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An *metabolomic* approach to identify the *endogenous* substrate of OCT1

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Transporters Play Critical Roles in Drug and Nutrients A.D.M.E.
Currently Utilized SLC-drug Targets

**Depression, epilepsy, addiction**
- SLC6 family (TC:2.A.22, APC)
  - SLC6A1, SLC6A2, SLC6A4, SLC6A3 (SSRI)

**Movement disorders, psychiatric disorders, addiction**
- SLC18 family (TC:2.A.1, MFS)
  - SLC18A2

**Epilepsy**
- SLC22 related (MFS)
  - SV2A

**Uricosuresis, gout**
- SLC22 family (TC:2.A.1.19, MFS)
  - SLC22A6 (OAT1)

**Diuresis**
- SLC12 family (TC:2.A.30)
  - SLC12A1, SLC12A2, SLC12A3, SLC12A4
  - SLC12A5 (NKCC)

**Antiosteoporotic, antineoplastic**
- SLC25 family (TC:2.A.29, MC)
  - SLC25A4, SLC12A5, SLC12A6

**Anti-diabetes**
- SLC5A2 (Canagliflozin)

The List is Increasing……..
Transporter as Important Disease Susceptible Genes in GWAS

- SLC24A4 for Alzheimer's Disease
- SLC39A6 for Breast/pancreatic cancer/esophageal squamous-cell carcinoma
- SLC16A9 in Metabolic disease
- SLC6A20 in Hyperglycinuria, and iminoglycinuria
- SLC7A9 in Chronic kidney disease
- SLC22A3 in Prostate cancer/heart disease
- SLC2A9 in Gout: Urate acid disease
- SLC1A1 in Pancreatic disease
- SLC30A8 in Diabetes
- SLC22A12 in Gout: Urate acid disease
- SLC45A2 in Melonoma
- SLC17A8 in Lung Cancer Han Chinese
- SLC2A13 in Parkinson’s Disease
- SLC6A4 in Schizophrenia

“HOT” Therapeutic Targets
Obesity and Diabetes Rising in the world: How a Rare Disease Becomes a Modern "Pandemic"?

Prevalence of obesity*, ages 20+, age standardized Both sexes, 2008

- Prevalence of obesity (%)
  - <10
  - 10–19.9
  - 20–29.9
  - ≥30
  - Data not available
  - Not applicable

350 million people world-wide have T2D (~1/20)

Diabetes affects 92 to 115 million people in China: 10% of the population (~1/10)
Nonalcoholic steatohepatitis (NASH) disease affects 35% of adults and an increasing number of children.

Currently, there is no effective treatment on fatty liver.
Major Transporters Expressed in Liver

Organic Cation Transporter 1 (OCT1) is highly and specifically expressed in Liver.

Metformin | Oxaliplatin
What **Phenotypes** do we see from the mouse studies?

Oct1+/+        Oct1-/-

Lean mice
When crossed with Ob/Ob mice (obesity mice), the liver size is more **apparently reduced** in KO mice.
OCT1 knockout mice showed less fat accumulation but higher glycogen in liver than WT.

- mOct1^{+/+}
- mOct1^{-/-}
- mOct1^{+/+, ob/ob}
- mOct1^{-/-, ob/ob}

**Media:**
- ORO
- PAS
- H&E
What’s the endogenous substrate of OCT1?
Thiamine (Vitamin B1) is one of the metabolites accumulated highly in HEK293-hOCT1

265.1 / 15.1
m/z / R.T.
OCT1 is **high capacity but low affinity** thiamine transporter.

**Kinetics**

- **mOct1**
- **hOCT1**
- **mTHTR1**
- **Control**

![Graph showing kinetics](image)

- Y-axis: nmol/mg protein/min
- X-axis: Thiamine (µM)
- Different lines represent different transporters and controls.
Oct1-/- mice has decreased thiamine distribution in liver

Tissue types
Carnitine and its derivatives are the most significant metabolites elevated in KO mice liver.
Fatty acid β-oxidation rate is higher in Oct1 KO mice but lower fatty acid synthesis rate.
Location, Location……

X-gal staining

Anti-beta Galactosidase
OCT1 only expressed in the hepatocytes around central vein

Glutamine synthetase

β-Galactosidase

Merge
The **enlarged liver** from human transgenic mice - magnetic resonance imaging (MRI) of liver **fat content**

The non-invasive method to monitor the fat amount in **living animal**.
OCT1 activates the P-AMPK to inhibit the fatty acid synthesis.
The **glycogenesis** pathways:

- **Glycogenesis**
- **Glycogenolysis**
- **Glycolysis**

Glucose metabolism

[Diagram showing pathways and proteins involved in glucose metabolism, including Glucose-6-phosphatase (G6pc), Glucose-6-phosphate (G6-P), Glucokinase (Gck), Pyruvate kinase (PK), and various protein expressions under different conditions.]
The OCT1--The molecular Switch (分子开关) of energy

TPP: Thiamine pyrophosphate

Turn on:
- Triglyceride
- Oxidation
- ACC

Turn off:
- Glycogen
- Pyruvate DH
- Fatty acid synthesis

- Acetyl CoA
- ATP

In Press in PNAS
In the news

Science Highlights our Discovery

F1000 Prime Wrote the Commentary

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**METABOLIC DISEASE**

**A vitamin’s dark side in liver disease**

Too much of a good thing can be bad for the liver. Chen et al. find that mice with high levels of thiamine (vitamin B₁) in their livers develop fatty liver disease, a metabolic disorder that affects one-third of adults in the United States. A protein called organic cation transporter 1 (OCT1) carries dietary thiamine into the liver. When the researchers deleted the Oct1 gene in mice or fed mice a diet low in thiamine, the mice did not develop the disease. OCT1 also carries the diabetes drug metformin into the liver, which might explain why metformin decreases symptoms of fatty liver disease: By competing with thiamine for OCT1, metformin reduces the amount of dietary thiamine that reaches the liver. — PAK


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