Arsenic exposure activates an oncogenic signaling pathway; leads to increased cancer risk

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Researchers have found a new oncogenic signaling pathway by which the environmental toxin arsenic may lead to adverse health effects, including bladder cancer. These study results are published in *Cancer Research*, a journal of the American Association for Cancer Research.

"In a collaborative investigation we found that arsenic, at environmentally relevant levels, is capable of activating the Hedgehog pathway and may represent a novel pathway of arsenic-associated diseases, such as bladder cancer," said Margaret R. Karagas, Ph.D., professor in the Department of Community and Family Medicine at Dartmouth Medical School.

"We provide important insight into the etiology of arsenic-induced disease, potentially relevant to the millions of people worldwide who are exposed to arsenic," she said.

Arsenic is a well-known environmental toxin and carcinogen. Studies to date have shown that individuals who live in arsenic contaminated areas of the world exhibit an elevated cancer rate. In many regions of the world, notably Taiwan, Bangladesh and Argentina, high levels of arsenic are detected in drinking water, according to Karagas. Here in the United States, Karagas said that arsenic concentrations above the current maximum contaminant level of 10 μg/L are often found in private, unregulated drinking water systems.

While the correlation between exposure to arsenic resulting in human tumors such as those derived from bladder, lung and skin is well established, the molecular mechanisms driving this connection is unclear.

Karagas and colleagues examined the hypothesis that the secreted protein called Hedgehog, a key oncogenic signaling pathway, might be activated by arsenic. Activation might underlie the mechanism by which arsenic acts as a co-carcinogen.

Using experimental data from cell cultures and results of epidemiologic studies, the researchers found that arsenic activates the Hedgehog signaling by decreasing the stability of the repressor form of GLI3, which is one of the transcription factors that regulate Hedgehog activity. Also, Karagas and colleagues found high levels of arsenic exposure associated with high levels of Hedgehog activity.

"Constitutive Hedgehog signaling has been implicated in a wide spectrum of solid tumors," said Anthony Capobianco, Ph.D., editorial board member of Cancer Research. "This group observed increased Hedgehog activity in a large set of human bladder tumors. Interestingly, they also detected a strong correlation between high-level Hedgehog activity and arsenic exposure in this cohort of bladder cancer patients, supporting their mechanistic findings."

Capobianco is director of the Molecular Oncology Research Program in the Division of Surgical Oncology at the Sylvester Comprehensive Cancer Center, University of Miami, and was not associated with this study.

"This report is the first to link arsenic exposure to activation of the signaling pathway and its potential mediator of arsenic-driven tumors," he said.