S04-2 **Arsenic biomethylation is obligatory for oxidative DNA damage but not for malignant transformation**

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Inorganic arsenic is a human carcinogen that acts by undefined mechanisms. In this study, the role of arsenic biomethylation (AsBM) in arsenic-induced oxidative DNA damage (ODD) was studied with the recently developed, highly reliable immuno-spin trapping method, which directly traps DNA radicals and measures them as stable nitrone derivates. The AsBM-capable rat liver epithelial line, TRL1215, and the AsBM-deficient human prostate cell line, RWPE-1, were exposed to low-levels ($\leq$ 5.0 μM) of arsenite that induce malignant transformation (MT). A remarkable, but delayed (>5 wks), increase in ODD occurred with arsenic only in TRL1215 cells prior to MT (18 wks), whereas the RWPE-1 cells were devoid of increased ODD despite being exposed past a point that induced MT (30 wks). In fact, peak ODD in TRL1215 cells directly correlated with signs of MT, including tumors upon inoculation into mice and increased matrix metalloproteinase-2 secretion. Selenite, which blocks AsBM, abolished arsenic-induced ODD and signs of MT in TRL1215 cells. The human urothelial cell lines UROtsa, which does not methylate arsenic, and its stable arsenic methyltransferase transductant, UROtsa/F35, similarly showed that arsenic-induced ODD occurred only in AsBM-competent cells and that ODD levels also directly correlated with biomarkers of MT. Thus, although neither arsenic-induced ODD nor AsBM are obligatory for MT, they likely hasten the process. However, mechanisms not requiring ODD are operative in target cells not biomethylating arsenic, and arsenic has multiple carcinogenic mechanisms.