Impairment of Calcium-dependent inactivation of TRPC6 Mediated by Calmodulin Underlies Renal Channelopathy

Onur K Polat¹, Masayuki X Mori¹, Masatoshi Uno², Hidehito Tochio², Yasuo Mori¹

¹Graduate School of Engineering, Department of Synthetic and Biological Chemistry, Japan, ²Kyoto University, Graduate School of Science, Department of Biophysics, Japan

TRPC6 channel activity is suppressed by the intracellular Ca^{2+} through a negative feedback regulation known as Ca^{2+} -dependent inactivation (CDI), in which calmodulin (CaM) has been proposed to play a critical role. Here, our molecular mutations and dissections with functional and biophysical analysis have revealed new detail that equal contribution of N- and C-lobes of CaM to CDI and which could be accomplished by Ca^{2+} -dependent CaM binding to the TRPC6 CaM-binding domain (CBD) in a 1:2 stoichiometry. This ensemble prerequisite was arranged via assembly of the coiled-coil segment adjacent to the CBD. The deletion of this segment markedly decelerated CDI of TRPC6 currents, suggesting that CDI is induced by bridging of two CBDs by a single CaM molecule. Naturally occurring gain-of-function TRPC6 mutations are involved in autosomal dominant focal segmental glomerulosclerosis (FSGS). Surprisingly, the FSGS-TRPC6 mutations in the coiled-coil severely hamper CDI and induce "rim-like" morphological changes in podocytes. Our study provides novel structural insights into the CDI of TRPC6 channel, and the disruption of CDI leads to the pathophysiological significance in kidney disease.