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***Research Article***

# miR-204-5p and miR-130a-3p in Focus: Computational Breakthroughs in Understanding Hypertension Pathogenesis

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**ABSTRACT**

Hypertension is a multifactorial disorder influenced by complex genetic and epigenetic interactions. Recent advancements in understanding the role of microRNAs (miRNAs) in regulating gene expression have provided new insights into the molecular mechanisms underlying hypertension. This study investigates the involvement of miRNAs in the pathophysiology of hypertension by analyzing gene expression profiles derived from multiple datasets obtained from NCBI and analyzed with GEOR. miR-DEGs were identified and subjected to the DAVID online tool for gene ontology study. BiBiServ2 was queried for miRNA/mRNA homology study. A total of 1,014 overlapping differentially expressed genes (DEGs) were identified across three datasets, revealing a significant dysregulation of the hypertensive transcriptome. The study further highlights the role of miRNAs, such as miR-29a-3p, miR-204-5p, miR-130a-3p, and miR-145-5p, in targeting these DEGs, with a predominant suppression of gene expression observed in hypertensive conditions. Functional enrichment analysis of miRNA-targeted DEGs revealed significant associations with key pathways involved in vascular remodeling, inflammation, and aldosterone regulation, including MAPK signaling, PI3K-Akt signaling, and the renin-angiotensin-aldosterone system (RAAS). Additionally, miRNA/gene homology studies demonstrated strong binding affinities between these miRNAs and genes involved in aldosterone synthesis, suggesting their pivotal role in modulating blood pressure regulation. The findings underscore the critical involvement of miRNAs in hypertension, proposing their potential as biomarkers and therapeutic targets for hypertension management. Future research should focus on validating these miRNA-targeted pathways and exploring miRNA-based therapeutics to restore homeostasis in hypertension.

**Keywords:** Aldosterone; Hypertension; miRNA; Genes; Pathways; Therapeutics

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## INTRODUCTION

Hypertension is a significant global health issue, affecting over 1.4 billion adults and serving as a primary risk factor for cardiovascular diseases, stroke, and kidney dysfunction (Mills *et al*., 2020). The disease is characterized by increased systolic and/or diastolic blood pressure, which if left untreated, can lead to serious health ailments involving organ failure, such as kidney and heart disease (Brenner *et al*., 2020). The pathogenesis of hypertension is multifactorial, involving complex interactions among genetic predispositions, environmental factors, and underlying biological mechanisms. While traditional risk factors, such as diet and lifestyle have been extensively studied, emerging evidence suggests that microRNAs (miRNAs) play a pivotal role in the regulation of gene expression. Thus, regulating many biochemical processes and their dysregulation remains a major factor in the development of numerous infectious and metabolic diseases, including cardiovascular diseases (Dandare, *et*

*al*., 2022; Jusic & Devaux, 2019; Khidr *et al*., 2023; Liu *et al*., 2021; Matshazi *et al*., 2021; Nunes *et al*., 2025; Shaheen *et al*., 2024).

miRNAs are small, non-coding RNA molecules that modulate gene expression by binding to complementary sequences in target mRNAs, leading to their degradation or translational repression (Rani & Sengar, 2022). Their involvement in cardiovascular physiology has garnered attention, with specific miRNAs linked to key processes such as vascular tone regulation, cardiac hypertrophy, and inflammation. Dysregulation of miRNAs has been observed in various forms of cardiovascular diseases, where alterations in their expression profiles can disrupt the balance of signaling pathways that govern vascular homeostasis and blood pressure control (Khidr *et al*., 2023). Furthermore, the implications of miRNA dysregulation have extended to organ failure, including heart failure, chronic kidney disease, liver cirrhosis, and stroke (Blaya *et al*., 2021; Liu *et al*., 2024; Xie *et al*., 2023). For instance, miR-155 and miR-126 have been implicated in mediating inflammatory responses and endothelial function (Li *et al*., 2018), which are critical in the pathophysiology of hypertension and its sequelae (Wang *et al*., 2012). Despite the significant therapeutic advancement in the management of hypertension, it remains one of the leading risk factors for several life-threatening diseases (Mills *et al*., 2016). Given their regulatory roles and the potential for miRNAs to serve as biomarkers or therapeutic targets, a deeper understanding of their involvement in hypertensive disorders could offer novel strategies for prevention and treatment.

This research explored the contributions of miRNAs to the pathogenesis of hypertension and its complications, highlighting their potential mechanisms of action and therapeutic implications. By synthesizing from existing literatures and presenting original findings, we seek to advance the understanding of miRNA involvement in hypertension, ultimately contributing to improved management strategies for this pervasive condition.

## MATERIALS AND METHODS

### Data mining for differentially expressed miRNA and target genes in hypertension

Gene expression profile datasets related to hypertension were retrieved from the NCBI Gene Expression Omnibus (GEO) database and analyzed using the Geo2R tool to identify significantly differentially expressed genes (DEGs). Three hypertension-related datasets, GSE113439 ( Mura *et al.*, 2019), GSE236251 (Kucherenko *et al*., 2023), and GSE33463 (Cheadle *et al*., 2012) were selected based on their relevance and quality for further analysis. Common differentially expressed genes (cDEGs) across these datasets were identified using a Venn diagram constructed with the Bioinformatics and Evolutionary Genomics tool (http://bioinformatics.psb.ugent.be/webtools/Venn/). Genes that were differentially expressed in at least two of the three selected datasets were prioritized for downstream analyses, ensuring a robust identification of candidates with potential roles in the pathogenesis of hypertension. The fold-change values for each gene, obtained from the selected experiments, were averaged and attributed to the corresponding gene. The dysregulated miRNAs implicated in hypertension were identified through a comprehensive and intensive review of the existing scientific literature.

### Prediction of miRNAs target differentially expressed genes (miR-DEGs).

miRNA target prediction database (miRDB) was queried to predict their target genes of the selected miRNAs. Subsequently, the miRNA-targeted DEGs (miR-DEGs) were determined following the approach described by Dandare *et al*., (2021). To focus on key regulatory interactions, the top three miRNAs with the highest number of target DEGs were selected for further downstream analyses.

### Functional enrichment analysis.

Database for Annotation, Visualization, and Integrated Discovery (DAVID) was queried for functional enrichment analysis. Three major GO terms, particularly biological processes, cellular compartments, molecular functions were used to predict the regulatory role of the miRNAs on cellular function linked to the development of diabetes mellitus (Sherman *et al*., 2022). Additionally, Kyoto Encyclopedia of Genes and Genomics mapper (KEGG) was used for the pathway enrichment analysis (Hu *et al*., 2019).

### miRNA/mRNA homology study

Mature miRNA sequences were obtained from the miRDB database, and the corresponding target gene sequences were retrieved in FASTA format from the NCBI database. The BiBiServ online tool was queried for homology analysis, in which the energy threshold was set at -25 kcal/mol (Krüger & Rehmsmeier, 2006; Rehmsmeier *et al*., 2004).

## RESULTS

### Differentially Expressed Genes in Hypertension

Volcano plots generated from the gene expression profiles of hypertensive subjects, derived from raw data of three selected experiments obtained from the NCBI database, reveal significant patterns of gene dysregulation (Fig. 1a). The Venn diagram constructed shows that 1014 DEGs are overlapping among the three selected experiments, and a total of 6917 DEGs are common in at least two of the three selected experiments (Fig 1D), thus considered as common

differentially expressed genes (cDEGs). Among the datasets, GSE113439 exhibited the highest number of differentially expressed genes (DEGs), with a total of 15,059 DEGs identified (Fig. 1A). This was followed by GSE33463 and GSE236251 with 8,962 and 7,971 DEGs respectively (Fig. 1B & C). Upon averaging the DEGs across the three experiments, it was observed that approximately 59% of the genes were upregulated**,** while 41% were down regulated in response to hypertension (Fig. 1E).

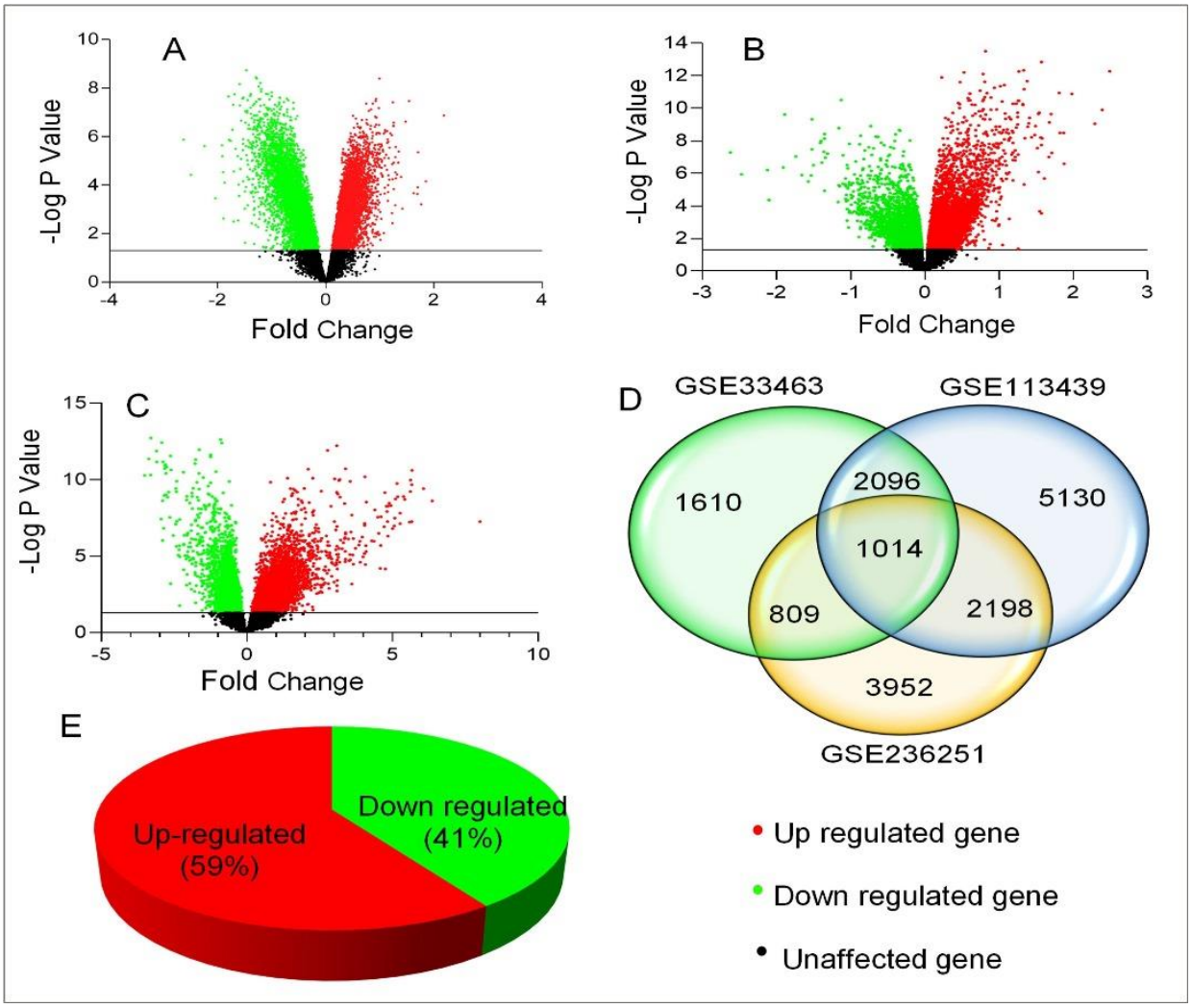


**Fig. 1: Gene expression analysis across three experiments. A, B, and C: Volcano plots displaying the differential gene expression results from three separate experiments. GSE113439, GSE33463 and GSE236251 respectively. D: Venn diagram illustrating the overlap and unique genes among the three experiments. E: Pie chart showing the percentage distribution of overlapping upregulated and downregulated genes across the three experiments**

**miRNA target differentially expressed genes (miR-DEGs) in hypertension**

Experimentally validated miRNAs that are dysregulated in hypertension were identified. However, only four of them were selected and presented owing to their great potential in the regulation of genes dysregulated due to hypertension (Fig. 2). The number of differentially expressed genes (DEGs) targeted by specific miRNAs, as presented. It was indicated that miRNAs, miR-29a-3p exhibited the highest number of targets DEGs, regulating a total of 404 genes, followed by miR-240-5p, which potentially regulates 380 DEGs. miR-130a-3p and miR-145-5p targeted the least number of DEGs, with 367 and 327 genes, respectively. Furthermore, it was observed that the number of downregulated genes targeted by these miRNAs was relatively higher compared to the upregulated genes, suggesting a stronger influence on gene suppression within the dataset.

**Functional Enrichment Analysis of miR-DEGs**

The gene ontology (GO) enrichment analysis of miRNA-targeted differentially expressed genes (miR-

DEGs) revealed their involvement in a wide array of critical biological processes that will directly or indirectly implicate hypertension. These include protein phosphorylation, MAPK signaling cascade, transcriptional regulation, modulation of PI3-kinase activity, apoptotic signaling pathways, aldosterone biosynthesis and secretion, and proliferation of cardiac muscle cells (Figure 3A). At the subcellular level, the miR-DEGs exhibited functional associations with several key cellular compartments. Each of the analyzed miRNAs (miR-130a-3p, miR-204-5p, miR-145-5p, and miR-29a-3p) demonstrated regulatory influence over a substantial number of genes localized within the cytosol, nucleus, nucleoplasm, centrosome, Golgi apparatus, and membranes (Fig. 3B), highlighting their widespread functional impact on cellular architecture and processes.

**Regulatory network of miRNAs and miR-DEGs in hypertension-associated biological processes**

A network was constructed to analyze the interactions between dysregulated genes critical to blood pressure regulation and the development of hypertension and the selected miRNAs (miR-130a-3p, miR-204-5p, miR-145-5p, and miR-29a-3p). The results revealed the extent to which each miRNA targets differentially expressed genes in the pathway. miR-29a-3p was found to target the highest number of differentially expressed genes (59), followed by miR-204-5p (55), demonstrating their significant regulatory potential (Fig. 4). miR-130a-3p and miR-145-5p each targeted 37 differentially expressed genes, representing the least number among the miRNAs studied. Notably, some genes, such as PTPRJ, CAMK2D, and FRS2, were targeted by at least three of the miRNAs under investigation, indicating their critical role as central regulatory nodes in the network.

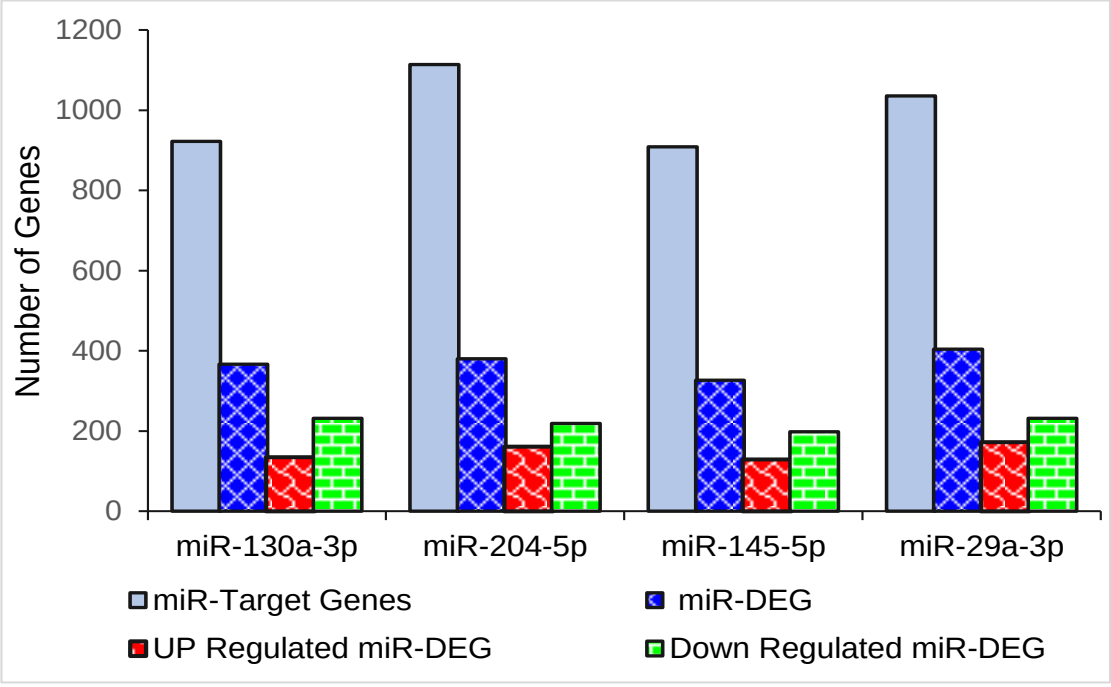


**Fig. 2: miRNA target differentially expressed genes (miR-DEGs) in hypertension**

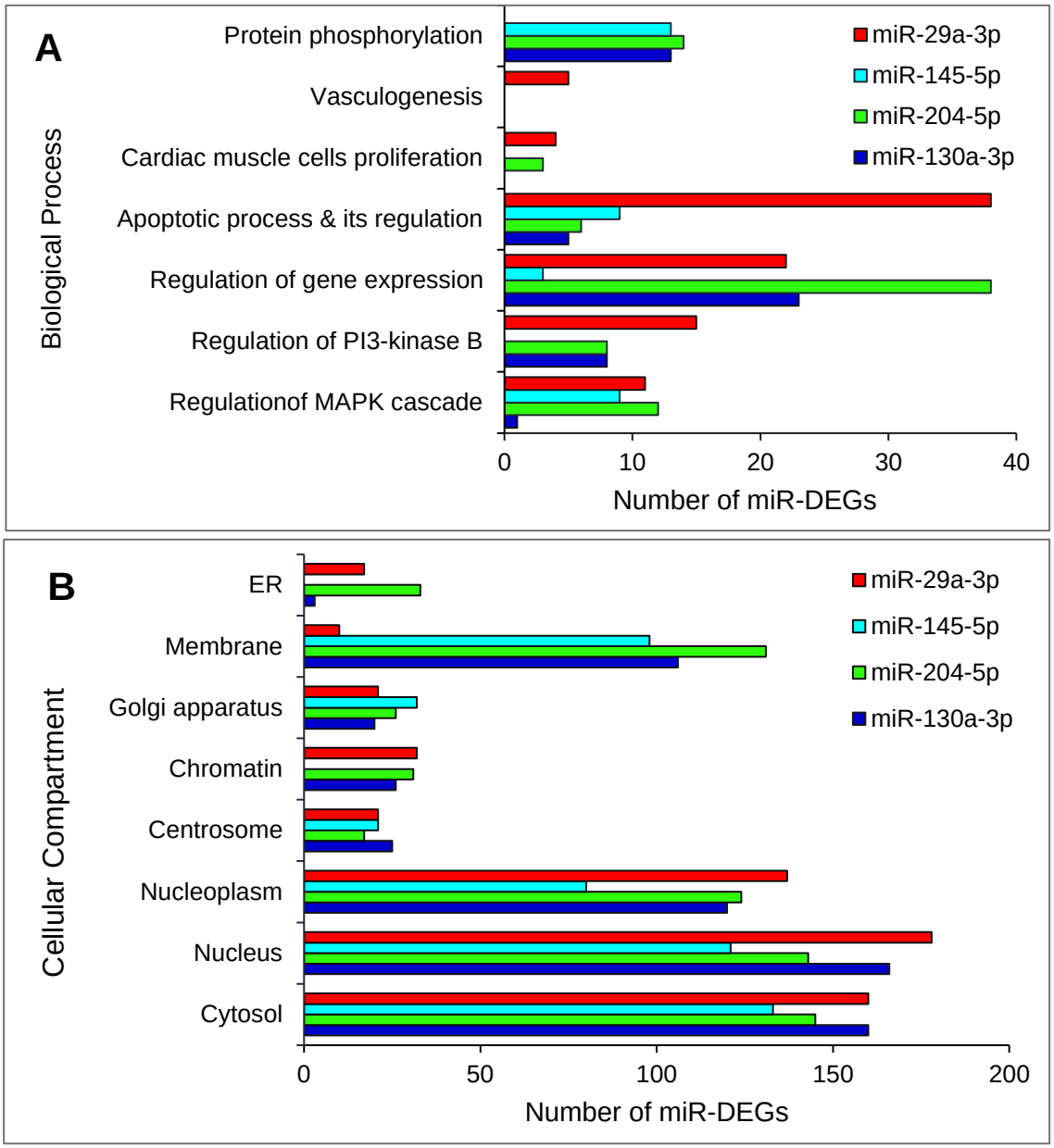


**Fig 3: Functional categorization miR-DEGs based on gene ontology terms (A) Biological processes, (B) cellular compartments**


**Fig 4. Regulatory network of miRNAs and dysregulated genes associated with key biological processes in hypertension**

**KEGG pathway analysis**

The KEGG pathway analysis of miR-DEGs implicated in hypertension revealed significant enrichment in several signaling pathways known to contribute to hypertension pathophysiology. These include the apelin signaling pathway, FoxO signaling pathway, p53 signaling pathway, TNF signaling pathway, MAPK cascade, PI3K-Akt signaling pathway, atherosclerosis-related pathways, mTOR signaling pathway, JAK/STAT signaling cascade, and VEGF signaling pathway, among others (Fig. 5). Particular emphasis was placed on the aldosterone synthesis and secretion pathway, given its critical role in blood pressure regulation. The analysis revealed that dysregulated miRNA-targeted genes (miR-DEGs) directly impact the aldosterone synthesis and secretion pathway, with 10 key genes showing altered expression patterns (Fig. 6). Specifically, ADCY1, ADCY6, ATP2B4, and LDLR were upregulated, while ATF2, CALML4, CAMK2D, CAMK2G, CAMK4, and PRKACB were downregulated (Fig. 6A). Furthermore, all analyzed miRNAs (miR-130a-3p, miR-204-5p, miR-145-5p, and miR-29a-3p) were shown to regulate at least one gene involved in this pathway (Fig. 6B). This observation highlights the collective influence of these miRNAs on aldosterone synthesis and secretion, demonstrating their potential as regulatory elements in hypertension-related processes.

**miRNA and Target Genes Homology Study**

The study evaluated the binding affinity of miR-130a-3p, miR-204-5p, miR-145-5p, and miR-29a-3p against dysregulated genes involved in the aldosterone synthesis and secretion pathway in hypertensive subjects. Using Bibiserv, the ten best miRNA-mRNA hybrids with minimum free energy (MFE) values of at most -28 kcal/mol were identified and presented (Fig. 7). The analysis revealed that, with the exception of

miR-29a-3p, all examined miRNAs demonstrated firm binding to at least two target genes in the pathway, with MFE values meeting or exceeding the threshold of -28 kcal/mol. Among these, the most stable hybrid was miR-204-5p/ATP2B4, which achieved the best MFE value of -36.4 kcal/mol, indicating the strongest binding affinity.

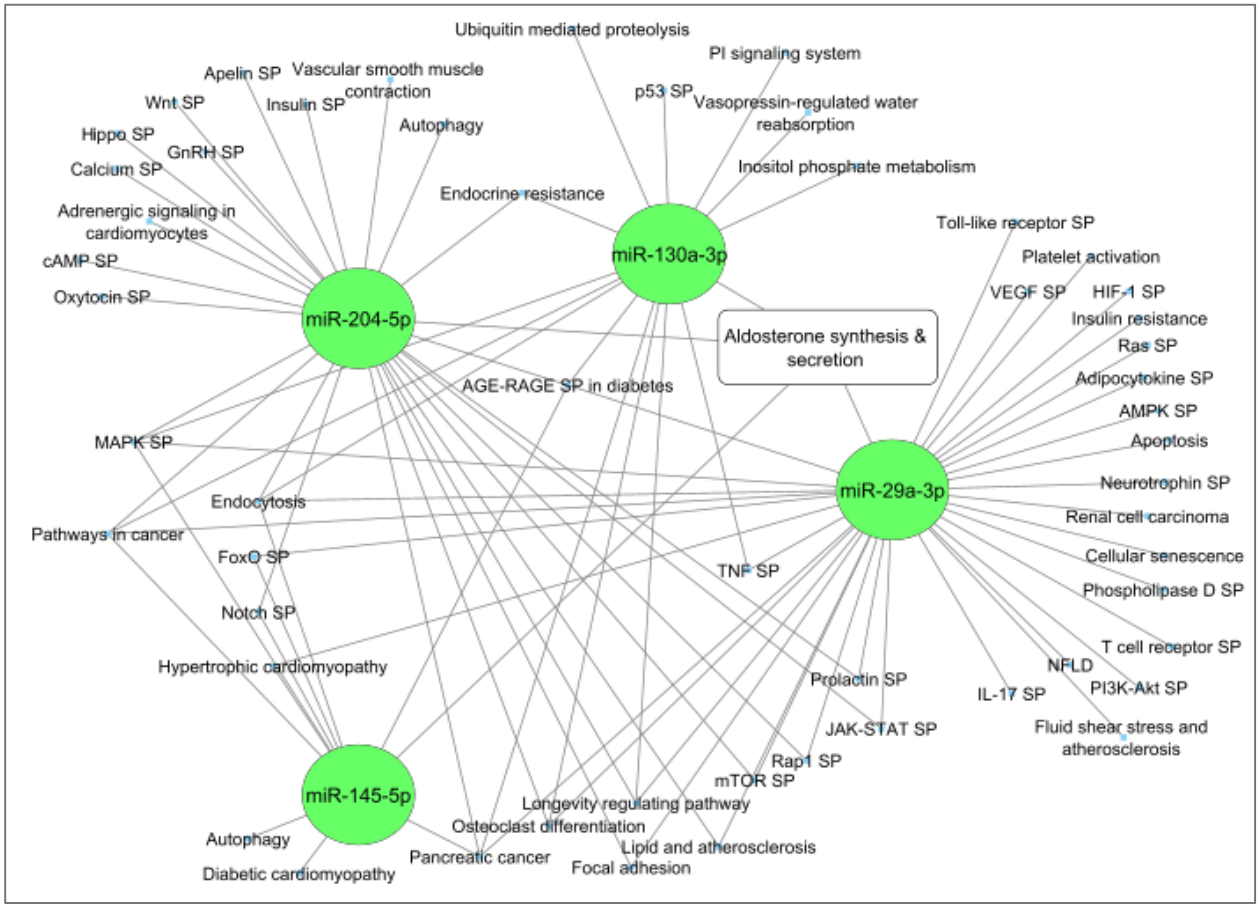


**Fig 5. Regulatory network of miRNAs and pathways enriched with hypertension-associated dysregulated genes. SP: signaling pathway, NAFLD: Non-alcoholic fatty liver disease, PI: Phosphatidylinositol**

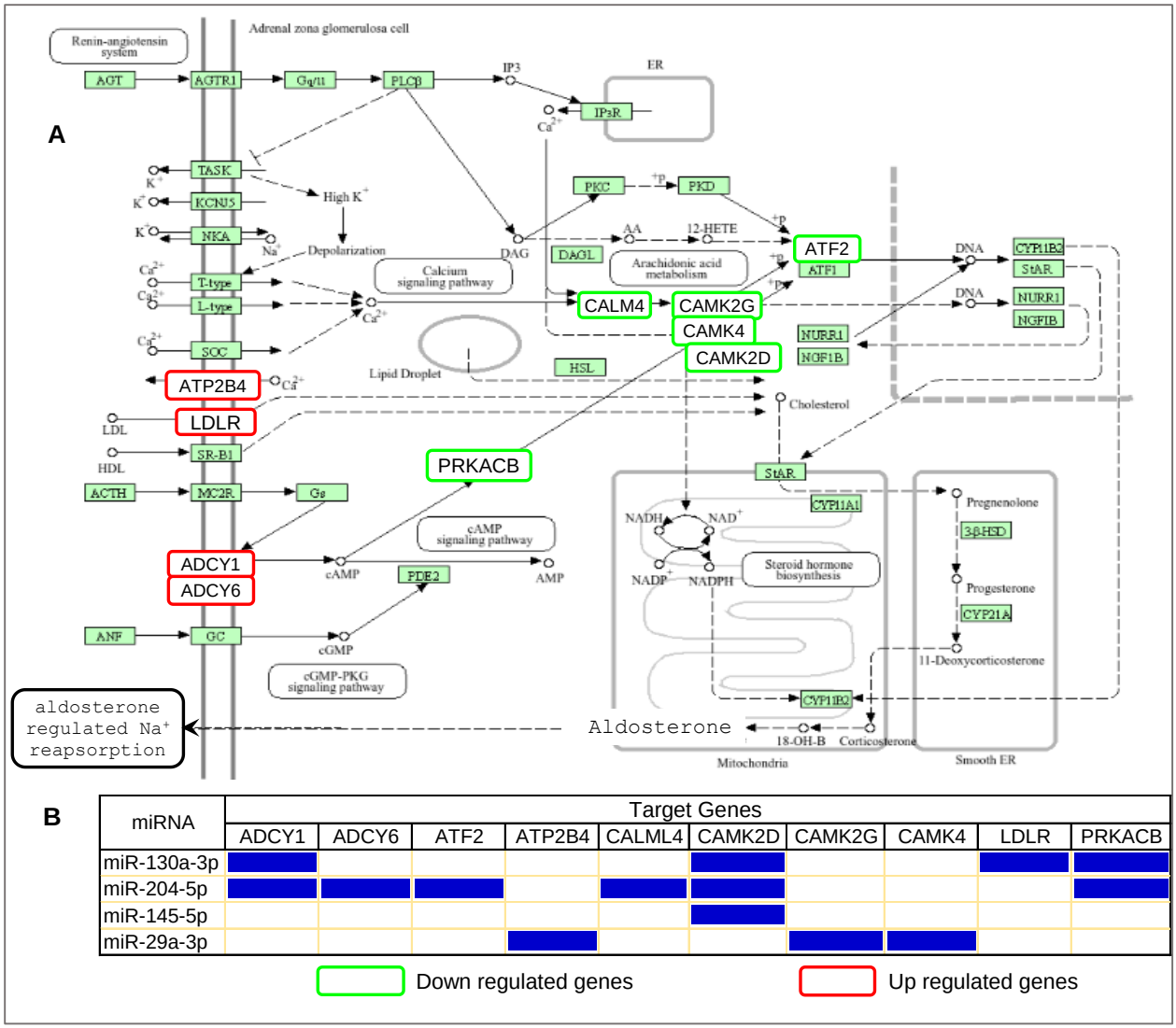


**Fig 6: miRNA-dysregulated target genes (miR-DEGs) in the aldosterone synthesis and secretion Pathway**

| S/No | miRNA | Target Genes | Binding Position | MFE (kcal/ mol) | Hybridazation Pattern |
|---|---|---|---|---|---|
| 1 | miR-204-5p | ATP2B4 | 1714 | -36.4 | Target 5' GGGCA AGGAUGACGAAGGGGA 3'<br>miRNA 3' UCCGU UCCUACUGUUUCCCUU 5' |
| 2 | miR-145-5p | ADCY1 | 615 | -34.8 | Target 5' GGGGUUCC GGGG GCUGGG 3'<br>miRNA 3' CCCUAAGG CCCU UGACCU 5' |
| 3 | miR-204-5p | ADCY1 | 5315 | -31.4 | Target 5' GGGCA GGAUGGC AGGGAA 3'<br>miRNA 3' UCCGU CCUACUG UCCCUU 5' |
| 4 | miR-204-5p | LDLR | 88 | -31.3 | Target 5 GGGG CCUGGGG GA GCUGGAC 3'<br>miRNA 3' UCCC GGACCCU UU UGACCUG 5' |
| 5 | miR-145-5p | CALML4 | 1532 | -30.1 | Target 5' GG UUUCUGGGAG AGCUGGA 3'<br>miRNA 3' UCCC AAGGACCCUU UUGACCUG 5' |
| 6 | miR-204-5p | ADCY6 | 4917 | -30.5 | Terget 5' GG AUGGGGUG G GAGGGAG 3'<br>miRNA 3' UCC UAUCCUAC U UUCCCUU 5' |
| 7 | miR-145-5p | ATP2B4 | 4016 | -30 | Terget 5' GUUCCUG GGAGGCUGGGC 3'<br>miRNA 3' UCCC UAAGGAC CUUUUGACCUG 5' |
| 8 | miR-204-5p | CAMK4 | 1355 | -29.1 | Terget 5' AGGCA AGGAU GAUAAAGG GG 3'<br>miRNA 3' UCCGU UCCUA CUGUUUCC CU 5' |
| 9 | miR-130a-3p | ADCY1 | 8838 | -28.4 | Terget 5' GCCCU GACA GCACUG 3'<br>miRNA 3' UA CGGGA UUGU CGUGAC 5' |
| 10 | miR-130a-3p | LDLR | 91 | -28.4 | Terget 5' GCCCU GGC AUUGCGCUG 3'<br>miRNA 3' UACGGGA UUG UAACGUGAC 5' |

**Fig 7: mRNA-miRNA hybrid characteristics showing the minimum free energy (MFE) of the duplexes and binding pattern at predicted target sites**

**DISCUSSION**

The analysis of gene expression profiles from hypertensive subjects highlights substantial dysregulation across multiple datasets. The volcano plots illustrate significant patterns of gene expression changes, underscoring the complexity of the hypertensive transcriptome. The identification of 1,014 overlapping DEGs among the three experiments and 6,917 DEGs shared by at least two datasets reinforces the robustness of these findings as common differentially expressed genes (cDEGs). Among the datasets analyzed, GSE113439 contributed the largest number of DEGs, reflecting its potential richness in capturing the transcriptional landscape of hypertension. The distribution of DEGs in GSE33463 and GSE236251 further complements this profile, collectively unveiling an average of 59% upregulated and 41% downregulated genes across the datasets. This upregulation/downregulation balance suggests a predominant activation of pathways associated with hypertension, aligning with previous studies linking hypertension to dysregulated inflammatory, metabolic, and vascular signaling pathways (Rabinovitch *et al*., 2014). Furthermore, it was observed that the number of downregulated genes targeted by these miRNAs was relatively higher compared to the upregulated genes**,** suggesting a stronger influence on gene suppression within the dataset. This pattern underscores the critical regulatory roles of these miRNAs in modulating gene expression, with implications for their functional involvement in the studied biological context.

The identification of miRNA-targeted differentially expressed genes (miR-DEGs) in hypertension highlights the intricate role of post-transcriptional

regulation in the pathophysiology of the condition. Among the analyzed miRNAs, miR-29a-3p was found to have the highest regulatory influence in hypertensive disorder. These findings align with prior studies indicating that miR-29a-3p plays a pivotal role in vascular remodeling and fibrosis, common features of hypertension (Hsu *et al*., 2021). Interestingly, the data revealed a higher proportion of downregulated DEGs targeted by these miRNAs compared to upregulated ones, underscoring the predominant role of miRNAs in gene suppression mechanisms. This observation corroborates previous findings, suggesting that miRNA-mediated repression of hypertension-relevant genes may significantly contribute to the molecular landscape of the disease (Shaheen *et al*., 2024).

The functional enrichment analysis of the identified miR-DEGs revealed that the analysed miRNAs are significantly associated with pathways critical to hypertension pathophysiology, including protein phosphorylation, MAPK signaling cascade, transcriptional regulation, modulation of PI3-kinase activity, apoptotic signaling pathways, aldosterone biosynthesis and secretion, and proliferation of cardiac muscle cells. Notably, previous studies demonstrated that alteration in these biological processes may lead to high blood pressure (Ma *et al*., 2023; Wu *et al*., 2024). Furthermore, the study is consistent with previous reports, highlighted the involvement of miR-204 in the regulation of blood pressure. Specifically, increased expression of miR-204 normalizes the dysregulated apoptosis and proliferation observed in hypertension (Liu *et al*., 2021). Additionally, elevated levels of circulating miR-143 and miR-145, have been correlated with hypertension-related complications, suggesting their potential utility in clinical settings (Murase *et al*., 2024; Xu *et al*., 2022). The roles of miR-29a3p, miR-204-5, miR-130a-3p, and miR-145-5p in hypertension pathology observed in the present study underline their distinct yet interrelated effects on cardiomyocyte proliferation and overall cardiac remodeling. At the subcellular level, the miR-DEGs were mapped to key cellular compartments, including the cytosol, nucleus, nucleoplasm, centrosome, Golgi apparatus, and membranes. This broad localization reflects the extensive functional influence of the analyzed miRNAs on cellular architecture and processes. The presence of miR-DEGs in centrosomes and the Golgi apparatus, for instance, highlights their role in regulating cell cycle dynamics and protein trafficking, processes that may contribute to vascular remodeling and hypertrophy observed in hypertension (Mascanzoni *et al*., 2022).

The network interaction of the four miRNAs, miR-130a-3p, miR-204-5p, miR-145-5p, and miR-29a-3p, revealed that PTPRJ, CAMK2D, and FRS2 were targeted by at least three of the miRNAs under investigation, indicating their critical role as central regulatory nodes in the network. These miRNAs strongly influence blood pressure via their interaction with genes involved in the pathogenesis of hypertension. The involvement of miR-130a-3p in hypertension pathology is in agreement with earlier report, which suggested that miR-130a influences vascular smooth muscle cell (VSMC) proliferation and contributes to vascular dysfunction in hypertensive mice by downregulating the expression of the growth arrest-specific homeobox (GAX) gene (Ali *et al*., 2022). The findings of the present study reveal that miR-204-5p regulates cellular processes associated with the pathogenesis of hypertension and its upregulation leads to hypertension. This result is in line with the previously reported data (Gabani *et al*., 2019; Liu *et al*., 2021). Contrary to our findings, miR-204 was reported to be downregulated in patients with pulmonary hypertension (Courboulin *et al*., 2011; Lee *et al*., 2012; Yu *et al*., 2018). The inconsistency in the results is attributed to the tissue-specific expression pattern of the miR-204. The over-expressed miRNA-204 influences hypertension suppressing the proliferation and migration of vascular smooth muscle cells thereby distorting the vascular tone and structure which consequently leads to hypertension (Gabani *et al*., 2019; Liu *et al*., 2021).

miR-29a-3p was linked to several diseases (Chen *et al*., 2016; Mo & Cao, 2022) including high blood pressure (Luo *et al*., 2015). Our data shows overexpression of miR-29a-3p has a strong link to the development of hypertension. This is consistent with the results from a previous study, which indicated that miR-29a-3p is also upregulated in hypertensive subjects and could be a potential target for prevention and therapy of hypoxic pulmonary hypertension(Luo *et al*., 2015).

Interestingly, the findings of this study underscore the complex interplay between dysregulated miRNA-targeted genes and signaling pathways implicated in hypertension pathophysiology. Through KEGG pathway analysis, multiple enriched pathways that are well-established in the etiology of hypertension were identified, including the apelin signaling pathway, FoxO signaling pathway, p53 signaling pathway, TNF signaling pathway, MAPK cascade, PI3K-Akt signaling pathway, atherosclerosis-related

pathways, mTOR signaling pathway, JAK/STAT signaling cascade, and VEGF signaling pathway. These pathways are integral to the regulation of vascular tone, inflammation, oxidative stress, and endothelial function, all of which contribute to hypertension development and progression (Ali *et al*., 2022; Martyniak *et al*., 2024; Stanciu *et al*., 2024). Moreover, the findings offer valuable insights into the broader implications of miRNA-gene interactions in hypertension. The significant enrichment of pathways, such as the PI3K-Akt and JAK/STAT signaling cascades, suggests that dysregulated miRNAs influence not only aldosterone production but also vascular remodeling, immune responses, and metabolic processes. These pathways' roles in promoting endothelial dysfunction and systemic inflammation align with the multifactorial nature of hypertension (Huang *et al*., 2008; Ramadan *et al*., 2021).

The aldosterone synthesis and secretion pathway emerged as a key regulatory hub, with dysregulated miRNA-targeted genes (miR-DEGs) significantly influencing its functionality. This pathway's pivotal role in modulating blood pressure via the renin-angiotensin-aldosterone system (RAAS) underscores its importance (Martyniak *et al*., 2024). Our analysis revealed 10 key genes with altered expression patterns: ADCY1, ADCY6, ATP2B4, and LDLR were upregulated, whereas ATF2, CALML4, CAMK2D, CAMK2G, CAMK4, and PRKACB were downregulated. These findings suggest a dual regulatory mechanism in which specific genes promote aldosterone synthesis and secretion, while others suppress it, contributing to dysregulated blood pressure homeostasis in hypertension. The upregulation of ADCY1 and ADCY6 suggests enhanced cyclic AMP (cAMP) production, which may stimulate aldosterone synthesis via activation of protein kinase A (PKA) (Gambaryan *et al*., 2006). Conversely, the downregulation of PRKACB, a key subunit of PKA, and calmodulin-dependent kinase genes (CAMK2D, CAMK2G, CAMK4) indicates impaired signaling downstream of cAMP, which could attenuate aldosterone release despite increased synthesis (Spät & Hunyady, 2004). This apparent dichotomy highlights the intricate feedback mechanisms within the aldosterone synthesis and secretion pathway.

Furthermore, the downregulation of ATF2, a transcription factor implicated in aldosterone biosynthesis, and CALML4, which regulates calcium signaling, underscores the role of transcriptional and post-transcriptional modulation in this pathway. ATP2B4, an essential calcium pump, was upregulated, potentially compensating for dysregulated calcium dynamics. Similarly, the observed upregulation of LDLR, a receptor involved in cholesterol uptake, could enhance substrate availability for aldosterone synthesis (Tsai *et al*., 2021), further emphasizing the multifaceted regulatory inputs in this pathway.

All analyzed miRNAs (miR-130a-3p, miR-204-5p, miR-145-5p, and miR-29a-3p) were shown to target at least one of these genes, reinforcing their collective influence on aldosterone regulation. Notably, miR-130a-3p and miR-204-5p have been previously associated with cardiovascular diseases, while miR-145-5p and miR-29a-3p are recognized for their roles in vascular remodeling and fibrosis. Their coordinated regulation of aldosterone-related genes demonstrates the potential of these miRNAs as key modulators of RAAS activity in hypertension (Wang & Yang, 2015).

The results of the miR: Genes homology study highlight significant binding specificity for most of the examined miRNAs, except for miR-29a-3p, which demonstrated weak or no substantial interaction within the pathway. miR-204-5p emerged as the most effective miRNA, forming a hybrid with ATP2B4 at an MFE value of -36.4 kcal/mol, indicating the highest binding stability. This strong affinity suggests a potential regulatory role for miR-204-5p in modulating ATP2B4 expression, a critical gene in the aldosterone synthesis and secretion signaling pathway. Thus, strengthen the role of the miRNA in the pathogenesis of hypertension. This evidence supports the earlier report that highlights the regulatory effect of miR-204-5p in the regulation of ATP1B4 (Tapia-Castillo *et al*., 2019). Other notable hybrids with good binding affinities (MFE: ≤ -28kcal/mol) include miR-145-5p with ADCY1 and CALML4, miR-204-5p with ADCY1 and LDLR, and miR-130a-3p with LDLR and ADCY1. These interactions established the regulatory effect of the miRNA on the target genes, as supported by previous studies (Alves-Junior *et al*., 2009; Dandare *et al*., 2023; Krüger & Rehmsmeier, 2006). The ability of miRNAs to perfectly interact with the multiple genes of the aldosterone synthesis and secretion pathway underscores their potential to regulate various components of the pathway, a crucial process in blood pressure control.

**CONCLUSION**

The study highlights the critical role of miRNA-gene interactions in elucidating the molecular mechanisms underlying hypertension. Gene Ontology (GO) enrichment analysis of miR-DEGs reveals their

extensive involvement in key biological processes and signaling pathways, including aldosterone synthesis and secretion, MAPK signaling, and PI3K-Akt signaling, which contribute to vascular remodeling, inflammation, and metabolic dysregulation. Affinities between miR-29a-3p, miR-204-5p, miR-130a-3p, and miR-145-5p with dysregulated genes. Through the homology study of miRNA and their target genes, strong binding affinities were identified between miR-29a-3p, miR-204-5p, miR-130a-3p, and miR-145-5p with key genes involved in the aldosterone synthesis and secretion pathway. Dysregulation of miR-29a-3p, miR-204-5p, miR-130a-3p, and miR-145-5p underscores their influence on hypertension pathophysiology and identifies them as potential biomarkers and therapeutic targets. These findings emphasize the potential of miRNA-based therapeutics to restore homeostasis within disrupted pathways, offering novel strategies for hypertension management. Future research should validate these findings across diverse populations and explore miRNA mimics or inhibitors in preclinical models to advance therapeutic development.

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