Epigenetic Regulation of Hepatic Efflux Transporters in Mice

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In hepatocytes, efflux transporters serve a protective mechanism to export environmental toxicants, drugs and xenobiotics into the systemic circulation or into the bile. Efflux pumps include the multidrug resistance protein 1 (MDR1), breast cancer resistant protein (BCRP), and different isoforms of the multidrug resistance-associated protein (MRP) family. Compromised function of these transport proteins has been associated with increased susceptibility to the toxicity of chemicals. Recent research has demonstrated that histone deacetylase (HDAC) inhibitors that enhance histone acetylation can alter the expression and function of efflux transporters in cancer cells. Currently, the ability of epigenetic pathways to regulate the expression of hepatic efflux transporters is unknown. In our study, we sought to investigate the ability of HDAC inhibitors to alter efflux transporter mRNA and protein expression in mouse livers. C57BL/6 mice (N=5) were administered daily intraperitoneal injections of one of three HDAC inhibitors including SAHA (75mg/kg), valproic acid (VPA, 200mg/kg), Apicidin (5mg/kg), or corresponding vehicles. After 7 days, livers were collected. Using qPCR and western blotting, alterations in the mRNA and protein levels of Mdr1, Bcrp, and Mrp1-4 were assessed. Apicidin treatment reduced the hepatic expression of Mrp2 mRNA by 22% and induced Mrp3 and Mrp4 mRNAs by 64% and 131%, respectively. Likewise, mice treated with apicidin exhibited enhanced histone H3 acetylation and up-regulation of Mdr1 (42%) and Mrp3 (72%) proteins. By comparison, the treatment of mice with SAHA and VPA for 7 days did not alter histone H3 acetylation although modest changes in transporter expression were observed. Notably, livers from VPA-treated mice exhibited modest reductions in Mdr1 and Bcrp protein expression. Taken together, these data demonstrate that HDAC inhibitors differentially alter the expression of hepatic efflux transporters with the most significant changes observed in mice treated with apicidin. Supported by NIH R01ES021800 and P30ES005022.