Arsenic: metabolism and transport mechanisms in human hepatocytes

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Arsenic is a human carcinogen known to induce tumors of the urinary bladder, skin, liver and lung (Dopp et al. 2009; Beyersmann and Hartwig 2008). Genotoxicity of arsenic is not caused by direct interaction with DNA but by indirect processes, including generation of reactive oxygen species and inhibition of DNA repair processes. Drinking water represents a common source of human exposure. Tens of millions of humans in Southeast Asia routinely drink ground water with too high arsenic concentrations (Polizzotto et al. 2008). Recently, indoor combustion of high arsenic-containing coal has been reported to contribute to human exposure (Chen et al. 2007a, b, 2009; Masoudi and Saadat 2008; Lin et al. 2007).

Besides its carcinogenicity, many further toxic effects of arsenic have been reported. Examples are its compromising effect of some immune functions (Kozul et al. 2009; Conde et al. 2007), induction of alterations in DNA methylation patterns (Jensen et al. 2009), decreased glucose tolerance (Ettinger et al. 2009), inhibition of neurite growth (Frankel et al. 2009) and oxidative myocardial and liver injury (Manna et al. 2008; Gonsebatt et al. 2007).

Today, it is well accepted that the +3 methylated arsenic species are more toxic compared to the inorganic counterparts (review: Dopp et al. 2009). Methylation of inorganic arsenic mostly occurs in the liver. In this issue of the *Archives of Toxicology*, Miroslav Styblo from the University of North Carolina reviews metabolic pathways of arsenic in human liver particularly focusing on transporter studies performed in hepatocytes in vitro. Cultivated

hepatocytes represent a well accepted in vitro system for the study of drug metabolism and toxicity (Kafert-Kasting et al. 2006; Schumann et al. 2009; Bauer et al. 2009; Godoy et al. 2009; Schug et al. 2008; Schön et al. 2008; Brulport et al. 2007; Carmo et al. 2005; Ringel et al. 2005) and have also been recommended for transporter studies (Hewitt et al. 2007). Styblo concludes that MRP2 is the most important mechanism responsible for efflux of arsenic metabolites into bile and excretion into feces. However, relatively little is known about the basolateral transport mechanisms that lead to excretion of arsenic metabolites via blood into urine.

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