Role of Zip8 in Cadmium (Cd) Uptake and Hypertension

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Abstract:

Cadmium (Cd) is a widely distributed pollutant, and its major sources are diet and cigarette smoking. Cd causes severe adverse effects in animals and humans. Elevated level of Cd in plasma and renal induces hypertension in animals including mouse, rat, and rabbit, rat and rabbit, and its level is highly associated with hypertension and hypertension-related death in humans. Cd accumulates in the body with an extremely long half-life of 15-30 years. Therefore, reducing Cd uptake is crucial for preventing the morbidity, but the underlying mechanism remains largely unknown. A previous genomic study reveals that Zip8, a divalent metal ion transporter, is associated with mouse sensitivity to Cd-induced testicular necrosis. Recent studies show that Zip8 promotes Cd uptake and accumulation, leading to a high susceptibility to Cd-induced cytotoxicity and diseases in animals. These results suggest a critical role of Zip8 in Cd uptake, which requires in vivo validation by gene ablation; however, Zip8 knockout causes embryonic lethality in mice. Our preliminary study takes advantage of an inducible global knockout system to generate viable adult mice with *Zip8* deletion. *Zip8* knockout induces a significant decrease in blood pressure. Interestingly, a recent genome wide association study shows that a nonsynonymous SNP in Zip8 is associated with blood pressure. Based on these results, we hypothesize that *Zip8 inhibition can reduce Cd uptake and accumulation, therefore attenuating Cd-induced cytotoxicity, hypertension and tissue damage*. To test this hypothesis, we will determine the effects of inducible *Zip8* knockout on Cd accumulation and Cd-induced hypertension and tissue damage. We will determine the underlying mechanism by examining the role of Zip8 in Cd uptake and Cd-induced cytotoxicity in vascular cells. Successful completion of this pilot study will establish an essential role of Zip8 in Cd tr nsportation and identify Zip8 as a crucial therapeutic target for Cd-induced diseases including hypertension.