Review article

MicroRNAs and Hypertension

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Abstract

MicroRNAs (miRNAs) are non-coding, highly conserved RNAs found in all biological fluids, that are emerging as master regulators of gene expression, consequently impacting a variety of biological processes in both healthy and diseased environments. There are still certain limitations regarding analysis of circulating miRNAs, specifically concerning standardisation and accuracy of obtained data. However, there is an indisputable therapeutic and diagnostic potential, confirmed by recent research. Hypertension, as one of the leading causes of death in modern world, has been in the focus of scientific society for several decades now. So, it is of outmost importance to investigate and pinpoint appropriate miRNAs for early indication and diagnosis of hypertension in general population. More in vivo and clinical research is necessary in animal and human models in order to exploit the full potential of this novel technology.

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Introduction

MicroRNAs (miRNAs) represent a class of short length (20-24 nucleotides), highly conserved, non-coding RNAs that have a role in regulation of gene expression through inhibition of transcription, translation or degradation of target genes, depending on their origin (1,2). MiRNAs can be categorized as tissue-derived miRNAs (t-miRNAs) and freely circulating miRNAs (c-miRNAs), with t-miRNAs being mainly associated with hypertension and cardiac function (more evidence needed), while the latter are described as a potential specific biomarkers for early disease detection, with their abnormal expression being largely associated with diseases in humans (1,3).

C-miRNAs or extracellular miRNAs can be found in all biological fluids, mainly carried in vesicles exosomes, such as serum, plasma, saliva, urine, while serving a hormone-like purpose in processes of signalisation, mediation and regulation of a variety of biological and cellular activities, physiological responses and pathological conditions (3–5). Even though the sampling is minimally invasive and there is a potentially high reproducibility of results, analysis of miRNAs still represents a challenge due to low concentrations of target compounds, lack of standardized methodology and eventual accuracy obtained regarding their in vivo role and therapeutic properties (1,6).

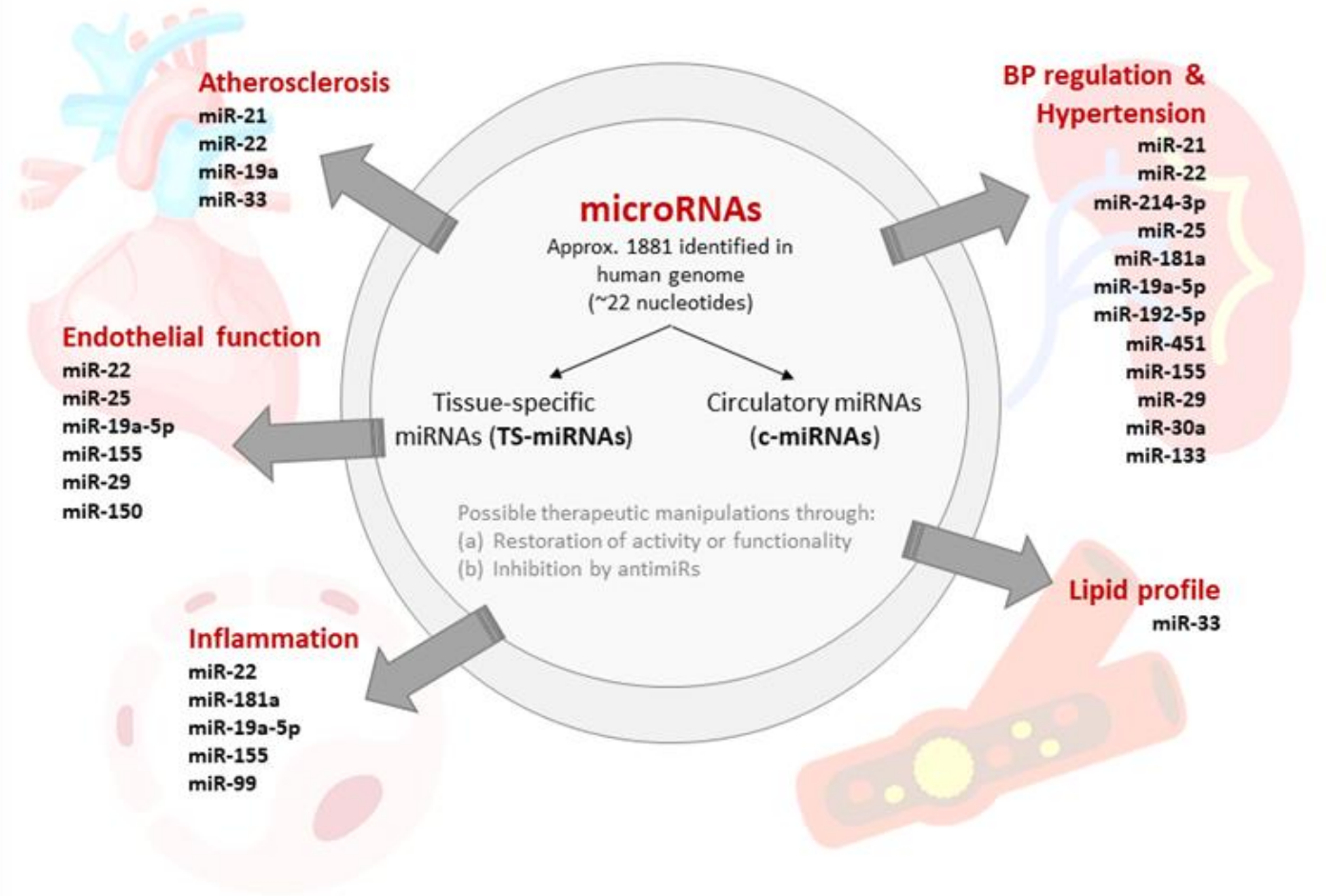

Figure 1. Schematic presentation of therapeutic and diagnostic potential of microRNAs in atherosclerosis, blood pressure regulation and hypertension, endothelial function, inflammation and lipid profile.
miR – microRNA; BP – blood pressure.

These highly stable regulators are primarily found in human serum and saliva (a total of 1881 miRNAs identified in human genome) and they can reduce gene expression post transcription by binding to the 3' untranslated region (UTR) of a messenger RNA (mRNA) leading to repression of translation and/or degradation of target (2,7). Lately, efforts are being made regarding investigation of therapeutic use of miRNAs in a wide variety of diseases, including cardiovascular disease, immune disorders, rheumatoid arthritis and cancer (8). The fact that mature miRNAs are highly conserved and short, makes them perfect for therapeutic manipulations towards modulation of cellular pathways and networks (9). There are two possible proposals for such actions: (1) therapeutic restoration of miRNA activity/functionality; and (2) inhibition of miRNA function by so-called antimiRs – antisense oligonucleotides (4,9,10). In order to draw firm conclusions, it is necessary to take into account that there are great variations in miRNA expression levels present, depending on their origin (tissue or cell type) and pathological state, which requires further extensive in vivo experiments in appropriate animal models. Schematic representation of miRNA breakdown regarding therapeutic/diagnostic potential is presented in Figure 1.

Emerging role of non-coding RNA in endothelial function and blood pressure regulation

Hypertension is, alongside diabetes and cancer, the most common chronic disease and leading cause of death in modern society (11). Yet, in a large number of affected individuals, the main cause of elevated blood pressure (BP) cannot be determined with certainty. Some of the risk factors associated with hypertension include genetic predisposition, advanced age, low physical activity, obesity and overall poor dietary habits characterized by high sodium chloride (NaCl) and low potassium intake (12,13). High-salt (HS) diet normally has a suppressive effect on renin-angiotensin system (RAS) – a physiological system that regulates BP – and leads to reduced renin, angiotensin II (Ang II) and aldosterone plasma levels (14,15), inciting endothelial dysfunction (16–18). However, in hypertensive and diabetic patients, RAS activation is not suppressed following salt loading, thus salt loading tends to aggravate the cardiovascular risks in those particular individuals (14,19,20).

So far, animal studies have shown that Ang II, HS diet and exercise change miRNA levels in hypertension (6). Several studies listed miR-22 (21), miR-181a (22) and miR-25 (23) as potential therapeutics in stress response, hypertension and vascular remodelling. Furthermore, it is necessary to address environmental factors in future research and find out what influence they could potentially have on miRNAs expression, especially in case of hypertension and related complications (6). Table 1 represents a cross-section of research studies regarding non-coding RNA role in endothelial function and BP regulation.

Non-coding RNAs in hypertension treatment

Currently, there is a lack of evidence supporting a significant role of non-coding RNAs in BP regulation and hypertension but it has been frequently mentioned that miRNA activity is deregulated in the state of illnesses.

MiR-21 is among the first identified non-coding RNAs (24) and has been suggested by several studies as a biomarker for early atherosclerosis and hypertension (25–27). In a study by Kara et al. (2021), significantly increased levels of miR-21 and aldosterone were found in patients with resistant hypertension compared to newly diagnosed hypertensive patients and healthy controls (28). Further, higher levels of miR-21 were reported in hypertensive, stroke and atherosclerotic patients compared with healthy controls, while it also negatively correlated with plasmatic levels of eNOS in hypertensive patients (29–31). Renal miR-214-3p has also been mentioned as a contributor to hypertension by directly targeting eNOS in rats and potentially humans (32,33).

Table 1. Cross-section of research studies regarding non-coding RNAs role in endothelial function and BP regulation

miRNAs	Study model	Targets	Effects	Reference
miR-21	Human model – hypertensive, ischemic stroke and atherosclerotic patients Rat model – SHR rats Mice model - C57BL/6J, TAC mice	mt-Cytb eNOS	↑ Mir-21 and aldosterone levels in RHT group Positive correlation with aldosterone, age, office SBP, 24-h ABPM all-day SBP; ↑ CRP level, plasma miR-21 expression level and CIMT in HT group ↓ NOx and eNOS levels in HT group ↑ miR-21 in stroke and atherosclerotic patients	(28) (29) (25) (27) (31)
miR-214-3p	Human model - HT and hypertensive nephrosclerosis patients Rat model – Dahl SS rat, SS.13^{BN26}(L26) rat	eNOS	Upregulated in kidneys of HT patients and HS–fed SS rats ↓ hypertension and albuminuria in SS model following inhibition of miR-214-2p	(33)
miR-22	Rat model – SHR rats Mice model – cardiac-specific knockout	Chga TGFβR I	↓ BP following inhibition ↓ cardiac hypertrophy and ↑ fibrogenesis of cardiac fibroblasts in knockout mice ↑ cardiac contractility and function following inhibition	(34) (36) (37)
miR-181a	Mice model – BPH/2J mice, miR-181a knockout	RAS	↑ BP and salt-sensitivity in knockout mice ↓ BP and renal renin mRNA following treatment with miR-181a mimic	(40) (41)

miR-19a	Human model – AMI and CAD patients, Rat model – Dahl SS rat Mice model - ApoE$^{-/-}$ mice, c57BL/6 mice	ADRB1 HBP-1	↑ proliferation and arteriogenesis ↓ apoptosis in endothelial cells ↓ atherosclerotic plaques and lipids load in mice fed with high-fat diet following administration of antagonist	(1) (83) (47) (84)
miR-192-5p	Human model - hypertensive and hypertensive nephrosclerosis patients Rat model – Dahl SS rat, SS.13^{BN26}(L26) rat Mice model – mir-192 knockout	Atp1b1	↓ miR-192-5p in hypertension animal model and following HS diet ↑ MAP following HS diet in antimiR-treated L26 model ↑ MAP, SBP, DBP following HS diet in knockout mice	(32)
miR-25	Human model – diabetic patients Rat model – SD rat Mice model – WT mice, C57BL/6 mice, *db/db* mice	CDC42	↑ RAS, hypertension, renal dysfunction following inhibition in normal mice ↓ glomerular fibrosis and BP following inhibition in *db/db* mice	(49)
miR-451	Human model – PAH and HCM patients Rat model – Wistar rat Mice model - miR-451 knockout	TSC1	Negatively correlated with mPAP, BNP and ADMA ↓ development of PAH in hypoxia-exposed rats following inhibition ↑ development of HCM following down-regulation	(51) (52)
miR-29a	Human model – hypertensive patients Rat model – SHR rat	PTEN/AKT /mTOR signalling pathway	Negatively correlated with the glomerular filtration rate, but positively with CRP, TGF-β1, and UACR ↓ hypertrophy and associated indices following inhibition	(57) (59)

	Mice model – TAC mice	(85)

SHR rats – spontaneously hypertensive rats; TAC mice – transverse aortic constriction mice; mt-Cytb - mitochondrially encoded cytochrome B; eNOS - endothelial nitric oxide synthase; HS – high-salt; RHT – resistant hypertension; SBP – systolic blood pressure; ABPM - ambulatory blood pressure monitoring; CRP – C-reactive protein ; CIMT - carotid intima-media thickness test; HT – hypertension; NO_x – nitric oxide; SS rat – salt-sensitive rat; SS.13^{BN26}(L26) rat – salt-insensitive rat; BP – blood pressure; Chga – chromogranin A; TGFβR I - transforming growth factor βR I; BPH/2J mice – hypertensive mice; RAS - renin–angiotensin system; AMI - acute myocardial infarction; CAD - coronary artery disease; ApoE$^{-/-}$ mice – model of atherosclerosis; ADRB1 - adrenoceptor beta 1; HBP-1 - HMG-box transcription factor 1; Atp1b1 - ATPase Na+/K+ transporting subunit beta 1; MAP – mean arterial pressure; DBP – diastolic blood pressure; SD rat – Sprague Dawley rat; WT mice – wild type mice; C57BL/6 mice – basic background mouse strain; *db/db* mice – type II diabetes model; CDC42 - cell division cycle 42; PAH – pulmonary arterial hypertension; HCM – hypertrophic cardiomyopathy; TSC1 - TSC complex subunit 1; mPAP - mean pulmonary artery pressure; BNP - brain natriuretic peptide; ADMA - asymmetric dimethylarginine.

The above mentioned miR-22 targets chromogranin A (Chga) mRNA – a protein expressed peripherally and in the central nervous system (CNS). Chga influences BP, vasodilatation, insulin sensitivity, and inflammation (34). Animal studies report overexpression of Chga and polymorphism of untranslated binding region (UTR) for miRNAs in Spontaneously Hypertensive Rat (SHR) animal model (13), which consequently increases the binding of miR-22 (34,35). Inhibition of miR-22 caused a decrease in BP of SHRs, which potentially makes it a therapeutic agent in terms of navigating hypertension treatment (7,34). Furthermore, results show that miR-22 is an essential regulator of cardiac function and remodelling, since its' genetic ablation suppresses induced cardiac hypertrophy and enhances fibrogenesis of cardiac fibroblasts in murine model (21,36,37). Wahlquist et al. (2014) suggested miR-25 inhibition as a treatment strategy for heart failure, since it improves cardiac contractility and function. It is a repressor of cardiac function and has been upregulated in heart failure events in both murine and human model (7,23).

MiR-181a is another miRNA that has a potential influence on BP. It is the most abundant miRNA in lymphoid tissue and it regulates T cell function (38). It showcases somewhat anti-inflammatory effect and contributes to adaptive immunity (39). In knock-out mice, deletion of miR-181a led to salt sensitivity and increased BP while it was downregulated in hypertensive murine and human model (40,41). In mice model of hypertension (Schlager BHP/2J mouse), treatment with miR-181a mimics resulted in decreased BP and renal renin mRNA (6). Recently, we published several papers concerning effects of high-salt intake on inflammation and endothelial function and found altered leukocyte activation status followed by advancement of vascular low-grade inflammation in both animal and human model (16,42), and also impaired microvascular reactivity in healthy individuals (43).

Langlo et al. (2021) exposed Dahl salt-sensitive (Dahl/SS) rats to low-salt (LS) and HS diet, with first resulting in mild to moderate hypertension over time, while the latter resulted in severe hypertension following severely increased systolic blood pressure (SBP) (1). Out of 145 studied c-miRNAs assessed in that study, 68 of them were associated significantly with hypertensive complications and can potentially serve as biomarkers for diagnostic purposes. Among others, miR-19a-5p was suggested as a biomarker in cases of hypertensive encephalopathy and endothelial dysfunction (ED), since it was recognized as the main regulator of platelet activation, coagulation and inflammation (44). Enhanced expression of c-miR-19a was reported in cases of pulmonary arterial hypertension (45), acute myocardial infarction (46), coronary artery disease and atherosclerotic patients (47).

Baker et al. (2019) reported antihypertensive effects of renal miR-192-5p in animal hypertension models with an emphasis on the role of Atp1b1 target genes (32). They noted decreased levels of miR-192-5p in L26 (SS.13BN26; mild hypertension) and Dahl/SS rats following HS loading, with more pronounced effect of HS diet in the latter model. Furthermore, when treated with antimiR-192-5p, L26 rats had increased mean arterial BP (MAP) following HS diet. Similar effect was detected in miR-192 knockout mice where MAP, systolic (SBP) and diastolic BP (DBP) increased significantly compared to wild type (WT) mice as a response to a HS diet. These results suggest that deletion or a decrease in miR-192-5p levels leads to exaggerated renal damage and hypertension, suggesting protective role of miR-192-5p against hypertension development.

In another study, high salt loading caused renal and cardiac dysfunction in uninephrectomized Sprague Dawley rats (SD) to a larger extent compared to normal rats fed a HS diet. This was accompanied by an increase in levels of miR-25, miR-451, miR-155 and a decrease in levels of miR-99 of the heart, with opposite effect on same circulatory miRNAs (48). According to Liu et al. (2017), miR-25 levels are lower in blood and tissue samples from diabetic patients/animals and cell cultures exposed to glucose when compared to controls (49). They investigated the effect of knock-down/inhibition of miR-25 on

BP, among other parameters, since hypertension is associated closely to diabetic nephropathy. In WT mice, such venture resulted in RAS activation and hypertension contributing to renal dysfunction. MiRNA-25 has also been described as an oncogenic miRNA and an important regulator in acute myocardial infarction, left ventricular hypertrophy and heart failure (50). Expression levels of miR-451 have been cited in literature as a diagnostic reference in pathogenesis of pulmonary hypertension (51–53), while circulating miR-155 has been positively correlated with BP (both SBP and DBP) and inflammatory markers, with significantly higher expression levels in hypertensive patients compared to healthy controls (54). As suggested by Sun et al. (2012), miR-155 acts as a key regulator of cardiovascular functions, since, when overexpressed, it targets endothelial nitric oxide synthase (eNOS) expression, decreases it and impairs endothelium-dependent vasorelaxation (55).

Another potential therapeutic target and diagnosis biomarker (e.g. early stages of hypertensive nephropathy) is miR-29, depicted as necessary for both normal endothelial function and its restoration in animals and humans (56–58). For example, hypertensive patients with left ventricular hypertrophy had significantly higher levels of miR-29a compared to patients with hypertension, while anti-miR inhibition in transverse aortic constriction (TAC) mice model resulted in suppressed hypertrophy and associated indices (59). Alongside miR-29, miR-30a and miR-133 were also assessed for diagnostic accuracy in case of white-coat hypertension, where their expression levels were associated with BP-related parameters and BP monitoring (60).

Potential of non-coding RNAs in endothelial dysfunction treatment

In the last decade, there has been a lot of research dealing with therapeutic inhibition of miR-33 in animal models. There are two isoforms of miR-33 present in humans, miR-33a and miR-33b, embedded within SREBF1 and SREBF2 genes (SREBP family of transcription factors), while there is only one isoform present in rodents and non-human primates – miR-33a (9,61,62). These serve a purpose in progression of cardiometabolic diseases such as atherosclerosis and obesity and are crucial factors in lipid metabolism regulation, since they are responsible for maintenance of cholesterol, fatty acid and triglyceride homeostasis (62,63).

Previous studies reported improved lipid profile (increased circulatory HDL-cholesterol levels), mitigated inflammation and decreased formation of atherosclerotic lesions following inhibition or genetic ablation of miR-33 in mice (63–65). Similar effects were also detected in case of inhibition by antimiR when administered subcutaneously in Ldlr-/- mice (deficient for LDL receptor) which resulted in reduced plaque size and atherosclerosis regression as well as improved HDL-cholesterol functionality (66,67). On another note, in non-human primates, both normal and metabolic disease model, treatment with miR-33 targeting antimiRs resulted in increased HDL-cholesterol levels, while in normal males' pharmacological inhibition also resulted in decreased VLDL triglycerides (68,69). These results suggest potential therapeutic utility of miR-33s in treatment of atherosclerosis, dyslipidaemia and related metabolic disorders.

Nuclear factor kappa B (NF-κB), a fairly general transcription factor, regulates a variety of biological processes, particularly in stress response and progression of inflammation, both playing large roles in vascular damage and onset of cardiovascular diseases (70,71). Downregulation or decreased expression of miR-150 occurs in acute coronary syndrome and correlates with its onset (72). It targets pentraxin-3 (PTX3) and negatively regulates it through inhibition of NF-κB signalling pathway, furthermore attenuating vascular remodelling and restoring endothelial cell function. Mir-150 has also been associated with therapeutic potential for thrombosis treatment, since its upregulation has an effect on endothelial progenitor cell differentiation and increases angiogenic potential (73). MiR-155, a master

regulator of inflammation, plays an important role in regulation of endothelial inflammation through targeting NF-κB pathway and suppression of inflammatory factors, since its inhibition results in significant inflammatory response (74,75). Another non-coding RNA potentially attenuating endothelial inflammation through effects on NF-κB pathway is miR-99 (76).

MicroRNA identification and screening

Choosing the right miRNA for diagnostic/therapeutic purposes and identification of key targets responsible for specific phenotype is somewhat of a challenge of its own (77). Understanding of phenotypes evoked by certain miRNAs requires usage of computational tools (databases of validated miRNAs, prediction algorithms) as well as an experimental approach (gene expression analysis and proteomics), in order to perform functional cell-based screenings in both health and disease conditions (77,78). Several reviews and research articles listed functional genomics for appropriate validation of critical proteins in biological networks for the purpose of creating prognostic risk models using miRNA data (77–79).

Eulalio et al. (2015) (77) provided a review of functional cell-based screening technologies for miRNA function, aimed at biological processes and illness-related events, including proliferation, signaling, cell maintenance and differentiation. For characterization of mechanisms of action, it is of crucial importance to identify potential key targets for different miRNAs. Such information can be detained from computational, prediction algorithms based on complementarity between miRNAs and target sequences (80–82).

Several prediction tools for miRNA targets have been developed in the last two decades (miRanda, miRanda-mirSVR, TargeScan, DIANA-microT-CDS, MirTarget2, rna22-GUI, TargetMiner, SVMicrO, PITA, RNAhybrid), although it should be clarified that despite the predictive power each approach has, there are also limitations and weaknesses calling for future efforts and research towards the upgrade of available tools (79,81).

Conclusions

Circulating miRNAs could have a potential for early diagnosis of end-organ injury in hypertension and hypertensive emergency. Pathway prediction tools elucidate possible mechanisms in hypertensive emergency that may be the subject for further investigations. Further mechanistic studies are needed (e.g. with miRNA-214-3p and miRNA-29, which have recently been shown to be involved in the development of hypertension). However, currently there are several limitations in using miRNAs in clinical diagnosis and therapy, such as large number of miRNAs as potential biomarkers that require high-throughput technology (e.g. functional screenings) for investigation, followed by mechanistic studies in animals and humans (the latter much more difficult).

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References

1. Langlo KAR, Silva GJJ, Overrein TS, Adams V, Wisløff U, Dalen H, Rolim N, Hallan SI. Circulating microRNAs May Serve as Biomarkers for Hypertensive Emergency End-Organ Injuries and Address Underlying Pathways in an Animal Model. Front Cardiovasc Med. 2021; 7:626699. doi: 10.3389/fcvm.2020.626699

2. Javadifar A, Rastgoo S, Banach M, Jamialahmadi T, Johnston TP, Sahebkar A. Foam Cells as Therapeutic Targets in Atherosclerosis

with a Focus on the Regulatory Roles of Non-Coding RNAs. Int J Mol Sci. 2021; 22:2529. doi: 10.3390/ijms22052529

3. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front Endocrinol. 2018; 9:402. doi: 10.3389/fendo.2018.00402

4. Ebert MS, Sharp PA. MicroRNA sponges: Progress and possibilities. RNA. 2010; 16:2043–2050. doi: 10.1261/rna.2414110

5. Gallo A, Tandon M, Alevizos I, Illei GG. The Majority of MicroRNAs Detectable in Serum and Saliva Is Concentrated in Exosomes. PLOS ONE. 2012; 7:e30679. doi: 10.1371/journal.pone.0030679

6. Marques FZ, Charchar FJ. microRNAs in Essential Hypertension and Blood Pressure Regulation. Adv Exp Med Biol. 2015; 888:215–235. doi: 10.1007/978-3-319-22671-2_11

7. Marques FZ, Booth SA, Charchar FJ. The emerging role of non-coding RNA in essential hypertension and blood pressure regulation. J Hum Hypertens. 2015; 29:459–467. doi: 10.1038/jhh.2014.99

8. Chakraborty C, Sharma AR, Sharma G, Lee S-S. Therapeutic advances of miRNAs: A preclinical and clinical update. J Adv Res. 2021; 28:127–138. doi: 10.1016/j.jare.2020.08.012

9. van Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med. 2014; 6:851–864. doi: 10.15252/emmm.201100899

10. Garzon R, Marcucci G, Croce CM. Targeting MicroRNAs in Cancer: Rationale, Strategies and Challenges. Nat Rev Drug Discov. 2010; 9:775–789. doi: 10.1038/nrd3179

11. Heart Disease and Stroke | CDC. (2022) https://www.cdc.gov/chronicdisease/resources/publications/factsheets/heart-disease-stroke.htm (Accessed February 28, 2022)

12. Drenjančević-Perić I, Jelaković B, Lombard JH, Kunert MP, Kibel A, Gros M. High-Salt Diet and Hypertension: Focus on the Renin-Angiotensin System. Kidney Blood Press Res. 2011; 34:1–11. doi: 10.1159/000320387

13. Lerman LO, Kurtz TW, Touyz RM, Ellison DH, Chade AR, Crowley SD, Mattson DL, Mullins JJ, Osborn J, Eirin A, Reckelhoff JF, Iadecola C, Coffman TM. Animal Models of Hypertension: A Scientific Statement From the American Heart Association. Hypertension. 2019; 73:e87–e120. doi: 10.1161/HYP.0000000000000090

14. Charytan DM, Forman JP. You are what you Eat: Dietary Salt Intake and Renin Angiotensin Blockade in Diabetic Nephropathy. Kidney Int. 2012; 82:257–259. doi: 10.1038/ki.2012.148

15. Rassler B. The Renin-Angiotensin System in the Development of Salt-Sensitive Hypertension in Animal Models and Humans. Pharmaceuticals. 2010; 3:940–960. doi: 10.3390/ph3040940

16. Knezović A, Kolobarić N, Drenjančević I, Mihaljević Z, Šušnjara P, Jukić I, Stupin M, Kibel A, Marczi S, Mihalj M, Stupin A. Role of Oxidative Stress in Vascular Low-Grade Inflammation Initiation Due to Acute Salt Loading in Young Healthy Individuals. Antioxidants. 2022; 11:444. doi: 10.3390/antiox11030444

17. DuPont JJ, Greaney JL, Wenner MM, Lennon-Edwards SL, Sanders PW, Farquhar WB, Edwards DG. High Dietary Sodium Intake Impairs Endothelium-Dependent Dilation in Healthy Salt-Resistant Humans. J Hypertens. 2013; 31:530–536. doi: 10.1097/HJH.0b013e32835c6ca8

18. Boegehold MA. The Effect of High Salt Intake on Endothelial Function: Reduced Vascular Nitric Oxide in the Absence of Hypertension. J Vasc Res. 2013; 50:458–467. doi: 10.1159/000355270

19. Price DA, De'Oliveira JM, Fisher ND, Williams GH, Hollenberg NK. The state and responsiveness of the renin-angiotensin-aldosterone system in patients with type II diabetes mellitus. Am J Hypertens. 1999; 12:348–355. PMID: 10232494

20. Stupin A, Drenjancevic I, Rasic L, Cosic A, Stupin M. A Cross-Talk between the Renin-Angiotensin and Adrenergic Systems in Cardiovascular Health and Disease. SEEMEDJ. 2017, 1:18. doi: 10.26332/seemedj.v1i1.33

21. Huang Z-P, Wang D-Z. miR-22 in Smooth Muscle Cells. Circulation. 2018; 137:1842–1845. doi: 10.1161/CIRCULATIONAHA.118.033042

22. Cheleschi S, Tenti S, Mondanelli N, Corallo C, Barbarino M, Giannotti S, Gallo I, Giordano A, Fioravanti A. MicroRNA-34a and MicroRNA-181a Mediate Visfatin-Induced Apoptosis and Oxidative Stress via NF-κB Pathway in Human Osteoarthritic Chondrocytes. Cells. 2019; 8:E874. doi: 10.3390/cells8080874

23. Wahlquist C, Jeong D, Rojas-Muñoz A, Kho C, Lee A, Mitsuyama S, van Mil A, Park WJ, Sluijter JPG, Doevendans PAF, Hajjar RJ, Mercola M. Inhibition of miR-25 improves cardiac contractility in the failing heart. Nature. 2014; 508:531–535. doi: 10.1038/nature13073

24. Jenike AE, Halushka MK. miR-21: a non-specific biomarker of all maladies. Biomark Res. 2021; 9:18. doi: 10.1186/s40364-021-00272-1

25. Li H, Zhang X, Wang F, Zhou L, Yin Z, Fan J, Nie X, Wang P, Fu X-D, Chen C, Wang DW. MicroRNA-21 Lowers Blood Pressure in Spontaneous Hypertensive Rats by Upregulating Mitochondrial Translation. Circulation. 2016; 134:734–751. doi: 10.1161/CIRCULATIONAHA.116.023926

26. Li X, Wei Y, Wang Z. microRNA-21 and hypertension. Hypertens Res Off J Jpn Soc Hypertens. 2018; 41:649–661. doi: 10.1038/s41440-018-0071-z

27. Watanabe K, Narumi T, Watanabe T, Otaki Y, Takahashi T, Aono T, Goto J, Toshima T, Sugai T, Wanezaki M, Kutsuzawa D, Kato S, Tamura H, Nishiyama S, Takahashi H, Arimoto T, Shishido T, Watanabe M. The association between microRNA-21 and hypertension-induced cardiac remodeling. PloS One. 2020; 15:e0226053. doi: 10.1371/journal.pone.0226053

28. Kara SP, Ozkan G, Yılmaz A, Bayrakçı N, Güzel S, Geyik E. MicroRNA 21 and microRNA 155 levels in resistant hypertension, and their relationships with aldosterone. Ren Fail. 2021; 43:676–683. doi: 10.1080/0886022X.2021.1915800

29. Cengiz M, Yavuzer S, Kılıçkıran Avcı B, Yürüyen M, Yavuzer H, Dikici SA, Karataş ÖF, Özen M, Uzun H, Öngen Z. Circulating miR-21 and eNOS in subclinical atherosclerosis in patients with hypertension. Clin Exp Hypertens N Y N 1993. 2015; 37:643–649. doi: 10.3109/10641963.2015.1036064

30. Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov. 2017; 16:203–222. doi: 10.1038/nrd.2016.246

31. Tsai P-C, Liao Y-C, Wang Y-S, Lin H-F, Lin R-T, Juo S-HH. Serum microRNA-21 and microRNA-221 as potential biomarkers for cerebrovascular disease. J Vasc Res. 2013; 50:346–354. doi: 10.1159/000351767

32. Baker MA, Wang F, Liu Y, Kriegel AJ, Geurts AM, Usa K, Xue H, Wang D, Kong Y, Liang M. MiR-192-5p in the Kidney Protects Against the Development of Hypertension. Hypertension. 2019; 73:399–406. doi: 10.1161/HYPERTENSIONAHA.118.11875

33. Liu Y, Usa K, Wang F, Liu P, Geurts AM, Li J, Williams AM, Regner KR, Kong Y, Liu H, Nie J, Liang M. MicroRNA-214-3p in the Kidney Contributes to the Development of Hypertension. J Am Soc Nephrol JASN. 2018; 29:2518–2528. doi: 10.1681/ASN.2018020117

34. Friese RS, Altshuler AE, Zhang K, Miramontes-Gonzalez JP, Hightower CM, Jirout ML, Salem RM, Gayen JR, Mahapatra NR, Biswas N, Cale M, Vaingankar SM, Kim HS, Courel M, Taupenot L, Ziegler MG, Schork NJ, Pravenec M, Mahata SK, Schonbein GWS, O'Connor DT. MicroRNA-22 and promoter motif polymorphisms at the Chga locus in genetic hypertension: functional and therapeutic implications for gene expression and the pathogenesis of hypertension. Hum Mol Genet. 2013; 22:3624–3640. doi: 10.1093/hmg/ddt213

35. O'Connor DT. Catecholamine storage vesicle protein expression in genetic hypertension. Blood Press. 1999; 8:285–295. doi: 10.1080/080370599439508

36. Hong Y, Cao H, Wang Q, Ye J, Sui L, Feng J, Cai X, Song H, Zhang X, Chen X. MiR-22 may Suppress Fibrogenesis by Targeting TGF β R I in Cardiac Fibroblasts. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol. 2016; 40:1345–1353. doi: 10.1159/000453187

37. Huang Z-P, Chen J, Seok HY, Zhang Z, Kataoka M, Hu X, Wang D-Z. MicroRNA-22 regulates cardiac hypertrophy and remodeling in response to stress. Circ Res. 2013; 112:1234–1243. doi: 10.1161/CIRCRESAHA.112.300682

38. Ye Z, Li G, Kim C, Hu B, Jadhav RR, Weyand CM, Goronzy JJ. Regulation of miR-181a expression in T cell aging. Nat Commun. 2018; 9:3060. doi: 10.1038/s41467-018-05552-3

39. Marques FZ, Romaine SPR, Denniff M, Eales J, Dormer J, Garrelds IM, Wojnar L, Musialik K, Duda-Raszewska B, Kiszka B, Duda M, Morris BJ, Samani NJ, Danser AHJ, Bogdanski P, Szczechowska EZ, Charchar FJ, Tomaszewski M. Signatures of miR-181a on the Renal Transcriptome and Blood Pressure. Mol Med. 2015; 21:739–748. doi: 10.2119/molmed.2015.00096

40. Jackson KL, Gueguen C, Lim K, Eikelis N, Stevenson ER, Charchar FJ, Lambert GW, Burke SL, Paterson MR, Marques FZ, Head GA. Neural suppression of miRNA-181a in the kidney elevates renin expression and exacerbates hypertension in Schlager mice. Hypertens Res Off J Jpn Soc Hypertens. 2020; 43:1152–1164. doi: 10.1038/s41440-020-0453-x

41. Paterson MR, Jackson KL, Dona MSI, Farrugia GE, Visniauskas B, Watson AMD, Johnson C, Prieto MC, Evans RG, Charchar FJ, Pinto AR, Marques FZ, Head GA. Deficiency of MicroRNA-181a Results in Transcriptome-Wide Cell-Specific Changes in the Kidney and Increases Blood Pressure. Hypertension. 2021; 78:1322–1334. doi: 10.1161/HYPERTENSIONAHA.121.17384

42. Mihalj M, Matić A, Mihaljević Z, Barić L, Stupin A, Drenjančević I. Short-Term High-NaCl Dietary Intake Changes Leukocyte Expression of VLA-4, LFA-1, and Mac-1 Integrins in Both Healthy Humans and Sprague-Dawley Rats: A Comparative Study. Mediators Inflamm. 2019; 2019:e6715275. doi: 10.1155/2019/6715275

43. Barić L, Drenjančević I, Matić A, Stupin M, Kolar L, Mihaljević Z, Lenasi H, Šerić V, Stupin A. Seven-Day Salt Loading Impairs Microvascular Endothelium-Dependent Vasodilation without Changes in Blood Pressure, Body Composition and Fluid Status in Healthy Young Humans. Kidney Blood Press Res. 2019; 44:835–847. doi: 10.1159/000501747

44. Eyileten C, Wicik Z, De Rosa S, Mirowska-Guzel D, Soplinska A, Indolfi C, Jastrzebska-Kurkowska I, Czlonkowska A, Postula M. MicroRNAs as Diagnostic and Prognostic Biomarkers in Ischemic Stroke—A Comprehensive Review and Bioinformatic Analysis. Cells. 2018; 7:249. doi: 10.3390/cells7120249

45. Jusic A, Devaux Y. Noncoding RNAs in Hypertension. Hypertension. 2019; 74:477–492. doi: 10.1161/HYPERTENSIONAHA.119.13412

46. Mansouri F, Seyed Mohammadzad MH. Molecular miR-19a in Acute Myocardial Infarction: Novel Potential Indicators of Prognosis and Early Diagnosis. Asian Pac J Cancer Prev APJCP. 2020; 21:975–982. doi: 10.31557/APJCP.2020.21.4.975

47. Chen H, Li X, Liu S, Gu L, Zhou X. MircroRNA-19a promotes vascular inflammation and foam cell formation by targeting HBP-1 in atherogenesis. Sci Rep. 2017; 7:12089. doi: 10.1038/s41598-017-12167-z

48. Amara VR, Surapaneni SK, Tikoo K. Dysregulation of microRNAs and renin-angiotensin system in high salt diet-induced cardiac dysfunction in uninephrectomized rats. PLOS ONE. 2017; 12:e0180490. doi: 10.1371/journal.pone.0180490

49. Liu Y, Li H, Liu J, Han P, Li X, Bai H, Zhang C, Sun X, Teng Y, Zhang Y, Yuan X, Chu Y, Zhao B. Variations in MicroRNA-25 Expression

Influence the Severity of Diabetic Kidney Disease. J Am Soc Nephrol JASN. 2017; 28:3627–3638. doi: 10.1681/ASN.2015091017

50. Sárközy M, Kahán Z, Csont T. A myriad of roles of miR-25 in health and disease. Oncotarget. 2018; 9:21580–21612. doi: 10.18632/oncotarget.24662

51. Grant JS, Morecroft I, Dempsie Y, van Rooij E, MacLean MR, Baker AH. Transient but not genetic loss of miR-451 is protective in the development of pulmonary arterial hypertension. Pulm Circ. 2013; 3:840–850. doi: 10.1086/674751

52. Long L, Xiao Y, Yin X, Gao S, Zhou L, Liu H. Expression of serum miR-27b and miR-451 in patients with congenital heart disease associated pulmonary artery hypertension and risk factor analysis. Exp Ther Med. 2020; 20:3196–3202. doi: 10.3892/etm.2020.9042

53. Song X, Zou L, Cui L, Li S, Qin Y, Zhao X, Jing Q. Plasma miR-451 with echocardiography serves as a diagnostic reference for pulmonary hypertension. Acta Pharmacol Sin. 2018; 39:1208–1216. doi: 10.1038/aps.2018.39

54. Huang Y, Huang C, Zhang B, Feng Y. Association of circulating miR-155 expression level and inflammatory markers with white coat hypertension. J Hum Hypertens. 2020; 34:397–403. doi: 10.1038/s41371-019-0250-7

55. Sun H-X, Zeng D-Y, Li R-T, Pang R-P, Yang H, Hu Y-L, Zhang Q, Jiang Y, Huang L-Y, Tang Y-B, Yan GJ, Zhou JG. Essential Role of MicroRNA-155 in Regulating Endothelium-Dependent Vasorelaxation by Targeting Endothelial Nitric Oxide Synthase. Hypertension. 2012; 60:1407–1414. doi: 10.1161/HYPERTENSIONAHA.112.197301

56. Han X, Wang C, Li Y, Jin Z, Zhang B, Dong Y. miR-29b in regulating blood pressure and cardiac function in the rat model of hypertension. Exp Ther Med. 2019; 17:3361–3366. doi: 10.3892/etm.2019.7335

57. Huang Y, Huang C, Li J, Zhang B, Feng Y. The association of miR-29a with proteinuria in essential hypertension. J Hum Hypertens. 2018; 32:775–780. doi: 10.1038/s41371-018-0097-3

58. Widlansky ME, Jensen DM, Wang J, Liu Y, Geurts AM, Kriegel AJ, Liu P, Ying R, Zhang G, Casati M, Chu C, Malik M, Branum A, Tanner MJ, Tyagi S, Usa K, Liang M. miR-29 contributes to normal endothelial function and can restore it in cardiometabolic disorders. EMBO Mol Med. 2018; 10:e8046. doi: 10.15252/emmm.201708046

59. Han W, Han Y, Liu X, Shang X. Effect of miR-29a inhibition on ventricular hypertrophy induced by pressure overload. Cell Biochem Biophys. 2015; 71:821–826. doi: 10.1007/s12013-014-0269-x

60. Huang Y, Huang C, Chen J, Li J, Feng Y. The association of circulating miR-30a, miR-29 and miR-133 with white-coat hypertension. Biomark Med. 2016; 10:1231–1239. doi: 10.2217/bmm-2016-0215

61. Näär AM. miR-33: a metabolic conundrum. Trends Endocrinol Metab TEM. 2018; 29:667–668. doi: 10.1016/j.tem.2018.04.004

62. Price NL, Goedeke L, Suárez Y, Fernández-Hernando C. miR-33 in cardiometabolic diseases: lessons learned from novel animal models and approaches. EMBO Mol Med. 2021; 13:e12606. doi: 10.15252/emmm.202012606

63. Horie T, Nakao T, Miyasaka Y, Nishino T, Matsumura S, Nakazeki F, Ide Y, Kimura M, Tsuji S, Rodriguez RR, Watanbe T, Yamasaki T, Xu S, Otani C, Miyagawa S, Matsushita K, Sowa N, Omori A, Tanaka J, Nishimura C, Nishiga M, Kuwabara Y, Baba O, Watanbe S, Nishi H, Nakashima Y, Picciotto MR, Inoue H, Watanbe D, Nakamura K, Sasaki T, Kimura T, Ono K. microRNA-33 maintains adaptive thermogenesis via enhanced sympathetic nerve activity. Nat Commun. 2021; 12:843. doi: 10.1038/s41467-021-21107-5

64. Nakao T, Horie T, Baba O, Nishiga M, Nishino T, Izuhara M, Kuwabara Y, Nishi H, Usami S, Nakazeki F, Ide Y, Koyama S, Kimura M, Sowa N, Ohno S, Aoki H, Hasegawa K, Sakamoto K, Minatoya K, Kimura T, Ono K. Genetic Ablation of MicroRNA-33 Attenuates Inflammation and

Abdominal Aortic Aneurysm Formation via Several Anti-Inflammatory Pathways. Arterioscler Thromb Vasc Biol. 2017; 37:2161–2170. doi: 10.1161/ATVBAHA.117.309768

65. Rayner KJ, Suárez Y, Dávalos A, Parathath S, Fitzgerald ML, Tamehiro N, Fisher EA, Moore KJ, Fernández-Hernando C. MiR-33 contributes to the regulation of cholesterol homeostasis. Science. 2010; 328:1570–1573. doi: 10.1126/science.1189862

66. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, Temel RE, Parathath S, van Gils JM, Rayner AJ, Chang AN, Suarez Y, Fernandez-Hernando C, Fisher EA, Moore KJ. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. J Clin Invest. 2011; 121:2921–2931. doi: 10.1172/JCI57275

67. Rotllan N, Ramírez CM, Aryal B, Esau CC, Fernández-Hernando C. Therapeutic silencing of microRNA-33 inhibits the progression of atherosclerosis in Ldlr−/− mice. Arterioscler Thromb Vasc Biol. 2013; 33:1973–1977. doi: 10.1161/ATVBAHA.113.301732

68. Rayner KJ, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, Temel RE, Moore KJ. Inhibition of miR-33a/b in non-human primates raises plasma HDL and reduces VLDL triglycerides. Nature. 2011; 478:404–407. doi: 10.1038/nature10486

69. Rottiers V, Obad S, Petri A, McGarrah R, Lindholm MW, Black JC, Sinha S, Goody RJ, Lawrence MS, deLemos AS, Hansen HF, Whittaker S, Henry S, Brookes R, Najafi-Shoushtari SH, Chung RT, Ehetstine JR, Gerszten RE, Kauppinen S, Naae AM. Pharmacological inhibition of a microRNA family in non-human primates by a seed-targeting 8-mer antimiR. Sci Transl Med. 2013; 5:212ra162. doi: 10.1126/scitranslmed.3006840

70. Fiordelisi A, Iaccarino G, Morisco C, Coscioni E, Sorriento D. NFkappaB is a Key Player in the Crosstalk between Inflammation and Cardiovascular Diseases. Int J Mol Sci. 2019; 20:1599. doi: 10.3390/ijms20071599

71. Jones WK, Brown M, Wilhide M, He S, Ren X. NF-kappaB in cardiovascular disease: diverse and specific effects of a "general" transcription factor? Cardiovasc Toxicol. 2005; 5:183–202. doi: 10.1385/ct:5:2:183

72. Luo X-Y, Zhu X-Q, Li Y, Wang X-B, Yin W, Ge Y-S, Ji W-M. MicroRNA-150 restores endothelial cell function and attenuates vascular remodeling by targeting PTX3 through the NF- κ B signaling pathway in mice with acute coronary syndrome. Cell Biol Int. 2018; 42:1170–1181. doi: 10.1002/cbin.10985

73. Du X, Hu N, Yu H, Hong L, Ran F, Huang D, Zhou M, Li C, Li X. miR-150 regulates endothelial progenitor cell differentiation via Akt and promotes thrombus resolution. Stem Cell Res Ther. 2020; 11:354. doi: 10.1186/s13287-020-01871-9

74. Mahesh G, Biswas R. MicroRNA-155: A Master Regulator of Inflammation. J Interferon Cytokine Res Off J Int Soc Interferon Cytokine Res. 2019; 39:321–330. doi: 10.1089/jir.2018.0155

75. Wu X-Y, Fan W-D, Fang R, Wu G-F. Regulation of microRNA-155 in endothelial inflammation by targeting nuclear factor (NF)- κ B P65. J Cell Biochem. 2014; 115:1928–1936. doi: 10.1002/jcb.24864

76. Bao M, Li J-M, Luo H, Tang L, Lv Q, Li G, Zhou H. NF- κ B-Regulated miR-99a Modulates Endothelial Cell Inflammation. Mediators Inflamm. 2016; 2016:5308170. doi: 10.1155/2016/5308170

77. Eulalio A, Mano M. MicroRNA Screening and the Quest for Biologically Relevant Targets. J Biomol Screen. 2015; 20:1003–1017. doi: 10.1177/1087057115578837

78. Lemons D, Maurya M, Subramaniam S, Mercola M. Developing microRNA screening as a functional genomics tool for disease research. Front Physiol. 2013; 4:11. doi: 10.3389/fphys.2013.00223

79. Zheng G, Zhang G, Zhao Y, Zheng Z. Screening of miRNAs as Prognostic Biomarkers for Colon Adenocarcinoma and Biological

Function Analysis of Their Target Genes. Front Oncol. 2021; 11:10. doi: 10.3389/fonc.2021.560136

80. Ritchie W, Rasko JEJ. Refining microRNA target predictions: sorting the wheat from the chaff. Biochem Biophys Res Commun. 2014; 445:780–784. doi: 10.1016/j.bbrc.2014.01.181

81. Peterson S, Thompson J, Ufkin M, Sathyanarayana P, Liaw L, Congdon CB. Common features of microRNA target prediction tools. Front Genet. 2014; 5:10. doi: 10.3389/fgene.2014.00023

82. Pallarès-Albanell J, Zomeño-Abellán MT, Escaramís G, Pantano L, Soriano A, Segura MF, Martí E. A High-Throughput Screening Identifies MicroRNA Inhibitors That Influence Neuronal Maintenance and/or Response to Oxidative Stress. Mol Ther - Nucleic Acids. 2019; 17:374–387. doi: 10.1016/j.omtn.2019.06.007

83. Solayman MH, Langaee TY, Gong Y, Shahin MH, Turner ST, Chapman AB, Gums JG, Boerwinkle E, Beitelshees AL, El-Hamamsy M, El-Wakeel L, Cooper-DeHoff RM, Badary OA, Johnson JA. Effect of plasma MicroRNA on antihypertensive response to beta blockers in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) studies. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2019; 131:93–98. doi: 10.1016/j.ejps.2019.02.013

84. Gao F, Kataoka M, Liu N, Liang T, Huang Z-P, Gu F, Ding J, Liu J, Zhang F, Ma Q, Wang Y, Zhang M, Hu X, Kyselovic J, Hu X, Pu WT, Wang J, Chen J, Wang DZ. Therapeutic role of miR-19a/19b in cardiac regeneration and protection from myocardial infarction. Nat Commun. 2019; 10:1802. doi: 10.1038/s41467-019-09530-1

85. Shi J-Y, Chen C, Xu X, Lu Q. miR-29a promotes pathological cardiac hypertrophy by targeting the PTEN/AKT/mTOR signalling pathway and suppressing autophagy. Acta Physiol Oxf Engl. 2019; 227:e13323. doi: 10.1111/apha.13323

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