MicroRNAs (miRNAs) Role in Hypertension: Pathogenesis and Promising Therapeutics

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Abstract

MicroRNAs (miRNAs) are small, non-coding RNA molecules that play a crucial role in regulating various cellular processes, including cell proliferation, differentiation, apoptosis, and disease development. Recent studies have highlighted the importance of miRNAs in the development and progression of essential hypertension, a common form of high blood pressure that affects millions of individuals worldwide. The molecular mechanisms by which miRNAs regulate hypertension are complex and multifaceted. MiRNAs target the 3' untranslated regions of mRNA molecules, thereby regulating the synthesis of specific proteins involved in cardiovascular function. For instance, miRNAs are known to regulate the expression of genes involved in blood vessel tone, cardiac function, and inflammation.

The growing body of research on miRNAs in hypertension has highlighted their potential as therapeutic targets for managing this condition. Studies have shown that miRNA-based therapies can modulate the expression of key genes involved in hypertension, leading to improvements in blood pressure and cardiovascular function. However, more research is needed to fully understand the mechanisms of miRNA-mediated hypertension and to develop effective therapeutic strategies.

In summary, this review highlights the current understanding of the role of miRNAs in essential hypertension, including their molecular mechanisms and potential therapeutic applications. Further research is needed to fully understand the impact of miRNAs on hypertension and to develop new treatments for this common and debilitating condition.

Introduction

Hypertension, also known as high blood pressure, is a chronic condition in which the systemic arterial blood pressure is elevated over a prolonged period of time. It is a major public health concern, as it can lead to a variety of clinical manifestations and complications, including end-organ damage such as cardiovascular disease, coronary artery disease, and renal failure [1–3].

According to the World Health Organization, hypertension is a leading cause of morbidity and mortality, with nearly 40% of individuals over 25 years of age affected by the condition. Hypertension can be classified into two main categories: primary hypertension and secondary hypertension. Primary hypertension, which accounts for the majority of cases, is of unknown aetiology [8][4]. In contrast, secondary hypertension is caused by an underlying medical condition. Despite extensive research, the underlying mechanisms of primary hypertension remain poorly understood. The identification of the etiological causes and pathophysiology of hypertension is crucial for the development of effective treatment strategies.

In recent years, the field of miRNA research has provided evidence that these small non-coding RNA molecules may play a role in the development of hypertension. MiRNAs are typically composed of 24 nucleotides and negatively influence gene expression at the post-transcriptional level. They are involved in a wide range of biological processes, including cell proliferation, differentiation, apoptosis, cancer, and
stress response[8, 9]. Specifically, studies have shown that miRNAs are involved in the regulation of genes involved in blood pressure regulation, suggesting that they may play a role in the development of hypertension. For example, some miRNAs have been found to regulate the expression of genes involved in the renin-angiotensin-aldosterone system (RAAS), which plays a critical role in blood pressure regulation [5].

Additionally, miRNAs have been found to be involved in the regulation of genes involved in other key physiological processes such as cell proliferation, differentiation, apoptosis, and stress response, which may contribute to the development of hypertension [4, 6].

Overall, while hypertension is a complex multifactorial disease, recent advances in the field of miRNA research have provided new insights into the underlying mechanisms of hypertension. These findings have the potential to lead to the development of new diagnostic and therapeutic strategies for hypertension, which may help reduce the burden of this debilitating condition. Further research is needed to fully understand the role of miRNAs in hypertension and to translate these findings into effective treatments for patients.

**Mirna Biogenesis And Function**

The understanding of the role of miRNAs in the development of hypertension is essential in the scientific literature. MiRNAs are small non-coding RNA molecules that play a critical role in regulating gene expression at the post-transcriptional stage, which occurs in the cytoplasm. However, miRNA residues can also be found in the nucleus, particularly in non-coding regions such as introns and exons, as well as in coding regions of the genome (introns only) [7].

There are many different types of miRNAs in the genome, each with a unique transcriptional unit or a collection of polycistronic units that contain information for multiple miRNAs. Once mature miRNAs are generated, they are able to target mRNA and negatively control gene expression by either mRNA degradation or translation inhibition.

MiRNAs are single-stranded strands that can attach to the 4’ end of other miRNAs and impede translation, which is why they are referred to as miRNAs. MiRNAs can target multiple mRNA, and several miRNAs can target a single mRNA, making this regulation effective and able to control at least 60% of protein coding genes in humans [8–11]. Determining the involvement of miRNAs in hypertension is challenging due to the many systemic disorders and comorbid conditions that are linked to it. Different enzymes are involved in synthesising mature miRNAs, which bind to specific proteins and regulate gene expression by acting on miRNA-specific regions of the genome and its products [12–14].

The generation of miRNAs begins with the transcription of miRNA genes by RNA Polymerase II, resulting in long primary transcripts (pri-miRNA) that are converted to the first precursor of mature miRNA (pre-miRNA) by Drosha [15]. The pre-miRNA is then imported into the cytoplasm by protein exporting 5 and processed by RNAse III protein Dicer to the second precursor of mature mi-RNA (miRNA-miRNA duplex),
an unstable miRNA duplex structure consisting of roughly 22 nucleotides [16]. By interacting with multiple-protein nuclease complexes, mature miRNAs produce a miRNA-induced slicing complex (RISC), the effector arm of miRNA influences gene expression. The complementary strand of miRNA that is not integrated with these complexes are destroyed. Mature miRNAs bind to target genes via 3'-UTR complementarity. The 4' ends of miRNAs bind with target mRNA (the "seed region") to stop gene translation [17, 18].

Research supports the efficiency of post-transcriptional regulation generated by miRNAs and epigenetic genome alterations, which may impair health and enable disease development if disrupted. Multiple hypertensive patients may now be recognized and treated based on alterations in the miRNA expression profile, which can be a consequence of DNA damage related to dysfunctions in DNA repairing pathways, as documented in pulmonary hypertension.

Despite the fact that the precise pathophysiology is unknown, miRNA expression identified using microarray has been demonstrated to be deregulated in hypertensive modules, while other studies have suggested that this modification may be owing to DNA repair disruption secondary to chronic inflammation as activation of poly ADP-ribose. In patients with Pulmonary Hypertension, polymerase-1 (PARP-1) increases miR-204 expression. Based on current findings, it is hypothesised that the pathophysiology of hypertension alters miRNA expression (as illustrated in Figs. 1, 2, and 3) [19–21].

Role Of Mirna In Pathogenesis Of Hypertension

Hypertension, a condition characterized by elevated blood pressure, is a complex and multifaceted disease that has long been a subject of scientific inquiry. Recent research has shed light on the crucial roles that miRNA-122 (miR-122) and the Renin-Angiotensin system (RAS) play in the development of cardiovascular damage in hypertensive patients [22–27].

Studies on hypertensive animal models have revealed that miR-122 plays a significant role in the cardiovascular remodeling and kidney damage observed in these models [28, 29]. The excessive activation of Angiotensin II in Neonatal Rat Ventricular Myocytes (NRVMs) leads to an increase in miR-122 production, which in turn promotes cardiovascular fibrosis and endovascular remodeling [29]. The Transforming Growth Factor-Beta (TGF-B) is a fibrotic signaling pathway that is suppressed by the administration of miR-122 inhibitors, further highlighting the role of miRNAs in fibrosis. Additionally, miR-122 is more prevalent in younger hypertensive patients, providing further evidence of its involvement in the development of hypertension. Endothelial dysfunction, a condition characterized by the impairment of the endothelial cells that line the blood vessels, is also induced by miR-122. The suppression of the cationic amino acid transporter by miR-122 results in endothelial dysfunction [22, 30]. The suppression of cationic amino acid transporter expression by miR-122 is responsible for the induction of endothelial dysfunction [31]. The administration of miRNA inhibitors has been shown to aid in the inhibition of fibrosis, the improvement of endothelial function, and the enhancement of cellular proliferation and migration, further emphasizing the role of miR-122 in hypertension. Recent studies have also shown that
the administration of miRNA mimics enhances the expression of BTB and CNC homology 1 Transcription factor (Bach-1) in mesangial cells. In contrast, the application of miRNA inhibitors to the Angiotensin II-induced hypertension model in elderly mice suppresses the expression of proinflammatory factors such as Bach1 and MCP-1, as well as profibrotic components such as collagen 1 alpha [23]. The pathophysiology of the bicuspid aortic valve, a congenital heart defect, is likewise linked to the production of apoptosis and the stimulation of the TGF-B-VEGF signalling pathway by miR-122 [32]. Moreover, targeting SIRT6 directly has been shown to lead to an increase in the levels of pAMPK alpha and ACE2 and a decrease in the production of CTGF, TGF-B, and collagen I and II in the cardiovascular system, further emphasising the importance of miR-122 in hypertension [33]. The connection between hypertension and cardiovascular and renal damage is undeniable, and miR-122 plays a crucial role in this complex process (Descriptive Figs. 4,5) (Table 1).

Table 1. **Summary describing the mechanism and net effect of different microRNA subtypes in the pathogenesis of different types of hypertensions.**
<table>
<thead>
<tr>
<th>Type of MiRNA</th>
<th>Type of Hypertension</th>
<th>Net effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>mi-RNA 204</td>
<td>Pulmonary Hypertension</td>
<td>● miR-204 is downregulated in the lung tissue of patients with pulmonary hypertension, and its expression is inversely correlated with the severity of the disease [62].&lt;br&gt;● Overexpression of miR-204 in animal models of pulmonary hypertension has been shown to reduce the development of the disease, while inhibition of miR-204 leads to an increase in the severity of pulmonary hypertension [63].&lt;br&gt;● miR-204 role in remodelling through inhibiting the SRC/Stat3 module in smooth muscle cells located in the pulmonary artery which provides a protection against monocrotaline-induced pulmonary arterial hypertension and also offers protection for pulmonary arterial hypertension patients from Dehydroepiandrosterone [64].</td>
</tr>
<tr>
<td>MiR-143</td>
<td>Pulmonary Hypertension</td>
<td>● inhibition of miR-143-3p blocked experimental pulmonary hypertension in mice exposed to chronic hypoxia, suggesting an important role for the miR-143/145 cluster in PAH pathobiology [65].</td>
</tr>
<tr>
<td>mi-RNA 122</td>
<td>Systemic (Reno-vascular Hypertension)</td>
<td>● MiR-122 has a role in regulation of lipid metabolism and glucose homeostasis and contributes to hypertension by promoting the growth and proliferation of smooth muscle cells in the blood vessels [66].&lt;br&gt;● Development of Renal hypertension, and cardio-renal injury, by their role in regulating lipoprotein metabolism and cholesterol homeostasis [66].&lt;br&gt;● Induce of fibrosis and inflammation, resulting in the occurrence of hypertension and heart failure [22].</td>
</tr>
<tr>
<td>miRNA-181 and miRNA-663</td>
<td>Renovascular Hypertension</td>
<td>● miRNA-181 targets genes involved in blood pressure regulation, including angiotensin II receptor type 1 and the renin-angiotensin-aldosterone system, contributing to the development of hypertension [67].&lt;br&gt;● Has-miRNA-663 reduces renal blood pressure by regulating the expression of renin gene expression that have a crucial role in regulating Blood pressure [67].</td>
</tr>
<tr>
<td>miRNA-155</td>
<td>Systemic Hypertension</td>
<td>● miR-15 plays a role in hypertension through its regulation of the TGFβ signal pathway, increasing the expression of miR-15b and miR-195 in Ang II-induced cardiac hypertrophy model through their suppressive effect on canonical and non-canonical TGFβ signal pathways at the same time [68].</td>
</tr>
</tbody>
</table>

In conclusion, the pathogenesis of hypertension is a complex and multifaceted process that involves the interplay of multiple genetic and environmental factors. Recent research has revealed the crucial role that miR-122 and the Renin-Angiotensin system (RAS) play in the development of cardiovascular damage in hypertensive patients. Studies on hypertensive animal models have shown that miR-122 plays a significant role in cardiovascular remodelling and kidney damage, with excessive activation of Angiotensin II leading to an increase in miR-122 production, thereby promoting fibrosis and endovascular...
remodelling in the cardiovascular system. The administration of miRNA inhibitors has been shown to aid in the inhibition.

The Role Of Mirna As A Sensitive Biomarker

The human body is a complex network of cells, tissues, and organs that work together in harmony to maintain our overall well-being. However, when something goes awry, it can result in serious health conditions that can be difficult to diagnose and treat. One area of research that is gaining momentum is the study of miRNA, a type of molecule that plays a critical role in regulating cell-cell interactions and may serve as biomarkers for related disorders. The interstitial fluid and plasma in our bodies contain miRNA, which can be released through vesicles to regulate cell-cell interactions or serve as biomarkers for related disorders [34, 35].

MiRNA was initially identified in the circulation in 2008, but it has since been revealed that it is present in platelets, RBCs, and other nucleated blood cells [35, 36]. There are many subtypes of miRNA, each unique to a particular tissue or pathology. Identifying their sequences depends on amplifying these specific sequences, which remain stable throughout time [37]. The potential for miRNA as a biomarker for cardiovascular disease diagnosis and prognosis is particularly promising. MiRNA types alter with cardiovascular disorders, including Primary Hypertension [38]. Studies have reported the presence of HcmvmiR-UL112 and has-miR-505 in individuals with systemic hypertension [39], placental specific C19MC miRNAs in gestational hypertension, and ley-7e in chronic thromboembolic pulmonary hypertension (CTEPH) [28, 40]. Another benefit of miRNA biomarkers is their potential for increased sensitivity and specificity. They also have the advantage of being low cost and easily accessible in plasma biomarkers [37]. These characteristics make miRNA an attractive target for therapeutic intervention in the treatment of cardiovascular disease [4, 41].

In conclusion, the study of miRNA has the potential to revolutionise the way we diagnose and treat cardiovascular disease. Further research is needed to fully understand the role of miRNA in the development and progression of these disorders and to uncover the most effective ways to target them therapeutically. With continued advancements in technology and research, we may soon be able to harness the power of miRNA to improve the lives of millions of people affected by cardiovascular disease.

Microrna As A Potential Therapeutic Target For Hypertension

Recent studies have revealed the potential role of miRNAs in modulating hypertension and cardiovascular diseases. miRNA-17 has been shown to act through the BMPR2 signalling pathway, while miRNA-22 modulates sympathetic activity by targeting AngII type 1 receptors in the periventricular nucleus [42, 43]. Intraperitoneal administration of miR-22 has been found to reduce systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 11 mmHg and 15 mmHg, respectively [44] (49). Furthermore, miR-25 has been shown to delay calcium uptake kinetics in failing cardiomyocytes in both humans and mice.
The loss of contractile function was confirmed when miR-25 was overexpressed in vivo. Targeting miR-25 in mice with antagomirs improved cardiac function and increased survival compared to control mice [45]. Physical exercise has been shown to be a favourable non-pharmacological therapy for hypertension, as it supports pharmacological therapies and increases their effectiveness [46]. Exercise modulates factors such as mechanical wall stress and metabolic changes that can disturb physiological cardiovascular function and induce vascular remodelling. This can reduce the changes and pathologies produced secondary to hypertension, improve perfusion to peripheral and vital organs, and even decrease the severity of resistant hypertension [47–52]. Furthermore, exercise produces signals that modulate EC phenotypes and SMC phenotype switching, which have a beneficial effect on overall cardiovascular function.

Several studies have also identified a relationship between miRNAs and exercise-induced mechanical wall stress. miRNA expressions in ECs are increased secondary to unidirectional shear wall stress, particularly miR-21, which increases eNOS phosphorylation and production of nitric oxide, inducing SMC proliferation and apoptosis [53]. Oscillatory shear stress elevates miR-19a, 23a/27b, and miR-21 subtypes [54–56]. However, these results were obtained from in vitro studies and more research is needed to confirm these findings in human cells. Hu et al. identified the crucial role of miR-145 in the process of exercise-induced SMC phenotype changing [57].

Previous studies have demonstrated a relationship between mechanical wall stress and miRNA release in in vitro settings. However, it is difficult to accurately replicate the pathologies and changes that occur in human vessels, highlighting the need for further studies to be conducted using human cells. To date, there have been no published studies that have investigated the relationship between miRNA and exercise-induced changes in SMC phenotype. However, Hu et al. [58] identified the crucial role of miR-145 in this process through the use of microarray analysis to identify miRNA profiles within mechanically-stressed, changed SMC phenotype. Animal studies have also provided insight into the relationship between exercise and miRNA expression. For example, a study in mice with atherosclerotic aorta found that twelve weeks of aerobic exercise led to increased expression of miR-146a and miR-126, and decreased expression of miR-155 [59]. Additionally, ten weeks of swimming training has been shown to increase capillary fibre ratio and angiogenesis, which may be controlled by MAPK and PI3K/Akt/eNOS signalling, and also increase expression of miR-126 which targets Spred-1 and PI3KR2 and is considered as modulator of angiogenesis, repair, vascular integrity and specific for endothelial cells [43].

**Limitation Of Mirna As Therapy For Hypertension**

MiRNA-based therapy has the potential to be a promising future treatment option, but there are still limitations that need to be addressed. These limitations include challenges such as low serum stability, nonspecific targeting, innate immune responses, and poor pharmacological properties. Additionally, miRNAs target multiple genes and may suppress the expression of genes that are not dysregulated. To overcome these limitations, research has focused on developing new in vivo delivery systems for miRNA
molecules that target specific cells. For example, the use of liposomal encapsulation technology has been shown to improve the half-life of therapeutic miRNAs in the blood.

Furthermore, several different carriers of miRNA molecules have been developed, such as biodegradable polymers, PEGylated liposomes, and lipidoids. These delivery systems are designed to protect the miRNA molecules from being removed by the kidney filter system, resulting in more efficient intracellular delivery [60, 61]. Microvesicles membrane markers would also be useful in determining the cell-tissue source of circulating miRNAs. Furthermore, Dluzen’s cohort study has shown that the expression of miRNAs can differ according to race, between African and White Americans [60], highlighting the importance of considering these variations in the development of miRNA-based therapeutics.

**Conclusion**

In conclusion, miRNAs play a critical role in regulating gene expression and have been found to be involved in the development of hypertension. MiRNAs can target multiple mRNA and several miRNAs can target a single mRNA, making this regulation effective and able to control at least 60% of protein coding genes in humans. Despite the complex and multifaceted nature of hypertension, research supports the efficiency of post-transcriptional regulation generated by miRNAs and epigenetic genome alterations in the pathogenesis of hypertension. Studies have suggested that alterations in miRNA expression may be a consequence of DNA damage related to dysfunctions in DNA repairing pathways or secondary to chronic inflammation.

Further research is needed to determine the precise pathophysiology of hypertension and how miRNA expression is altered in hypertensive patients. However, based on current findings, it is hypothesised that miRNA expression is altered in hypertension and miRNA-based therapies may offer a potential treatment option for hypertension.

**Declarations**

**Ethical Approval**

Not applicable

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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Availability of Data and Materials

The data supporting this study's findings are available from the first author, [Nour Shaheen], upon reasonable request.

Authors' contributions

Nour Shaheen: Conceptualization, Writing-Original draft, review, and editing.

Rehab Adel Diab Mariam Tarek Desouki, Ahmed Shaheen, Mohamed Elmasry, Mayssa Rebei, Sarya Swed: Writing-Review and editing.

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None

References


**Figures**
The miRNA gene is activated and produces pri-miRNA, which then goes through two stages of processing - the first in the nucleus to become pre-miRNA, and the second in the cytoplasm to become mature miRNA. This process is aided by enzymes Drosha, dicer, and helicase. Once mature, the miRNA binds to the 3' end of mRNA and regulates gene expression [15–17].

Figure 2

After the mi-RNA has been translated into a protein, a mi-RNA inhibits the mRNA's ability to be transcribed, preventing the protein from being encoded [17, 18, 69].
Figure 3

The following graphic illustrates another mechanism by which mi-RNA regulates the expression of mRNA-encoded genes. When mi-RNA binds with mRNA in this instance, mRNA is degraded, hence removing its existence [17, 18, 69].
Excessive angiotensin II synthesis in the ventricular myocytes causes the creation of mi-RNA 122, which in turn decreases the amount of cationic amino acid transporters and increases the release of collagen I, TGFB, CTGF. This results in both cardiac fibrosis and endothelial dysfunction [32, 33].
Angiotensin II synthesis by ventricular myocytes increases mi-RNA-122 production, increasing TGF-B release and elevating the expression of MCP-1, collagen 1 alpha, and BACI I 1, all of which contribute to kidney injury [32, 33].