Clues to the Genotoxicity of Arsenic

The metalloid arsenic, a natural component of the earth's crust and an anthropogenic soil, sediment and water pollutant, is a serious environmental concern and a global health threat impacting millions of people. Epidemiologic data have shown that chronic exposure of humans to inorganic arsenic is associated with liver injury, peripheral neuropathy, and an increased incidence of cancer of the lung, skin, bladder, and liver. However, the mechanism underlying arsenic's carcinogenicity is poorly understood. Dr. Tom Hei of the Columbia University SBRP believes that a better understanding of arsenic's mutagenic/carcinogenic mechanism(s) could increase the accuracy of risk assessments and provide a basis for better interventional approaches for both treatment and prevention of arsenic-related diseases.

Dr. Hei and researchers in his laboratory are conducting a series of studies aimed to increase our understanding of arsenic's carcinogenic mechanism. In earlier SBRP-funded studies, Dr. Hei found that arsenite is a potent gene and chromosomal mutagen, debunking the characterization of arsenic as a nongenotoxic carcinogen. He also showed that reactive oxygen species (superoxides and hydrogen peroxides) are important mediators in the genotoxicity of arsenic. This was the first clear-cut evidence of an environmental carcinogen acting predominantly through a free radical pathway. (See Research Brief 78.)

In recent studies, Dr. Hei has worked to uncover the origin of the oxyradical species and to determine if other secondary radical species are involved in the processes mediating the genotoxic effects of arsenic. The researchers used enucleation and fusion techniques with human-hamster hybrid (A_L) cells to test the hypothesis that mitochondria are an important target of arsenic-induced genotoxicity. As the metabolic center of a cell, mitochondria are intimately involved in the production of reactive oxygen species, mainly superoxides and hydrogen peroxides.

Dr. Hei and his research team conducted experiments to determine if the nucleus is the critical target for arsenite-induced genotoxicity:

- They removed the nuclei of A_L cells, yielding enucleated cytoplasts. They exposed the cytoplasts to 2 ppm arsenite and determined that the cytoplasts were able to generate reactive oxygen species, even in the absence of nuclei.
- They exposed enucleated cytoplasts to 2 ppm arsenite and later fused the treated cytoplasts with untreated nuclei to see if gene mutations would be induced. They detected significant mutant induction, indicating that, even in the absence of direct nuclear damage by arsenite, cytoplasts can initiate the signaling pathways that result in genotoxic damage.

To assess the role of the mitochondria in mediating the genotoxic response, Dr. Hei exposed A_L cells either lacking mitochondrial DNA (rho zero cells) or having diminished mitochondrial membrane potential to arsenite. The treatments produced few or no mutations. These data strongly suggest that mitochondrial function is necessary for arsenic-induced genotoxicity.

They also determined that mitochondrial damage can lead to the release of superoxide anions which then react with nitric oxide in the cytoplasm to produce the highly reactive peroxynitrites (ONOO-), which are potent and versatile oxidants that can attack a wide range of biological molecules including DNA, proteins, and lipids.

These studies lead to several important conclusions:

- The nucleus is not necessarily the only and sufficient target for environmental carcinogens
- Mitochondria are a primary target in arsenic-induced genotoxic response
- The genotoxicity of arsenic is mediated by a combination of reactive oxygen species and reactive nitrogen species.

Dr. Hei believes that mitochondria are an important target for arsenic-induced genotoxicity and the current findings should provide an additional impetus for focusing on mitochondria as an interventional target in the management of arsenic-induced diseases.

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To learn more about this research, please refer to:

Liu S-X, M.M. Davidson, X. Tang, W. F. Walker, M. Athar, V. Ivanov and T. K. Hei. April 15, 2005**.** Mitochondrial Damage Mediates Genotoxicity of Arsenic in Mammalian Cells. *Cancer Research* 65(8): 3236-3242.