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Hepatic GNMT Protects Mice from Aristolochic Acid Nephropathy by Increasing Transcription of Female-specific CYP3A44 and Decreasing NQO1

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Aristolochic acid (AA), a natural component of Aristolochia plants, is a nephrotoxic carcinogen responsible for acute kidney injury, chronic renal failure, and associated urothelial cancers. Glycine N-methyltransferase (GNMT) acts to bind environmental carcinogens, e.g. Benzo(a)pyrene and alfatoxin B1, translocate into nucleus and detoxify them in the liver. The function of nuclear GNMT is unknown. This study aims to determine the role of GNMT in AA-induced nephropathy and clarify the molecular mechanism underlying its action. We first established an experimental AA nephropathy animal model by 3-week intraperitoneal injection of AA type I (AAI) into mice. We found that AAI induced kidney injury at a lower concentration in male (2 mg/kg/day) than in female mice (5 mg/kg/day). This implies that there are gender-differences in AAI resistance. Microarray analysis and AAI treatment of human GNMT transgenic mice suggest that GNMT reduces AAI-induced kidney injury by increasing female-specific *CYP3A44/CYP3A41* transcription and inhibiting *NQO1* transcription. The protective effects of GNMT were absent in GNMT knockout in mice. AAI-induced nephropathy decreased in these mice after GNMT expression was induced in the liver via the adeno-associated virus type 8 (AAV8)-mediated gene transfer system. Mechanism-wise, AAI increased GNMT nuclear translocation. *Chromatin immunoprecipitation* (ChIP) assay results suggest that, in GNMT transgenic mice receiving a high dose of AAI (5 mg/kg/day), nuclear GNMT interacts with *Nrf2* transcripts, the transcription factor for *NQO1*, in liver and resulting serious kidney injuries; whereas in human GNMT transgenic mice, 5 mg/kg/day AAI exposure resulted in increased interaction between GNMT and transcripts of *CAR* and *PXR*, the transcription factors for *CYP3A44/CYP3A41*, and mildly impaired kidneys. In summary, hepatic GNMT protects mice from AAI nephropathy by reducing *Nrf2/NQO1* transcription and enhancing *CAR/PXR* and female-specific *CYP3A44/ CYP3A41* transcription.