Functional analysis of mutant SLCO2A1 transporter responsible for human intractable small intestinal ulcer

Seki Satowa[1], Gen Tanaka[2], Tadakazu Hisamatsu[1], Hiroyuki Sakurai[2]

[1]*Dept. Gastroenterology. Hepatology., Kyorin Univ.,* [2]*Dept. Pharmacology. Toxicology., Kyorin Univ.*

【Background】

Chronic nonspecific multiple ulcers of the small intestine (CNSU) is an intractable disease presenting with chronic anemia and hypoalbuminemia. Recently, mutations in *slco2a1* gene coding prostaglandin (PG) transporter protein have been shown to be causative for CNSU and a new disease entity "chronic enteropathy associated with SLCO2A1 (CEAS)" has been proposed. However, detailed mechanisms of how mutant SLCO2A1 protein involved in the development of CEAS has not been fully elucidated. In this study, we investigated transporter function of mutant SLCO2A1 proteins identified in the patients with CEAS.

【Method】

Synthesized cRNAs for wild type or 5 known mutants were injected into Xenopus oocytes. After 2 days incubation, these oocytes were treated with various concentrations of 3H-PGE2 for 30 min and amount of transport was measured by counting radioactivity of cell lysates.

【Results and discussion】

Consistent with previous reports, wild type SLCO2A1-expressed oocytes took up PGE2. A mutant with 97GC showed comparable PGE2 transport capability to wild type, while 3 mutants, 1647GT, 830dupT, and 830delT exhibited very little PGE2 transport activity. Another mutant, 1372GT, transported some PGE2 with markedly suppressed Vmax with little change in Km value. Most mutations in SLCO2A1 gene present in CEAS patients affected Vmax suggesting these mutations inhibited cell surface expression of the transporter rather than changing the affinity to the substrate. Since this assay employed a heterologous overexpression system, transport activity of 97GC mutant should be evaluated in a mammalian expression system.