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Review Article

A Novel Biomarker MicroRNA-92a-3p as a Link between Cardiovascular Disease and Chronic Kidney Disease

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ABSTRACT

The emergence of microRNAs (miRNA) as significant regulators of pathophysiological processes has provided new therapeutic strategies in atherosclerotic status. Recently, the author has described that microRNA-92a-3p (miR-92a-3p), having pleiotropic manner is a potential therapeutic target in atherosclerosis-related diseases. The author has previously described that mild renal dysfunction was associated with endothelial dysfunction in women and that the cardio-renal interrelationship may be also suggested under mild renal dysfunction. Shang et al. suggested mcroiRNA-92a (miR-92a) as a crucial link between chronic kidney disease (CKD) and cardiovascular disease (CVD) by mediating uremia-impaired endothelial dysfunction. On the evidences of relationships between miR-92a and flow-mediated vasodilation (FMD) and between miR-92a and estimated glomerular filtration rate (eGFR) level, the author indicates that miR-92a gene expression profile in endothelial cell and the circulating level reflecting FMD study and eGFR level which were established indicators may be an early diagnostic biomarker in atherosclerosis-related CKD, having a link between CVD and CKD. Shang et al. also indicated miR-92a as a link among CKD-induced uremia, oxidative stress, and endothelial dysfunction. On the proof of the interrelationship among miR-92a profile, FMD study, and eGFR level, the author suggests that atherosclerosis-related CKD cause oxidative stress, leading to miR-92a expression, endothelial dysfunction, and renal dysfunction. In CKD with advanced stage, oxidative stress derived from uremic toxin mainly contributes to miR-92a gene expression profile, endothelial dysfunction, and renal failure. Wiese et al. showed that renal injury significantly increased endothelial miR-92a-3p and dual inhibition of miR-92a-3p and miR-489-3p significantly reduced atherosclerotic lesion compared to control, thereby, suggesting that miR-92a-3p and/or miR-489-3p are potential therapeutic targets in atherosclerosis-related CKD. The author emphasizes that clinically and genetically, the studies have provided a link between CVD and CKD mediated by endothelial dysfunction even at early stage.

Keywords: Endothelial dysfunction; MicroRNA-92a-3p; MicroRNA-489-3p; Atherosclerosis-related CKD; Link between CVD and CKD

INTRODUCTION

The emergence of miRNA as significant regulators of pathophysiological processes has indicated novel molecular insights and provided new treatment strategies in atherosclerotic status [1]. Recently, the author has described that miR-93a-3p, having pleiotropic manner is a potential therapeutic target in atherosclerosis-related diseases [2]. Several clinical studies suggested the associations of CVD and CKD mediated by endothelial dysfunction. Our previous study [3] and other reports [4-6] restricting analysis to subjects with eGFR>60 mL/min/1.73m^2 namely early decline in kidney diseases showed relation between FMD study and eGFR value. The author has previously described that mild renal dysfunction was associated with endothelial dysfunction in women and that the cardio-renal interrelationship may be also suggested under mild renal dysfunction [3]. Shang et al. [7] suggested miR-92a as a crucial

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link between CKD and CVD by mediating uremia-impaired endothelial dysfunction. On the evidences of relationships between FMD and miR-92a [8] and between eGFR and miR-92a [7], the author indicates that miR-92a gene expression profile in endothelial cell and circulating level reflecting FMD study and eGFR level may be an early diagnostic biomarker in atherosclerosis-related CKD, having a link between CVD and CKD. Shang et al. also indicated miR-92a as a link among CKD-induced uremia, oxidative stress, and endothelial dysfunction [7]. The author suggests that atherosclerosis-related CKD cause oxidative stress, leading to miR-92a expression, endothelial dysfunction, and renal dysfunction. In CKD with late stage, oxidative stress derived from uremic toxin mainly contributes to miR-92a gene expression profile, endothelial dysfunction, and renal failure. Wiese et al. [9] showed that renal injury significantly increased endothelial miR-92a-3p and dual inhibition of miR-92a-3p and miR-489-3p significantly reduced atherosclerotic lesion compared to control. Furthermore they indicated that Tgfb2 and Fam220a were ascertained by gene receptor assays as direct targets of miR-489-3p and miR-92a-3p, respectively. The current knowledges of miR-92a-3p and miR-489-3p as novel multifunctional biomarkers in atherosclerosis-related CKD, namely a link between CVD and CKD will be reviewed in this article.

ASSOCIATIONS OF CVD AND CKD WITH EARLY STAGE MEDIATED BY ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction has been implicated as one of the main pathophysiological mechanisms contributing to the relation of CVD and CKD [10]. Endothelial dysfunction, so-called endothelial activation is regarded as a key initiation process in atherosclerotic condition and also contributed to arteriosclerotic status (arterial stiffness) [10]. Endothelial dysfunction caused by chronic inflammation and oxidative stress is traditionally thought to be an early and significant aspect of CKD [10,11]. Systemic inflammation and oxidative stress are almost universal in CKD, leading to endothelial dysfunction [10,12]. Previous studies have suggested that eGFR level [13] is associated with endothelial dysfunction in community-based [4-6,14,15]. With regard to the restricting analysis to subject with eGFR>60 mL/min/1.73m^2, a few reports has been studied [4-6]. Flow-mediated vasodilation (FMD), and nitroglycerin-mediated vasodilation (NMD) in the brachial artery is a potent procedure for estimating vascular endothelial and vascular smooth muscle cell (VSMC) function [16]. FMD and NMD examinations are useful tool of the vascular reactivity. The author has reported some studies on FMD and NMD including migraine, CVD, CKD, and dyslipidema [3,17-20]. The author has described that mild renal dysfunction with eGFR>60 mL/min/1.73 m^2 was associated with endothelial dysfunction in women and the cardio-renal interrelationship may be also suggested under mild renal dysfunction [3]. It can be suggested that mild renal dysfunction might be a cardiovascular risk factor in women as previously described [3].

miR-92A AS THERAPEUTIC TARGET IN ATHEROSCLEROSIS-RELATED DISEASE

miR-92a as pleotropic biomarker in atherosclerosis

Kumar et al. [21] mentioned that atherosclerosis occurs in arterial regions under disturbed flow condition, partially caused by changings in gene expression. miRNAs are small, noncoding genes that post-transcriptionally regulate gene expression by targeting messenger RNA transcripts. miR -92a is one of the flow-sensitive miRNA, so-called mechano-miRs, regulate endothelial gene expression, endothelial dysfunction, and atherosclerotic condition. The key signaling pathways that are targeted by these flow-sensitive microRNAs include the endothelial cell cycle, inflammation, apoptosis, and NO signaling [21]. Furthermore, Kumar et al. [22] also studied the role of flow-sensitive microRNAs and long noncoding RNAs (lncRNAs) in vascular dysfunction and atherosclerosis. While, extracellular vesicles (EVs) are emerging as important regulators of vascular homeostasis and cardiovascular disease progression [23]. Atherosclerotic stimuli such as oxidized low-density-lipoprotein (ox LDL) or interleukin (IL)-6, increase miR-92a-3p expression in endothelial cells, as well as in corresponding endothelial microvesicles in vitro [23]. Liu et al [23] demonstrated that clinical and experimental atherosclerotic conditions such as ox LDL and IL-6 can promote the packaging of functional miR-92a-3p into endothelial microvesicles, thereby promoting angiogenic responces in the recipient endothelial cells in a STAT3 (signal transducer and activator of transcription 3)-THBS1 (thrombospondin 1)- dependent manner [23]. Chang et al. [24] suggested that miR-92a exerts its effects on physiological responses in a novel biological manner. They have demonstrated that miR-92a-containing extracellular vesicles from endothelial cells modulate macrophage functions and phenotypes [24].

Inhibition of miR-92a in atherosclerosis - related CVD

Loyer et al. [25] mentioned that microRNA, selectively regulated by ox LDL and share stress are called as atheromiRs. They suggested that increased miR-92a expression and proinflammatory markers are recognized under the exposure condition of endothelial cells to oxidized LDL and low share stress [25]. Furthermore, they demonstrated that inhibition of miR-92a prevents endothelial dysfunction and atherosclerosis in mice. Inhibition of miR-92a improves neovasculization after myocardial or hind limb ischemia [26]. Hinkel et al. [27] suggested that inhibition of miR-92a protected against ischemia/reperfusion injury in a large-animal study. Daniel et al. indicated that inhibition of endothelial miR-92a improves re-endothelialization and prevents neointima lesion after vascular injury [28]. These evidences have provided endothelial and cardioprotective effects of genetic inhibition of miR-92a. miR-92a-3p has many targets including KLF2, KLF4 [29,30], the fibronectin adhesion molecule integrin α 5 (ITGA5), SOCS5, and SIRT1 [31,32]. Recently, Rogg et al. [31] studied miR target regulation using miR-92a-3p and suggested that miRs have cell type-specific effects in vivo. A novel function of miR-92a-3p in endothelial cell autophagy and cardiomyocyte metabolism was discovered by analysis of miR-92a targets in cell subtypes. Rogg

et al. [31] also indicated that inhibition of miR-92a-3p regulates endothelial cell autophagy through Atg4a and cardiomyocyte metabolic switching through Abca8b and Cd36 regulation. Gou et al. [33] also suggested that miR-92a overexpression reduces endothelial function and suppresses the heme oxygenase-1 (HO-1) expression. They demonstrated that inhibition of miR-92a suppresses oxidative stress and improves endothelial function by upregulating HO-1 in db/db mice.

miR-92A IN ATHEROSCLEROSIS - RELATED CAD (INVERSE RELATIONSHIP BETWEEN miR-92A EXPRESSION AND FMD STUDY)

Endothelial innate immunity has emerged as a significant mechanism underlying the interaction among oxidative stress condition, inflammation status, and endothelial dysfunction. Chen et al [8] reported that miR-92a is inversely correlated with endothelial function assessed by FMD study and is positively correlated with serum interleukin-1 β in patient with CAD. They suggested that sterol regulatory element-binding protein 2 (SREBP2) – miR-92a-inflammasome exacerbates endothelial dysfunction under oxidative stress condition. The reports [7,8] indicated the significant relationship between miR-92a and FMD study, showing close relation of vascular reactivity and gene expression, thereby it is putative that FMD examination, surrogate marker of endothelial dysfunction may partially reflect miR-92a gene expression profile as previously described [2].

miR-92A IN ATHEROSCLEROSIS-RELATED CKD

Interrelationship among FMD study, eGFR level, and miR-92a gene profile

As our previous study [3] and other reports [4-6] restricting analysis to subjects with eGFR>60 mL/min/1.73m^2, namely early decline in kidney diseases showed relation between FMD study and eGFR value, these result support that both FMD and eGFR are early and sensitive markers reflecting systemic atherosclerotic condition and renal function. Chen et al. [8] demonstrated a significantly inverse relationship between FMD test and miR-92a expression. Shang et al. [7] revealed a significantly inverse correlation between eGFR and miR-92a expression even at the early stage in CKD after adjusting confounding factors. They suggested that miR-92a level has promise as a diagnostic marker or early predictor of CKD-associated vascular impairment. On the evidences of relationships between FMD and miR-92a [8] and between eGFR and miR-92a [7], the author indicates that miR-92a may be an early diagnostic marker as atherosclerosis-related CKD, because both FMD study and eGFR value are established indicators. Chen et al. [8] showed that miR-92a is upregulated in endothelial cells by elevated oxidative stress in patients with stable CAD. Shang et al. [7] mentioned that CKD causes increased oxidative stress in the vessel wall, suggesting endothelial dysfunction as a common complication of renal failure [7]. They indicated miR-92a as a link among CKD-induced uremia, oxidative stress, and endothelial dysfunction [7]. The author suggests that atherosclerosis-related CKD cause oxidative stress, in turn leading to miR-92a gene expression in endothelial cell and circulating level, systemic endothelial dysfunction assessed by FMD, and renal dysfunction estimated by eGFR level even at the early stage in CKD.

Interrelationship among uremic toxin, endothelial dysfunction, and miR-92a profile

Oxidative stress originating from accumulated uremic toxins is also considered as a contributing factor in endothelial dysfunction. Indoxyl sulfate (IS) and p-cresylsulfate (pCS), protein-bound uremic toxins can damage vascular endothelial cells. IS and pCS have been found to associate with CV events [34]. Some studies which show significantly correlation between uremic toxin and vascular reactivity, namely endothelial dysfunction, have been reported [35-38]. Yu et al. [35] described that an oral absorbent to decrease IS level improved endothelial function assessed by FMD. Six I et al. [36] indicated the deleterious vascular effects of IS and reversal by oral adsorbent AST-120 in CKD by using Pulse Wave Velocity (PWV) for evaluation of vascular reactivity. Wang et al. also suggested the significantly inverse correlation between IS level and vascular reactivity index (VRI) value in patients with stage 3-5 CKD [37]. Meanwhile, Matsumoto et al. noted that IS directly affects the vascular function, particularly, endothelium-dependent vasorelaxation, suggesting this effect due to the increased oxidative stress [38]. The endothelial toxicity due to IS was established, including increased oxidative stress, inhibition of NO production, and endothelial inflammation [39]. Shang et al. [7] also showed a positive correlation between IS and circulating miR-92a in patients with CKD, demonstrating the evidence for the causal relation between uremic toxin and miR-92a-mediated endothelial dysfunction. They suggest that miR-92a is a crucial marker, linking between CKD and CVD by mediating uremia-impaired endothelial dysfunction. In addition, they provided miR-92a as a potent treatment target in patients with CVD and CKD. The author suggests that CKD in advanced stage cause oxidative stress mainly derived from uremic toxin, in turn leading to miR-92a gene expression in endothelial cell and circulating level, endothelial dysfunction, and renal failure.

DUAL INHIBITION of miR-92A-3P and miR-489-3P in ATHEROSCLEROSIS-RELATED CKD

miR-92a-3p as a pleiotropic biomarker in atherosclerosis-related CKD

Endothelial dysfunction encompasses a spectrum of biological processes and miRNAs, small non-coding RNAs that post-transcriptional regulate gene expression, have emerged as critical regulators of endothelial gene regulatory networks [9,21]. miR-92a-3p has emerged as a significant regulator of both angiogenesis and endothelial dysfunction through targeted suppression of protective endothelial genes. miR-92a-3p was also demonstrated as a pro-atherogenic miRNA in endothelial cells. The author previously described that miR-92a-3p, having pleiotropic manner is a potential therapeutic target in atherosclerosis-related disease [2]. Clinical evidences have suggested that CKD is associated with endothelial dysfunction and the author has described the association of brachial artery measures with estimated GFR >60 mL/min/1.73 m^2 in a cross-sectional study of the community-based women, indicating a

potent link between CVD and CKD even at the early stage [3]. Recently, miR-92a-3p was found to be elevated in serum from CKD patients and aortic miR-92a-3p was raised in rats with adenine-induced CKD [7,9]. In addition, the study indicated that inhibition of endothelial miR-92a-3p has a potential therapeutic strategy in atherosclerosis-related CKD.

miR-489-3p as a novel biomarker in renal disease

With respect to miR-489, Wei et al. suggested that miR-489 acts as a tumor suppresser and plays roles in cardiac hypertrophy and mouse stem cell quiescence and that be upregulated in clear cell papillary renal cell carcinoma [40-42]. They suggested that miR-489 is induced *via* hypoxia-inducible factor (HIF-1) during ishemic kidney disease to protect kidneys by targeting proinflammatory genes such as CXCL2 and CXCL10 [40,43]. Wiese et al. [9] revealed a novel role for miR-489-3p in endothelial cells by demonstrating that miR489-3p directly targets Tgfb2 in endothelial cells and locked-nuucleic acid (LNA) inhibition of miR-489-3p in vivo significantly increased Tgfb2 expression in aortic endothelium.

miR-92a-3p and miR-489-3p in atherosclerosis-related CKD

Wiese et al. [9] showed that renal injury significantly increased endothelial miR-92a-3p and dual inhibition of miR-92a-3p and miR-489-3p significantly reduced atherosclerotic lesion compared to control. Tgfb2 and FAM220A were ascertained by gene receptor assays as direct targets of miR-489-3p and miR-92a-3p, respectively. They also revealed that in human coronary artery endothelial cells, over-expression of miR-92a-3p decreased FAM220A expression and inhibition of miR-92a-3p increased FAM220A expression. Furthermore, miR-92a-3p overexpression increased STAT3 phosphorylation, through direct regulation of FAM220A [9]. They concluded that dual inhibition of endothelial miR-92a-3p and miR-489-3p decreases CKD-associated atherosclerosis and that inhibition of miR-92a-3p and miR-489-3p through a dual LNA therapy markedly decreased atherosclerotic lesion and altered endothelial gene expression profile.

SUMMARY

The author has previously described that mild renal dysfunction was associated with endothelial dysfunction in women and that the cardio-renal interrelationship may be also suggested under mild renal dysfunction. On the basis of the evidence of interrelationship among miR-92a profile, FMD study, and eGFR level, the author indicates that miR-92a gene expression profile may be a diagnostic early biomarker in atherosclerosis-related CKD, having a connection between cardiovascular disease and chronic kidney disease. The author suggests that atherosclerosis-related CKD cause oxidative stress, in turn leading to miR-92a gene expression in endothelial cell and circulating level, systemic endothelial dysfunction assessed by FMD, and renal dysfunction estimated by eGFR level. This mechanism may be present even at early stage in CKD, as cardio-renal interrelationship may be also suggested under mild renal dysfunction. In CKD with advanced stage, the author suggests that oxidative stress derived from uremic toxin mainly contribute to miR-92a profile, endothelial dysfunction, and renal failure on the basis of the proof of relationship among uremic toxin, FMD study, and miR-92a expression profile. Results provided that miR-92a-3p and/or miR-489-3p are potential treatment targets in atherosclerosis-related chronic kidney disease.

CONCLUSIONS

1. The author indicates that microRNA-92a gene expression profile in endothelial cell and circulating level reflecting flow-mediated vasodilation study and estimated glomerular filtration rate level may be an early diagnostic biomarker in atherosclerosis-related chronic kidney disease, having a link between cardiovascular disease and chronic kidney disease.

2. It is putative that microRNA-92a, having multifunctional manner show a link between cardiovascular disease and chronic kidney disease mediated by endothelial dysfunction.

3. The author suggests that atherosclerosis-related chronic kidney disease cause oxidative stress, in turn leading to microRNA-92a expression, endothelial dysfunction, and renal dysfunction. In addition, especially in chronic kidney disease with late stage, oxidative stress derived from uremic toxin mainly contributes to microRNA-92a gene expression profile, endothelial dysfunction, and renal failure.

4 It is strongly suggested that mcroRNA-92a-3p and/or microRNA-489-3p are potential therapeutic targets in atherosclerosis-related chronic kidney disease.

5. The author emphasizes that clinically and genetically, the studies have provided a link between cardiovascular disease and chronic kidney disease mediated by endothelial dysfunction even at early stage.

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REFERENCES

1. Feinberg MW, Moore KJ. MicroRNA regulation of atherosclerosis. Circ Res. 2016;118(4):703-720.
2. Fujioka K. Effect on microRNA-92a in atherosclerosis along with flow-mediated vasodilation study. J Cancer Oncol. 2020;4(1):153.
3. Fujioka K, Oishi M, Nakayama T, Fujioka A. Association of brachial artery measures with estimated GFR>60 mL/min/1.73 m^2 in a cross-sectional study of the community-based women. Angiology Open Access. 2019;7(3):231.
4. Reffelmann T, Krebs A, Ittermann T, Empen K, Hummel A, Dorr M, et al. Mild renal dysfunction as a non-traditional cardiovascular risk factor? Association of cystatin C-based glomerular filtration rate with flow-mediated vasodilation. Atherosclerosis. 2010;211(2): 660-666.
5. Peralta CA, Jacobs DR Jr, Katz R, Ix JH, Madero M, Duprez DA, et al. Association of pulse pressure, arterial elasticity, and endothelial function with kidney function decline among adults with estimated GFR>60 mL/min/ 1.73m^2: The Multi-Ethnic Study of Atherosclerosis(MESA). Am J Kidney Dis. 2012;59(1): 41-49.

6. Neprin E, Ingelsson E, Riserus U, Helmersson-Karlqvist J, Sundstrom J, Jobs E, et al. Association between glomerular filtration rate and endothelial function in an elderly community cohort. Atherosclerosis. 2012;224(1):242-246.
7. Shang F, Wang SC, Hsu CY, Miao Y, Martin M, Yin Y, et al. MicroRNA-92a mediates endothelial dysfunction in CKD. J Am Soc Nephrol. 2017;28(11):3251-3261.
8. Chen Z, Wen L, Martin M, Hsu CY, Fang L, Lin FM, et al. Oxidative stress activates endothelial innate immunity via sterol regulatory element binding protein 2 (SREBP2) transactivation of microRNA-92a. Circulation. 2015;131(9): 805-814.
9. Wiese CB, Zhong J, Xu ZQ, Zhang Y, Ramirez Solano MA, Zhu W, et al. Dual inhibition of endothelial miR-92a-3p and miR-489-3p reduces renal injury-associated atherosclerosis. Atherosclerosis. 2019;282(3):121-131.
10. Moody WE, Edwards NC, Madhani M, Chue CD, Steeds RP, Ferro CJ, et al. Endothelial dysfunction and cardiovascular disease in early-stage chronic kidney disease: cause or association? Atherosclerosis. 2012;223(1):86-94.
11. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. Circulation. 2007;116(1): 85-97.
12. Endemann DH, Schiffrin EL. Endothelial dysfunction. J Am Soc Nephrol. 2004;15(8):1983-1992.
13. Foundation NK. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2):S1-266.
14. Stam F, van Guldener C, Becker A, Dekker JM, Heine RJ, Bouter LM, et al. Endothelial dysfunction contributes to renal function-associated cardiovascular mortality in a population with mild renal insufficiency: The Hoorn study. J Am Soc Nephrol. 2006;17(2): 537-545.
15. Foster MC, Keyes MJ, Larson MG, Vita JA, Mitchell GF, Meigs JB, et al. Relations of measures of endothelial function and kidney disease: The Framingham Heart Study. Am J Kidney Dis. 2008;52(5):859-867.
16. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39(2): 257-265.
17. Fujioka K, Oishi M, Fujioka A, Nakayama T. Increased nitroglycerin-mediated vasodilation in migraineurs without aura in the interictal period. J Med Ultrason. 2018;45(5):605-610.
18. Fujioka K. Reply to: Endothelium-dependent and –independent functions in migraineurs. J Med Ultrason. 2019;46(10):169-170.
19. Fujioka K. Propensity to the vascular smooth muscle cell abnormality in migraine without aura and vasospastic angina along with a genome-wide association studies. J Carcinog Mutagene. 2019;10(2):1-4.
20. Fujioka K, Oishi M, Fujioka A, Nakayama T, Okada M. Interrelationship among lipid profiles, arterial stiffness, and nitroglycerin-mediated vasodilation in the community-based setting of Japanese women. Angiology Open Access. 2019;7(3): 235.
21. Kumar S, Kim CW, Simmons RD, Jo H. Role of flow-sensitive microRNAs in endothelial dysfunction and atherosclerosis: Mechanosensitive athero-miRs. Arterioscler Thromb Vasc Biol. 2014;34(10):2206-2216.
22. Kumar S, William D, Sur S, Wang JY, Jo H. Role of flow-sensitive microRNAs and long noncording RNAs in vascular dysfunction and atherosclerosis. Vascul Phamacol. 2019;114(3):76-92.
23. Liu Y, Li Q, Hosen MR, Zietzer A, Flender A, Levermann P, et al. Atherosclerotic conditions promote the packaging of functional microRNA-92a-3p into endothelial microvesicles. Circ Res. 2019;124(4): 575-587.
24. Chang YJ, Li YS, Wu CC, Wang KC, Huang TC, Chen Z, et al. Extracellular microRNA-92a mediates endothelial cell-macrophage communication. Arterioscler Thromb Vasc Boil. 2019;39(12): 2492-2504.
25. Loyer X, Potteaux S, Vion AC, Guerin CL, Boulkroun S, Rautou PE, et al. Inhibition of microRNA-92a prevents endothelial dysfunction and atherosclerosis in mice. Circ Res. 2014;114(3): 434-443.
26. Bonauer A, Carmona G, Iwasaki M, Mione M, Koyanagi M, Fischer A, et al. MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. Science. 2009;324(5935):1710-1713.
27. Hinkel R, Penzkofer D, Zuhlke S, Fischer A, Husada W, Fu Xu QF, et al. Inhibition of microRNA-92a protects against ischemia/reperfusion injury in a large-animal model. Circulation. 2013; 128(10):1066-1077.
28. Daniel JM, Penzkofer D, Teske R, Dutzmann J, Koch A, Bielenberg W, et al. Iinhibition of miR-92a improves re-endothelialization and prevents neointima formation following vascular injury. Cardiovasc Res. 2014;103(4):564-572.
29. Wu W, Xiao H, Laguna-Fernandez A, Villarreal G Jr, Wang KC, Geary GG, et al. Flow-dependent regulation of Kruppel-like Factor 2 is mediated by microRNA-92a. Circulation. 2011;124(5): 633-641.
30. Liu H, Li G, Zhao W, Hu Y. Inhibition of miR-92a may protect endothelial cells after acute myocardial infarction in rats: Role of KLF2/4. Med Sci Monit. 2016;22(5):2451-2462.
31. Rogg EM, Abplanalp WT, Bischof C, John D, Schulz MH, et al. Analysis of cell type-specific effects of microRNA-92a provides novel insights into target regulation and mechanism of action. Circulation. 2018;138(22):2545-2558.
32. Liu P, Su J, Song X, Wang S. miR-92a regulates the expression levels of matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase 3 via sirtuin 1 signaling in hydrogen peroxide-induced vascular smooth muscle cells. Mol Med Rep. 2018;17(1): 1041-1048.
33. Gou L, Zhao L, Song W, Wang L, Liu J, Zhang H, et al. Inhibition of miR-92a suppresses oxidative stress and improves endothelial function by upregulating heme oxygenase-1 in db/db mice. Antioxid Redox Signal. 2018;28(5):358-370.
34. Wu IW, Hsu KH, Hsu HJ, Lee CC, Sun CY, Tsai CJ, et al. Serum free p-cresyl sulfate levels predict cardiovascular and all-cause mortality in elderly hemodialysis patients-a prospective cohort study. Nephrol Dial Transplant. 2012;27(3):1169-1175.
35. Yu M, Kim YJ, Kang DH. Indoxyl sulfate-induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress. Clin J Am Soc Nephrol. 2011;6(1): 30-39.
36. Six I, Gross P, Remond MC, Chillon JM, Poirot S, Drueke TB, et al. Deleterious vascular effects of indoxyl sulfate and reversal by oral adsorbent AST-120. Atherosclerosis. 2015;243(1):248-256.
37. Wang CH, Lai YH, Kuo CH, Lin YL, Tsai JP, Hsu BG. Association between serum indoxyl sulfate levels and endothelial function in non-dialysis chronic kidney disease. Toxins. 2019;11(10):E589.
38. Matsumoto T, Takayanagi K, Kojima M, Taguchi K, Kobayashi T. Acute exposure to indoxyl sulfate impairs endothelium-dependent vasorelaxation in rat aort. Int J Mol Sci. 2019;20(2):E338.

39. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: A systematic review. J Am Soc Nephrol. 2014;25(9):1897-1907.

40. Wei Q, Liu Y, Liu P, Hao J, Liang M, Mi QS, et al. MicroRNA-489 induction by hypoxia-inducible factor-1 protects against ischemic kidney injury. J Am Soc Nephrol. 2016;27(9):2784-2796.

41. Cheung TH, Quach NL, Charville GW, Liu L, Park L, Edalati A, et al. Maintenance of muscle stem-cell quiescence by microRNA-489. Nature. 2012;482(7386):524-528.

42. Wang K, Liu F, Zhou LY, Long B, Yuan SM, Wang Y, et al. The long noncoding RNA CHRF regulates cardiac hypertrophy by targeting miR-489. Cir Res. 2014;114(9):1377-1388.

43. Zhou X, Qu Z, Zhu C, Lin Z, Huo Y, Wang X, et al. Identification of urinary microRNA biomarkers for detection of gentamicin-induced acute kidney injury in rats. Regul Toxicol Pharmacol. 2016;78(7):78-84.