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EDITORIAL

Severe arsenic poisoning: one of the largest man-made catastrophies

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More than 50 million people in Bangladesh are at risk of arsenic-induced disease (Ahmad 2001; Bae et al. 2002). In the 1970s, a nationwide WHO-initiated campaign switched water from ponds and open dug wells to groundwater as a source of drinking water. About 4 million wells have been installed for this purpose. Indeed, this measure reduced waterborne diseases, such as gastrointestinal diseases and infant mortality, as a consequence of drinking bacterial-contaminated water. However, the natural contamination of the groundwater with arsenic because of its contact with arsenic-rich rocks was neglected. Meanwhile, at least 100,000 people have been observed with skin lesions caused by arsenic; however, the real number is probably much higher. Arsenic poisoning is not limited to populations in Bangladesh. In Chile, arsenic in drinking water has been linked to lung and bladder cancer (Orellana 2001). Cases of severe arsenic poisoning as a consequence of fires fueled with high-arsenic coal have also been reported in Guizhou Province in China (Finkelman et al. 1999; Chen et al. 2007, 2009; Lin et al. 2010b). The alarming extent of arseniasis due to drinking water naturally contaminated with arsenic is illustrated by the fact that more than 2 million rural residents in Chinese mainland are at risk (Lin et al. 2010a). Large studies in an area with more than 2,000 arsenic-related skin lesions have shown that the *XPD/ERCC2* $G_{23591}A$ and $A_{35931}C$ polymorphisms modulate the risk for arsenic-induced skin disease (Lin et al. 2010a). Also the *GSTP1* $A_{1578}G$ and the GSTM1 polymorphisms might be susceptibility factors for arsenic-related skin lesions (Lin et al. 2007; 2006).

Because of the high relevance and consequences of arsenic poisoning to many of the world's populations, the toxic mechanisms of arsenic have been a central topic in the Archives of Toxicology (Wang et al. 2009; Xi et al. 2009; Juárez-Reyes et al. 2009; Mahmud et al. 2009; Naraharisetti et al. 2008; Beyersmann and Hartwig 2008; Manna et al. 2008; Kobayashi et al. 2008). The editors are happy that Ingrid Druwe and Richard Vaillancourt from The University of Arizona College of Pharmacy, Tucson, have accepted our invitation and reviewed the most up-to-date information available on how arsenate and arsenite influence signal transduction:

- Arsenate enters the cell through transporters that normally transport phosphate into the cell.
- In the cell, arsenate is reduced to arsenite that may undergo a Fenton reaction to produce reactive oxygen species (ROS).
- ROS interacts with Nrf2 resulting in dissociation of Nrf2 from the Keap1-Cul3 complex and its translocation to the nucleus.
- In the nucleus, Nrf2 induces transcription of a battery of genes, including NQO1, GST and HO-1.
- Importantly, arsenite activates the G-protein-coupled receptor in S1P1, which leads to activation of the Ras-Raf pathway.
- Arsenite inhibits the phosphorylation of Akt, thereby preventing the translocation of the GLUT4 transporter to the cell membrane. This mechanism contributes to arsenic-induced insulin resistance.

These examples illustrate that the current review by Druwe and Vaillancourt (this issue) is a "must-read" for anyone interested in the molecular mode of action of arsenate and arsenite.

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