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The discovery of a novel protein in regulating manganese metabolism

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Abstract

Manganese is essential for life. Tight homeostatic regulation is required to prevent manganese deficiency and avoid manganese overload. ZIP14 is a newly identified manganese importer. It is abundantly expressed in the liver and small intestine, the two major organs involved in the control of manganese metabolism. Patients with loss-of-function mutations in ZIP14 developed severe childhood-onset neurological disorder due to manganese hyper-accumulation in the brain; similarly, mice with whole-body Zip14 knockout displayed manganese loading in the blood and brain, indicating an indispensable role for ZIP14 in maintaining systemic Mn homeostasis. Through the deletion of ZIP14 in enterocytes, we have identified ZIP14 as the major transporter mediating basolateral manganese uptake. Lack of ZIP14 severely impaired basolateral-to-apical manganese transport, but strongly enhanced manganese transport in the apical-to-basolateral direction. Mechanistic studies demonstrated that ZIP14 limits manganese absorption via direct reuptake of freshly absorbed manganese. we propose a novel model for the control of systemic manganese homeostasis by ZIP14 that takes into account both manganese absorption by enterocytes and manganese clearance from the portal blood by hepatocytes.

Biography:

Ningning Zhao received his Ph.D. in Nutritional Science from the University of Florida. His postdoctoral training at Oregon Health & Science University was focused on molecular cell biology of metal metabolism. The research in his lab has been focused on examining the basic cell biology of membrane proteins involved in metal metabolism and investigating the role of these proteins in human diseases including hereditary hemochromatosis, cancer, and metal-related neurodegeneration.

Speaker Publications:

1. Felber DF, Wu Y, Zhao N*, Regulation of metal transporter, ZIP14 and ZnT10, by manganese intake in mice. Nutrients, 2019, under review.
2. Scheiber IF, Alarcon NO, Zhao N*, Manganese uptake by A549 cells is mediated by both ZIP8 and ZIP14. Nutrients, 2019; 11(7): 1473. PMID: 31261654.
3. Scheiber IF, Wu Y, Morgan SE, Zhao N*, The intestinal metal transporter ZIP14 maintains systemic manganese homeostasis. The Journal of Biological Chemistry, 2019; 294(23): 9147-9160. PMID: 31028174.
4. Zhao N*, Zhang AS, Wortham AM, Jue S, Knutson MD, and Enns CA, The Tumor Suppressor, P53, Decreases the Metal Transporter, ZIP14. Nutrients, 2017; 9 (12): 1335. PMID: 29292794.
5. Wahedi M, Wortham AM, Kleven MD, Zhao N, Jue S, Enns CA, Zhang AS. Matriptase-2 Suppresses Hepcidin Expression by Cleaving Multiple Components of the Hepcidin Induction Pathway. The Journal of Biological Chemistry, 2017; 292(44):18354-18371. PMID: 28924039.

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