The manganese efflux transporter SLC30A10 is essential for gastrointestinal manganese excretion

Courtney Mercadante, Ph.D.
Bartnikas Laboratory
Brown University, Providence, RI
September 5, 2019
Acquisition of Manganese (Mn)

- Cofactor of essential proteins
- Oxidant defense, bone growth, immunity
- Men and women require 2.3 and 1.8 mg/day, respectively
- Plentiful dietary sources
- Only 3-5% of dietary Mn is absorbed
- Mn deficiency is very rare
- Mn related diseases are often diseases of excess

http://www.chemistryexplained.com/elements/L-P/Manganese.html
Manganese in excess is toxic

- Mitochondrial dysfunction, compromised antioxidant defense mechanisms

- Manganism: Parkinson’s- like disorder
  - Behavioral changes, slow and clumsy movements, tremors, cock-walk gait

Quadri et al., 2012. *J. Human Genetics*
Physiological Mechanisms of Mn Homeostasis

Modified from: https://www.78stepshealth.us/human-physiology/images/3204_738_974-liver-gallbladder-portal-vein-intestines.jpg; Created using Biorender.com
Manganese excess: Acquired vs. Inherited

- **Deficiency**
  - Inherited: SLC39A8 Deficiency
  - Acquired: ?

- **Sufficiency**
  - Acquired: Occupational

- **Excess**
  - Inherited: SLC30A10 or SLC39A14 Deficiency

References:
Manganese excess: Acquired vs. Inherited

SLC30 family of proteins
- Originally thought to be a zinc transporter (Znt10)
- SLC30 proteins- cation diffusion facilitator superfamily of metal transporters
  - Transport divalent metal cations (Fe, Zn, Cu, Ni, Co, Cd, Mn)
  - Efflux metals from cytosol to extracellular space
- 6 transmembrane domains with a cytoplasmic N and C termini
Manganese excess: Acquired vs. Inherited

SLC30A10 deficiency

- Autosomal recessive
- Mutations in *SLC30A10* identified in patients with hepatic cirrhosis, polycythemia, manganism, and high Mn levels

* No history of environmental Mn exposure
Generating Slc30a10-deficient mice

Whole body Slc30a10 deficiency

\textbf{Slc30a10}^{\text{KO/KO}}

Hepatic Slc30a10 deficiency

\textbf{Slc30a10}^{\text{lox/lox}} \text{Alb}
Slc30a10-deficient mice recapitulate human disease phenotypes

Hypermanganesemia

Polycythemia

Decreased weight

![Graphs showing Slc30a10+/- and Slc30a10KO/KO for RBCs, Mn/mL whole blood, and Mouse weight](image)
Wild-type mice on high Mn diet accumulated high Mn levels
Slc30a10-deficient mice have impaired Mn excretion
Slc30a10-deficient mice have impaired Mn excretion

Control Mn diet 10 ppm

High Mn diet 2400 ppm

Hepatic-Slc30a10 deficiency leads to minimal Mn excess
Hepatic Slc30a10-deficient mice have impaired biliary Mn excretion, but minimal Mn excess.

Why do hepatic Slc30a10-deficient mice have minimal Mn excess?

Hepatic Slc30a10 is essential for hepatobiliary Mn excretion, but hepatic Slc30a10 deficiency only results in a minimal Mn excess?

- Late onset of Albumin-Cre transgene (P21)
- Another tissue contributes to Mn excretion
Slc30a10 is highly expressed in intestines.
Generating $\text{Slc30a10}$-deficient mice

Whole body $\text{Slc30a10}$ deficiency

$\text{Slc30a10}^{\text{KO/KO}}$

Hepatic $\text{Slc30a10}$ deficiency

$\text{Slc30a10}^{\text{lox/lox}} \text{ Alb}$

Hepatic and Intestinal $\text{Slc30a10}$ deficiency

$\text{Slc30a10}^{\text{lox/lox}} \text{ Alb Vil}$

Intestinal $\text{Slc30a10}$ deficiency

$\text{Slc30a10}^{\text{lox/lox}} \text{ Vil}$
Intestinal and hepatic Slc30a10 contribute to Mn homeostasis
Intestinal Slc30a10 contributes to intestinal Mn excretion

Conclusions

• Slc30a10-deficient mice have impaired Mn excretion
• Hepatic Slc30a10 is essential for hepatobiliary Mn excretion
• Hepatic and intestinal Slc30a10 contribute to manganese homeostasis
• Intestinal Slc30a10 contributes to excretion of Mn into intestinal lumen
Future Directions

• Determine the contribution of Slc30a10 to Mn homeostasis in developing mice
• Determine the role of Slc30a10 in cecum and large intestine to Mn homeostasis
• What about Mn absorption?
Acknowledgments

Bartnikas laboratory
Dr. Tom Bartnikas
Dr. Milan Prajapati
Heather Conboy
Miriam Dash
Carolina Herrera
Mike Pettiglio

Genomics Core
Dr. Christoph Schorl

Metal analysis
Dr. Joseph Orchardo

Funding
NIDDK- R01 DK110049, F31 DK117524
NIEHS- T32 ES007272