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αKlotho protects podocyte injury by upregulated calcium channels in diabetic nephropathy

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Objectives: αKlotho is mainly expressed in the renal tubules and protects the kidney filter via regulating renal Ca^{2+} ion channels. The abnormal activation of Orai1 and TRPC5/6 channels in podocyte disorganizes actin-cytoskeleton and leads to proteinuria in diabetic nephropathy (DN). It is still unknown whether and how αKlotho regulates multiple podocyte Ca^{2+} channels to protect DN. Here we demonstrated that αKlotho ameliorates podocytes injury by stabilizing Orai1 and TRPC5/6 channels-mediated Ca^{2+} signaling to prevent DN.

Methods: Type 2 diabetic *db/db* mice received *i.p.* injections of Klotho protein three times a week. Live-cell imaging and immunocytochemistry were performed in immortalized mouse podocytes.

Results: The mice were administered with recombinant αKlotho peptide through *i.p.* injections. αKlotho was reduced along with podocyte markers such as synaptopodin and nephrin, while Orai1, and TRPC5/6 were overexpressed in early and late periods in *db/db* mice, respectively. Administration of αKlotho protein ameliorated podocyte foot process disruption and proteinuria in *db/db* mice with decreased expression of channel proteins and the dissolution of synaptopodin. *In vitro*, αKlotho suppressed Orai1- and TRPC5/6-mediated Ca^{2+} entry in cultured murine podocytes via inhibiting growth factors and/or insulin signaling. Mechanistically, αKlotho acutely reduced cell-surface abundance of Orai1 by suppressing phosphoinositide-3-kinase-dependent trafficking of the channel, whereas TRPC5/6 channels were slowly decreased by inhibiting growth factor-driven SGK1 activation. All the total channel proteins were reduced in long-term treatment (~24 h) of αKlotho. Functionally, exacerbated actin remodeling by Orai1 and TRPC6 activation was ameliorated by αKlotho.

Conclusions: Taken together, our results reveal an underlying mechanism by which αKlotho protects proteinuria and podocyte actin remodeling through stabilizing Ca^{2+} signaling mediated by Orai1 and TRPC5/6, and offer a new potential therapeutic strategy for the treatment of DN.
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