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Simplified uremic vasculopathy model using induced pluripotent stem cells and uremic toxin mixture

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Objectives: Cardiovascular complications still remain as major causes of morbidity and mortality in end-stage renal disease (ESRD) patients. Although uremic vasculopathy is the corner stone of cardiovascular complications in ESRD, it is difficult to establish a proper animal model and simulate uremic vasculopathy. In this study, we evaluated simplified uremic toxin mixtures for disease modeling of uremic vasculopathy using endothelial cells differentiated from induced pluripotent stem cells (iPSCs-ECs).

Methods: Peripheral blood mononuclear cells from a normal control and an ESRD patient was reprogrammed to iPSCs using Sendai virus, then iPSC-ECs were differentiated from iPSCs. Uremic toxins such as urea, creatinine, uric acid, indoxyl sulfate, and advanced glycation end-product were tested in a cell culture model of iPSC-ECs. Reactive oxygen species (ROS) and tube formation were measured to evaluate dysfunction of iPSC-ECs. Media alone was used as a negative control and 15% serum from end-stage renal disease patients receiving hemodialysis was used as a positive control.

Results: Urea, uric acid, and indoxyl sulfate significantly decreased the tube formation ability of iPSC-ECs. Creatinine alone did not affect ROS levels or the tube formation ability of iPSC-ECs. Uremic toxin mixtures comprised of high concentration of urea, creatinine, uric acid, and indoxyl sulfate increased ROS production and apoptosis, whereas decreased tube formation ability of iPSC-ECs similar to the effect of ESRD patients' uremic serum. ESRD patient-specific iPSC-ECs showed impaired wound healing potential which was partially restored by losartan and TGF-β inhibitor.

Conclusions: Our study showed that simplified uremic vasculopathy model can be developed using uremic toxin mixtures comprised of urea, uric acid, and indoxyl sulfate in iPSC-ECs. This novel model may be used as a new research tool and drug screening system.