S17-1 Hyperuricemia and renal urate transporters

◯Naohiko ANZAI[1], Promsuk JUTABHA[1], Toru KIMURA[1], Toshiyuki FUKUTOMI[1], Hiroyuki SAKURAI[1]

[1]Kyorin Univ Sch Med

Reanl tubular reabsorption of urate occurs in two steps: (1) urate is taken up from the tubular lumen by apical transporter(s), (2) it is effluxed into the peritubular space by distinct basolateral transporter(s). In 2002, we identified a long-hypothesized urate–anion exchanger, URAT1 (*SLC22A12*), localized at the apical side of the renal proximal tubule that mediates the first step of urate reabsorption (Enomoto *et al., Nature*). Using *Xenopus* oocytes expression system, we found that an extended (class II) sugar transport facilitator family protein SLC2A9 transported urate in a voltage-sensitive manner, favoring urate efflux from the cell. Considering its basolateral localization, SLC2A9 is likely to be the transporter mediating the second step of urate reabsorption, and we renamed this protein as voltage-driven urate transporter (URATv1). Urate transport via URATv1 was affected by uricosuric agents probenecid, benzbromarone, phenylbutazone and losartan, but not by monocarboxylates such as lactate, nicotinate, orotate, pyrazinoate (PZA), or beta-hydroxybutyrate. Furthermore, we have identified an *SLC2A9* mutation P412R from Japanese renal hypouricemia patients who had no detectable mutations in *SLC22A12*. This missense mutation reduced urate uptake activity when expressed in *Xenopus* oocytes. Plasma membrane expression of this mutant was confirmed. (Anzai *et al., J Biol Chem*, 2008). In summary, although both transported urate, URATv1 showed different substrate selectivity than URAT1, suggesting that targeting URATv1 may lead to a novel therapy for hyperuricemia.