Combined Effects of Arsenic and Radiation

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Introduction

- Arsenic has been used successfully to treat several diseases and is approved by the U.S. Food and Drug Administration for the treatment of acute promyelocytic leukemia (APL).
- The mechanism(s) of arsenic therapeutic effects are not fully understood. However, arsenic has been shown to inhibit cellular repair of DNA damage. Radiation therapy induces cancer killing by causing DNA damage.
- We aim to study the combined effects of arsenic and radiation, with the long-term objective of using arsenic for potential radiosensitization in cancer therapy.
- Materials and Methods: We reviewed published studies on the combined treatment of human cancer cells with arsenic and radiation. We also treated a panel of normal and cancer cells with arsenic, and genotoxic agents, either alone or in combination; and examine the combined effects. We focused on mechanistic understanding of the observed effects, including cell-killing, DNA damage, and effects on DNA repair and cell cycle signaling.

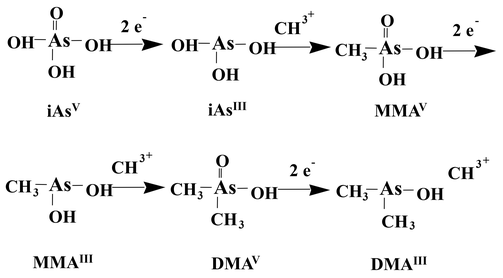

Fig. 1. Methylation as the main pathway of arsenic metabolism. Inorganic arsenate (As^{V}) is reduced to inorganic arsenite (As^{III}) before the addition of a methyl group to form monomethylarsonic acid (MMA^{V}). The pentavalent MMA^{V} is reduced to trivalent MMA^{III}, which is then methylated to dimethylarsinic acid (DMA^{V}). Reduction of DMA^{V} to produce DMA^{III}. The trivalent As^{III}, MMA^{III}, and DMA^{III} are more toxic than their pentavalent counterparts.

Results

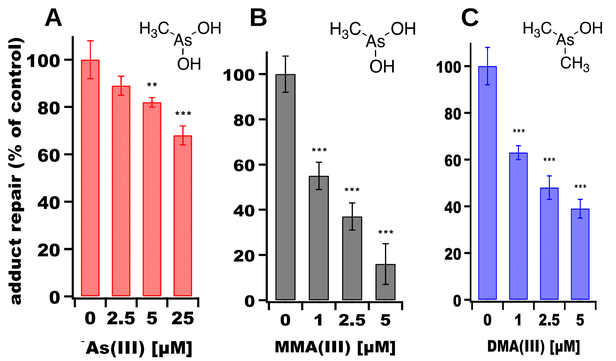

Fig. 2. Trivalent arsenic compounds impair BPDE-DNA adduct repair. Benzo(a)pyrene diol epoxide (BPDE) forms adducts with DNA to mimic DNA damage. Concentration-dependent inhibition of BPDE-DNA adduct repair by trivalent arsenic compounds. Human fibroblasts are incubated with BPDE and allowed to repair in the presence of As^{III} (A), MMA^{III} (B), or DMA^{III} (C) at various concentrations. A capillary electrophoresis laser-induced fluorescence immunoassay was used to detect BPDE-DNA adducts. ** p<0.05; ***p<0.01. n=3.

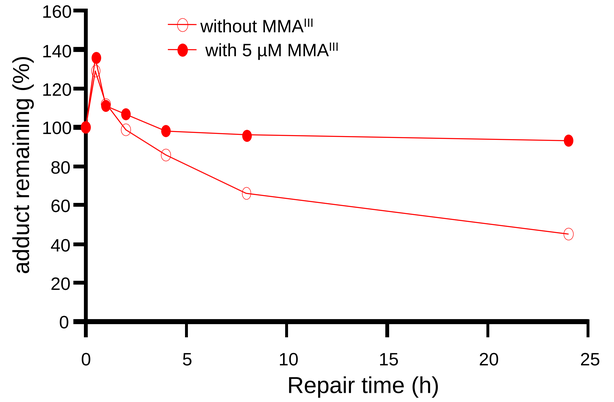

Fig. 3. MMA^{III} alters repair kinetics of BPDE-DNA adducts. Human fibroblasts were incubated with BPDE and allowed to repair in the absence (open circle) or presence of MMA^{III} (filled circle). BPDE-DNA adducts at various time points were analyzed with a capillary electrophoresis laser-induced fluorescence immunoassay. n=3.

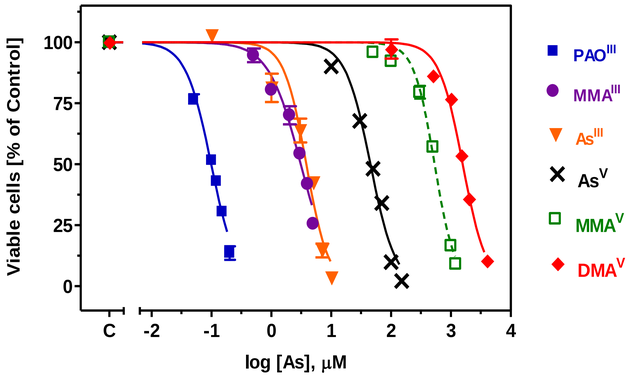

Fig. 4. Concentration dependent cytotoxicity of arsenic compounds. A human promyelocytic leukemia cell line was exposed to increasing concentrations of arsenic compounds: phenylarsine oxide (PAO^{III}), MMA^{III}, As^{III}, As^{V}, MMA^{V}, and DMA^{V}. Viable or apoptotic cells were quantified with staining of annexin V-PE and 7-aminoactinomycin D. n=3.

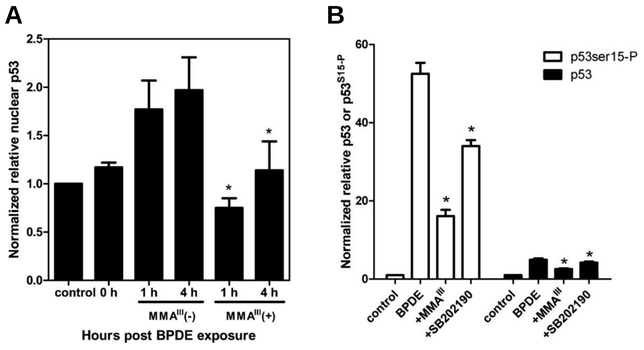

Fig. 5. MMA^{III} suppresses nuclear p53 and phosphorylated p53 expression. Quantification of nuclear p53 (A) and p53 phosphorylated at serine 15 (B) from Western blot analysis. Protein levels are normalized to the corresponding unexposed control.*, p<0.05. n=3.

Conclusions and Future Directions

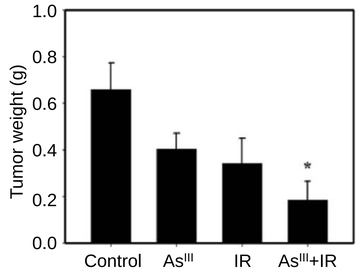

Fig. 6. Arsenite (As^{III}) has added effect to radiation of tumors in a mouse model. Tumor weight of tumor-bearing mice treated with irradiation (IR, 6Gy) or As^{III} alone or in combination.

- Arsenic compounds impair DNA repair and impact cell death, in part through suppression of p53 expression and activity.
- Arsenic compounds have been shown to cause radiosensitization
- MMA^{III} is more potent than arsenite at impairing DNA repair

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