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In vitro modeling of uremic cardiomyopathy using induced pluripotent stem cell-derived cardiomyocytes and simplified uremic toxin mixture

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Objectives: Cardiovascular diseases are the leading cause of death among patients with chronic kidney disease (CKD). Uremic cardiomyopathy (UCM) describes the cardiac abnormalities caused by chronic kidney disease, especially end-stage kidney disease (ESKD). Pathogenic mechanisms leading to uremic cardiomyopathy are complex and remain unresolved. We aimed to model uremic cardiomyopathy in vitro using patient-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) and simplified uremic toxin mixtures (UTs).

Methods: The patient-specific iPSCs were reprogrammed from peripheral blood mononuclear cells (PBMCs) of ESKD patients with and without UCM, respectively (UCM iPSC-CMs and control iPSC-CMs). In order to simulate the uremic condition of ESKD, iPSC-CMs were treated with various combinations of UTs.

Results: PBMCs were collected from three controls (ESKD patients with no significant cardiac abnormalities) and three UCM patients and reprogrammed to iPSCs using Sendai virus. Then, the control iPSC-CMs and UCM iPSC-CMs were generated. UCM iPSC-CMs treated with UTs showed the abnormal contractile properties including decreased spike amplitude and increased beat period in field potential analysis using multielectrode array. Compared to control iPSC-CMs, UCM iPSC-CMs treated with UTs showed increased abnormal sarcomere alignments. In transcriptome analysis, UCM iPSC-CMs exhibited upregulated gene expression associated with cell adhesion and cytokine stimulation compared with the control iPSC-CMs.

Conclusions: We demonstrated that iPSC-CMs with simplified uremic toxin mixtures can successfully recapitulate the phenotypes of uremic cardiomyopathy.