Efflux Transporter Genetics and Heavy Metal Toxicity in Mice

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Cadmium is a highly toxic, naturally occurring metal classified as a probable human carcinogen by the U.S. Environmental Protection Agency. Cadmium can accumulate in the liver and cause organ toxicity. Breast Cancer Resistant Protein (BCRP) is an efflux transporter that removes toxins from the body and protects organs from injury. A reduced function polymorphism in BCRP (Q141K in humans; Q140K in mice) can alter BCRP transport activity and in turn, xenobiotic disposition. The purpose of this study was to evaluate the ability of BCRP to influence cadmium concentrations and toxicity in the liver using transgenic mice with the Q140K polymorphism. Adult, male wild-type and Q140K mice were exposed to regular drinking water or water containing 50 ppm cadmium chloride for 14 days. Liver tissues were then collected and homogenized for analysis for protein expression by western blotting. We observed that compared to wild-type mice, those with the Q140K variant had 1) ~50% reduced BCRP expression and function leading to higher cadmium levels and 2) a 35% greater up-regulation of cellular stress protein HO-1. These studies provide insight into how genetic variation in BCRP can alter the susceptibility of the liver to cadmium-induced toxicity. Supported by the NIH R25ES020721 Grant and the Society of Toxicology Intern Program.