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REVIEW

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The role of MicroRNAs in mesenchymal stem cell differentiation into vascular smooth muscle cells

Sakhavat Abolhasani^{1*} , Yasin Ahmadi^{2*} , Yavar Rostami¹ and Davood Fattahi³

Abstract

MicroRNAs (miRNAs) are small, noncoding RNA molecules that play a vital role in regulating gene expression, especially in the differentiation of mesenchymal stem cells (MSCs) into vascular smooth muscle cells (VSMCs). MSCs hold considerable promise for vascular repair and regenerative medicine, given their ability to differentiate into smooth muscle cells (SMCs) under specific molecular cues. Recent studies have shown that miRNAs, through complex regulatory networks, influence MSC differentiation by targeting essential signaling pathways and modulating the expression of differentiation markers, underscoring the intricate roles of these molecules in cellular development.

This review comprehensively examines the functions of various miRNAs in MSC differentiation, focusing on miR-143 and miR-145, which are upregulated by transforming growth factor beta 1 (TGF- β 1), a key growth factor in SMC development. These miRNAs enhance differentiation by promoting the expression of SMC markers, including α -smooth muscle actin (α -SMA) and calponin, and by inhibiting factors that preserve MSCs in an undifferentiated state. This review further discusses the roles of miR-503, which supports SMC differentiation through SMAD7 inhibition via the TGF- β pathway, and miR-222-5p, which counteracts differentiation by downregulating ROCK2 and α -SMA. By highlighting these regulatory mechanisms, this review aims to clarify the bidirectional and multifaceted role of miRNAs in VSMC differentiation. This study offers insights into the therapeutic potential of miRNA-mediated MSC differentiation for vascular repair and regeneration, ultimately contributing to improved cardiovascular outcomes.

Keywords MicroRNAs (miRNAs), Mesenchymal stem cells (MSCs), Vascular smooth muscle cells (VSMCs), Differentiation

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Introduction

The differentiation of mesenchymal stem cells (MSCs) into vascular smooth muscle cells (VSMCs) is a fundamental process vital for maintaining cardiovascular health and facilitating proper developmental mechanisms. A comprehensive understanding of the molecular pathways that govern this differentiation is critical for advancing tissue regeneration strategies and developing innovative therapies for various cardiovascular diseases [1]. MicroRNAs (miRNAs), which are small noncoding RNAs typically ranging from 18 to 22 nucleotides in length, play a critical role in the post-transcriptional regulation of gene expression. They exert their regulatory effects by binding to the 3' untranslated regions (UTRs) of target messenger RNAs (mRNAs), leading to either mRNA degradation or inhibition of translation [2]. Due to their significant impact on the differentiation processes of multiple cell types, including those of muscle and adipose origin, miRNAs present promising avenues for therapeutic intervention in tissue regeneration and repair [3]. VSMCs are integral components of the cardiovascular system, contributing to vascular tone, structural integrity, and the pathophysiology of various vascular diseases [4]. Therefore, elucidating the mechanisms underlying the differentiation of MSCs into VSMCs is essential for the development of targeted therapeutic strategies aimed at addressing VSMC-related conditions [5]. Recent studies have identified miRNAs as critical noncoding RNA factors that facilitate the effective transition of MSCs into VSMCs [6]. This review consolidates current research on miRNAs in VSMC differentiation from MSCs, categorizing key miRNAs to reveal therapeutic targets that may promote vascular repair and regeneration. This exploration highlights miRNAs as noncoding RNA-based tools with potential for advancing vascular regeneration.

MSCs: characteristics and differentiation potential

MSCs are multipotent progenitors capable of differentiating into several lineages, including smooth muscle cells (SMCs) [7]. MSCs, which are isolated from various sources, such as bone marrow, adipose tissue, and the umbilical cord, express the surface markers CD90, CD105, and CD73 but lack hematopoietic markers, such as CD34 and CD45, as defined by the International Society for Cellular Therapy [8]. MSC-to-SMC differentiation is regulated by growth factors, primarily transforming growth factor beta 1 (TGF- β 1), which activates pathways that promote the expression of SMC-specific genes [9, 10]. Additionally, the Wnt and Notch pathways and factors such as hypoxia contribute to MSC differentiation, enhancing their potential for vascular repair [11].

MSC definition and characteristics

MSCs are unique in their self-renewal capacity and ability to differentiate into osteocytes, chondrocytes, adipocytes, and myocytes. Initially, isolated from bone marrow, MSCs have been identified in various tissues, including adipose and umbilical cord tissue, expanding their therapeutic applications [12]. Characterized by specific surface markers, MSCs exhibit immunomodulatory properties and secrete growth factors crucial for tissue regeneration, positioning them as valuable candidates in regenerative medicine [13, 14].

MSC differentiation pathways

The differentiation of MSCs into VSMCs is predominantly regulated by signaling molecules such as TGF- β 1, which activate the TGF- β /Smad pathway and upregulate the expression of SMC markers such as α -SMA, calponin, and SM22 α [15]. Other pathways, including the Wnt/ β -catenin pathway, further enhance MSC myogenic differentiation [16]. Growth factors such as PDGF also play a role, synergistically working with TGF- β 1 to accelerate MSC differentiation [17]. This process involves intricate interactions among signaling pathways and miRNAs, underscoring the complexity of MSC-to-VSMC differentiation.

VSMCs: function and importance

VSMCs are crucial for maintaining vascular tone and regulating blood flow, primarily through contraction and relaxation. VSMCs are innervated by the sympathetic nervous system and respond to adrenergic signals that induce vasoconstriction or vasodilation [18]. Beyond contraction, VSMCs are involved in pathological conditions such as atherosclerosis, transitioning from a contractile to a synthetic phenotype that contributes to vascular disease progression [19]. This plasticity underscores the importance of understanding VSMC behavior in both health and disease [20, 21].

MiRNA biogenesis and regulation

MiRNAs are essential noncoding RNAs involved in gene regulation. MiRNA biogenesis begins with the transcription of primary miRNAs (pri-miRNAs), which are processed by the microprocessor complex (Drosha and DGCR8) into precursor miRNAs (pre-miRNAs). These proteins are further processed in the cytoplasm by Dicer to form mature miRNAs, which associate with Argonaute proteins to form the RNA-induced silencing complex (RISC) [22]. miRNA interaction with target mRNAs occurs mainly at the 3' UTR, leading to mRNA degradation or translational repression [23]. MiRNA regulation involves complex feedback and is modulated by transcriptional control, RNA-binding proteins, and environmental stimuli [24, 25]. These mechanisms enable

miRNAs to finely tune gene expression across a range of cellular processes, making them potential therapeutic targets [26].

Role of miRNAs in MSC differentiation into VSMCs

MiRNAs are central to the differentiation of MSCs into VSMCs by modulating gene expression and signaling pathways essential for this transition [27]. Key miRNAs, including miR-143 and miR-145, are significantly upregulated following TGF- β 1 treatment, aiding in VSMC differentiation by promoting the expression of SMC-specific markers such as α -SMA, calponin, and SM22 [28, 29]. Additionally, miR-503 enhances SMC differentiation by targeting SMAD7, a known inhibitor of TGF- β signaling, amplifying the TGF- β pathways critical for VSMC formation [30]. Conversely, miR-222-5p inhibits differentiation by downregulating proteins such as ROCK2 and α -SMA, underscoring the regulatory balance of miRNAs in the MSC-to-VSMC transition [31]. This interplay highlights the therapeutic potential of miRNAs in vascular development and regenerative medicine, especially for engineered vascular grafts [32].

Specific miRNAs involved in the differentiation of MSCs into VSMCs

Certain miRNAs play crucial roles in guiding the differentiation of MSCs into VSMCs [33]. Among these, miR-143 and miR-145 are particularly noteworthy.

These miRNAs are significantly upregulated in response to TGF- β 1 stimulation, promoting the expression of smooth muscle cell markers such as α -smooth muscle actin (α SMA) and calponin [34]. By targeting and inhibiting factors that maintain the undifferentiated state of MSCs, miR-143 and miR-145 facilitate the transition into mature VSMCs, highlighting their importance in regulating the differentiation process (Table 1) [35]. Another key player, miR-503, also promotes SMC differentiation by directly targeting SMAD7, a negative regulator of TGF- β signaling. This inhibition amplifies TGF- β 1-mediated signaling, which is essential for developing the SMC phenotype, underscoring the complexity of regulatory mechanisms involved in differentiation [36, 37]. Conversely, miR-222-5p acts as an inhibitor of SMC differentiation by downregulating proteins such as Rho-associated protein kinase 2 (ROCK2) and α -SMA, illustrating the balance between miRNAs that promote and those that inhibit differentiation [38]. Other miRNAs, such as miR-221, influence MSC differentiation, with their roles varying based on cellular context and environmental conditions [39]. This complex network of miRNA interactions highlights both the challenges of regulating MSC differentiation into VSMCs and the potential therapeutic targets for vascular regeneration [40]. Understanding these mechanisms enables researchers to determine specific miRNAs that promote vascular repair and regeneration (Table 1).

Table 1 Specific miRNAs involved in the differentiation of MSCs into VSMCs

Types of miRNAs	Role in MSC to SMC Differentiation	Mechanism of Action	Target Genes/Pathways	Ref
miR-503	Promotes differentiation	Upregulated during early differentiation; enhances TGF- β signaling	Targets SMAD7, regulated by SMAD4	[30]
miR-222-5p	Inhibits differentiation	Decreased expression during differentiation; affects cytoskeletal dynamics	Targets ROCK2, potential regulatory roles of passenger strand	[41]
miR-1	Positive regulator	Essential for promoting SMC lineage; interacts with KLF4	HDAC4, Srsf9	[42]
miR-206	Essential for myogenic differentiation	Similar to miR-1. Promotes muscle differentiation.	HDAC4, Utrn, Fstl1, Srsf9	[43]
miR-145	Promotes differentiation	Induces expression of smooth muscle-specific genes	Targets KLF4, influences myogenic factors	[44]
miR-143	Promotes differentiation	Upregulated by TGF- β 1; enhances expression of SMC-specific markers like α SMA and calponin by inhibiting undifferentiated state factors	Targets ELK-1, factors maintaining undifferentiated state	[45]
miR-221	Enhances MSC function	Upregulated in response to HGF; promotes migration and survival of cardiomyocytes through Akt pathway activation via PTEN inhibition	Targets PTEN, enhances Akt signaling	[46]
miR-24	Enhances differentiation	Overexpression can counteract TGF- β effects	Modulates TGF- β signaling	[33]
miR-181	Promotes myoblast differentiation	Inhibits Hox-A11, facilitating smooth muscle lineage progression	Targets Hox-A11	[47]
miR-133	Dual role: promotes proliferation and later differentiation	Suppresses excessive proliferation through SRF targeting	Targets SRF	[48]

SMAD: Smad proteins, KLF4: Krüppel-like factor 4, HDAC: Histone Deacetylase, ROCK2: Rho-associated protein kinase 2, HGF: Hepatocyte Growth Factor, PTEN: Phosphatase and Tensin homolog, Akt: Protein kinase B, ELK-1: ETS domain-containing protein 1, SRF: Serum Response Factor, Utrn: Utrophin, Fstl1: Follistatin-like 1, Hox-A11: homeobox-A11

Table 2 Mechanisms by which miRNAs influence the differentiation of MSCs into VSMCs

Mechanism	miRNAs	Role in MSC to SMC Differentiation	Target/Effect	Ref
TGF- β 1	miR-143	Upregulated in response to TGF- β 1, promoting SMC differentiation	Inhibits pluripotent factors.	[53]
Signaling Interaction	miR-145	Enhances expression of smooth muscle-specific genes; represses KLF4	Targets KLF4 to promote differentiation	[38]
	miR-503	Upregulated during early differentiation phases; targets SMAD7 to promote TGF- β signaling	Enhances transcriptional activity of SMAD4.	[30]
	miR-222-5p	Downregulated during differentiation; inhibits SMC differentiation by targeting ROCK2	Impedes cytoskeletal dynamics	[38]
Wnt/ β -Catenin Pathway Interaction	miR-503	Modulates β -catenin stability and activity; may enhance Wnt signaling in response to TGF- β 1	Targets negative regulators of Wnt pathway.	[30]
	miR-1	Positive regulator of MSC to SMC differentiation; loss-of-function leads to reduced SMC marker expression	Interacts with KLF4 to repress its expression.	[64]

Mechanisms of action of miRNAs

MiRNAs play vital roles in the differentiation of MSCs into VSMCs by modulating the Wnt/ β -catenin signaling pathway. The regulatory impact of miRNAs on this pathway highlights the important role that miRNAs play in guiding the developmental processes of MSCs [49]. This differentiation is vital in the field of vascular tissue engineering or regenerative medicine since VSMCs are critical cells that maintain the structure and function of blood vessels [50]. The processes through which miRNAs mediate this process are complex and involve several pathways, with the TGF- β signaling pathway being a major pathway [33].

Interaction with TGF- β 1 signaling

The mechanism of action of TGF- β signaling involves TGF- β 1, which functions as a principal regulator that initiates the differentiation of MSCs into VSMCs by activating the canonical TGF- β /Smad signaling cascade [51]. Upon ligand binding to its receptor, TGF- β 1 catalyzes the phosphorylation of Smad2 and Smad3, resulting in their subsequent association with Smad4. This resulting complex translocate to the nucleus, where it coordinates the transcriptional regulation of SMC-specific genes, thereby promoting the expression of markers such as α -SMA, calponin, and SM22 α [52]. Certain miRNAs, notably miR-143 and miR-145, are upregulated in response to TGF- β 1 stimulation. These miRNAs support SMC differentiation by targeting and inhibiting pluripotent factors that maintain MSCs in an undifferentiated state [53]. For example, miR-145 enhances the expression of smooth muscle-specific genes while repressing KLF4, a factor linked to less differentiated states. MiR-503- promotes differentiation: miR-503 is markedly upregulated during the initial phases of MSC differentiation into VSMCs. It facilitates this differentiation by specifically targeting SMAD7, an established inhibitor of TGF- β signaling [30]. The expression levels of miR-503 are modulated by SMAD4, which binds to its promoter region upon TGF- β 1 stimulation,

thereby augmenting its transcriptional activity [30]. MiR-222-5p inhibited differentiation; in contrast, miR-222-5p expression was reduced during the differentiation of MSCs into VSMCs. It impedes this process by targeting ROCK2, a protein integral to cytoskeletal dynamics relevant to SMC differentiation [54]. Recent investigations have suggested that the passenger strand of miR-222 may play significant regulatory roles within this framework [55]. (See Table 2)

Interaction with the Wnt/ β -catenin pathway

The Wnt/ β -catenin pathway is crucial in the regulation of various cellular processes, including differentiation [56]. Although direct interactions between miRNAs and this pathway during the transition of MSCs into VSMCs necessitate further exploration, several inferred mechanisms have been proposed: MiRNAs possess the ability to modulate the expression of components within the Wnt pathway [57]. For example, miR-503 may affect the stability and activity of β -catenin by targeting negative regulators that operate within this pathway [58]. The interaction between TGF- β 1 signaling and the Wnt/ β -catenin pathway is critical for VSMC differentiation [59]. The upregulation of miR-503 in response to TGF- β 1 implies that it may function as a mediator that enhances Wnt signaling, thereby promoting the expression of SMC-specific genes [30].

In addition, other miRNAs, including miR-1, also contribute significantly to the differentiation of MSCs into VSMCs [38]. MiR-1 exerts a positive regulatory effect on the differentiation of MSCs into VSMCs; loss-of-function experiments revealed that its absence results in diminished expression of SMC-specific markers [60]. Furthermore, miR-1 interacts with KLF4, an antimitogenic factor, by binding to its 3' untranslated region (UTR) and repressing its expression [61]. In addition, during retinoic acid-induced SMC differentiation from embryonic stem cells (ESCs), an increase in miR-1 was observed alongside other myomiRs, such as miR-145, suggesting a

coordinated regulatory network encompassing multiple miRNAs [62].

While miR-1 is indispensable, other miRNAs such as miR-503 and miR-222-5p, also play significant roles in this biological process [63]. Specifically, miR-503 facilitates the differentiation of MSCs into VSMCs by targeting SMAD7, whereas miR-222-5p inhibits this differentiation by targeting ROCK2. This dynamic interaction exemplifies a complex regulatory framework which various miRNAs can either collaborate with or counteract each other's influences on the fate of MSCs [38]. (See Table 2).

Functional implications

The successful differentiation of MSCs into functional VSMCs involves the expression of SMC-specific markers, such as α -SMA, SM22, and calponin, at both the mRNA and protein levels [65]. Differentiated VSMCs can contract and contribute to vascular structure formation, indicating their potential in tissue-engineered vascular grafts [6].

Feedback mechanisms

The interaction between TGF- β signaling and miRNA regulation engenders a feedback loop that meticulously modulates MSC differentiation into VSMCs. Certain miRNAs can regulate the expression levels of TGF- β receptors or their downstream effectors, thereby affecting the overall response to TGF- β 1 and subsequently influencing differentiation outcomes [66]. miRNAs serve as crucial regulators in the differentiation of MSCs into VSMCs through their interactions with various signaling pathways, particularly the TGF- β and Wnt/ β -catenin pathways [67]. Exploring the role of specific miRNAs in modulating the expression of key transcription factors could unveil novel strategies to increase the efficiency of MSC differentiation and improve outcomes in tissue engineering [38].

MiRNA and VSMCs connection with vascular grafting and disease

The intricate interplay between miRNAs and VSMCs is crucial for comprehending the pathophysiology of vascular diseases and the cellular response to injury, especially within the context of vascular grafts [68]. This section examines how miRNAs orchestrate VSMC behavior under pathological conditions and their consequential implications for the success of vascular grafting procedures.

Role of VSMCs in vascular disease and grafting

VSMCs are fundamental to maintaining the structural and functional integrity of blood vessels. However, their phenotypic plasticity enables them to play both

protective and pathological roles in vascular diseases and vascular grafting [69].

In vascular diseases, such as atherosclerosis, VSMCs undergo a phenotypic transition from a contractile to a synthetic state, characterized by the downregulation of contractile markers and the upregulation of synthetic markers. This facilitates increased cellular proliferation, migration, and extracellular matrix deposition, processes critical for vascular remodeling and plaque formation [27, 69]. These changes are governed by intricate molecular mechanisms, including the influence of microRNAs (miRNAs) and cytokines, which modulate gene expression related to inflammation and cellular responses. miRNAs, such as miR-143-5p and miR-145-5p, play a vital role in regulating VSMC behavior under shear stress conditions [70, 71]. Mechanotransduction processes, such as increased shear stress from interstitial fluid, activate signaling pathways that promote the synthetic phenotype of VSMCs, enhancing their involvement in atherosclerosis [72]. While these adaptive processes contribute to vascular homeostasis under normal conditions, the pathological phenotypic shift of VSMCs drives the progression of vascular diseases [72].

In the context of vascular grafting, VSMCs exhibit a dual role, balancing repair and pathology. Upon vascular injury, VSMCs transition to a synthetic state, enabling their proliferation and migration toward the intimal layer to facilitate repair. However, excessive proliferation and migration can lead to intimal hyperplasia, a primary cause of graft failure [72]. This pathological process is mediated by molecular regulators, including miRNAs and growth factors released from activated macrophages and platelets during inflammation and endothelial damage. For instance, dysregulation of miRNAs, such as miR-143-5p and miR-145-5p, can impair VSMC-endothelial cell interactions and exacerbate intimal hyperplasia following vascular injury [71].

Additionally, matricellular proteins like cysteine-rich protein 61 (CYR61) are overexpressed in VSMCs within atherosclerotic lesions and promote their migration and proliferation. Suppressing CYR61 has been shown to reduce neointimal formation, highlighting its importance in vascular remodeling and its potential as a therapeutic target [73]. During vein grafting, the surgical procedure triggers inflammatory responses and endothelial damage, further stimulating VSMC migration and extracellular matrix deposition, leading to potential graft dysfunction and failure [74]. Consequently, VSMCs are central to vascular health, disease, and grafting outcomes. Their phenotypic plasticity enables essential reparative processes; however, dysregulated VSMC behavior can result in adverse effects, such as atherosclerosis and graft failure. Therapeutic strategies targeting molecular regulators, including miRNAs and CYR61, hold promise in

mitigating these pathological effects and improving clinical outcomes.

MiRNAs in vascular injury response

Following instances of vascular injury, such as those occurring during grafting procedures, miRNAs play a critical regulatory role in managing the healing processes [75]. Their effects manifest in various ways, for instance, certain miRNAs have shown the ability to regulate inflammatory responses that arise after vascular injury, directing the migration and activation of immune cells to the affected area. This regulation significantly impacts the healing trajectory and the risk of negative outcomes. Additionally, certain miRNAs facilitate the differentiation of MSCs into VSMCs, enhancing the tissue's repair and regeneration capacity at the injury site [38, 76]. This regenerative function is vital for reestablishing proper vascular function following injury.

MiRNA-mediated effects on vascular graft

The effectiveness of vascular grafts is often compromised by neointimal hyperplasia, which involves the excessive growth of VSMCs at the graft site [77]. Certain miRNAs, particularly miR-143 and miR-145, promote the differentiation of MSCs into mature VSMCs, helping to mitigate neointimal hyperplasia by ensuring a balanced cellular response to vascular injury [78]. In contrast, miR-222-5p may inhibit this differentiation, leading to poorer graft outcomes [79]. Understanding these molecular mechanisms is essential for designing approaches to improve the longevity and effectiveness of vascular grafts. Investigating the role of specific miRNAs in VSMC behavior during vascular diseases presents significant opportunities for therapeutic interventions aimed at improving graft results [80]. Targeted therapies that focus on particular miRNAs could promote MSC differentiation into VSMCs, reduce inflammatory responses, or limit excessive VSMC proliferation in grafts, potentially leading to better integration and functionality of the grafts [81]. Additionally, identifying unique miRNA expression patterns associated with successful graft integration could provide valuable biomarkers for predicting patient outcomes, enabling more personalized treatment strategies in clinical settings [82].

Clinical implications of miRNAs in VSMC differentiation

MiRNAs play indispensable roles in the regulation of gene expression, particularly during the differentiation of VSMCs from MSCs [83, 84]. Gaining insight into the intricate regulatory mechanisms governed by miRNAs holds substantial promise for advancing clinical strategies within the realm of cardiovascular medicine.

Regulation of VSMC differentiation

MiRNAs exert a significant influence over various signaling pathways that are fundamental to the differentiation of VSMCs. Numerous studies have identified specific miRNAs that either facilitate or inhibit the transition of MSCs into VSMCs by targeting essential transcription factors and growth factors critical to this differentiation process [49]. Certain miRNAs are known to promote signaling cascades crucial for smooth muscle identity, while others may act to suppress alternative differentiation pathways [85]. Strategic modulation of these miRNA pathways could enhance VSMC differentiation, offering a novel therapeutic approach for regenerative medicine [86]. While exploring the potential of miRNAs offers promising therapeutic possibilities, it is important to recognize the complexity of their interactions and the risks of unintended effects when manipulating these pathways. Continued research is essential to fully comprehend the implications of miRNA regulation on VSMC differentiation and its overall influence on vascular health.

Therapeutic applications

Targeting miRNAs presents numerous promising therapeutic opportunities. For instance, in the realm of cardiovascular regeneration, employing miRNA mimics or inhibitors to promote the differentiation of VSMCs could significantly enhance tissue engineering and regenerative therapies aimed at vascular repair [87]. By selectively enhancing the expression of advantageous miRNAs, it may be feasible to restore vascular integrity following injury or disease [68]. Moreover, modifying miRNA expression profiles could lead to innovative treatments for vascular disorders associated with dysfunctional VSMC activity [88]. Atherosclerosis and restenosis, characterized by abnormal SMC proliferation and migration, may be effectively managed with miRNA-targeted therapies, providing more personalized treatment options [89]. Furthermore, a comprehensive understanding of individual miRNA expression profiles can facilitate the development of personalized treatment plans that provide each patient's unique vascular characteristics, then, enhancing the potential for therapeutic efficacy and advancing the field of precision medicine in cardiovascular care.

Limitations

This review offers a focused and insightful analysis of selected miRNAs involved in MSC differentiation, providing valuable contributions to understanding VSMC differentiation. Given the intricate and dynamic nature of miRNA interactions, a broader exploration of additional miRNAs and their complex regulatory networks could offer deeper insights. However, due to the challenging complexity of these interactions, this review intentionally narrows its focus to key miRNAs, providing a clear and

manageable scope that we believe significantly advances the field. While the therapeutic potential of miRNAs is discussed, there is limited coverage of the clinical challenges in applying these findings, such as delivery methods and patient variability. Additionally, conclusions drawn from primarily in vitro studies may not fully reflect in vivo realities. While miR-143 and miR-145 are emphasized for their prominent roles, other potentially important miRNAs may not be as extensively explored. The study selection process may also introduce some bias, which could influence interpretations. Addressing these gaps in future research will be essential for advancing the application of miRNAs in vascular repair and regenerative medicine.

Conclusion and future perspectives

Investigating the role of miRNAs in the differentiation of MSCs into VSMCs presents a remarkable opportunity for the advancement of regenerative medicine and tissue engineering. miRNAs serve as vital regulators that orchestrate a multitude of signaling pathways, particularly in response to critical growth factors such as TGF- β 1, which play indispensable roles in facilitating the differentiation of VSMCs from MSCs. Among the numerous miRNAs implicated in this process, miR-503 and miR-222-5p have emerged as pivotal contributors. MiR-503 enhances the differentiation of MSCs into VSMCs by specifically targeting and downregulating SMAD7, a negative regulator of the TGF- β signaling pathway. In contrast, miR-222-5p has been identified as an inhibitor of differentiation, exerting its effects by downregulating key proteins such as ROCK2 and α SMA. This duality in miRNA function underscores the intricate balance of regulatory mechanisms that govern MSC differentiation. Future research must investigate the complex regulatory networks that encompass not only miRNAs but also long noncoding RNAs (lncRNAs) in greater depth. A thorough understanding of these interactions is essential for advancing our knowledge of MSC biology and for developing novel therapeutic strategies aimed at addressing vascular diseases. By clarifying these relationships, researchers can create targeted interventions that effectively address these conditions, potentially improving patient outcomes in vascular health. The prospect of engineering MSCs to express specific miRNAs holds the promise of creating personalized therapies that actively promote tissue repair and regeneration, particularly in conditions such as atherosclerosis and vascular graft failure. Furthermore, the use of MSC-derived exosomes, which are rich in functional miRNAs, represents a promising method for noninvasive therapeutic applications. These exosomes may function as effective carriers, delivering miRNAs to specific tissues and consequently influencing cell responses to improve regenerative

results. In conclusion, the integration of miRNA research into the differentiation of MSCs offers transformative potential for the field of regenerative therapies. Ongoing investigations into the mechanisms that govern miRNA function will not only deepen our understanding of MSC dynamics but also facilitate the development of precision medicine approaches that connect the innate regenerative capabilities of MSCs. This, in turn, promises to significantly improve patient outcomes across a spectrum of clinical scenarios.

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Author contributions

The author contributions for the manuscript are outlined as follows: Sakhavat Abolhasani: Responsible for conceptualizing the study, acquiring funding, managing the project, supervising the research, validating results, and writing both the original draft and subsequent revisions. Yasin Ahmadi: Contributed to the conceptual framework, provided resources, and assisted in writing both the original draft and revisions. Yavar Rostami: Involved in editing and resource provision. Davood Fattahi: Responsible for the final revision of the manuscript. This clear delineation of roles emphasizes each author's specific responsibilities and contributions to the research project.

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No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Conflict of interest

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