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Effect of Klotho on Autophagy Clearance in Tacrolimus-induced Renal Injury

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Objectives: Recently, we showed that tacrolimus-induced renal injury is closely associated with impairment of autophagy clearance, and Klotho deficiency aggravates tacrolimus-induced renal injury. In this study, we evaluated the effect of Klotho treatment on autophagy clearance in tacrolimus-induced renal injury.

Methods: We evaluated the effect of Klotho on tacrolimus-induced renal injury in an experimental mouse model and in vitro by treatment with tacrolimus and/or recombinant mouse Klotho.

Results: In vivo and in vitro studies showed that tacrolimus treatment impaired lysosomal acidification and decreased cathepsin B activity, expression of lysosome-associated membrane protein 2, and transcription factor EB (TFEB), a master regulator for lysosomal biogenesis. These results were improved by Klotho treatment. Moreover, addition of bafilomycin A1, an inhibitor of lysosomal function, abolished the protective effect of Klotho, indicating that the protective effect of Klotho was closely associated with lysosome function. Klotho induced nuclear translocation of TFEB through inhibition of phosphorylation of glycogen synthase kinase 3β (GSK3β) by confirming using CHIR99021, a GSK3β inhibitor.

Conclusions: Collectively, our data suggest that Klotho improves autophagy clearance via activation of lysosomal function in tacrolimus-induced nephrotoxicity.