

INHIBITION OF DNA REPAIR AS A MECHANISM OF ARSENIC CARCINOGENESIS

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Arsenic is a metalloid that is widely distributed in the environment. Exposure to arsenic has been associated with an increased risk of a variety of cancers, including skin, liver, bladder, kidney and lung cancer. However attempts to prove arsenic carcinogenesis in animals have been unsuccessful. A hypothesis has been proposed that arsenic might act as a co-carcinogen instead of a carcinogen itself. Recently Rossman's group demonstrated that arsenic enhanced the induction of skin tumors by UV irradiation in hairless Skh1 mice (Rossman, 2001). Consistent with its co-carcinogenic activity, arsenic by itself does not seem to induce point mutations in most of the bacteria and mammalian systems tested. Instead, it can potentiate the mutagenicity of other mutagens, such as UV (Hartmann, 1996), Benzo(a)Pyrene (Maier, 2002) and N-methyl-N-nitrosourea (NMU)(Li, 1989). The mechanism of this co-mutagenicity remains unknown. The most tempting hypothesis is that arsenic can inhibit DNA repair. We have used arsenite at low concentrations in cultured human cells to test this hypothesis, in the hope of shedding light on the mechanism of arsenic mutagenesis and co-mutagenesis. Our study shows that (1) Arsenic at 1 μ M is not mutagenic, but induces deletion/insertion mutations at 2.5 μ M. Arsenic synergistically enhances UV mutagenicity at 2.5 μ M, but not at 1 μ M. (2) Arsenic treatment does not alter the UV mutation spectra. (3) Arsenic at 1-5 μ M enhances and prolongs RPAp34 phosphorylation induced by UV irradiation, suggesting the persistence of the DNA damage signal that induces the phosphorylation response. This effect is less prominent in NER-deficient XPA cells. (4) Arsenic does not increase the generation of thymine dimers induced by UV assayed by FACS with thymine dimer-specific antibody, but it inhibits the removal of thymine dimers. All of these results suggest that arsenic inhibits DNA repair, probably nucleotide excision repair. Further work will be required to identify the mechanism of this inhibition. This work is supported by NIEHS Superfund Basic Research grant ES04908.