothelium within the TME may lead to the identification of novel targets for tumor development. Additionally, it may offer novel insight and strategies for combating tumors.

4. Role of exosomes in the TME

The TME is composed of a diverse array of elements, such as cancerous cells, different types of stromal cells, cytokines, growth factors, enzymes and the surrounding environment where they are located. It plays a critical role in controlling the development, advancement and spread of cancer, as shown by extensive evidence available across various types of cancer. As tumors advance and spread to other parts of the body, the cancer cells do not function in isolation; instead, they engage in interactions with the entirety of the TME (112,113). A growing body of research suggests that exosomes serve an important role in the regulation of the TME (114). CAFs, CSCs, MSCs and tumor microenvironmental immune cells (TMICs) are the most important types of cells in the TME. In the following sections, we examine the key cells within the TME and their significant associations with exosomes (Fig. 4).

CAFs and exosomes. In most types of solid cancer, CAFs are the major cellular component of the TME (115). Cancer-associated fibroblast-derived exosomes (CDEs) are one of the key factors in oncogenic transformation (116).

In colorectal cancer (CRC), the role of CDEs in enhancing resistance to cancer drugs and facilitating metastasis cannot be overlooked. For instance, CDEs have the ability to stimulate angiogenesis and the advancement of tumors in colorectal cancer (CRC). Moreover, they can trigger the dedifferentiation of cancer cells via the Wnt signaling pathway, thereby contributing to the development of resistance to chemotherapy in CRC (117). CAF-induced activation of the Wnt signaling pathway enhances cell stemness, promotes EMT, the development of metastasis and resistance to chemotherapy in CRC by upregulating miR-92a-3p expression (118). CDEs in CRC exhibit elevated miR-93-5p levels compared with normal fibroblasts. This increased miR-93-5p content promotes the proliferation of SW480 cells and imparts radioresistance to these cells (119). Resistance to treatment with 5-fluorouracil is frequently observed in patients with CRC. miR-181d-5p, an exosome originating from CAFs, directly inhibits neurocalcin delta, thereby reducing sensitivity to 5-fluorouracil in CRC cells (120). Exosome miR-200b-3p deletion in hypoxic CAFs decreases sensitivity to treatment with 5-fluorouracil in CRC through high mobility group box 3 targeting (121). CDEs promote CRC progression and metastasis through miR-181b-3p and miR-345-5p (122,123). CDEs harbor the long non-coding RNA (lncRNA) long intergenic non-protein coding RNA 659 (LINC00659), which enhances the proliferation, invasion, migration and EMT advancement of CRC cells by modulating the miR-342-3p/annexin A2 signaling pathway (124). CDE circular RNA-NEDD4 binding protein 2 like 2 enhances the stemness of CRC cells and their resistance to oxaliplatin by increasing the expression of eukaryotic translation initiation factor 4A3 (125).

Elevated expression levels of miR-21, miR-378e and miR-143 are observed in CDEs of patients with breast cancer. The introduction of these three miRNAs into breast cancer cells induces an increase in stemness and facilitated the EMT process (126). CDEs exhibit a more potent effect on promoting breast cancer cell migration and invasion, compared with exosomes derived from normal fibroblasts. Moreover, the expression of miR-18b is

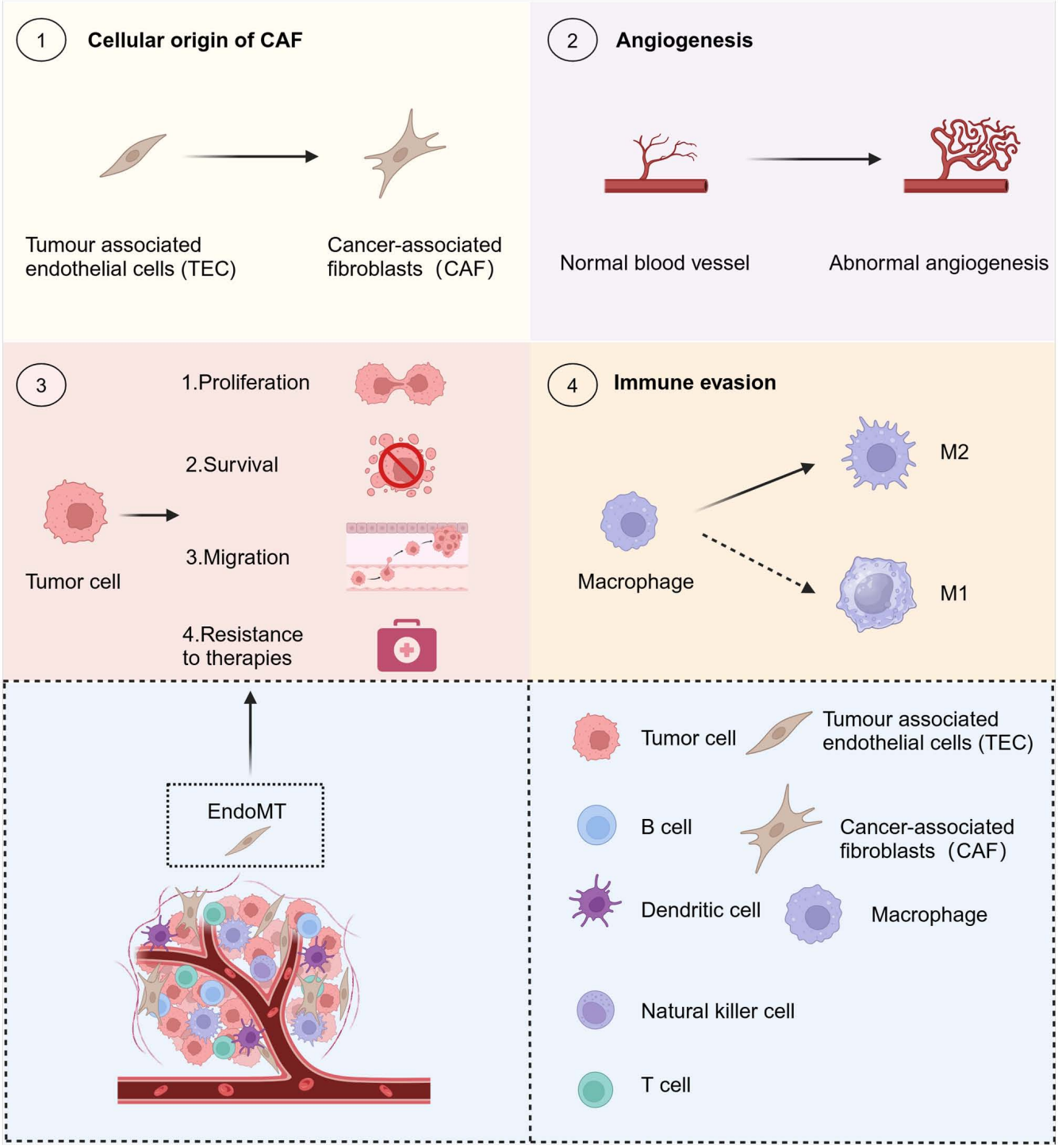

Figure 3. EndoMT promotes tumor progression. 1. Endothelial cells undergo EndoMT-mediated cellular origins of (CAFs). 2. EndoMT promotes angiogenesis. 3. EndoMT promotes tumor cell proliferation, survival and metastasis, including EMT, migration, invasion, endocytosis and exocytosis, as well as resistance to chemotherapy, radiotherapy and anti-angiogenic therapy. 4. EndoMT enhances tumor cell immune escape by inducing macrophage M2 polarization. EndoMT, endothelial-to-mesenchymal transition; CAFs, cancer-associated fibroblasts; EMT, epithelial-to-mesenchymal transition. Created with BioRender.com.

increased in CDEs. The presence of miR-18b in CDEs facilitates breast cancer cell invasion, migration and EMT progression through its specific interaction with the 3'untranslated region of transcription elongation factor A-like 7 (127). Exosomes transfer miR-20a-5p from CD63 CAFs to breast cancer cells, leading to the development of resistance to cyclin dependent kinase 4/6 (CDK4/6) inhibitors through the miR-20a-5p/retinoblastoma 1 (miR-20a-5p/RB1) axis (128).

Cancer cell growth is promoted by CDEs through the inhibition of mitochondrial oxidative phosphorylation. Additionally, CDEs increase glycolysis and reduce glutamine-dependent carboxylation in pancreatic cancer cells (115). Furthermore, miR-106b promotes gemcitabine resistance by directly targeting tumor protein 53-induced nuclear protein-1 in cancer cells (129). Exosomal miRNA-320a derived from CAFs induces M2 polarization

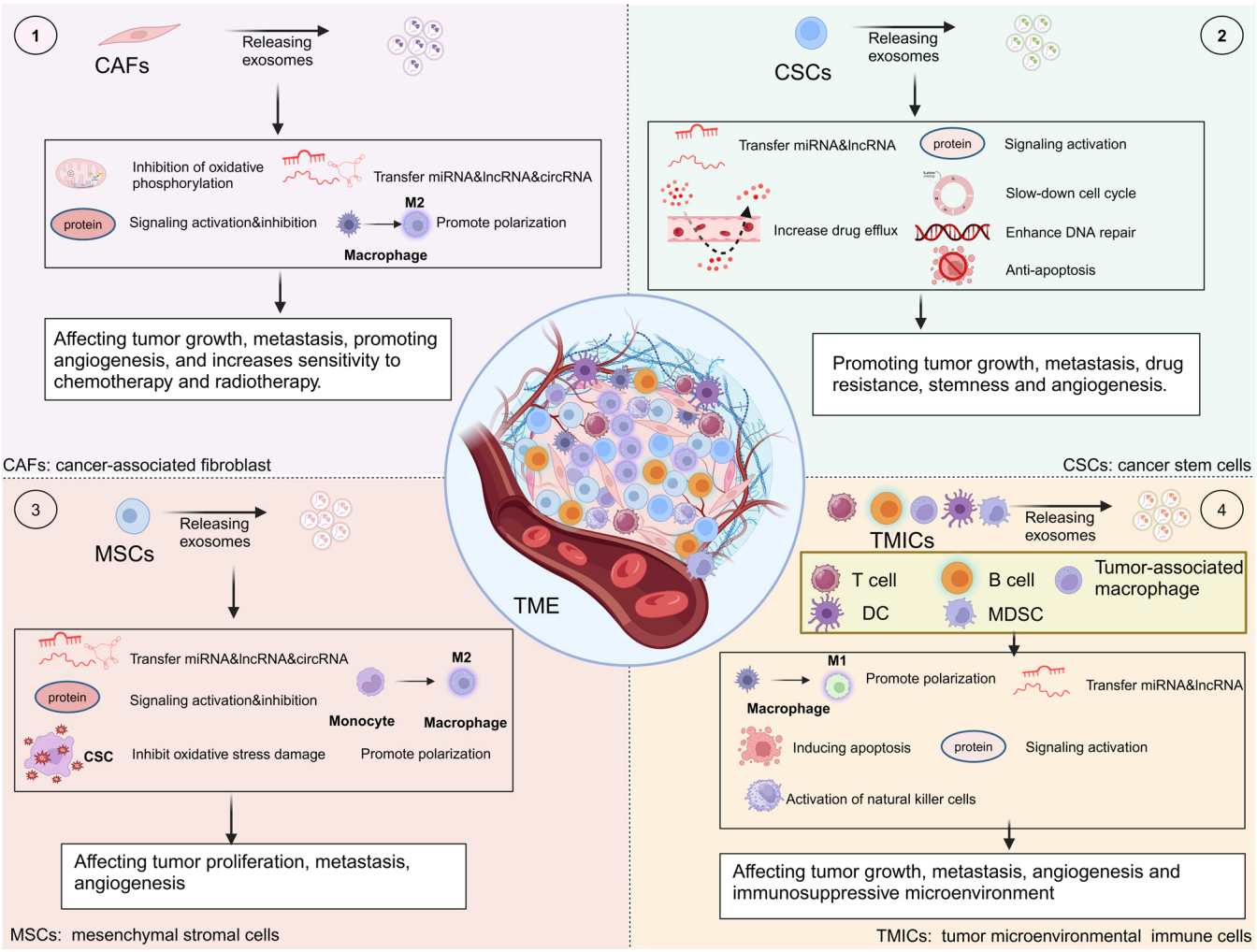

Figure 4. Pathways of exosomes in the TME. The most important cells in the TME are CAFs, CSCs, MSCs and TMICs. These four types of cells use exosomes to influence angiogenesis as well as tumor growth, metastasis and sensitivity to radiotherapy and chemotherapy through multiple mechanisms. TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; CSCs, cancer stem cells; MSCs, mesenchymal stromal cells; TMICs, tumor microenvironmental immune cells; circRNA, circular RNA; DC, dendritic cell; lncRNA, long non-coding RNA; MDSC, myeloid-derived suppressor cell; miRNA, micro-RNA; Treg, regulatory T. Created with BioRender.com.

of macrophages to enhance cell proliferation and invasion in pancreatic cancer (130).

In ESCC cells, the promotion of proliferation, invasion and migration is facilitated by two proteins found in CDEs, namely tumor necrosis factor receptor superfamily member 10b and interleukin enhancer binding factor 3 (131). Additionally, experiments conducted *in vitro* and *in vivo* demonstrate that CDEs are able to enhance the proliferation and spread of esophageal squamous cell carcinoma (ESCC) (132). LINC01410, a lncRNA secreted by CDEs, enhances metastasis and EMT of ESCC both *in vitro* and *in vivo* through the miR-122-5p/pyruvate kinase M1/2 axis (133).

miR-210 is expressed at high levels in NSCLC and acts through CDEs to enhance the migration and invasion of NSCLC cells. This is achieved by directly targeting Up frameshift 1, leading to activation of the PTEN/PI3K/AKT pathway involved in the process of EMT (134). CDEs confer resistance to cisplatin in NSCLC cells by transferring miRNA-130a (135).

Emerging data indicate that taurine upregulated gene 1 (TUG1) plays a vital role in cancer advancement, with CDE TUG1 stimulating the movement, penetration and glucose metabolism of HCC cells through the miR-524-5p/SIX homeobox 1 pathway (136). The circular RNA-zinc finger RNA binding protein (circZFR) exhibits high expression levels in CAFs and CDEs. Moreover, the addition of CAFs to the culture medium enhances resistance to cisplatin in HCC cells. Xenograft studies demonstrate that depletion of circZFR suppressed tumor progression and reduced resistance to cisplatin. Conversely, exposure to CDEs upregulated circZFR levels, suppressed the signal transducer and activator of transcription 3/nuclear factor-κB (STAT3/NF-κB) signaling pathway, facilitated tumor growth and heightened resistance to cisplatin (137). Bladder cancer CDEs increase HCC cell metastasis through lncRNA zinc finger E-box binding homeobox 2-antisense RNA 1 by stimulating invasion and EMT (138).

Exosomal miR-199a-5p from CAFs promotes gastric tumorigenesis *in vivo* (139). In gastric cancer, the lncRNA disheveled binding antagonist of beta catenin 3-antisense RNA 1 (DACT3-AS1), a regulatory inhibitor, suppresses malignant transformation and overcomes resistance to oxaliplatin. DACT3-AS1 is a valuable tool for diagnosing and treating gastric cancer (140).

By contrast, certain CDEs may also possess oncostatic properties. For instance, in HCC, a notable decrease in miR-150-3p is observed in CDEs, resulting in the inhibition of tumor cell migration and invasiveness (141). Additionally, diminished miR-150-3p expression in HCC tissues poses a significant risk for recurrence in patients with HCC. Importantly, individuals displaying low levels of miR-150-3p in plasma exosomes exhibit notably reduced survival rates compared with those with elevated miR-150-3p levels (141). CDEs transport circular RNA-interferon gamma receptor 2 (circIFNGR2) and suppress the malignant advancement of ovarian cancer through the circIFNGR2/miR-378/ST5 pathway (142).

CSCs and exosomes. Cancer-initiating cells, commonly referred to as CSCs, constitute a minority of the diverse cell population found within tumor tissues. Nevertheless, CSCs do not remain stagnant, as they continuously shift between self-differentiation and de-differentiation, leading to a constant state of transformation alongside non-CSCs. These CSCs possess an infinite capacity for self-renewal and variation, contributing significantly to the development of tumors, their recurrent nature, metastatic spread and resistance to treatment (143). Exosomes are carriers of information in the transition from non-CSCs to CSCs and in the regulation of CSC homeostasis through specific mechanisms (144). The dynamic interconversion state of CSCs is maintained by exosomal lncRNA fragile X messenger ribonucleoprotein 1-antisense RNA 1 via a mechanism that triggers Toll like receptor 7-NF-κB signaling (145). Exosomes from CSCs deliver miR-19b-3p into cells of clear cell renal carcinoma and trigger EMT, leading to the enhancement of metastasis (146). Furthermore, exosomes originating from HCC cells contain p120 catenin, which hinders the growth of HCC cells, as well as the spread and growth of CSCs by targeting the STAT3 pathway (147).

Exosomes serve a critical role in CSC drug resistance due to various mechanisms. These include increased efficiency of DNA repair, enhanced anti-apoptotic abilities, delayed progression of the cell cycle, drug expulsion and the activation of detoxification enzymes (148). EVs originating from pancreatic CSCs resistant to gemcitabine facilitate the transfer of drug resistance characteristics to gemcitabine-sensitive pancreatic cancer cells via transfer of miR-210 (149). RAB27B in breast cancer facilitated the transfer of exosomes from stromal cells to breast cancer cells containing exosomal 5'-triphosphates. This transfer led to the activation of the retinoic acid-inducible gene I (RIG-I) signal in recipient cells, subsequently triggering the interferon-related DNA damage resistant signature (IRDS) genes to confer resistance to DNA damage. Additionally, the notch receptor 3 (NOTCH3) pathway was concurrently activated to modulate the proliferation of CSCs (150). Of note, aside from pro-angiogenic factors (such as IL-8 and VEGF), CSCs serve a role in promoting angiogenesis through exosome secretion. They exhibit resistance to intratumor hypoxia by accessing blood supply via autophagy or directly forming tube-like structures (150). Conversely, the vascular niche within the TME also secretes growth factors through autocrine and paracrine pathways to facilitate CSC growth and preserve their stem-like properties. This mutual enhancement mechanism between angiogenesis and CSCs is present in the liver TME and contributes to the progression and unfavorable outcome of HCC (151).

In addition, exosome miR-26a from glioma stem cells stimulates angiogenesis in human brain microvascular VECs by activating the PI3K/AKT signaling pathway (152). The piwi-like RNA-mediated gene silencing 2-induced CSCs secrete exosomes with the ability to transform normal fibroblasts into CAFs, ultimately facilitating tumor progression (153). Lung CSC-derived exosome miR-210-3p targets fibroblast growth factor receptor like 1 to promote lung cancer metastasis (154). Exosomal lncRNA dedicator of cytokinesis 9-antisense 2 derived from thyroid-like carcinoma (papillary thyroid carcinoma) CSCs stimulates the Wnt/β-catenin pathway, enhancing proliferation, migration, invasion, EMT and stemness in this type of cancer (155). CSCs secrete exosomes in a RAB27A-dependent manner to trigger the expression of Nanog and resistance to regorafenib in differentiated cells. Exosomal lncRNA cyclin dependent kinase inhibitor 2B-antisense 1 derived from CSCs enhances the growth and spread of thyroid cancer through the TGF-β1/Smad2/3 signaling pathway or the miR-122-5p/prolyl 4-hydroxylase subunit alpha 1 axis (156,157). MSCs, highly metastatic melanoma CSCs, release exosomes that enhance the invasiveness of melanoma parental cells, low metastatic melanoma cells and hasten metastatic advancement through miR-1268a (158). In addition, circular RNA-zinc finger E-box binding homeobox 1 and circular RNA-actin filament associated protein 1 derived from exosomes of HCC CSCs were significantly linked to the stemness of HCC and unfavorable prognosis and were able to control the process of EMT (159).

MSCs and exosomes. MSCs are recognized as a highly promising cell source for tissue engineering owing to their convenient availability and pluripotent characteristics, which enable their differentiation into adipocytes, osteoblasts, cardiomyocytes and neurons. Exosomes are the primary paracrine mediators of MSCs (160). Exosomes derived from MSCs control cancer indicators and boost tumor advancement through the transfer of particular miRNAs to adjacent cells. Specifically, MSCs from bone marrow discharge exosomes containing miR-214; this suppresses oxidative stress-induced harm in CSCs, thus supporting tumor growth (161). Exosomes from MSCs associated with tumors have elevated concentrations of miR-155. Uptake of miR-155 by tumor cells resembling atypical teratoma/rhabdomyosarcoma leads to suppression of the tumor inhibitory gene SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (a target of miR-155) and promotes the migration of these tumors (162). Exosomes derived from human MSCs associated with glioma and containing miR-1587 serve a role in enhancing the proliferation and formation of clones of glioma stem cells. This is achieved by reducing the expression of the tumor suppressor nuclear receptor corepressor 1 in glioma stem cell-like cells (163). Exosomes derived from MSCs suppress EndoMT, promote angiogenesis and uphold vascular equilibrium. Of note, exosomes derived from MSCs harbor miRNAs with anti-angiogenic properties, including miR-16 and miR-100, which hinder angiogenesis in breast cancer cells within the TME by suppressing VEGF (164-166). Biswas *et al* (167) showed that exosomes released by

tumor-educated MSCs from humans and mice promote the rapid advancement of breast cancer. This is achieved through the conversion of monocytic MDSCs into M2-polarized macrophages with strong immunosuppressive abilities at the tumor sites. Exosomes derived from MSCs containing miR-133b suppresses the proliferation, invasion and migration of glioma cells by blocking the enhancer of zeste 2 polycomb repressive complex 2 subunit and Wnt/β-catenin signaling pathways (168). In addition, exosomes derived from MSCs regulate osteosarcoma progression through miR-150 as well as miR-21-5p (169,170). Exosome miR-3940-5p from MSCs inhibits the invasion, EMT, metastasis and growth of CRC cells by targeting integrin subunit α6 (171). Exosomes derived from MSCs suppress the proliferation, migration, invasion and angiogenesis of CSCs originating from HCC through the lncRNA chromosome 5 open reading frame 66-antisense 1/miR-127-3p/dual specificity phosphatase 1/extracellular signal-regulated kinase axis (172). In a study, MSCs exhibit anti-HCC activity through the exosomal circ563/miR-148a-3p/metal regulatory transcription factor 1 pathway (173).

TMICs and exosomes. TMICs predominantly consist of myeloid cells (such as tumor-associated macrophages, dendritic cells, MDSCs) and lymphocytes (T cells and B cells) (174). Macrophages are classified into two major macrophage subsets. M1 macrophage-derived exosomes (M1-Exos) can inhibit tumor progression by directly promoting apoptosis or enhancing tumor immune response (175). In addition, M1-Exos could also reduce the expression of PD-L1 in gastric cancer cells through miR-16-5p, thereby promoting the activation and killing ability of T cells (176). Notably, Jiang *et al* (177) found that M1-Exos could also serve a dual role as a tumor suppressor. M1-Exos highly expressed the lncRNA HOXA distal transcript antisense RNA (HOTTIP), which inhibited the proliferation, invasion and metastasis of head and neck squamous cell carcinoma cells by upregulating the TLR5/NF-κB signaling pathway. In addition, it polarizes circulating monocytes into antitumor M1 macrophages thereby inhibiting cancer progression. M1-Exos may serve a greater role as a regulator of other immune cell functions in the TME. Thus, further research on M1-Exos is warranted. M2 macrophage-derived exosomes (M2-Exos) miR-221-3p promotes tumor cell proliferation and G_1/S transformation by decreasing the levels of CDKN1B in tumor cells (178). M2-Exos miR-501-3p downregulates transforming growth factor beta receptor 3 expression and finally promotes pancreatic ductal adenocarcinoma cell invasion and migration through the TGF-β signaling pathway (179). M2-Exos also promote esophageal cancer invasion and metastasis by downregulating miR-26a and upregulating activating transcription factor 2 via lncRNA AFAP1-AS1 (180). Moreover, M2-Exos can carry miR-155-5p and miR-221-5p to ECs and promote angiogenesis in pancreatic ductal adenocarcinoma by targeting E2F2 (181).

Exosomes secreted by dendritic cells induce $CD8^+$ T cell proliferation, cytotoxicity and a strong tumor immune response to cervical cancer (182). They activate natural killer cells to inhibit tumor progression (183). In colorectal cancer, exosomes from MDSCs promote the growth of colorectal cancer cells through S100A9 (184). In lung cancer, they promote tumor proliferation by activating the PI3K/AKT signaling pathway through downregulation of membrane protein 2B by miR-143-3p (185).

$CD8^+$ T cells are a subgroup of T cells, also termed cytotoxic T cells, which are among the most toxic T cells. Exosomes derived from $CD8^+$ T cells limit the tumor-promoting effects of estrogen on uterine corpus endometrial cancer by regulating the miR-765/proteolipid protein 2 axis (186). In addition to inhibiting tumor progression, Cai *et al* (187) found that exosomes secreted by $CD8^+$ T cells activated the ERK and NF-κB pathways in tumor cells, which in turn increased the expression of matrix metallopeptidase 9 (MMP9) and promoted tumor cell invasion and metastasis. Xie *et al* (188) found that exosomes secreted by regulatory T cells inhibit $CD8^+$ T cell responses and antitumor immunity, which may render them an option for immunotherapy of autoimmune diseases. T cells promote the release of exosomal miR-4315 under anti-PD1 treatment which mediates the downregulation of the pro-apoptotic protein Bim in tumor cells, thereby increasing resistance to conventional chemotherapeutic agents (189). Exosomes secreted by B cells inhibit the proliferation and killing ability of $CD8^+$ T cells (190). Plasma cell-secreted exosomes increase the expression of attachment adhesion molecule B on non-mesenchymal subtypes of ovarian cancer cells via miR-330-3p, thereby promoting their transformation into mesenchymal subtypes (191).

Engineered exosomes have become a research hotspot in recent years. However, exosomes extracted from different cells of different populations are heterogeneous. How can we overcome the heterogeneity and find the exosomes that can serve the most important role? Tumor heterogeneity is also extensive. How can we select the exosomes that serve the most effective role specifically for different tumors? In addition, the tumor immune microenvironment is complex. Can exosomes overcome the functions of immunosuppressive factors and immunosuppressive cells, thus allowing immune killer cells to serve a greater role? Further research on exosome-based antitumor therapies and efficacy is warranted.

5. Exosomes and tumor angiogenesis

Angiogenesis is a process that plays an important role in the development of cancer, from the beginning of carcinogenesis to the advanced stages of cancer (192). Tumor cells use different strategies to communicate with neighboring tissues to promote tumor progression; one such strategy is the release of exosomes (193,194). Exosomes contain various cargoes that can accelerate angiogenesis and serve an important role in cancer invasion (195). Evidence suggests that ncRNAs, particularly lncRNAs and miRNAs, serve an important role in the regulation of angiogenesis (196). Angiogenesis in tumor tissues is a dynamic process with spatio-temporal specificity. Do exosomes serve different roles at different stages of angiogenesis? Is the relationship between exosomes and angiogenesis the same in tumors of different tissue origins? These questions should be explored in detail.

Tumor angiogenesis. Cancer cells have specific mechanisms of vascular development, including the unique ability of host blood vessels to adulterate tumors or to express EC phenotypes

and form structures that resemble blood vessels (197). At the initial stage of tumor progression, tumor tissues develop independently of the structure of the vascular network, oxygen and nutrients and growth factors. They reach the tumor cells mainly due to the diffusion of nearby blood vessels. At later stages of development, tumor growth is dependent on further blood supply (198). Tumor neovascularization promotes tumor growth by providing oxygen, nutrients and metabolite replacement. Adequate blood supply to the tumor promotes the entry of tumor cells into the bloodstream, which initiates the metastatic process (199).

The development of blood vessels involves two primary processes, namely vasculogenesis and angiogenesis. A key distinction between them lies in their mechanisms; angiogenesis refers to the creation of new blood vessels from those that already exist, whereas vasculogenesis pertains to the generation of new blood vessels from precursors termed ECs or angioblasts originating from the mesoderm. This process subsequently leads to the formation of basic capillary networks that eventually mature into fully developed blood vessels (200).

The generation of new blood vessels begins in the early stages of cancer development and is related to the amount of exosomes produced by the tumor. A proangiogenic effect is observed using exosomes derived from cancer cell lines, as well as exosomes isolated from blood samples of patients with cancer and urine of patients with bladder cancer (201). Notably, gliomas have a more abundant vascular system compared with other solid tumors. *In vitro* and *in vivo* studies have shown that exosomes secreted by gliomas are rich in angiogenic proteins (202,203). In addition, other solid tumors, such as pancreatic and breast cancers, produce exosomes that promote angiogenesis (195). In addition to solid tumors, chronic granulocytic leukemia cells also produce exosomes that interact directly with ECs and have an effect on angiogenesis (204).

One of the factors determining the development and progression of cancer is an adequate supply of oxygen and nutrients (205). During the initial stages of tumor development, vascular organization in the TME is poor. Pro-angiogenic signaling predominates, which activates clusters of angiographically inactive cancer cells. This mechanism is termed the angiogenic switch. In the TME, this is achieved by transferring angiogenic factors from cancer cells to VECs (206).

In TME remodeling, angiogenesis is induced, involving a number of molecules transported by TEX. The angiogenic potential of TEX depends on the conditions under which they are secreted. It has been shown that HUVECs cultured with esophageal squamous-cell carcinoma-secreted exosomes under hypoxic conditions have improved angiogenic capacity compared with those cultured under normal conditions (207). Studies show that miR-23a, an exosome derived from hypoxic lung cancer cells and HCC, stimulates angiogenesis (208,209). Hypoxia may be an influential factor in the role of exosomes at different stages of tumor vascularization.

TEXs target VECs to influence tumor progression. Tumor cell exosomes are able to influence EC characteristics via their internal cargo. This can lead to stimulation of angiogenesis or changes in vascular endothelial permeability, ultimately affecting tumor spread (Fig. 5). Following exposure to low oxygen levels, exosomes containing the tetraspanin protein CO-029 can enhance tumor development by boosting angiogenesis (210). Relevant pathways and regulatory mechanisms identified in studies are listed (Table II) (208,211-220).

Exosomes in the pre-metastatic microenvironment. Primary tumors release systemic signals, such as exosomes, to promote the formation of a pre-metastatic microenvironment. Studies have revealed the importance of exosomes in the establishment of a pre-metastatic microenvironment by cancer cells. For example, melanoma cell-derived exosomes promote angiogenesis in lymph nodes or lung tissue, thus creating a favorable microenvironment for melanoma cell metastatic colonization and growth (221,222). Exosomes from melanoma cells deliver MET (a tyrosine kinase receptor) to myeloid progenitor cells. In addition, they induce vascular leakage at pre-metastatic sites and reprogram myeloid progenitor cells to a pro-angiogenic phenotype that promotes bone metastasis (223).

By contrast, exosomes from parental lung cancer cells contain miR-192, which effectively blocks metastatic angiogenesis and inhibits cancer cell colonization by suppressing the expression of IL-8, intercellular adhesion molecules and CXCL1 in endothelial precursor cells of the bone microenvironment. Moreover, exosomes from a highly metastatic subpopulation contained less miR-192, which promoted the formation of the pre-metastatic microenvironment of bone metastasis (224).

There are 10 major tumor angiogenesis process, including hypoxia, extracellular matrix (ECM) organization, vascular development, cell migration, cell proliferation, VEGF response, wound healing, lipid response, hemostasis and platelet aggregation (27). Exosomes influence the progression of these processes through the cargoes they carry. For example, hypoxia plays a key role in tumor angiogenesis (27), hypoxia-inducible factor 1 (HIF-1) plays an essential role in the hypoxic tumor microenvironment (225). In breast cancer, MSC-derived exosomal miR-100 induces VEGF expression by regulating HIF-1α (166). In pancreatic cancer, TEX-enriched protease regulates ECM as demonstrated for degradation of collagens, laminin and fibronectin; this has important implications for tumor adhesion, motility and invasiveness (226). Exosomal regulation of the ECM may contribute to physiologic and pathologic angiogenesis, wound healing and coagulation after vessel rupture (226). Xie *et al* (227) demonstrate that exosomal miR-582-3p promotes gastric cancer progression by regulating VEGF expression. One study suggests that EVs, containing both microvesicles and exosomes, derived from breast-cancer cell lines induce tissue factor (TF)-independent platelet activation and aggregation, as well as TF-dependent plasma clotting and platelet aggregation by means of thrombin generation (228). These roles may vary depending on the tumor type and microenvironment. Further studies will help to reveal the specific mechanism underlying the role of exosomes in tumor angiogenesis and provide new strategies for tumor therapy.

6. Application of engineered exosomes and vascular endothelium in cancer progression

With the development of and advances in exosome research, the use of engineered exosomes in cancer is gaining attention.

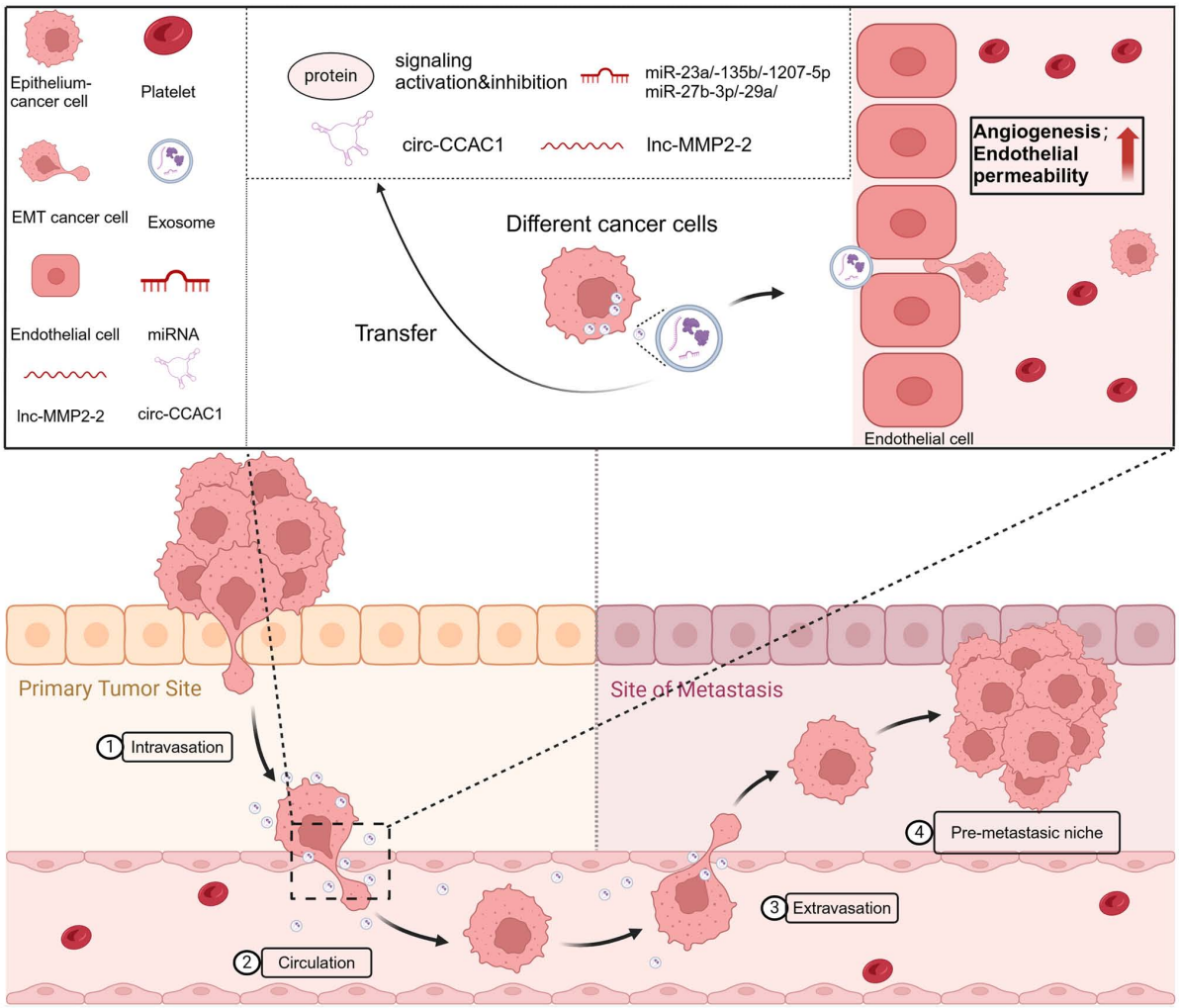

Figure 5. Tumor cell-derived exosomes promote the metastatic process through multiple pathways. Exosomes secreted by a variety of tumors accelerate the metastatic process by activating or inhibiting multiple signaling pathways, or by translocating various non-coding RNAs that encapsulate and act on endothelial cells. This process increases the permeability of the vascular endothelium and promotes angiogenesis through several mechanisms. circ-CCAC1, circular RNA-cholangiocarcinoma-associated circular RNA 1; EMT, epithelial-to-mesenchymal transition; lnc-MMP2-2, long non-coding RNA-matrix metalloproteinase 2-2; miR, microRNA. Created with BioRender.com.

Although natural exosomes can deliver antitumor drugs, they are mostly retained in the liver or spleen rather than in tumor tissue. Consequently, the therapeutic effect is unsatisfactory (229). Thus, engineering technology provides exosomes with more specific targeting and clinical application potential (Fig. 6).

Isolation of exosomes. The isolation of exosomes is important for the study of their application in tumor therapy. Conventional methods for exosome isolation include ultracentrifugation, size-based filtration, size exclusion chromatography and polymer precipitation (230). They are typically subject to various constraints with regard to clinical applications, such as cumbersome procedures, high costs and limited throughput.

Microfluidic-based separation techniques have recently attracted increasing attention for the microscale separation, detection and analysis of exosomes. The technique uses innovative sorting mechanisms such as acoustic, electrophoretic, electromagnetic manipulation, nanowire-based traps, nanoscale deterministic lateral displacement and viscoelastic flow (231). This results in a five-fold increase in the number of key liposarcoma-associated EV cargoes in 30 min (232).

In short, isolation of high-purity exosomes is the first step in studying the therapeutic function of engineered exosomes. Conventional methods alone are often unable to meet separation requirements, such as high purity, high yield and low cost. Microfluidic-based isolation techniques are capable of recovering, analyzing and quantifying exosomes in limited clinical samples in a high-throughput manner with higher sensitivity and multiplexed detection capabilities. This is the basis for the development of efficiently engineered exosomes.

Modification, labeling and imaging of engineered exosomes. Biomodification is currently the most widely used membrane modification strategy, including targeted peptide modification and biomimetic exosome modification. For example, cyclo(Arg-Gly-Asp-D-Tyr-Lys) peptide is a cyclic Arg-Gly-Asp peptide, which endows the natural exosome with significant tumor-targeting ability and high affinity for tumor vascular ECs in osteosarcoma (233,234). Notably, this opens up the possibility of exosome-based anti-angiogenic therapies. Triple-negative breast cancer is a form of breast cancer characterized by a high likelihood of metastasis and recurrence.

Table II. Tumor-derived exosome-mediated regulation of endothelial cells.

First author/s, year	Origin of exosomes	Functional Molecules	Mechanism of Action	(Refs)
Nazarenko, *et al* 2010	Pancreatic cancer cells	TSPAN8	Stimulation of angiogenic factor transcriptions induces systemic angiogenesi	(220)
Sheldon, *et al* 2010	Human glioma cells	DLL4	Inhibition of the Notch signaling pathway induces angiogenesis	(211)
Tang, *et al* 2018	Ovarian cancer cells	E-cadherin	Activates β-catenin and NF-κB signaling to promote angiogenesis	(212)
Svensson, *et al* 2011	Hypoxic glioblastoma cells	TF	PAR2/ERK1/2-dependent activation of the pro-angiogenic growth factor HB-EGF pathway promotes angiogenesis	(213)
Hsu, *et al* 2017	Hypoxic lung cancer cells	miR-23a	Inhibition of tight junction protein ZO-1 expression increases vascular permeability and tumor transendothelial migration	(208)
Umezu, *et al* 2014	Hypoxic myeloma cells	miR-135b	Inhibition of HIF1AN-induced angiogenesis in endothelial cells	(214)
Wu, *et al* 2021	Non-small cell lung cancer	lnc-MMP2-2	Promotion of vascular endothelial permeability through the miR-1207-5p/EPB41L5 axis	(215)
Dou, *et al* 2021	EMT colorectal cancer	miR-27b-3p	Targeting of VE-cadherin and p120 catenin and inhibition of their expression to increase vascular endothelial permeability	(216)
Liu, *et al* 2023	EMT colorectal cancer	miR-29a	Increase in endothelial permeability by targeting KLF4 and decreasing expression of ZO-1, claudin-5 and occludin	(217)
Yi Xu, *et al* 2021	Cholangiocarcinoma	circCCAC1	Elevation of SH3 domain-containing GRB2-like protein 2 expression to reduce the levels of intercellular junction proteins	(218)
Li, *et al* 2024	Colorectal cancer	ADAM17	Targeting of vascular endothelial cells to enhance vascular permeability by affecting endothelial calcineurin cell membrane localization	(219)

TSPAN8, tetraspanin 8; DLL4, delta like canonical Notch ligand 4; PAR2, protease-activated receptor 2; ERK1/2, extracellular signal-regulated kinase; TF, tissue factor; miR, microRNA; KLF4, Krüppel-like factor 4; lnc, long non-coding; circCCAC1, circular RNA-cholangiocarcinoma-associated circular RNA 1; ZO-1, zonula occludens-1; EPB41L5, erythrocyte membrane protein band 4.1 like 5; EMT, epithelial-to-mesenchymal transition; GRB2, growth factor receptor bound protein 2; HB-EGF, heparin-binding epidermal growth factor-like growth factor; HIF1AN, hypoxia-inducible factor 1-alpha inhibitor; lnc-MMP2-2, lncRNA-matrix metalloproteinase 2-2; NF-κB, nuclear factor-κB; VE-cadherin, vascular endothelial-cadherin; ADAM17, ADAM metallopeptidase domain 17.

Raghav *et al* (235) altered the surface of exosomes using a peptide that targets the c-Met gene, a receptor for hepatocyte growth factor or scatter factor. This modification causes an increase in c-Met on the surface of triple-negative breast cancer cells. Studies conducted in living organisms showed that the engineered nanoparticles enclosed within exosomes markedly increases the efficiency of cellular absorption and effectiveness of adriamycin against tumors. This approach demonstrates remarkable effectiveness in targeting tumors, resulting in improved inhibition of tumor growth and triggering robust tumor cell death (236). Modification of exosomes with peptides is a promising engineering approach.

Labeling strategies are necessary for imaging engineered exosomes *in vivo*. Lipid dyes, luminal dyes and gene markers are the main strategies for labeling engineered exosomes. For example, lipid dyes such as PKH67, DiR/DiD and MemGlow have been used to label engineered exosomes (237). However, the half-life of the lipid dyes greatly exceeds that of the engineered exosomes. This would result in the degradation of the exosomes after cellular uptake being masked by the recovery and redistribution of the fluorescent dyes (238). Bioluminescence-based reporter proteins, such as glucose-lactate adhesin and glucose b, are recommended for labeling engineered exosomes in small animal models (239,240).

Real-time imaging of engineered exosomes through stochastic optical reconstruction microscopy, structured illumination microscopy and confocal laser scanning microscopy is also important in *in vivo* studies. Structured illumination microscopy and confocal laser scanning microscopy can track the dynamic intracellular distributions of exosomes within

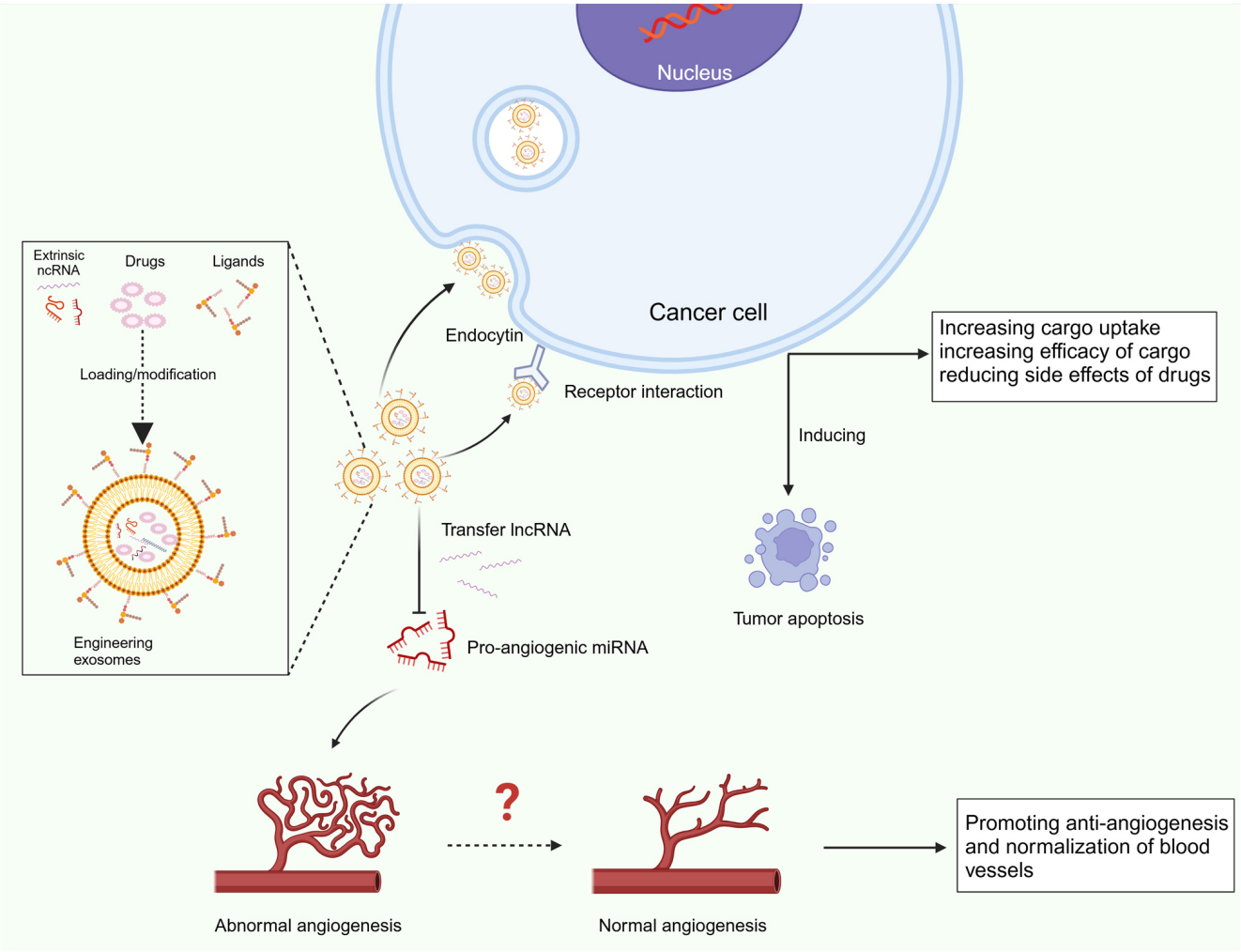

Figure 6. Precise tumor targeting with engineered exosomes as carriers. Exosomes are carriers with natural delivery capabilities, characterized by precise targeting and high bioavailability. After anticancer drugs and/or exogenous ncRNAs are loaded into exosomes, they can directly target the specific pathways of cancer cells or cancer stem cells and prevent further tumor development. In addition, ligands corresponding to overexpressed receptors on the surface of cancer cells can also modify the surface of exosomes, thus improving the efficiency of exosome uptake by cancer cells. The value of engineered exosomes in anti-angiogenic therapy needs to be further investigated. ncRNA, non-coding RNA; lncRNA, long non-coding RNA; miRNA, micro-RNA. Created with BioRender.com.

seconds. This approach is suitable for studying the physiological and tumor-killing effects of engineered exosomes on cancer cells (241,242). It is important to choose a particular combination of reporter and microscope based on the biological question and the actual imaging equipment available at this time.

Possibilities of engineered exosomes in anti-angiogenic therapy. Gene therapy is the transfer of genetic molecules to a patient for the treatment of a disease (243). The ncRNAs can be used as gene therapy vectors for a wide range of diseases, including cancer. However, great challenges remain for the controlled expression of ncRNA therapeutics in terms of the level, timing and location of gene therapy. Engineered exosomes offer promise in this field; it is realistic to deliver ncRNAs to the tumor site in a precise temporal, spatial and dosage manner through engineered exosomes (244-247). For instance, antimiRNA-21 and antimiRNA-10b were encapsulated within polymeric nanocarriers and subsequently coated with urokinase plasminogen activator-engineered exosomes to improve the affinities for targeting tumors. As a result, the systemic delivery of the urokinase plasminogen activator-engineered exosomes polymeric nanocarriers nanococktail *in vivo* demonstrated significant cancer inhibition, thereby supporting the evidence for the combined antitumor impacts of ncRNAs and engineered exosomes (248).

Exosomes serve a role in cancer progression by promoting angiogenesis through the transportation of various pro-angiogenic molecules, including VEGF and miRNAs (249). Numerous lncRNAs are dysregulated in the context of angiogenesis within human malignant tumors. Moreover, exosomes secreted by cancer cells harbor a multitude of lncRNAs that promote angiogenesis. Consequently, exosomes derived from tumors containing lncRNAs are perceived as potent modulators of angiogenesis. Moreover, as aforementioned, exosomes encapsulate miRNAs that serve a role in the regulation of angiogenesis. The effect of these miRNAs on angiogenesis is manifested through the direct modulation of VEGF or activation of signaling pathways (such as NF-κB). Hence, targeting lncRNAs and miRNAs presents a promising therapeutic

approach to manipulating the angiogenic process in diverse human ailments. The advances in high-throughput sequencing techniques have simplified the recognition of ncRNA characteristics involved in angiogenesis and the correlation between the expression levels of various ncRNA subclasses, thereby delineating the intricate network of interactions between miRNAs and lncRNAs. Such strategies facilitate the development of novel therapeutic interventions to modulate angiogenesis. The aforementioned ncRNAs have emerged as valuable diagnostic and prognostic indicators for human diseases, particularly types of cancer (250). Further research is warranted to investigate the potential value of ncRNA-based anti-angiogenic therapies by targeting engineered exosomes. Specifically, determining whether the translocation of certain lnRNAs against pro-angiogenic miRNAs to the endothelium of tumor blood vessels can effectively inhibit aberrant angiogenesis in tumors is a major area of study.

7. Conclusions and future prospects

To create a conducive environment for cancer cell survival and immune system suppression, cancer cells manipulate the properties of stromal cells through various means, including the release of exosomes. Research indicates that the impact of cancer cells on the vascular endothelium plays an important role in establishing and sustaining an immunosuppressive TME (31). Specifically, the vascular network of the tumor hinders the infiltration of T cells, selectively eliminates them and attracts immunosuppressive cells, thereby hampering antitumor immune responses. Emerging evidence suggests that strategies aimed at normalizing the tumor vasculature can temporarily enhance its structural and functional abnormalities, reduce hypoxia within the tumor, improve drug delivery, facilitate immune cell penetration and synergize with immunotherapy for prolonged efficacy. These discoveries hold significant implications for the development of vascular normalization therapies; nonetheless, numerous unanswered questions and obstacles persist. Examples include lack of therapeutic efficacy, drug resistance and prevalence of treatment modalities. These limitations encourage researchers to develop novel angiogenesis inhibitors, explore the druggability of additional targets, validate specific biomarkers and offer more treatment options to patients with cancer. Whether ncRNA-based anti-angiogenic therapy is feasible and has clinical translational value through engineered exosomes should be further investigated.

Novel approaches are required to enhance the outcomes of anti-angiogenic treatment beyond VEGFR blockade. Investigating the metabolic profiles and transport mechanisms of VECs may unveil promising alternatives for therapy. Enhancing the delivery of pharmacological inhibitors to these targets via exosomes, natural drug carriers, could be a fruitful avenue. Additionally, the role of stromal cells, such as CAFs, in promoting angiogenesis should not be overlooked. Exploring potential targets to hinder the recruitment of immunosuppressive cells that fuel tumor growth, in light of the interactions between VECs and immune cells, is of great importance.

In summary, directing efforts towards vascular normalization in tumor vasculature could enhance the effectiveness of current immunotherapies by reducing immunosuppression within the TME. EndoMT encourages various malignant biological behaviors within tumors. Potentially beneficial therapeutic effects could be achieved by inhibiting or reversing EndoMT during tumor advancement. For instance, it fosters tumor growth by stimulating the proliferation, survival and angiogenesis of tumor cells, promotes tumor metastasis by influencing critical processes (such as EMT, cell migration, invasion, endocytosis and exocytosis) and facilitates tumor immune evasion and resistance to therapy. Nonetheless, limited research has been conducted thus far on EndoMT in tumor therapy.

In theory, suppressing molecules and signaling pathways initialized and sustained by EndoMT or effector molecules enhancing tumor biological behavior could effectively impede tumor progression. Nevertheless, only a small number of studies have attempted to tackle these obstacles, primarily concentrating on evaluating the efficacy of current medications. Markedly, EVs from MSCs possess the ability to reverse EndoMT in VECs exposed to tumor cells (84). More in-depth understanding of the molecules and signaling pathways triggered and sustained by EndoMT or effector molecules that enhance tumor biological behaviors, coupled with the creation of specific inhibitors, will enhance treatment plans and improve the outlook for patients with cancer.

Cancer-related exosomes within the TME encompass a variety of molecules, including proteins, DNA, mRNA, miRNA, lncRNA and circular RNA. In cancer, some of these components function as biomarkers, aiding in the early detection, diagnosis, prognosis and evaluation of treatment effectiveness. Additionally, certain molecules serve as messengers for intercellular communication between cancer cells and surrounding cells or within the TME, influencing processes such as tumor progression, invasion, metastasis and resistance to therapies. Notably, exosomes derived from tumors can enhance metastasis by modifying the behavior of VECs. Notably, research has shown that exosomes serve a role in connecting cardiovascular disease to cancer. For instance, exosomes released by cardiomyocytes during heart failure facilitate intercellular communication using miR-22-3p, which decreases the vulnerability of cancer cells to iron-induced cell death, thereby supporting tumor growth (251). In a recent study, Caller *et al* (252) reported that hearts following myocardial infarction, specifically cardiac MSCs (cMSCs), generate an increased amount of cardiac small extracellular vesicles (sEVs) containing tumorigenic material compared with healthy hearts. Following a heart attack, cMSC-sEVs also transform inactive macrophages into a state that promotes angiogenesis and tumorigenesis in laboratory settings. Furthermore, the absorption of cMSC-sEVs by cancer cells enhances the growth of tumors.

Engineered exosomes offer a number of advantages over natural exosomes as drug delivery platforms. Nevertheless, there are several challenges to the clinical application of engineered exosomes. First, there is a lack of consensus on standardized methods for isolating, quantifying and analyzing engineered exosomes from complex tissues (such as blood, tissues and urine) in the clinical stage. Second, the process

through which we can accurately quantify exosomes and their contents, including the exosome number, protein content and ratio of these two remains elusive. Finally, exosomes from different sources have different functions and compositions. Hence, it is important to develop methods for the selection of suitable and available exosomes. This must be addressed before clinical development of exosome-based drug delivery systems.

Numerous investigations have examined the molecular mechanisms that drive the biological function of exosomes in advancing tumors. Nevertheless, additional research is essential to deepen our understanding and translate the diagnostic and therapeutic potential of exosomes into practical use in clinical settings. It is anticipated that through research, we can effectively harness the benefits of exosomes as inherent transporters and address their limitations in the immediate future. The use of exosome-based strategies may lead to significant advancements in the treatment of cancer.

In brief, both the endothelium and exosomes possess the ability to affect tumor advancement in distinct manners and are consistently associated with tumor progression, each fulfilling crucial functions. The functions of the vascular endothelium and exosomes in cancer are interconnected and reciprocally influential. VECs aid in promoting tumor expansion and dissemination by regulating the TME, whereas exosomes alter the activities of tumor cells and adjacent stromal cells (including VECs) through the transport of signaling molecules, collectively promoting tumor progression. Consequently, a thorough examination of the mechanisms involving vascular endothelium and exosomes in cancer could uncover novel pathways of tumor formation and offer new perspectives and strategies for cancer therapy and prevention.

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Authors' contributions

Writing of the original draft was by YD. Writing, reviewing and editing was by YY. Supervision was by YH. Supervision, writing, reviewing and editing was by XH. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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