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Chemical and Biological Studies for the Molecular Mechanisms of Human Trivalent Dimethylarsenic Metabolite-Induced Cytolethality; Chemical Biology of Arsenicals

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Abstract:
Although inorganic arsenicals are toxic and carcinogenic in humans, inorganic arsenite (As^{III}) has recently emerged as a highly effective chemotherapeutic agent for acute promyelocytic leukemia (APL). Inorganic arsenicals are enzymatically methylated to weakly toxic dimethylarsinic acid ($DMAs^{V}$) that is a major pentavalent dimethylarsenic metabolite. Recent reports have indicated that trivalent methylarsenicals are produced through methylation of inorganic arsenicals and participate in arsenic poisoning. Trivalent methylarsenicals may be generated as arsenical-glutathione conjugates, such as dimethylarsinous glutathione ($DMAs^{III}G$), during the methylation process. However, less information is available on the cytolethality of $DMAs^{III}G$. We easily synthesized and purified $DMAs^{III}G$ by a new high performance thin layer chromatography (HPTLC) method, and observed the cytolethality of the synthesized $DMAs^{III}G$ using rat liver TRL 1215 cells. The cytolethality of $DMAs^{III}G$ was very strong because of its high cellular uptake; its lethal concentration *in vitro* in 50% of the population (LC_{50}) was about 160 nM. We also found that $DMAs^{III}G$ itself was not transported efficiently into the cells and was not cytotoxic; however it readily became strongly cytotoxic by dissociating into trivalent dimethylarsenicals and glutathione (GSH). The addition of GSH in micromolar physiological concentrations maintained the chemical form of $DMAs^{III}G$, and prevented $DMAs^{III}G$-induced strong cytolethality. Physiological concentrations of normal human serum (HS), human serum albumin (HSA), and human red blood cells (HRBC) also reduced both the cytolethality and

cellular arsenic uptake induced by $DMAs^{III}G$ exposure. These findings suggest that the significant cytolethality induced by $DMAs^{III}G$ may never manifest in healthy humans even if $DMAs^{III}G$ is formed in the body from inorganic arsenicals. This study may provide important information to determine the role of metabolic methylation and GSH in arsenic toxicity in patients with chronic arsenic poisoning who regularly ingest inorganic arsenic-contaminated well water and/or in APL patients who are injected with As^{III} as a chemotherapeutic agent.

Key words: arsenic, arsenite, dimethylarsenic, trivalent dimethylarsenic, dimethylarsinous, GSH, chemical biology

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