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Understanding toxic arsenic

Arsenic is a well-known environmental contaminant, and chronic exposure to it is associated with multiple human diseases, including cancer and diabetes. However, it is also used as a clinical drug for the treatment of acute promyelocytic leukemia. To understand the toxicity of arsenic as both a toxin and a drug, it is important to elucidate the transport and metabolic mechanisms of arsenic.

Zijuan Liu asks the question: how does arsenic get inside cells, which is the first step for arsenic to exert its toxicity? Liu has identified two uptake pathways for arsenic, which include aquaglyceroporins and glucose transporters. These are important nutrient transporters that are closely related to normal cell function. The toxicity of arsenic is partly caused by its accidental uptake through nutrient transporters, which is explained by arsenic existing in forms that are molecular mimics of nutrients such as glycerol and phosphate. In Liu's lab, researchers are trying to understand the mechanisms of arsenic translocation through these transporters using molecular and biochemical approaches.

To understand the arsenic metabolism, Liu's team uses zebrafish as an animal model to study arsenic detoxification and metabolism. The zebrafish has many advantages, including its shorter generation time, fully available genomic information and multiple feasible molecular operations. Liu plans to identify the transporters and enzymes that are involved in arsenic uptake, cellular methylation and efflux pathways to elucidate the entire arsenic metabolic mechanisms and evaluate whether zebrafish could be used as an animal model to simulate human diseases.

In addition, Liu and her coworkers are interested in understanding the transport of metalloid selenium. Selenium is a required human nutrient and a deficiency of selenium is related to human diseases. Selenium has a thin boundary between toxicity and nutrition. It has been used to treat cancer, and is also an antidote for arsenic toxicity. Due to its important roles for human health, Liu plans to identify selenium's transport mechanisms in both prokaryotes and eukaryotes. She is using microbial systems to identify these mechanisms and hopes to apply their findings to humans. In addition, Liu is trying to understand the antagonistic relationship between arsenic and selenium.

Representative Recent Publications

1. Li M, Zhang Y, Liu Z, Bharadwaj U, Wang H, Wang X, Zhang S, Liuzzi JP, Chang SM, Cousins RJ, Fisher WE, Brunicardi FC, Logsdon CD, Chen C, Yao Q. 2007. Aberrant expression of zinc transporter ZIP4 (SLC39A4) significantly contributes to human pancreatic cancer pathogenesis and progression. *Proc Natl Acad Sci USA* 104:18636-18641.

2. Liu Z, Styblo M, Rosen BP. 2006. Methylarsonous acid transport by aquaglyceroporins. *Environ Health Perspect* 114:527-531.

3. Liu Z, Sanchez MA, Jiang X, Boles E, Landfear SM, Rosen BP. 2006. Mammalian glucose permease GLUT1 facilitates transport of arsenic trioxide and methylarsonous acid. *Biochem Biophys Res Commun* 351:424-430.

4. Meng Y, Liu Z, Rosen BP. 2004. As(III) and Sb(III) uptake and efflux in Escherichia coli. *J Biol Chem* 279:18334-18341.

5. Liu Z, Carbrey JM, Agre P, Rosen BP. 2004. Arsenic trioxide uptake by human and rat aquaglyceroporins. *Biochem Biophys Res Commun* 316:1178-1185.

6. Liu Z, Boles E, Rosen BP. 2004. Arsenic trioxide accumulation by hexose permeases in Saccharomyces cerevisiae. *J Biol Chem* 279:17312-17318.

7. Liu Z, Shen J, Carbrey JM, Mukhopadhyay R, Agre P, Rosen BP. 2002. Arsenite transport by mammalian aquaglyceroporins AQP7 and AQP9. *Proc Natl Acad Sci* 99:6053-6058.