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The effect of increased blood microRNA on autophagy dysregulation in cardiac cells and cardiac complications in chronic kidney disease

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Objectives:

Increased cardiovascular morbidity and mortality is the conundrum in chronic kidney disease (CKD). Although hemodynamic change has been blamed for the extremely high incidence of cardiovascular disease in CKD, the retention of uremic toxins might be directly associated with it, including decreased heart function and induction of serious arrhythmia. This study aimed to investigate the association between the cardiac fibrosis and uremic toxin in CKD. Furthermore, we will try to investigate the role of the alteration of blood microRNA (miRNA) levels like other uremic toxin on cardiac fibrosis.

Methods:

We induced CKD in rats by 5/6-STNx. We investigated the changes in the renal function and the levels of blood miRNA by affymetrix miRNA array. Renal and cardiac fibrosis was evaluated by Masson's trichrome(MT) staining. We also isolated sinus nodal cells from cardiac atria of C57BL/6 mice, and treated a representative protein-bound uremic toxin, indoxyl sulfate (IS) and probenecid into the cells for 48 h, and evaluated the changes in the expression of fibrosis-related molecules.

Results: Serum creatinine(Cr) and blood urea nitrogen(BUN) were significantly higher in the 5/6-STNx than controls, while echocardiography were lower in the 5/6-STNx. The miRNA profiles of blood serum of 5/6-STNx were significantly different compared to controls. We focus on the significant decrease in the level of miRNA let-7 family for now. Additionally, MTstaining for the assessment of fibrosis showed the increased fibrosis in the heart and kidney of 5/6-STNx compared with controls. *In vitro,* protein expressions of fibronectin, phospho-p38 MAP kinase and LC3-II after IS stimulation were significantly higher at 48 h, which was blocked by organic anion transporter inhibitor, probenecid.

Conclusions: These findings suggested that there was a direct effect of uremic toxin on the induction of fibrosis by MAPK activation in sinus nodal cells. The relationship between miRNA and cardiac fibrosis would be investigated down the road.