Loss-of-Function Variant in the BCRP/*ABCG2* Transporter Increases Cadmium Renal Injury *In Vitro*

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Cadmium is a high priority environmental pollutant present in tobacco smoke and contaminated foods. With chronic exposure, cadmium accumulates in multiple tissues including the kidneys where it causes toxicity. The breast cancer resistance protein (BCRP, *ABCG2*) is an efflux transporter in kidney tubules that facilitates the urinary secretion of drugs and toxins. Our previous studies indicate that the *ABCG2* genetic variant Q141K (C421A) reduces transport of BCRP substrates due to altered membrane trafficking. In the current study, we sought to 1) assess the *in vitro* ability of BCRP to efflux cadmium and protect kidney cells from injury and 2) determine whether this protection is disrupted by the Q141K variant. Cadmium ($CdCl_2$) accumulation and cellular stress and toxicity were assessed in human embryonic kidney 293 (HEK293) cells stably expressing plasmids containing an empty vector (EV), BCRP wild-type (WT), or BCRP variant (Q141K) gene. Intracellular $CdCl_2$accumulation was significantly higher in EV cells compared to BCRP WT cells, confirming that cadmium is a novel substrate of BCRP. Following exposure to $CdCl_2$ (2.5 to 10 µM) for 48 h, greater apoptosis (100-300%) was observed in EV cells compared to WT BCRP cells. Exposure to $CdCl_2$ (0.5 and 1 µM) induced mRNA and protein expression of stress-related genes including metallothionein 1A and 2A (MT-1A and 2A), NAD(P)H quinone dehydrogenase 1 (Nqo1), and heme oxygenase (HO-1) to a greater extent in EV cells compared to WT BCRP cells. While the BCRP Q141K variant protected against $CdCl_2$-induced activation of stress pathways and cytotoxicity compared to EV cells, the extent of protection was less than that observed with WT BCRP. In conclusion, the BCRP/*ABCG2* transporter protects against cadmium toxicity through active efflux from kidney cells, a response that is limited by the loss-of-function Q141K genetic variant. *Supported by R01ES029275 and P30ES005022.*