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Review article

Exosomal non-coding RNAs in angiogenesis: Functions, mechanisms and potential clinical applications

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ABSTRACT

Exosomes are extracellular vesicles that can be produced by most cells. Exosomes act as important intermediaries in intercellular communication, and participate in a variety of biological activities between cells. Non-coding RNAs (ncRNAs) usually refer to RNAs that do not encode proteins. Although ncRNAs have no protein-coding capacity, they are able to regulate gene expression at multiple levels. Angiogenesis is the formation of new blood vessels from pre-existing vessels, which is an important physiological process. However, abnormal angiogenesis could induce many diseases such as atherosclerosis, diabetic retinopathy and cancer. Many studies have shown that ncRNAs can stably exist in exosomes and play a wide range of physiological and pathological roles including regulation of angiogenesis. In brief, some specific ncRNAs can be enriched in exosomes secreted by cells and absorbed by recipient cells through the exosome pathway, thus activating relevant signaling pathways in target cells and playing a role in regulating angiogenesis. In this review, we describe the physiological and pathological functions of exosomal ncRNAs in angiogenesis, summarize their role in angiogenesis-related diseases, and illustrate potential clinical applications like novel drug therapy strategies and diagnostic markers in exosome research as inspiration for future investigations.

1. Introduction

Extracellular vesicles (EVs), including exosomes and microvesicles, can be secreted by almost every cell [1]. Exosomes are derived from the multivesicular endosome pathways, different from microvesicles formed from the plasma membrane [2]. It has been demonstrated that EVs, including exosomes, are involved in intercellular communication [2] and usually deliver signals by following three ways: binding to receptors on the surface of the cell membrane, transferring surface receptors to target cells, and delivering related functional proteins or RNAs to target cells [3]. Exosomes are nanosized EVs measured 30–150 nm in diameter [4]. At present,

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the main role of exosomes seems to involve intercellular signal transduction and material transport [5]. Exosomes contain biologically active substances including proteins, lipids, and genetic material [2]. For example, in recent years a variety of non-coding RNAs (ncRNAs) have been found in exosomes, such as microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) [6]. Therefore, the primary physiological function of exosomes is to serve as intermediaries for the transfer of vesicle material between cells. This action mediates various biological processes such as immune functions [7], intercellular signals, cell growth and differentiation, and gene transcription and expression [8]. However, it is unclear whether the transport of exosome content is random or specific. Interestingly, a novel study demonstrated that a zipcode-like sequence mediated mRNA enrichment in exosomes [9]. In that study, a zipcode-like sequence containing a short CTGCC core domain and a miRNA-1289 binding site in the 3′-untranslated region (3′-UTR) was found to bind directly with miRNA-1289 and increase the levels of specific mRNAs in EVs. Although exosomes were previously thought to have only transport functions, a new study has found that breast cancer-associated exosomes process precursor microRNAs (miRNAs) into mature miRNAs through Dicer, Argonaute2 (AGO2), and trans-activation response RNA-binding protein (TRBP) [10]. Exosomes also exert pathological effects under certain conditions. Taking the tumor microenvironment for example, hypoxia-derived tumor cells can secrete exosomes to activate the NF-κB pathway and upregulate the expression of hypoxia-inducible factor-1α (HIF-1α) to promote tumor cell proliferation [11]. Additionally, non-coding RNA may also participate in this process, the study showed that the 50 miRNAs were found to significantly upregulate in exosomes of hypoxia induced-esophageal squamous cancer cells and further KEGG pathway analysis revealed that they are related to tumor-associated pathways [12]. Moreover, exosomes can also promote tumor metastasis, enhance radiation resistance of tumor and induce tumor angiogenesis [13–15].

Vascular dysfunction and neovascularization are associated with the development and progression of many diseases, including angiogenesis-related, ischemic, inflammatory, and immune diseases and cancer [16]. The formation of new blood vessels is a sophisticated process that includes vasculogenesis and angiogenesis [17]. Vasculogenesis is the early stage of new vessel formation from endothelial progenitor cells, or angioblasts. Angiogenesis is the proliferation and migration of endothelial cells (ECs) from existing mature blood vessels in tissues [18]. Both neovascularization patterns are closely related to the functional status of ECs [19]. Related cytokines, functional proteins, and some RNAs can influence endothelial cell metabolism and thus participate in angiogenesis.

NcRNAs are a large family of RNAs that have been extensively researched in the past. They include lncRNA, miRNA, circRNA, transfer RNA (tRNA), ribosome RNA (rRNA), small interfering RNA (siRNA), small nuclear RNA (snRNA) and piwi-interacting RNA (piRNA) which perform several functions, including amino acid transport, mRNA modification, editing, gene silencing, and recognition [20]. NcRNAs participate in regulating cellular physiological processes through different levels of gene regulation. The aberrant expression of various ncRNAs may induce pathological effects and even become a sign of disease. Recently, the role of lncRNA and miRNA in pathological angiogenesis has been studied in depth [21]. Increasing evidence indicates that lncRNAs serve as molecular switches during cellular differentiation, movement, apoptosis, and reprogramming of cell states by shifting gene expression patterns [22,23]. One of the major functional mechanisms of miRNAs is to regulate post-transcriptional expression by gene silencing [23]. Moreover, depletion of Dicer1 in miRNAs (miRNA-21a, miRNA-125b, miRNA-let-7) suppresses tumor angiogenesis [24]. MiRNAs are involved in diabetic retinopathy, etc [25].

This review describes the roles and mechanisms of several important types of exosomal ncRNAs in angiogenesis and clarifies their participation in pathological angiogenesis. In addition, we discuss the clinical applications of exosomal ncRNAs in angiogenesis-related diseases, as well as their potential capabilities as therapeutic targets and the prospect of related studies.

2. Exosomal miRNAs in angiogenesis

MiRNAs are small ncRNAs with 20-24 nucleotides (nt) in length, made from single-stranded RNAs with a hairpin precursor structure about 70–90 nt in size processed by the Dicer enzyme [23]. MiRNAs could bind to the open reading frame (ORF) region or 3′-UTR of target mRNAs and play a moderating role [26]. MiRNAs have two modes of action: binding closely to the ORF region of mRNA and forming a double-stranded structure that leads to mRNA degradation or loosely binding to the 3′-UTR region of mRNA and inhibiting the post-transcriptional translation of mRNA [27]. Furthermore, miRNAs have been verified to be involved in many biological processes, including cell growth, differentiation, and disease development [28].

MiRNAs are stable in body fluids like blood, urine, saliva, and breast milk [29–31]. In addition, extracellular miRNAs can be loaded into EVs, like exosomes, which prevent their degradation, ensuring their stability [32]. Thus, given the transportation role of exosomes, miRNAs can be delivered by exosomes to specific cells. MiRNAs are not only loaded into exosomes randomly, but also through a sorting mechanism [33], such that some types of miRNAs (miRNA-150, miRNA-142-3p, and miRNA-451) have a higher priority for entering exosomes than other miRNAs [34]. This sorting mechanism may be based on the specific sequences of certain miRNAs, some enzymes, or other proteins [33]. MiRNAs can be transferred between cells by exosomes and participate in many pathological processes such as inflammation, tumor metastasis, and angiogenesis [6]. The role of exosomal miRNAs has attracted greater attention in recent years, and more reports have shown that exosomal miRNAs play an important role in regulating angiogenesis [33]. Exosomal miRNA-214, secreted by human microvascular endothelial cells (HMECs), promoted nearby HMEC migration and blood vessel formation [35]. This study utilized *in vivo* and *in vitro* methods to prove that exosomal miRNA-214 could mediate the interaction between endothelial cells. Exosomal miRNA could not only participate in crosstalk between homogeneous cells like endothelial cells, but also involved in signal transduction in different cells. Exosomal miRNA-92a, derived from the K562 leukemic cell line, could be absorbed by human umbilical vein endothelial cells (HUVECs) and induce HUVEC migration and tube formation [36]. However, this result was mainly based on *in vitro* approaches and how did leukemia cells affect angiogenesis *in vivo* still need further exploration. Exosomal miRNAs could also change the tumor microenvironment and lead to angiogenesis in cancer [37]. The uptake of related angiogenic exosomal miRNAs by normal ECs could activate the angiogenesis-related signaling pathways and stimulate new blood vessel formation

[38]. A recent study showed that exosomes derived from senescent ECs include several pro-angiogenesis miRNAs [39]. The further study revealed that these exosomal miRNAs could regulate endothelium dysfunction and promote angiogenesis of normal ECs. Another research showed that miRNA-155 and miRNA-182 differently expressed between H_2O_2 treated and normal HUVEC-derived exosomes, and they were involved in cellular senescence and autophagy [40]. Those are interesting findings which suggested that these exosomal miRNAs may be a potential biomarker [39] and therapeutic target [40] of age-related vascular diseases. For example, exosomal miRNA-210 from lung could activate the PI3K/AKT/HIF-1 pathway and promoted angiogenesis [41]. Meanwhile, lung cancer-derived exosomal miRNA-21 could activate the STAT3 pathway, increasing the expression of vascular endothelial growth factor (VEGF) and accelerating angiogenesis in bronchial epithelial cells [42]. Exosomal miRNA-126 was found to upregulate the AKT/ERK signal pathway and inhibit downstream p53 to regulate angiogenesis [25]. On the other hand, exosomal miRNAs could modulate the ECs to take part in the new blood vessels [43]. Furthermore, M2 macrophage-derived exosomal miRNA-155-5p and miRNA-221-5P acted on ECs and induced angiogenesis [44]. Exosomal miRNAs, such as miRNA-132 and miRNA-378, could promote proliferation, migration, and tube formation of ECs, and subsequently regulated sprout formation [45,46]. Similarly, exosomal miRNAs such as exosomal miRNA-210, miRNA-10b, and miRNA-9b increased capillary formation, ECs chemotaxis, and proliferation in response to VEGF [47, 48]. Moreover, tumor-derived exosomal miRNAs could target ECs and accelerate tumor angiogenesis. So, it is clear that exosomal miRNA could also regulate angiogenesis by directly affecting ECs.

Taken together, current evidence indicates that exosomal miRNAs play a non-negligible role in angiogenesis. The related mechanisms of exosomal miRNAs in angiogenesis are summarized in Table 1 and Fig. 1, and we look forward to providing more inspiration for potential clinical applications.

3. Exosomal lncRNAs in angiogenesis

In contrast to miRNAs, lncRNAs are ncRNAs longer than 200 nt, the largest category among the ncRNAs [84]. LncRNAs are known to take part in many physiological and pathological processes: for example, fibrosis in various organs such as liver, heart, lung, and kidney [85], regulation of synaptogenesis in the human nervous system through modulation of gene expression [86], and adjustment of reprogramming of human induced pluripotent stem cells [86]. In other words, lncRNAs are involved in gene regulation at multiple

Table 1
The mechanisms of exosomal ncRNAs in angiogenesis.

Exosomal ncRNAs		Mechanism	Refs.
miRNA	miRNA-21	activate STAT3, increase the expression of VEGF	[42]
	miRNA-126	regulate AKT/ERK pathway	[25]
	miRNA-210	target SMAD4 and STAT6 in ECs	[49]
	miRNA-9	enhance ECs chemotaxis in response to VEGF	[50]
	miRNA-23a	target PHD1, PHD2 and tight junction protein ZO-1	[51]
	miRNA-192	repression of proangiogenic IL-8, ICAM and CXCL1	[52]
	miRNA-16	downregulate VEGF expression	[53]
	miRNA-130a	regulate PTEN pathway	[54]
	miRNA-135b	downregulate the expression of VEGF	[55]
	miRNA-6785-5p	inhibit inhibin subunit beta A (INHBA)	[56]
	miRNA-378b	inhibit TGF-β receptor III	[57]
	miRNA-29a	suppress the expression of VEGF	[58]
	miRNA-150-3p	promote tumor angiogenesis	[59]
	miRNA-155	target the c-MYB/VEGF axis of ECs	[60]
	miRNA-21-3p	inhibit ECs proliferation and migration	[61]
	miRNA-17-3p	target PETN pathway	[62]
	miRNA-486-3p	participate in TLR4/NF-κB axis repression	[63]
	miRNA-202-5p	target TGF-β receptor II	[64]
lncRNA	lncRNA-p21	inhibit p53	[65]
	lncRNA-01435	facilitate YY1-mediated HDAC8 expression	[66]
	lncRNA OIP5-AS1	regulate miR-153 and ATG5	[67]
	lncRNA-HOTAIR	target the VEGFA	[68]
	lncRNA-H19	increase the level of VEGF and ICAM-1 in ECs	[69]
	lncRNA-NR2F1-AS1	enhance the production of VEGF in ECs	[70]
	lncRNA-PCAT6	activate IGF-1/ERK pathway	[71]
	lncRNA-TUC339	activate VEGFR/AKT/mTOR pathway	[72]
	lncRNA-SNHG16	regulate miR-195/MFN2 axis	[73]
	lncRNA-CCAT2	activate the Wnt/β-catenin pathway	[74]
	lncRNA-UCA1	regulate miRNA-96-5p/AMOTL2 axis	[75]
circRNA	circRNA -ANRIL	combine with PES1 protein	[76]
	circRNA-100338	interact with NOVA2 and activate mTOR pathway	[77]
	circRNA-SHKBP1	upregulate the expression of HUR	[78]
	circRNA-PWWP2A	regulate the level of Ang-1	[79]
	circRNA-0005015	increase the expression of STAT3	[80]
	circRNA-HIPK3	upregulate the level of VEGF-C	[81]
	circRNA-DNMT3B	regulate miR-20b-5p/BAMBI axis	[82]
	circRNA-ZNF609	regulate MEF2A and suppress angiogenesis	[83]

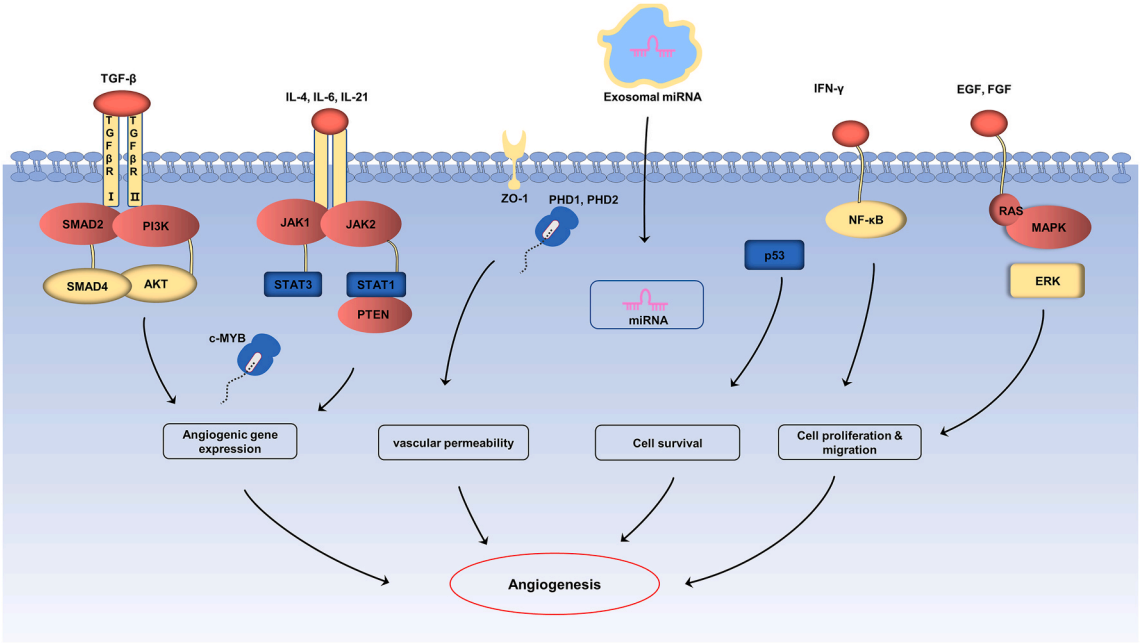

Fig. 1. The mechanisms of exosomal miRNAs in angiogenesis. Exosomal miRNAs target angiogenesis related pathways (TLR-4/NF– NF-κB, JAK/STAT, TGF-β/SMAD4, PI3K/AKT, PTEN and MAPK/ERK pathway) in ECs or act on downstream target genes (PHD1, PHD2, c-MYB) to increase the expression of angiogenesis related factors (VEGF, TGF-β, HIF-1α) and promote proliferation of endothelial cells, leading to angiogenesis.

levels, incorporating epigenetic, transcriptional, and post-transcriptional regulation [87].

LncRNAs have four classical modes of action [88]. The first mode of action is as signals: in particular situations, some lncRNAs will be transcribed and participate in specific signal pathways as signal transduction molecules [88]. For example, lncRNA-p21 located upstream of the cyclin-dependent kinase inhibitor 1A (CDKN1A) gene, was reported as a transcription inhibitor of the classic p53 pathway [65]. The second mode of action is as decoys: when these lncRNAs are transcribed, they will bind directly to RNA or proteins, blocking molecular action and signaling pathways [88]. For instance, lncRNA PANDA could bind directly with the apoptotic program nuclear transcription factor NF-YA and thereby block the inhibit cells apoptosis to some extent [89]. The third mode of action is as guides: some types of lncRNAs could guide binding protein binding with transcription product and regulate the transcription of downstream molecules [88] such as lncRNA-HOTTIP [90]. The riboprotein body complex could be guided to a specific target by this pattern. The last mode of action is a molecular scaffold: lncRNAs can act as a platform upon which other relative molecules can assemble [88].

A wide range of lncRNAs have also been found in exosomes [91], where they play an important role in angiogenesis [92]. Studies have proved that tumor-derived exosomal lncRNAs could stimulate tumor angiogenesis by activating angiogenic cells [93]. Furthermore, exosomes secreted by different types of cells, such as mesenchymal stem cells and endothelial cells, were involved in tumor angiogenesis [94,95]. According to Wang et al., lncRNA HITT and HIF-1α form a loop to regulate angiogenesis and tumor growth in colon cancer [96]. Exosomal lncRNA OIP5-AS1 induces the angiogenesis in osteosarcoma by regulating miRNA-153 and autophagy-related protein 5 (ATG5) [67]. According to these results, some exosomal lncRNAs could affect relative protein level like ATG5 to regulate tumor cells autophagy and thereby promote tumor angiogenesis. Exosomal lncRNAs could also regulate angiogenesis by affecting the expression of angiogenic factors [97]. For instance, LncRNA HOTAIR was highly expressed in glioma cells [98] and transferred from glioma cells to ECs, where it prompted tumor angiogenesis by increasing the expression of VEGFA [68]. In addition, exosomal lncRNAs can also act directly on the ECs involved in angiogenesis [43]. Researchers recently identified lncRNA H19-enriched $CD90^{+}$ liver cancer cells-derived exosomes, which were delivered to ECs, where they enhanced the production of VEGF [69]. Thus, some kind of exosomal lncRNAs are capable of activating ECs, which means that they can promote ECs proliferation and migration, as well as increase the level of pro-angiogenic factors such as VEGF. Meanwhile, overexpression of lncRNA HOTAIR and MALAT1 was found in ethanol-induced endothelial cell-derived exosomes, which related to alcohol-induced tumor angiogenesis. This might suggest that ECs-derived exosomal lncRNAs could induce angiogenesis by targeting other ECs [99], and that exosomal lncRNAs could serve as competing endogenous RNA (ceRNA) [100]. CeRNAs are RNA transcripts with miRNA binding sites that competitively bind miRNA and inhibit miRNA regulation on target genes, including mRNAs, lncRNAs, pseudogenes, and circRNAs [100]. CeRNAs regulate and communicate with each other by competing for binding to specific miRNAs. They are called miRNA sponges since they could block miRNAs from their original targets by binding with them [101]. For example, lncRNA NR2F1-AS1 acts as a sponge by binding to miRNA-338-3p and suppressing the expression of insulin-like growth factor-1 (IGF-1), thus increasing the expression of IGF-1 and activating the IGF-1/IGF-1R/ERK pathway, both of which play an important role in the angiogenesis of breast cancer [70]. Furthermore, M2 macrophage-induced lncRNA PCAT6 upregulates VEGF receptor (VEGFR) through ceRNA and activates

VEGFR/AKT/mTOR signaling pathway to accelerate angiogenesis in breast cancer [71].

To summarize, exosomal lncRNAs participate in angiogenesis via multiple mechanisms, such as regulating the proliferation of ECs and enhancing VEGF expression; acting as ceRNA for miRNAs and thereby suppressing miRNA-mediated inhibition of angiogenesis, and activating related signal pathways in ECs (Fig. 2).

4. Exosomal circRNAs in angiogenesis

CircRNAs are prevalent in eukaryotic cells and have a closed-loop structure, making them more stable than other ncRNAs [102]. As a novel member of the ncRNAs, circRNAs have multiple functions in gene regulation [103]. New research shows that circRNAs can act as miRNA sponges and inhibit miRNA function [104], regulate transcription of cells (cell nucleus) [105], take part in splicing of the target gene, and interact with RBPs [106]. Moreover, recent studies have shown the stability and enrichment in exosomes of circRNAs [107]. Over one thousand circRNAs can be found in human serum exosomes [108], and they play a role in many human systems, such as the nervous [109,110], immune [111], and hematopoietic systems [112], and also participate in pathological angiogenesis [113].

In recent years, the roles of exosomal circRNAs in tumor angiogenesis and cardiovascular disease have been studied extensively [78,114,115]. Exosomal circRNAs could regulate angiogenesis by interacting with RBPs; for example, Holdt et al. found that circRNA-ANRIL could induce nucleolar stress and regulate ribosomal RNA maturation by combining with PES1 protein (a protein-coding gene) [76]. After combining with PES1 protein, circRNA-ANRIL modulated pre-rRNA processing and ribosome synthesis in macrophages and vascular smooth muscle cells, thereby serving as a protective factor in atherosclerosis. Moreover, Huang et al. demonstrated that HCC cell-derived exosomal circRNA-100,338 might regulate tumor angiogenesis through interacting with the RBP NOVA2 [77]. Their results showed that transferring the exosomal circRNA-100,338 to recipient receptor cells could increase angiogenesis and activate the mTOR pathway. Similar to lncRNA, exosomal circRNA could also act as miRNA sponge to participate in the regulation of angiogenesis [116]. Exosomal circ-SHKBP1 produced by gastric cancer cells could sponge miRNA-582-3p and upregulate the expression of HUR (downstream target gene of miRNA-582-3p). HUR activated the translation of VEGF and increased tumor angiogenesis [78]. Meanwhile, circRNA-PWWP2A could be delivered from pericytes to ECs through exosomes, and inhibited miRNA-579 by acting as an endogenous miRNA-579 sponge. CircRNA-PWWP2A was proved to regulate vascularization via the circRNA-PWWP2A-miRNA-579-angiopoietin 1(Ang-1) axis [79].

Second, the n6-methyladenosinde (m^6A) modification mechanism also participates in the regulation of circRNA and angiogenesis [117]. M^6A is the most common modification of RNAs in eukaryotic cells, and regulates RNA transcription, processing, splicing, degradation and translation [118–120]. The functions of the m^6A modification are mediated by three kinds of methylase called "writers," "erasers," and "readers" [121]. "Writers" are involved in the formation of the methyltransferase complex [122], "erasers" act as demethylases, and "readers" serve as binding proteins [123]. For example, METTL14 and ALKBH5 ("erasers") inhibited YTHDF3 ("readers") by controlling each other's expression and then regulated the m^6A modification of transforming growth factor–β(TGF-β), which played an important role in the angiogenesis of diabetic retinopathy [124]. A recent study showed that m^6A-modified circRNAs could also be endoribonuclease-cleaved via a YTHDF2-HRSP12-RNase P/MRP axis [125]. However, these studies did not address

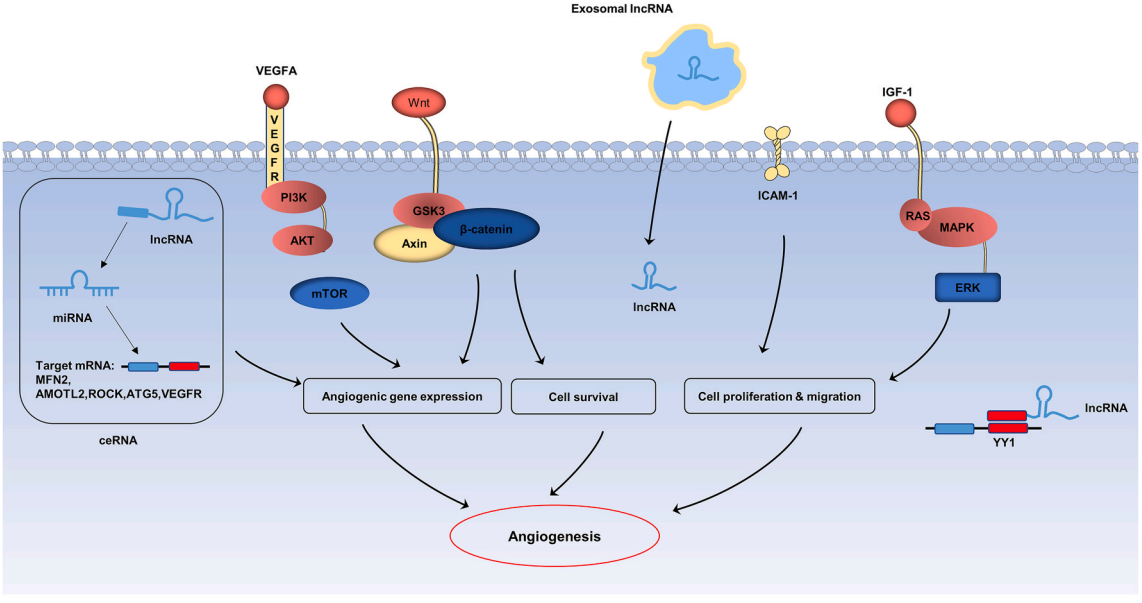

Fig. 2. The mechanisms of exosomal lncRNAs in angiogenesis. Exosomal lncRNAs participate in the regulation of angiogenesis through a variety of mechanisms, including the regulation of ECs related signaling pathways (mTOR, Wnt/β-catenin and ERK pathway), the increase of target gene expression by ceRNA mechanism, and the regulation of ECs proliferation, differentiation and migration (ICAM-1, YY-1 and HDAC8).

exosome pathways. Another study revealed the role of m6A modification in exosomal circRNA. In this study, m^6A methylase METTL3 and ALKBH5 could regulate the molecular sponge effect of circ-0008542 in osteoblast exosomes [126]. Notably, m^6A modification is also present in other types of ncRNAs [127], but how m^6A modification plays its biological role by regulating ncRNAs through exosomes in angiogenesis remains to be further studied.

In conclusion, circRNA could assemble in exosomes and be delivered to recipient cells. After exosomes were ingested by the recipient cells, circRNA played a regulatory role in the nucleus or cytoplasm as follows: acting as a miRNA sponge, interacting with RNA-binding proteins, and depending on pathways of RNA modifications such as m^6A methylation. We summarized the mechanisms of exosomal circRNA in angiogenesis (Table 1 and Fig. 3).

5. Other exosomal ncRNAs in angiogenesis

Other types of exosomal ncRNAs have been shown to play essential roles in angiogenesis, including transfer RNA-derived small RNA (tsRNA), snRNA, and siRNA.

TsRNAs are small ncRNAs with 18–40 nt in length, produced by precursor or mature tRNAs [128]. Many studies have revealed that the expression of tsRNAs is controlled under certain physiological conditions and plays a vital role in many biological processes and diseases such as genetic, metabolic, and cancer [129,130]. Many types of ncRNAs exist stably in exosomes and play diverse roles in physiological and pathological processes [6]. A study by Dou et al. showed that MSC-secreted exosomal tsRNA-21109 might suppress M1 macrophage polarization by reducing the expression of Ras, mitogen-activated protein kinase (MAPK), and transforming growth factor-β (TGF-β) signal pathways and thereby stimulate the inflammatory response in systemic lupus erythematosus [131]. TsRNAs are also found involved in angiogenesis. Ischemia is defined as the interruption of tissue blood supply [132], and angiogenesis could also be found in ischemic tissue. According to Li et al., two tsRNA fragments generated from tRNA-Val and tRNA-Gly were highly expressed in the brain ischemia and hindlimb ischemia mouse model [133]. Their study proved that tsRNAs upregulated in the model possessed the capacity to inhibit angiogenesis and significantly inhibit the proliferation, migration, and tube formation of ECs. Moreover, a recent study showed that tsRNA contributed to angiogenesis in moyamoya disease (MMD) [134], a cerebrovascular disease characterized by chronic, progressive stenosis or occlusion [135]. Researchers found four differentially expressed (DE)-tsRNAs: tsRNA-Glu-TTC-010, tsRNA-Glu-CTC-003, tsRNA-Val-AAC-017, and tsRNA-Arg-CCT-008. Further research revealed that DE-tsRNAs activated the HIF-1 pathway and then played a compensatory role in angiogenesis of MMD [134].

SnRNA as a type of ncRNA is mainly involved in the processing of mRNA precursors [136]. Exosomal snRNA could activate Toll-like receptor 3 (TLR3) in lung epithelial cells, change tumor microenvironment, and promote tumor metastasis [137]. SiRNAs are double-strand RNAs 19–24 nt in length, which can serve as an RNA-induced silencing complex (RISC) and play a part in gene silencing in the post-transcriptional stage [138]. Recently, the feasibility of exosomes as carriers to inhibit tumor angiogenesis was verified by Zhang, et al., who proved that exosomes with hepatocyte growth factor (HGF) siRNA significantly suppressed tumor angiogenesis of gastric cancer *in vitro* and *in vivo* via the HGF/cMET axis [139]. Furthermore, another study demonstrated that bone mesenchymal stem

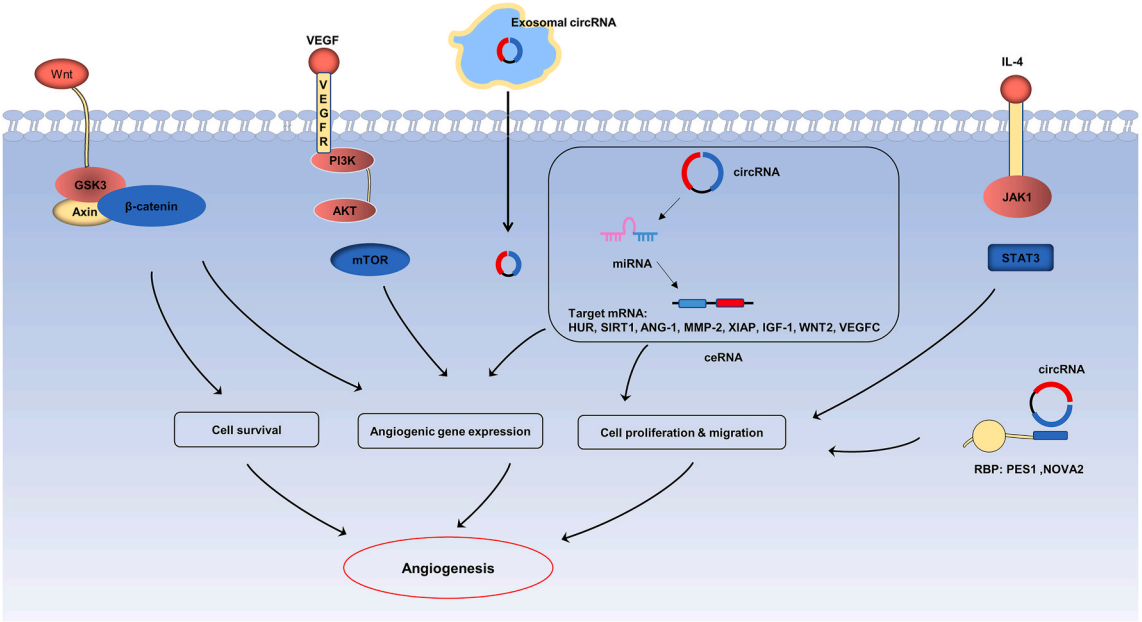

Fig. 3. The mechanisms of exosomal circRNAs in angiogenesis. Exosomal circRNAs mainly participate in angiogenesis through the mechanism of ceRNA, but also modulate related signaling pathways (mTOR, Wnt/β-catenin and JAK/STAT pathway) and interact with RNA-binding proteins (PES1, NOVA2) to regulate angiogenesis and tube formation.

cells (BMSCs)-derived exosomal siRNA enhanced the proliferative ability of ECs, stimulated angiogenesis, and inhibited osteonecrosis of the femoral head by suppressing related gene expression including FGF2, WNT-11, and S100A9 [140].

In summary, current evidence indicates that diverse exosomal ncRNAs play an indispensable role in the progression of angiogenesis. The modes of action of exosomal ncRNAs involved in the regulation of angiogenesis have been described (Fig. 4). Notably, other ncRNAs such as small nucleolar RNA (snoRNA) and PIWI-interacting RNA (piRNA) also play critical roles in physiological or pathological processes through exosomes [141,142], while their roles and mechanisms in angiogenesis need to be further studied.

6. Exosomal ncRNAs in tumor angiogenesis

Tumor angiogenesis is one of the common characteristics of cancer, essential for the growth and development of tumor cells, and plays a vital role in tumor invasion and metastasis [143]. The formation of tumor blood vessels is dependent on the regulation of the tumor microenvironment [144]. High expression of angiogenic factors, inflammatory cytokines, and HIF-1α in the tumor microenvironment induces tumor angiogenesis [145]. In addition, cancer-derived exosomes are involved in tumor angiogenesis, and some of the ncRNAs in cancer-derived exosomes are closely related to them [146]. Further elucidation of the mechanism of exosomes in tumor proliferation, invasion and angiogenesis is helpful for future clinical application such as cancer diagnosis and novel therapeutic target [147].

Lung cancer cells could secret exosomal miRNA-23a to promote angiogenesis by inhibiting the tight junction protein ZO-1 [51]. It has been reported that breast cancer (BC) cells-derived exosomal miRNA-210 can stimulate angiogenesis [148]. In particular, researchers have revealed that miRNA-210 could be delivered from hepatocellular carcinoma (HCC) cells to ECs via exosomes and thus promote angiogenesis by targeting SMAD4 and STAT6 pathways [49]. Meanwhile, exosomal miRNA-155 secreted by HCC cells in hypoxia could accelerate tube formation in ECs [149]. In addition to the exosomal miRNAs that can promote tumor angiogenesis mentioned above, there are also exosomal miRNAs could suppress tumor angiogenesis. A study by Lee et al. showed that miRNA-16 and miRNA-100 in exosomes derived from mesenchymal stem cells (MSCs) suppress angiogenesis by reducing the production of VEGF in BC cells [53]. Valencia et al. reported that exosomal miRNA-192 could also suppress the expression of angiogenic factors such as IL-8, ICAM, and CXCL1, consequently impairing tumor-induced angiogenesis in lung cancer [52].

In addition, lncRNA-H19 is highly expressed in exosomes released by CD90+liver cancer cells and is proved to be involved in regulating tumor angiogenesis [69]. Exosomal lncRNA-TUC339 from HCC cells could regulate M2 macrophage polarization and participate in the migration of liver cancer cells [72]. Moreover, Huang et al. found that highly metastatic HCC cells-secreted exosomal circRNA-100338 was enriched in HUVECs [77].

Exosomal miRNA-25-3p is related to tumorigenesis and angiogenesis in colorectal cancer [150,151]. Similarly, exosomal ncRNAs participate in gastric carcinoma (GC) angiogenesis. Investigators have shown that GC cells-derived exosomal miRNA-let-7 promotes tumor angiogenesis by regulating HMGA2 and RAS [152]; meanwhile, miRNA-130a has been highly expressed in GC cells-secreted

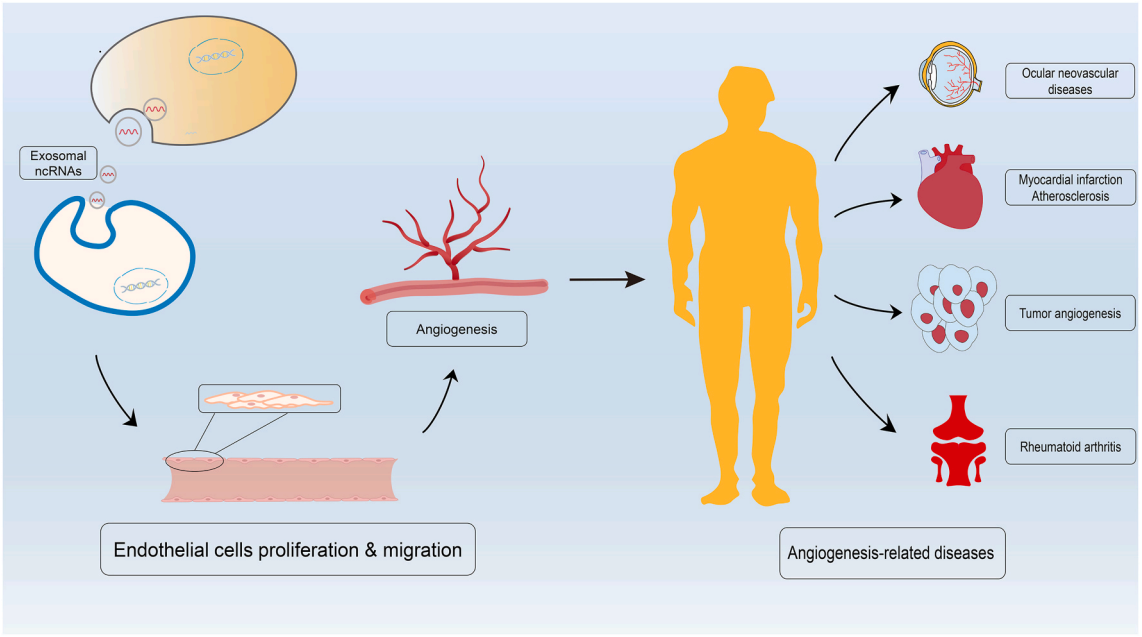

Fig. 4. The process of exosomal ncRNAs involved in the regulation of angiogenesis and angiogenesis-related diseases. Exosomal ncRNAs derived from donor cells can be absorbed by target cells and activate angiogenesis related signal pathways. After that, the activated endothelial cells will proliferate and migrate to form new blood vessels which also called angiogenesis. Abnormal angiogenesis will cause a series of pathological changes and ultimately induce angiogenesis-related diseases like ocular neovascular diseases, atherosclerosis, rheumatoid arthritis and cancer.

exosomes and could be delivered to ECs where they induced angiogenesis [153]. In addition, exosomal circRNA-SHKBP1 from GC cells could act as miRNA sponge and enhance angiogenesis via miRNA-582-3p/HUR/VEGF axis [78].

7. Exosomal ncRNAs in ocular neovascular diseases

Ocular neovascularization diseases are divided into two main types, retinal and choroidal neovascularization [154]. Various diseases that cause vision loss are associated with ocular neovascularization [155,156].

7.1. Diabetic retinopathy

Diabetic retinopathy (DR) is one of the complications of diabetes. Multiple mechanisms are involved in the development of DR, including dysfunction of multiple cell-signaling pathways, inflammation and oxidative stress resulting from hyperglycemia, and dyslipidemia [156]. DR is divided into two types: non-proliferative DR (NPDR) and proliferative DR (PDR). The exosomes in plasma of patients with diabetic retinopathy were found to upregulate the expression of angiogenic factors, revealing that exosomes may be involved in the delivery of angiogenic factors and participate in DR [157]. In addition, many *in vitro* and *in vivo* experiments have shown that exosomal ncRNAs are closely related to DR [158,62]. Maisto et al. found that VEGF was increased, and the level of anti-angiogenic miRNAs was decreased in photoreceptor cells exosomes of a high glucose model used to simulate DR [159]. Moreover, Cao et al. indicated that MSC-derived exosomal lncRNA-SNHG7 was involved in DR retinal angiogenesis [158]. MiRNA-15a was found to be produced by pancreatic cells and delivered to the retina through exosomes in the blood circulation, where they induced oxidative stress and promoted type 2 diabetes (T2D)-induced DR [160]. Researchers also reported that circRNA-cPWWP2A could be transferred by exosomes from pericytes to ECs in the retina and mediate the function of diabetic retinal microvasculogenesis [79].

7.2. Retinopathy of prematurity

Retinopathy of prematurity (ROP) is one of the leading causes of vision loss in children [161]. Despite some differences in mechanisms, the oxygen-induced retinopathy (OIR) mouse model is widely used in the study of retinal neovascular diseases, especially ROP [162]. Scott and Fruttiger found that the reduction of circRNA-ZNF609 suppressed pathologic angiogenesis in the OIR mouse model [83]. Likewise, the role of microglia in the pathophysiology of retinal diseases has been studied extensively [163]. Xu et al. used intravitreal injections with microglial cells-derived exosomes in the OIR mouse model and found smaller avascular areas and fewer neovascular tufts in treated eyes. Further research revealed that microglial cells-derived exosomal miRNA-24-3p downregulated the levels of VEGF and TGF- β in photoreceptors [164]. Novel clinical research proved that intravitreal injections of MSCs-secreted exosomes could effectively protect hyperoxia-induced retinopathy [165].

7.3. Age-related macular degeneration

Age-related macular degeneration (AMD) is divided into dry AMD and wet AMD according to the clinical features and pathological changes [166]. Wet AMD is characterized by choroidal neovascularization [167]. In the past decades, many studies implicated aging, circulation disorders, photodamage and oxidative damage, inflammatory responses, and related genetic changes in the pathogenesis of AMD [168]. Oxidative stress was proved to be one of the most important factors in AMD [169]. Shah et al. showed that oxidative-injured retinal pigment epithelium (RPE) cells could secrete exosomes with oxidative stress signals to normal RPE cells and contributed to angiogenesis [170]; additionally, RPE and retinal astroglial cells (RACs) are involved in AMD [171]. Researchers demonstrated that RACs-derived exosomes could reduce angiogenesis via anti-angiogenic components, including proteins, lipids, mRNA, and miRNA [172], and that RPE cells and RACs could serve as feasible therapeutic targets for AMD. Furthermore, a bioinformatics study revealed that AMD-derived exosomes acted as miRNA cargo and played a key role in the pathological angiogenesis of AMD, such as exosomal miRNA-126 and miRNA-410 [173], which might be a novel diagnostic and therapeutic approach for AMD.

8. Exosomal ncRNAs in other angiogenesis-related diseases

In addition to the diseases mentioned above, there are many other angiogenesis-related diseases including cardiovascular diseases, rheumatoid arthritis, and diabetic microangiopathy.

Hypoxic-treated cardiomyocytes were found to release exosomes containing circRNA-HIPK3 to cardiac microvascular ECs [174]. This finding indicated that exosomal circRNA could target ECs. Interestingly, a recent study also supported this conclusion. Wang et al. found that vascular ECs in a high glucose environment could release exosomal circRNA-0077930 to regulate senescence in vascular smooth muscle cells [175].

Angiogenesis also participates in the inflammatory process of autoimmune diseases such as rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, systemic sclerosis, and atherosclerosis [176]. As proof, exosomes from IL-1β-treated fibroblast-like synoviocytes have been found to lead osteoarthritic changes in chondrocytes [177]. Exosomes derived from rheumatoid models have also been shown to induce the secretion of COX-2 and promote angiogenesis [178].

Atherosclerosis is generally recognized as a chronic, lipid-induced inflammatory disease associated with endothelial cell damage [179]. Results from a study by Chen et al. suggest that human leukemia monocytic cell line (THP-1)-derived exosomes could promote the apoptosis of vascular ECs by transporting lncRNA-GAS5 [180]. In another study, Cheng et al. found high expression of miRNA-1

and miRNA-208 in exosomes from the urine of patients with acute myocardial infarction [181]. Moreover, higher levels of exosomal miRNAs were found in a rat model of myocardial infarction [182]. Furthermore, a cardio-protective miRNA-214 has been shown to be upregulated in the heart after ischemia and secreted by exosomes from human ECs [35]. The ncRNAs associated with angiogenesis-related diseases were summarized in Table 2. The ncRNAs mentioned in the review and the corresponding Gene Symbol and ENSEMBL ID are summarized in Supplementary Table S1.

9. Potential clinical application of exosomal ncRNAs

The stable expression and enrichment of ncRNAs in exosomes has been confirmed through a large number of studies. Exosomal ncRNAs are widely studied in disease diagnosis and prognosis, drug resistance research, and new therapeutic targets [196,197]. Many studies have proved that exosomal miRNAs are abnormally expressed in certain types of cancer: for example, miRNA-17 and miRNA-21 were upregulated in colon, lung, stomach, prostate, and pancreatic cancer, and miRNA-155 was overexpressed in breast, lung, and colon tumors [198].

The blood levels of lncRNA-POU3F3 were identified as a diagnostic marker in esophageal squamous cell carcinoma [199], while lncRNA-MALAT-1 was overexpressed in prostate cancer [200]. Meanwhile, the overexpression of circRNA-IARS were identified in pancreatic cancer tissues and blood [201]. Due to the significant differential expression between patients and healthy groups, there is no doubt that exosomal ncRNA could be a promising biomarker in cancer. Besides, miRNA-122-5p from serum exosomes were found differentially expressed between multiple sclerosis patients and healthy individuals [202]. The exosomes with miRNA-223, miRNA-339 and miRNA-21 from platelets could suppress the PDGFR-β in SMCs and thereby proved to be biomarkers of atherosclerotic thrombosis [203]. Similarly, exosomal ncRNAs could also be biomarkers for early diagnosis of ischemic diseases [204].

Exosomal miRNA-21 is a proven biomarker of treatment outcome in non-small cell lung cancer (NSCLC); inhibiting miRNA-21 increases the sensitivity to chemotherapy of NSCLC by suppressing PI3K/AKT pathway [205,206]. Unlike miRNA, the specificity of

Table 2
Expression of exosomal ncRNAs in angiogenesis-related diseases.

Angiogenesis-related diseases	Exosomal ncRNAs	Expression	Refs.
Lung cancer	miRNA-9	↑	[50]
	miRNA-21	↑	[42]
	miRNA-23a	↑	[51]
	miRNA-126	↑	[183]
	miRNA-210	↑	[41]
Breast cancer	miRNA-192	↑	[52]
	miRNA-210	↑	[148]
	miRNA-16	↑	[53]
	miRNA-100	↑	[53]
Hepatocellular carcinoma	lncRNA-TUC339	↑	[72]
	miRNA-21	↑	[184]
	miRNA-210	↑	[49]
	circRNA-100338	↑	[77]
	miRNA-155	↑	[149]
	miRNA-378b	↑	[57]
	lncRNA-SNHG16	↑	[185]
	miRNA-130a	↑	[186]
Gastric cancer and colorectal cancer	circRNA-0044366	↑	[187]
	miRNA-135b	↑	[55]
	circRNA-SHKBP1	↑	[78]
Pancreatic cancer	miRNA-27a	↑	[188]
	miRNA-501-3p	↑	[59]
	lncRNA-CCAT1	↑	[189]
	lncRNA-UCA1	↑	[75]
Diabetic retinopathy	miRNA-17-3p	↓	[62]
	miRNA-486-3p	↓	[62]
	miRNA-202-5p	↓	[64]
	miRNA-377-3p	↓	[190]
	lncRNA SNHG7	↓	[191]
	circRNA-cPWWP2A	↑	[79]
Retinopathy of prematurity	miRNA-24-3p	↓	[164]
Age-related macular degeneration	miRNA-486-5p	↑	[192]
	miRNA-626	↑	[192]
	miRNA-885-5p	↓	[192]
Myocardial infarction	miRNA-214	↑	[182]
Atherosclerosis	miRNA-21-3p	↑	[61]
	miRNA-155	↑	[193]
	lncRNA GAS5	↑	[180]
Rheumatoid arthritis	miRNA-150-5p	↓	[194]
	circRNA-EDIL3	↓	[195]
Diabetic microangiopathy	circRNA-PWWP2A	↑	[79]

lncRNA in tissue expression and the stability of circRNA in exosomes make them better biomarkers for molecular diagnosis and disease prognosis [107]. For example, exosomal lncRNA-SNHG15 is an indicator of poor prognosis in HCC [207].

Given the abilities of miRNAs to target multiple genes, targeting miRNA could be a promising therapeutic approach. There are two miRNA-based therapeutic modalities: miRNA mimics and anti -miRNA [208]. MiRNA mimics are small, double-stranded RNA molecules that can mimic miRNAs [208]. A previous study showed that miRNA-210 mimic enhanced angiogenesis in myocardial infarction mouse model [209]. Anti-miRNAs are antisense oligonucleotides with the complementary reverse sequences of miRNAs. They play a role in inhibiting miRNAs by interacting and combining with them. Costa et al. used anti-miRNA gene therapy approach to inhibit the proliferation and tumor size of glioblastoma in mice [210]. Although further research is needed to evaluate its clinical efficacy, this result suggested that miRNA targeted therapy is a promising new treatment. Moreover, exosomes, as intercellular mediators, have potential applications as drug carriers [211]. Dong et al. found that in the OIR model, using an exosome loading system with VEGF inhibitors to inhibit angiogenesis was superior to using VEGF inhibitors alone [212]. Actually, exosomes have been used in several clinical therapeutic tests such as NSCLC and colorectal cancer since 2000s [213,214]. It is feasible to target exosomes as vectors and exosomal miRNAs as new therapeutic strategies. In 2020, Peng et al. found the correlation of plasma exosomal miRNAs and efficacy of immunotherapy between NSCLC patient and healthy individuals, and predicted the possible miRNA therapeutic targets [215]. A clinical trial demonstrated the potential function of miRNAs derived from adipose extracellular vesicles in type 2 diabetes with pioglitazone treatment [216]. Besides, there was study showed that MSC-derived exosomes played an angiogenic effect under concentration of 100 μg/mL, while other result showed that lower concentration of MSC exosomes (10 μg/mL) maybe more effective than high concentration in tube formation [94,217]. The different results may be attributed to the differences in exosome size, purity, and surface molecules during the isolation of the MSC-derived exosomes [218,219]. The targets and mechanisms, as well as clinical therapeutic effects of exosomal ncRNAs should be further studied on this basis. Moreover, tumor-released exosomal ncRNAs were found to interfere with the sensitivity to radiotherapy and efficiency of treatment [220]. Consequently, exosomal ncRNAs are of great significance in the study of drug resistance.

10. Prospect and challenges of exosome research

Currently, the study of exosomes has been developed extensively; however, challenges still exist. EVs are divided into exosomes and microvesicles. Microvesicles are generated by budding from the plasma membrane, while exosomes are produced via the multivesicular endosome pathway. Microvesicles and exosomes have similar size, density, and biological composition; therefore, current methods cannot effectively distinguish them [221]. In addition, the relative ratio of exosomes and microvesicles released by cells is highly variable, depending on the cell type, environmental conditions, and other factors (such as infection or artificially induced).

Although currently no technology can completely isolate and purify exosomes [222], there are still some feasible isolation and purification techniques based on exosome characteristics [223]: 1) density-gradient separation enhances the purity of exosomes by further separating particles by density and effectively removing non-exosomes; 2) size-exclusion chromatography separates exosomes via a stationary phase composed of a porous polymer and is mainly used to separate exosomes from plasma; 3) immunological isolation based on immune affinity interactions between proteins present on the membrane of exosomes and their antibodies. Till now, the most common method of exosome isolation is ultracentrifugation, which is complex, tedious and time-consuming [211]. However, Heller et al. showed a novel alternating current electrokinetic microarray chip device which makes the isolation of exosomes convenient and fast [224]. It also makes exosome analysis suitable for point-of-care diagnostic applications. Such study revealed the application prospect of exosome research.

Notably, study indicated that exosomes secreted from red blood cells are more likely to be absorbed by the liver and bone while melanoma-derived exosomes are mainly uptake by the lung and spleen [225]. It suggested that exosomes derived from different cell may have different targets. Indeed, the mechanism of exosomes and surface receptors of target cells deserves in-depth study. Since the prospects for the treatment of angiogenesis diseases based on exosomal ncRNAs have been mentioned above, we should also set sights on the best way of exosome delivery and exosome concentration of exosome-based therapies [93].

Despite their great potential, our understanding of exosomal ncRNAs is still in the preliminary stages. The current understanding of the physiology, diversity, internalization, and molecular transport of exosomes is too limited to accurately draw conclusions about the mechanisms by which exosomes interact with and modify recipient cells [226]. Moreover, the interaction mechanisms between donor cells, recipient cells, and exosomes are unclear, such as how recipient cells recognize and ingest the donor cells-derived exosomes and whether the transport of exosome content is random or specific. Therefore, it is necessary to conduct comprehensive research, including biogenesis formation and sorting, to make progress in the field of exosomal ncRNAs [227–229].

11. Conclusion

Increasing attention has been paid to the physiological and pathological roles of exosomal ncRNAs. As a frontier research area, exosomal ncRNAs revealed increasing research value. This review described the roles and mechanisms of several main exosomal ncRNAs in angiogenesis. Exosomes as EVs exist widely in various body fluids and could mediate cell to cell communication. NcRNAs, as one of the components of exosomes, can be expressed stably in exosomes and can play an accurate role in regulation. In addition to the roles and mechanisms of exosomal ncRNAs in angiogenesis, we should also attach great importance to their potential clinical applications, such as in disease diagnosis based on their stable expressions in exosomes. Exosomal ncRNAs also play an important role in pharmacology, for instance, exosomes can serve as a new drug delivery vector, exosomal non-coding RNAs can act as a novel therapeutic target and drug resistance research. Therefore, further studies should emphasize the use of ncRNAs as clinical therapeutic

targets in tumor angiogenesis and ocular neovascular disease. On the other hand, the study of exosomal ncRNAs as disease biomarkers is very valuable and important, and may greatly improve the diagnosis of some angiogenesis-related diseases. In summary, the study of exosomal ncRNAs in the future is promising.

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Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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