No. 2320

Molecular Mechanisms of LRBA-Mediated Sodium Reabsorption in Renal Tubules

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Summary

Lipopolysaccharide-responsive beige-like anchor protein (LRBA) is a protein kinase A (PKA) anchoring protein that creates compartmentalized PKA signaling in renal collecting ducts which is responsible for aquaporin-2 (AQP2) phosphorylation. *Lrba* knockout mice exhibit a polyuric phenotype with severely impaired AQP2 phosphorylation. However, the molecular mechanisms by which LRBA mediates vasopressin-induced AQP2 phosphorylation remain unknown.

To investigate AQP2 intracellular localization and phosphorylation status *in vivo*, a density gradient ultracentrifugation technique was combined with super-resolution structured illumination microscopy. AQP2 and LRBA were colocalized on the recycling endosome in the absence of vasopressin stimulation. The LRBA-PKA complex created compartmentalized PKA signalling at the recycling endosome, which facilitated AQP2 phosphorylation in response to vasopressin.

Although low urinary concentrating ability usually induces hypernatremia due to free-water diuresis, serum sodium level of *Lrba* knockout mice was low. The diuretic loading test revealed that thiazide diuretics, which is an inhibitor of sodium-chloride cotransporter (NCC), did not increase urinary sodium excretion in *Lrba* knockout mice. As a result of the impairment of NCC activity, baseline blood pressure was low in *Lrba* knockout mice, and their blood pressure was unresponsive to thiazide treatment. We finally examined the molecular mechanisms of LRBA-mediated NCC regulation. WNK-SPAK-NCC signaling is a main trigger to promote sodium reabsorption from urine via NCC. LRBA was colocalized with SPAK at intercellular vesicles in the distal convoluted tubules. In *Lrba* knockout mice, the protein expression level of SPAK was decreased and that of WNK was compensatorily increased. LRBA directly bound to SPAK and inhibited its lysosomal degradation.

In this study, we demonstrated that LRBA is essential for the activation of both NCC and AQP2, thereby ensuring sodium and water homeostasis in renal tubules. We now establish an international observational registry to examine these renal phenotypes in patients with LRBA deficiency.