Abstract Submission No. : 9017
May 26(Thu),10:40-13:10 Basic Science Symposium: A Session of the ISN North and East Asia Regional Board

Identification of an A-Kinase Anchoring Protein Essential for Urinary Concentration

Fumiaki Ando
Tokyo Medical and Dental University (TMDU), Japan

Protein kinase A (PKA) directly phosphorylates aquaporin-2 (AQP2) water channels in renal collecting ducts to reabsorb water from urine for the maintenance of systemic water homeostasis. Over 50 functionally distinct PKA-anchoring proteins (AKAPs) respectively create compartmentalized PKA signaling to determine the substrate specificity of PKA. Identification of an AKAP responsible for AQP2 phosphorylation is an essential step toward elucidating the molecular mechanisms of urinary concentration. We used PKA activators as novel screening tools to uncover PKA substrates whose phosphorylation levels were nearly perfectly correlated with that of AQP2.

The leading candidate in this assay proved to be an AKAP termed lipopolysaccharide-responsive and beige-like anchor protein (LRBA). We found that LRBA colocalized with AQP2 *in vivo*, and *Lrba* knockout mice displayed polyuric phenotype, with severely impaired AQP2 phosphorylation. Most of the PKA substrates other than AQP2 were adequately phosphorylated by PKA in the absence of LRBA, demonstrating that LRBA preferentially mediated AQP2 signaling in renal collecting ducts. Furthermore, PKA activators robustly dissociated the LRBA–PKA interaction, rather than other AKAP–PKA interactions. AKAP–PKA interaction inhibitors have attracted attention for their ability to directly phosphorylate AQP2. Therefore, the LRBA–PKA interaction is a promising drug target for the development of anti-aquaretics.