

Ke Jian “Jim” Liu

**University of New Mexico, Department of Pharmaceutical Sciences,
College of Pharmacy**

Oxidative stress and DNA repair inhibition in arsenic carcinogenesis

Abstract

Inorganic arsenic is a complete carcinogen and enhances tumor development when combined with other carcinogens including ultraviolet radiation (UVR). Arsenite stimulates reactive oxygen and nitrogen species (ROS/RNS) in keratinocytes leading to DNA damage. We have observed that low arsenite concentrations enhance UVR-induced 8-hydroxyl-2'-deoxyguanine (8-OHdG) formation, DNA strand break, and cyclobutane pyrimidine dimers (CPDs). Biochemical studies suggest that disruption of zinc finger DNA repair protein function may represent an underlying mechanism for arsenic carcinogenicity. We find that i) activity of the DNA repair zinc finger protein poly(ADP ribose) polymerase-1 (PARP-1) is impaired at 200 nM arsenite concentration, ii) oxidative DNA damage is enhanced in the presence of a PARP-1 inhibitor, and iii) inclusion of zinc counteracts arsenite-enhancement of UVR-induced 8-OHdG lesions on DNA. Mass spectrometry analysis provides evidence that arsenite binds to the vicinal thiols of the zinc finger moiety of PARP-1, preventing zinc binding, thus interrupting the function of PARP-1. Collectively our studies demonstrate that two properties of arsenite, namely binding of trivalent arsenicals to sulfhydryls and ROS/RNS formed by arsenic exposure, can modify PARP-1 protein and function leading to elevated oxidative DNA damage.

Bio

Ke Jian "Jim" Liu, PhD, Professor & Assistant Dean for Research, Center Director & Director, EPR Core Facility, UNM BRAIN Center, UNM Partnersite Director for the MIND Institute, Associate Professor of Neurology (UNM SOM), Specialty: Chemistry, Department of Pharmaceutical Sciences. Dr. Liu has broad scholarly interests, ranging from the study of the toxicity and carcinogenesis of metal ions (such as arsenic and chromium), to the brain injury due to stroke, with a central focus on the role of free radicals (such as oxygen radicals, and nitric oxide) and oxidative stress in signal transduction, and its associated oxidative damage.