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Roles of renal transporters in health and disease

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The kidney is one of the most active organs in transmembrane transport of water, electrolytes, and inorganic and organic compounds. Several renal transporters play important roles in maintenance of health or normalization of disease states. In this presentation, the following transporters will be discussed for drug targets.

SGLT2 (SLC5A2)/anti-diabetes

Within the proximal tubules, two isoforms of sodium glucose co-transporters (SGLT1 and 2) were identified. SGLT1 is localized in the terminal portion (S3) of the proximal tubule and SGLT2 is in the early portion (S1). Their properties are high and low affinity transporters, respectively. In 1999, we have characterized analogs of Pflorizin, (a classical glycosuric agent), T-1095 and its metabolite, T-1095A clearly showing that IC50 value of T-1095A was fairly lower against SGLT2 (IC50=50 nM) and oral administered T-1095 (as a prodrug) revealed higher glucose excretion into urine and lowered blood glucose in diabetic rats (Diabetes 48: 1794, 1999).

In 2001 and 2002, the analogs of T-1095A were synthesized as much better compounds from pharmacokinetic viewpoints. Now, several compounds were launched as new anti-diabetic drugs. Thus, SGLT2 is one of most influential drugs for a typical common disease, diabetes mellitus.

URAT1 (SLC22A12)/anti-hyperuricemia

In 2002, we could identify URAT1 using a 'dry cloning' strategy (Nature 417: 447). URAT1 was characterized as an exchanger of uric acid with endogenous and exogenous anionic substances. Moreover, URAT1 was so powerful in absorbing uric acid from urine that the modification of its function could increase and/or decrease blood level of uric acid. Since various mutations of URAT1 decreases/loses its functions and since most uricosuric agents inhibit URAT1, compounds which inhibit URAT1 could become novel anti-hyperuricemia. Several trials have been carried out to develop new agents worldwide using hURAT1 expression systems as a screening method.

LAT1 (SLC7A5)/anti-polycystic kidney disease

Prior to entering genome era, we could identify two types of heterodimeric transporters for branched-chain amino acid (BCAA) transport, named LAT1 (J. Biol Chem. 273:23629, 1998) and LAT2 (ibid 274: 19745, 1999). Both members required a glycosylated chaperon, 4F2hc (CD98) in addition to 12 transmembrane non-glycosylated subunits, LAT1 and LAT2. LAT1 is an oncofetal transporter whereas LAT2 is a normal type in their functions. Although

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LAT1 is a good biomarker of cancers to supply essential amino acids, one of pathogenesis reveals that BCAA supply would be a crucial component. Recently, LAT1 has been identified to show its strong expression in cyst cells lining the autosomal dominant polycystic kidney disease. In addition, BCAA supply stimulates mTOR and MAPK/ERK pathways for cyst formation. Thus, inhibitors of LAT1 may be therapeutic agents.
In conclusion, renal transporters may play essential roles in maintenance of physiological and pathophysiological states not only within the kidney, but also in the whole body.