Advances in microRNA regulation of deep vein thrombosis through venous vascular endothelial cells (Review)

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Abstract. Deep vein thrombosis (DVT) is a prevalent clinical venous thrombotic condition that often manifests independently or in conjunction with other ailments. Thrombi have the propensity to dislodge into the circulatory system, giving rise to complications such as pulmonary embolism, thereby posing a significant risk to the patient. Virchow proposed that blood stagnation, alterations in the vessel wall and hypercoagulation are primary factors contributing to the development of venous thrombosis. Vascular endothelial cells (VECs) constitute the initial barrier to the vascular wall and are a focal point of ongoing research. These cells exert diverse stimulatory effects on the bloodstream and secrete various regulatory factors that uphold the dynamic equilibrium between the coagulation and anticoagulation processes. MicroRNAs (miRNAs) represent a class of non-coding RNAs present in eukaryotes, characterized by significant genetic and evolutionary conservation and displaying high spatiotemporal expression specificity. Typically ranging from 20 to 25 bases in length, miRNAs can influence downstream gene transcription through RNA interference or by binding to specific mRNA sites. Consequently, advancements in understanding the molecular mechanisms of miRNAs, including their functionalities, involve modulation of vascular-associated processes such as cell proliferation, differentiation, secretion of inflammatory factors, migration, apoptosis and vascular remodeling regeneration. miRNAs play a substantial role in DVT formation via venous VECs. In the present review, the distinct functions of various miRNAs in endothelial cells are outlined and recent progress in comprehending their role in the pathogenesis and clinical application of DVT is elucidated.

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Contents

1. Introduction

MicroRNAs (miRNAs) are a class of non-coding RNAs characterized by very short sequences, typically containing approximately 20-25 bases (1-3). Traditionally, miRNAs exert their biological functions by binding to specific sites on mRNA molecules, thereby influencing the transcription of downstream genes. This binding occurs through essentially complementary pairing with gene sequences on the target mRNAs, organizing the translation process of the bound mRNA and thus regulating the expression levels of corresponding proteins. In addition to the classical mechanism of gene expression downregulation, miRNAs exhibit other non-classical regulatory mechanisms that warrant further investigation (4-7). Research into miRNAs has seen a significant increase, revealing their involvement in the development of various systemic diseases such as cardiovascular (8), digestive (9) and respiratory (10) diseases. Moreover, they play a unique and biologically significant role in numerous biological processes.

Previous research suggests that the canonical pathways for miRNA production play critical roles in multiple biological processes. Genes containing miRNAs undergo transcription, translation and initial processing into pre-miRNAs within the nucleus. These pre-miRNAs then traverse the nuclear membrane via transmembrane proteins into the cytoplasm, where they undergo further processing and modifications to become mature miRNAs. Initially, genes harboring miRNAs are transcribed by RNA polymerase II into primary miRNAs (pri-miRNAs), characterized by one or more hairpin

structures with 5' caps and 3' polyadenylate (A) tails (11-13). Within the nucleus, a microprocessor complex, consisting of a DROSHA endonuclease molecule and two molecular chaperones, including DGCR8 with an RNase III structural domain, cleaves and modifies pri-miRNAs into 50-70 nucleotide pre-miRNAs (14). Subsequently, pre-miRNAs are transported across the nuclear membrane to the cytoplasm by the transmembrane protein exportin 5. In the cytoplasm, Dicer, containing two RNase III endonuclease structures, cleaves pre-miRNAs into mature miRNA duplexes ~22 nucleotides in length (15). Finally, with the assistance of molecular chaperones such as HSC70/HSP90 (16,17), duplex miRNAs form a silencing complex known as the RNA-induced silencing complex (RISC), which includes the Argonaute (AGO) protein possessing shearing functionality (18,19). This complex catalyzes the separation of duplex miRNAs into two single-stranded miRNAs by disrupting the hydrogen bonds of the base complementary sequences. The strand with a stronger binding affinity to the 5' end of the AGO protein within its inner pocket is designated as the guide strand (20,21), while the other strand, known as the passenger strand (22), undergoes degradation by cytoplasmic RNA enzymes. Once a stable RISC structure forms, miRNAs bind to specific sites on mRNA molecules, thereby silencing mRNA transcription and exerting biological effects. This process delineates the classical formation pathway of miRNAs.

It is generally accepted that miRNAs interact with target genes by inhibiting translation. However, some miRNAs interact with target genes with less complementarity, overlooking the fact that certain miRNAs can lead to target gene degradation (23). Numerous studies suggest that, contrary to the common misconception, miRNAs typically do not fully silence target gene mRNAs but rather decrease their expression (24,25). However, over time, miRNAs exhibit both temporal and tissue expression specificity, which explains why mere inhibition or promotion does not fully reflect the biological functions of miRNAs (26). A number of studies have reported that miRNAs have seven non-classical regulatory molecular mechanisms (27); however, this does not fully outline the non-classical regulatory functions of miRNAs. Despite the current limited understanding of the biological functions of miRNAs, further investigation into cellular function regulation by miRNAs is warranted (2,28,29).

Cardiovascular endothelial cells serve dual roles in blood coagulation, with both anticoagulant and procoagulant functions, thereby preserving the equilibrium necessary for proper blood flow (30). Initially, the intact endothelium acts as a physical barrier, segregating platelets, clotting factors and the highly procoagulant endothelial matrix from the bloodstream (31). Furthermore, endothelial cells contribute to anti-platelet aggregation mechanisms. They produce prostacyclin (32-34) and nitric oxide (NO) (35-37), which inhibit platelet aggregation, along with adenosine diphosphatase (38-40), which degrades ADP and prevents platelet agglutination. Additionally, the vascular endothelium synthesizes antithrombin and coagulation factors. It generates thrombomodulin, which binds to circulating thrombin, triggering the activation of the anticoagulant factor protein C. This synergistic action with protein S, also synthesized by the endothelium, leads to the inactivation of coagulation factors V and VIII (41-44). They synthesize membrane-associated heparin-like molecules that bind to antithrombin III and inactivate thrombin, as well as coagulation factors X and IX (45,46). Additionally, VECs promote fibrinolysis. They internalize tissue-type plasminogen activator, leading to the degradation of fibrin deposited on the endothelial cell surface into fibrin degradation products. The latter exhibits anticoagulant effects (47-49). Damage to the cardiovascular endothelium constitutes one of the three major pathological processes of thrombosis. Following endothelial cell injury, subendothelial collagen becomes exposed, activating platelets and coagulation factor VII, thereby initiating the endogenous coagulation pathway (50,51). Simultaneously, injured endothelial cells release tissue factor (TF), which activates coagulation factor VII and triggers the exogenous coagulation pathway (52,53). Consequently, VECs play a multidimensional role in thrombus formation and regulation, serving as key cells in maintaining the dynamic balance between the coagulation and anticoagulation systems. Recently, miRNAs have been recognized as common risk factors for deep vein thrombosis (DVT) (54). Therefore, in the present review, the diverse functions of different miRNAs in endothelial cells are summarized and recent advances in their pathogenesis and clinical application in DVT are discussed.

2. miRNAs in endothelial cells regulate DVT

miRNAs reverse DVT. Several studies on DVT have highlighted the role of miRNAs in directly regulating or indirectly influencing the function of venous VECs, thus impacting thrombosis (30,54). In recent years, researchers have employed genetic techniques to initially screen for aberrantly expressed miRNAs in the blood of patients with DVT. Subsequently, the target genes these miRNAs act upon, their effects on the function of VECs and their involvement in DVT formation have been investigated. These miRNAs play a crucial role in regulating the function of VECs, inhibiting apoptosis and ultimately preventing thrombus formation. For instance, a previous study revealed that miR-9-5p (55) reduces TRPM7 expression by activating the PI3K/Akt/autophagy pathway, thereby enhancing endothelial progenitor cell migration, invasion and angiogenesis. Conversely, the upregulation of histone deacetylase 3 can elevate miR-19b levels, which in turn mediates peroxisome proliferator-activated receptor γ to deactivate nuclear factor-κB (NF-κB), thus mitigating inflammation (56). Decreased levels of miR-125a-5p (57) have been shown to lead to increased expression of myeloid cell leukemia sequence 1, promoting VEC migration and angiogenesis, consequently inhibiting DVT. miRNAs with similar biological functions include miR-9 (55,58), miR-19b (56,59), miR-29c-3p (60), miR-125a-5p (57), miR-126 (61), miR-143-3p (62), miR-150 (63-65), miR-205 (66), miR-411 (67) and miR-3120 (68), which primarily regulate the autophagic pathway in PI3K/Akt cells, thus exerting influence on this pathway. Li and Ni (69) found that miR-26a regulates the NF-κB signaling pathway by binding to protein kinase C-δ mRNA, thereby inhibiting the expression levels of inflammatory factor mRNAs and reducing the risk of DVT. Sun *et al* (70) revealed that miR-103a-3p can inhibit the expression of inflammatory factors such as TF, plasminogen activator inhibitors, interleukin

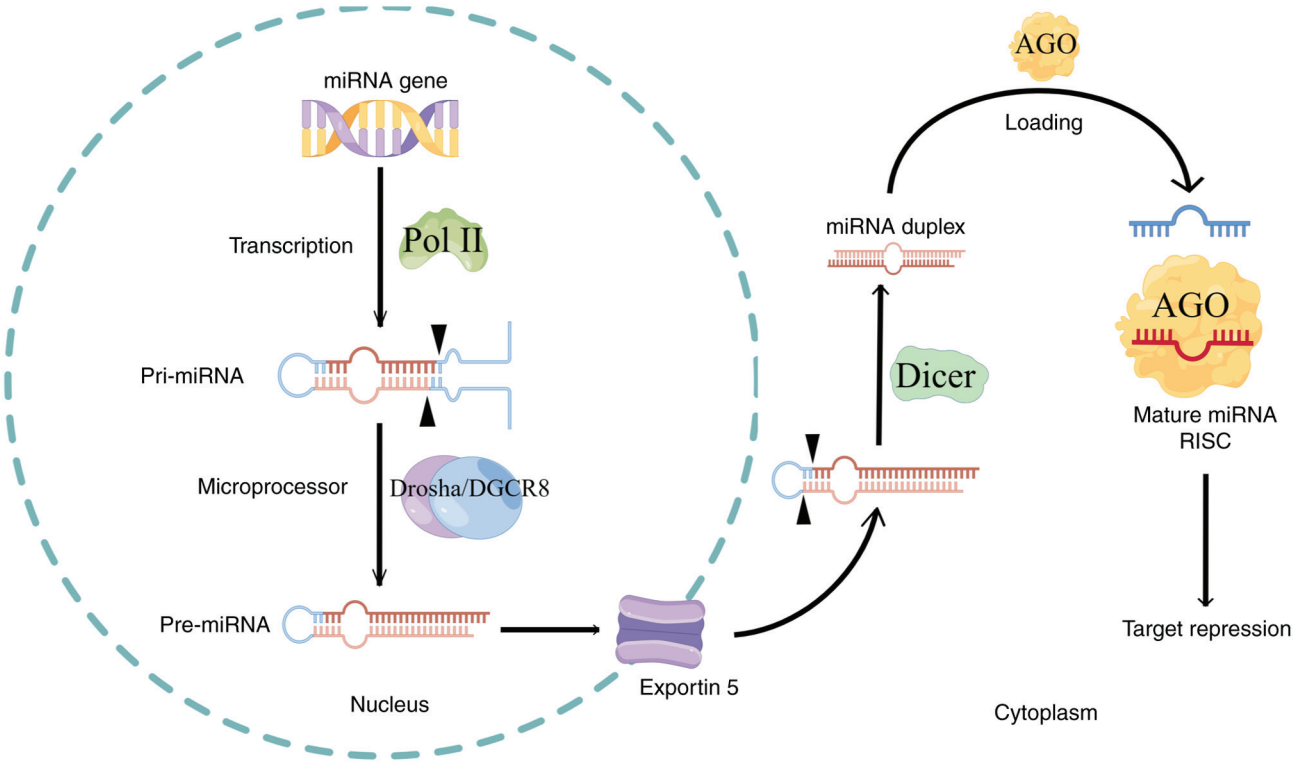

Figure 1. Schematic diagram of the formation and function of typical miRNAs. The miRNA-containing gene is transcribed by Pol II to produce a pri-miRNA, which is then sheared using a microprocessor to produce pre-miRNAs. Pre-miRNA crosses the nuclear membrane, enters the cytoplasm with the help of exportin 5 and is subsequently sheared by Dicer to form a double-stranded miRNA. Finally, miRNAs and AGO form RISC with a silencing effect and RISCs then act on the translation process of target genes to exert biological effects. This figure was created using FigDraw (www.figdraw.com). miRNA, microRNA; Pol II, polymerase II; pri-miRNA, primary miRNA; AGO, Argonaute; RISC, RNA-induced silencing complex.

(IL)-6 and IL-8, ultimately disrupting the inflammatory response. miR-5189-3p can inhibit apoptosis of VECs through the Notch signaling pathway (71); miR-195/582 (72) maintains the homeostasis of the intracellular environment by targeting and inhibiting the 3'-UTR of post-transcriptional nitric oxide synthase 3 in VECs, which in turn inhibits NO release. The miR-125a-3p/IL-1 receptor type 1 axis and miR-136-5p inhibit the secretion of inflammatory mediators in the blood of rat femoral veins, resulting in morphological changes in thrombus length and weight, and inhibition of thrombus formation (73,74). A number of miRNAs inhibit thrombosis by promoting the proliferation of VECs, increasing their viability and attenuating cellular damage. These miRNAs are summarized as miR-21 (75,76), miR-195 (77), miR-204-5p (78), miR-296-5p (79), miR-342-3p (80) and miR-361-5p (81). The aforementioned studies demonstrated that among various miRNAs, some could inhibit VEC injury, improve endothelial cell inflammation and autophagy and inhibit thrombus formation. Therefore, miRNA mimics or inhibitors may serve as potential anticoagulants (Fig. 1; Table I).

miRNAs promote DVT. Functionally, miRNAs can enhance the secretion of inflammatory factors, proliferation, migration and VEC angiogenesis. They accelerate injury and apoptosis of VECs and cause shape elongation, aggregation and cytoskeletal rearrangement of VECs, thereby promoting DVT formation. Previous studies have reported that miR-122 (82), miR-181a-5p (83), miR-195-5p (84), miR-206 (85), miR-338-5p (86), miR-383-5p (87), miR-448 (88), miR-483-3p (89), miR-525p-5p (90) and let-7e-5p (91) can act on their respective target proteins to promote DVT formation. These aforementioned studies suggest that miRNAs can promote the release of inflammatory factors and accelerate oxidative stress-mediated cellular injury, leading to the loss of barrier and material transport functions and exacerbation of ischemic and hypoxic damage to the vascular microenvironment. The various damaging effects aforementioned disrupt the blood system balance and the procoagulant state accelerates DVT formation.

Additionally, miRNAs have been found to promote thrombus formation in patients with cancer. Venous thromboembolism (VTE) poses a significant risk to individuals with cancer, leading to increased morbidity and mortality, with miRNAs playing a role in this process (92-94). For instance, miRNA-135a directly affects forkhead box M1 and metastasis suppressor 1, thereby promoting metastasis of hepatocellular carcinoma cells and facilitating portal vein thrombosis (95). Oto *et al* (96) identified seven miRNAs, including miR-423-5p, as biological markers capable of predicting venous thrombosis in pancreatic ductal adenocarcinoma and distal extrahepatic cholangiocarcinoma. Similarly, four miRNAs, including miR-3652, were found to be significantly downregulated in patients with colorectal cancer with VTE, suggesting their potential as novel predictive biomarkers (97). Morelli *et al* (98) observed a positive correlation between plasma levels of miR-145 and the absence of VTE, proposing miR-145 as a potential target for VTE prevention (98). These studies collectively demonstrate the

Table I. miRNAs and target proteins that reverse DVT formation.

miRNA	Change in expression	Target gene(s)	(Refs.)
miR-9	Upregulation	FGF5/TRPM3	(55,58)
miR-19b	Upregulation	PPARγ/NF-κB	(56)
miR-19b	Upregulation	TGFβ2	(59)
miR-29c-3p	Downregulation	MDM2	(60)
miR-125a-5p	Downregulation	MCL-1	(57)
miR-126	Upregulation	PIK3R2	(61)
miR-143-3p	Upregulation	ATG2B	(62)
miR-150	Downregulation	SRCIN1	(63)
miR-150	Upregulation	Akt/FOXO1	(64)
miR-150	Upregulation	c-Myb	(65)
miR-205	Upregulation	PTEN	(66)
miR-411	Downregulation	HIF-2α	(67)
miR-3120	Downregulation	MMP1	(68)
miR-26a	Downregulation	PRKCD	(69)
miR-103a-3p	Upregulation	CXCL12	(70)
miR-125a-3p	Downregulation	IL1R1	(73)
miR-136-5p	Upregulation	IL-6 and CRP	(74)
miR-5189-3p	Downregulation	JAG1	(71)
miR-195/582	-	NOS3	(72)
miR-21	Upregulation	FASLG	(75)
miR-21	Upregulation	IL6R	(76)
miR-195	Downregulation	GABARAPL1	(77)
miR-204-5p	Upregulation	SPRED1	(78)
miR-296-5p	Upregulation	S100A4	(79)
miR-342-3p	Upregulation	EDNRA	(80)
miR-361-5p	Downregulation	FGF1	(81)

miRNA, microRNA; DVT, deep vein thrombosis.

dysregulated expression of miRNAs in the plasma of patients with cancer, their involvement in cancer cell metastasis and their role in promoting cancer-associated thrombosis formation. Consequently, numerous investigations have centered on utilizing miRNAs as biological markers for cancer-associated thrombosis (99) (Table II).

miRNAs can promote thrombus dissolution. Fibrinolytic enzyme activation within the newly formed thrombus and the release of lysozyme from cell disintegration allow for gradual thrombus dissolution. The lysis of thrombi depends on numerous factors and previous studies suggest that miRNAs are among them. miR-21 (75), miR-92a-3p (100), miR-126 (61,101), miRNA-136-5p (102) and miR-361-5p (81) increase the expression level of fibrinolytic enzymes, inhibiting the production and activity of fibrinogen and thrombin while promoting thrombus lysis. Additionally, seven additional miRNAs have been reported to be aberrantly expressed in patients with DVT after anticoagulation therapy and stable thrombosis (103). These studies could provide new targets and insights for thrombolysis. While miRNAs have the function of promoting DVT, this effect did not result in complete thrombus lysis and miRNAs were not identified as the most direct or critical factors for thrombus dissolution. The aforementioned studies have only demonstrated reduced thrombus size in animal models and have not been applied in a clinical setting (Table III).

miRNAs play a crucial role as transcriptional regulators within the human blood system, with considerable research centered on human umbilical vein endothelial cells or endothelial progenitor cells. Consequently, the present review emphasized the role of miRNAs in the regulation of VEC injury, which in turn affects DVT formation by modulating cellular injury. Previous studies have highlighted the involvement of miRNAs in various facets of thrombosis. miRNAs not only impact the function of VECs but also influence platelet activation (104), coagulation factor secretion (105,106) and fibrinolytic enzyme function (107). However, of note, while miRNAs are not primary determinants in thrombus formation and dissolution, they play a significant regulatory role in these processes. These investigations reveal that individual miRNAs can modulate different proteins in VECs and conversely, the same proteins may be subject to regulation by multiple miRNAs. This complexity suggests that the mechanisms through which miRNAs regulate thrombosis are highly intricate.

Table II. miRNA and target proteins that promote DVT formation.

miRNA	Change in expression	Target gene(s)	(Refs.)
miRNA-122	Upregulation	p53	(82)
miR-181a-5p	Downregulation	Pcyox1l	(83)
miR-195-5p	Upregulation	Bcl-2	(84)
miR-206	Upregulation	GJA1	(85)
miR-338-5p	Downregulation	IL-6	(86)
miR-383-5p	Downregulation	BCL2L11	(87)
miR-448	Downregulation	SIRT1	(88)
miR-483-3p	Downregulation	SRF	(89)
miR-525p-5p	Downregulation	Bax	(90)
let-7e-5p	Downregulation	FASLG	(91)
miRNA-135a	Upregulation	FOXM1	(93)

miRNA, microRNA; DVT, deep vein thrombosis.

Table III. miRNAs and target proteins that promote thrombus dissolution.

miRNA	Change in expression	Target gene(s)	(Refs.)
miR-21	Upregulation	FASLG	(75)
miR-92a-3p	Downregulation	Hmgcr	(100)
miR-126	Upregulation	PIK3R2	(61,101)
miR-136-5p	Upregulation	TXNIP	(102)
miR-361-5p	Downregulation	FGF1	(81)

miRNA, microRNA.

3. Clinical application of miRNAs in DVT

Extraction and detection techniques for miRNAs in the clinic. With the increasing focus on research regarding DVT, a growing number of researchers have turned their attention to utilizing miRNAs as biomarkers for DVT (108). Currently, miRNAs are primarily extracted and detected from plasma (109). In patients with DVT, various factors influence changes in miRNA expression in plasma (110), including: i) Active release from VECs, ii) platelet and red blood cell lysis, iii) cellular exosome secretion and iv) the influence of other unknown factors. miRNAs that enter the circulatory system are primarily in the form of nucleic acid-protein complexes (111). Conversely, miRNAs present as monomers are small in molecular weight, convey limited genetic information and are highly susceptible to degradation. Therefore, the majority of miRNAs detected in the circulatory system are in the form of nucleic acid-protein complexes rather than miRNA monomers (110). Detecting circulating miRNAs relies on two main methods: i) Microarrays/chips and ii) reverse transcription-quantitative PCR (RT-qPCR) (112). While microarrays excel at screening hundreds of miRNAs per sample and offer quantitative analysis, their complexity, high cost and limitation to small sample sizes hinder their clinical use, relegating them mainly to research purposes (113). RT-qPCR stands out due to its affordability, ease of use and ability to perform both relative and absolute quantification, rendering it the preferred choice for clinical applications (114). Therefore, the current clinical approach for miRNA detection involves initially using miRNA microarrays to screen out miRNAs with aberrant expression profiles, followed by validation through RT-qPCR to identify the target miRNAs (112).

miRNAs as markers for diagnosing DVT. As miRNAs are highly conserved genetically and stable within the circulatory system, investigations have been initiated into the utilization of aberrantly expressed miRNAs in plasma of patients, as markers for early DVT diagnosis (108). miRNAs present in the circulatory system offer diagnostic advantages over traditional biomarkers for several reasons: i) Circulating miRNAs demonstrate greater stability and reproducibility; ii) they impose less damage to samples, are more convenient to detect and are easier to analyze and iii) alterations in circulating miRNA expression occur earlier, facilitating early detection and diagnosis (115). The high early diagnostic value of miR-582, miR-195, miR-532 (116) and miR-488 (88) in serum for the development of DVT has been well-documented. Similarly, upregulation of miR-424-5p and miR-125a-5p expression levels, alongside downregulation of miR-136-5p and miR-223-3p expression levels, has been observed in patients with DVT compared with healthy participants (108,117). These alterations are associated with a hypercoagulable state of the blood, indicating potential diagnostic value for these miRNAs. By contrast, the diagnostic potential of miRNAs has been investigated by examining their relationship with D-dimers. For instance, the simultaneous detection of D-dimer and miR-96 (118) or miRNA-320a/b (119) has been shown to enhance the diagnostic accuracy of DVT. However, this does not imply that miRNAs surpass D-dimers in diagnostic value; the latter remain indispensable. In summary, the fluctuation in miRNA levels in blood during DVT is influenced by various factors and their specificity is not high. Consequently, studies utilizing miRNAs as diagnostic markers for VTE are still in the experimental stage and have not been extensively implemented in clinical settings. Nevertheless, monitoring changes in miRNA expression levels may offer a more precise assessment of risk levels in patients with DVT (54). Further research into miRNAs is likely to uncover their diagnostic potential to a greater extent.

Advances in miRNA therapy for DVT. Recent studies on miRNA therapy for patients with DVT have revealed significant progress (120). Research into miRNA therapy for various diseases has indicated that miRNA overexpression effectively regulates the transcriptional process of various genes, inhibits tissue inflammatory responses and reduces adverse effects in patients with DVT (121,122). A previous study suggested that when miRNAs enter the pulmonary veins following a DVT episode, they regulate and control cardiomyocyte activity, thus protecting the heart from DVT-induced damage (103). There is potential for treating vascular endothelial cell injury through miRNA upregulation or downregulation, which could

pave the way for new therapeutic approaches to DVT intervention. However, challenges persist for miRNA-based therapies, including the need for specific miRNA delivery within tissues, targeted receptor binding and dose optimization (61). To date, the direct miRNA use for DVT therapy has not been reported. Nonetheless, in the future, integrating miRNAs into novel therapeutic strategies may revolutionize DVT treatment.

4. Conclusions and future perspectives

miRNAs play a crucial role in regulating DVT formation via VECs, rendering them a valuable addition to clinical studies on DVT. These small RNA molecules exert biological effects on DVT formation by modulating VECs. However, there have been no reports of direct antagonistic effects between functionally distinct miRNAs regulating DVT formation. Consequently, the complexity of the miRNA regulatory network in DVT surpasses previous understanding. The vascular endothelium, being in direct contact with the vein wall, maintains a dynamic balance between procoagulation and anticoagulation. miRNAs influence the function of VECs through various pathways, including autophagy and inflammation, disturbing this delicate balance between pro- and anti-coagulation systems. Ultimately, this disruption indirectly regulates thrombus formation. It is unclear whether miRNAs mainly act on venous VECs, thereby regulating the biological function of these cells and potentially exacerbating the coagulation process following vascular endothelium damage. Thus, miRNAs do not directly participate in the endogenous coagulation pathway but rather modulate the process of thrombus formation. Furthermore, the expression levels of miRNAs in plasma are influenced by numerous factors, diminishing their sensitivity and specificity. There is no evidence indicating that the diagnostic efficacy of miRNAs surpasses that of traditional coagulation function tests. Similarly, while the thrombolytic potential of miRNAs may equal or exceed that of conventional thrombolytic drugs, no targeted thrombolytic medications or therapeutic approaches utilizing miRNAs have been developed. Consequently, there has been no significant clinical breakthrough or application of miRNAs in the diagnosis and treatment of DVT. Nevertheless, studying the biological interactions between miRNAs and VECs is crucial for advancing the comprehension of the intricate process of thrombosis. Continuous research and development of extraction, detection and analytical techniques for miRNAs will provide robust support and technical assurances for DVT research. As exploration in this field advances, the future holds promise for expanded applications of miRNA-based disease prevention and treatment. Investigating the regulatory mechanisms of miRNAs in thrombosis holds significant value, offering new insights for early DVT diagnosis and identifying fresh targets for thrombolysis and personalized therapy.

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Availability of data and materials

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Authors' contributions

JMo conceived the theme and reviewed the manuscript. CF and FH wrote the first draft of the manuscript. ZW, MY and JMa revised parts of the manuscript. DW, TG and FZ helped revise the manuscript and reviewed the literature. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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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