DIFFERENTIAL MODULATION OF CANCER-RELATED MOLECULAR NETWORKS IN HUMAN AND RAT URINARY BLADDER CELLS EXPOSED TO TRIVALENT ARSENICALS

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Arsenic (As) is classified as a known human carcinogen with primary targets of urinary bladder (UB), skin and lung. The most prevalent source of As exposure in humans is drinking water contaminated with inorganic As (iAs). The mode of action (MOA) of As carcinogenesis in target cells is largely undefined, including which arsenical(s) elicit a carcinogenic response. Two urinary metabolites of iAs, monomethylarsonous acid and dimethylarsinous acid (MMAIII and DMAIII, respectively), are attractive candidates as UB carcinogens. Human and rat UB cells are both targets of As carcinogenesis, and although DMAIII has long been considered the primary carcinogenic arsenical in the UB of both species, recent experimental evidence suggests MMAIII may play a more significant role than DMAIII in the UB, particularly in humans. We used a transcriptomics approach to examine the altered molecular pathways and networks in human and rat UB cells after exposure to individual arsenicals to investigate the MOA of As-driven UB carcinogenesis. UROtsa (human) and MYP3 (rat) cells were exposed to relatively non-cytotoxic (>75% cell viability), environmentally-relevant concentrations (1 μM) of iAsIII, MMAIII, and DMAIII for 24 h. Differentially expressed genes were determined for each treatment group relative to controls and analyzed for statistically significant biological functions, molecular networks and canonical pathways using Ingenuity Pathway Analysis software. Each treatment group elicited a distinct transcriptional profile with few shared genes in top networks or canonical pathways, although lipid metabolism was a function associated with all top networks. Distinct from the other groups, MMAIII exposure in UROtsa cells generated changes in several molecular networks that are consistent with pathways suspected to play key roles in human UB carcinogenesis, suggesting that common factors may drive UB carcinogenesis in humans and that they may be distinct from those in rats.

[This abstract does not necessarily reflect EPA policy.]

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