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# Effect of the Interaction between a Novel PDZ Protein and $Na^+$-Dependent Lactate Transporter SMCT1 on Renal Urate Transport

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Summary

Urate is the major end product of purine degradation in humans because of the genetic silencing of hepatic oxidative enzyme uricase. The kidney plays a dominant role in urate elimination. Therefore, it is important to understand renal urate handling mechanism because the underexcretion of urate has been implicated in the development of hyperuricemia that leads to gout. In 2002, we identified the urate-anion exchanger URAT1 (*SLC22A12*) in the human kidney and found that defects in *SLC22A12* lead to idiopathic renal hypouricemia. URAT1 is targeted by uricosuric and antiuricosuric agents that affect urate excretion. Using yeast two-hybrid approach, we identified the multivalent PDZ domain-containing protein PDZK1 as an apparent partner of URAT1 in the kidney. Co-expression experiments demonstrated that URAT1 transport activities are increased by PDZK1/URAT1 interactions. In 2004, Ganapathy and his colleagues identified that SLC5A8 is a sodium-coupled monocarboxylate transporter1 (SMCT1). Through the $Na^+$-coupled reabsorption of lactate, the counterion for URAT1, the modulation of SMCT function may affect the URAT1-mediated urate transport. Because we found that SMCT1 C-terminal that has PDZ motif binds to PDZK1, physical coupling between URAT1 and SMCT via PDZK1 forms a single functional complex and mediates $Na^+$-dependent reabsorption of urate in the renal proximal tubules. In this study, we characterized the interaction of a novel PDZ protein PDZRN3 with SMCT1 in the yeast two-hybrid system. Localization of PDZRN3 was detected at the cytoplasmic region of the proximal tubules in human kidney. The association of hSMCT1 with PDZRN3 did not enhanc SMCT1-mediated [$^3$H] nicotinate transport activity in HEK293 cells. Based on these results, we speculate that the interaction of PDZRN2 with SMCT1 is involved in the regulation of $Na^+$-dependent urate transport.