Interaction of the BCRP Transporter with Cadmium in Human Placentas and Cultured Trophoblasts

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Cadmium (Cd) is a ubiquitous environmental metal that is detectable in 97% of pregnant women. Animal and human studies have demonstrated that *in utero* Cd exposure reduces birth weight and perinatal growth. The developmental toxicity is due in part to the accumulation of Cd in the placenta which induces cellular stress, disrupts hormone production, and limits nutrients transfer to offspring. One mechanism to limit Cd accumulation in the placenta is through regulation of uptake and efflux transporters. The BCRP/ABCG2 efflux transporter is highly expressed on syncytiotrophoblasts in the placenta, however, its ability to remove Cd and protect the fetus against toxicity is unknown. In the current study, we sought to 1) assess relationships between Cd concentrations and transporter expression in healthy, term human placentas (N=28) and 2) investigate responses to Cd in cultured human BeWo trophoblasts with reduced BCRP expression. In human placentas, there was a 10-fold range in Cd (as measured by ICP/MS) with a median Cd concentration of 2.9 ng/g. Placentas with Cd > 2.9 ng/g (N=14) had higher mRNA expression of BCRP (*p=0.04),* as well as the Cd uptake transporters DMT1 (*p=0.07*) and ZIP8 (*p=0.04*) compared to placentas with Cd < 2.9 ng/g (N=14). Birthweights were also lower among offspring with placental Cd>2.9 ng/g (mean difference=285 g, *p=0.06*). Knockdown of BCRP expression and function in human BeWo trophoblasts using shRNA heightened susceptibility to Cd cytotoxicity as assessed by alamarBlue and propidium iodide staining. Taken together, these data indicate a dynamic relationship between the placental BCRP transporter and Cd accumulation in the placenta, which may impact the sensitivity of the fetus to Cd-induced developmental toxicity. *Supported by R01ES029275 and P30ES005022.*