Deterioration of skeletal myocyte myomixer expression and fusogenic activity in uremic sarcopenia

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Elderly people often have physiologically decreased renal function, and the influence of decreased renal function may not be ignored as a factor in sarcopenia in the elderly.In the context of declined skeletal muscle mass and function, the muscle regeneration and differentiation process has not been extensively studied. In mice with kidney dysfunction induced by adenine-containing diet compared to control mice, the tibialis anterior muscle damage was poorly recovered after muscle injury. In the cultured murine skeletal myocytes, stimulation with indoxyl sulfate (IS), a representative uremic toxin, morphologically jeopardized the differentiation, which was counteracted by L-ascorbic acid (L-AsA) treatment. Transcriptome analysis for those cultured myocytes identified a set of genes the expression of which was reduced by IS stimulation but reascended by L-AsA treatment. Silencing of myomixer, one of those genes, impaired myocyte fusion during the differentiation. In contrast, lentiviral overexpression of myomixer compensated a hypomorphic phenotype caused by IS treatment. The split-luciferase technique demonstrated that IS stimulation negatively affected early myofusion activity that was rescued by L-AsA treatment. Lastly, in mice with kidney dysfunction compared to control mice, myomixer expression in the muscle tissue in addition to the muscle weight after the injury were reduced, both of which were restored with L-AsA treatment. Collectively, the uremic milieu impairs the expression of myomixer and impedes the myofusion process. Considering frequent musculoskeletal injuries in those patients, defective myocyte fusion followed by delayed muscle damage recovery could underlie the muscle loss and weakness.