KSN SEOUL, KOREA 2023
April 27(Thu) - 30(Sun), 2023
Coex, Seoul, Korea

Submission No.: DKD1-9002
Session Title: Diabetic Kidney Disease
Date & Time, Place: April 29 (Sat), 08:30 - 10:30, Room 3

Klotho Protects Diabetic Nephropathy via Regulating Podocyte Ca2+-Permeable Channels

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Klotho is an anti-aging protein predominantly produced in the kidney that protects the kidney filter and renal diseases via regulating renal Ca^{2+} ion channels. Intracellular Ca^{2+} homeostasis in podocytes is vital for maintaining proper filter function, and the deregulation of Ca^{2+} signaling via TRPC5 or 6 channels has been implicated in proteinuria in diabetic nephropathy (DN). Recently, we reported that exaggerated Orai1-mediated store-operated Ca^{2+} entry in a hyperinsulinemic early period of DN causes proteinuria, while TRPC5 and 6 channels were increased in the late period of DN leading to proteinuria. However, it is still unknown whether and how Klotho integrates multiple podocyte Ca^{2+} channels to protect DN. This lecture will provide current research progress of Klotho and Ca^{2+} signaling targeting DN and suggest future direction. Briefly, in the progression of DN, Klotho has been reduced along with podocyte markers, while Orai1 and TRPC5/6 were overexpressed in early and late periods in DN mice, respectively. Administration of Klotho protein ameliorated podocyte foot process disruption and proteinuria in DN mice. Klotho suppressed Orai1- and TRPC5/6-mediated Ca^{2+} entry in mouse-cultured podocytes via inhibiting growth factor-driven channel activation. Mechanistically, Klotho acutely reduced cell surface abundance of channels by suppressing their phosphoinositide-3-kinase-dependent trafficking. Functionally, actin remodeling driven by Orai1 and TRPC6 overactivation was ameliorated by Klotho. These findings propose that Klotho ameliorates podocyte injury by stabilizing Orai1 and TRPC5/6 channels-mediated Ca^{2+} signaling to prevent DN. This lecture reveals an underlying mechanism by which Klotho protects proteinuria and podocytopathy through stabilizing Ca^{2+} signaling mediated by Orai1 and TRPC5/6, and offers a new potential therapeutic strategy for the treatment of DN.