could subsequently lead to permeability transition and apoptosis. Subcytotoxic arsenite also induced translocation of phosphatidylserine to the outer layer of the plasma membrane, indicative of apoptosis. To confirm whether subcytotoxic arsenite induces cellular and/or mitochondrial morphological alterations consistent with apoptotic cell death, HK-2 cells were evaluated with both light and transmission electron microscopy. Classic morphological changes indicative of apoptosis were not observed at either the light microscopic nor the electron microscopic level with subcytotoxic arsenite exposures; however, evidence of necrotic changes in cytoplasmic structure and morphology, particularly in the mitochondria, were apparent. Therefore, based on the externalization of phosphatidylserine, HK-2 cells appear to initiate apoptosis following subcytotoxic arsenite insult, but based on the morphological changes seen, fail to complete apoptosis and undergo necrosis instead. Subcytotoxic arsenite can be sufficiently toxic to mitochondria that they lose their ability to keep the cell on course for apoptotic cell death. (NIH ES 04940, ES 06694)

1146 ARSENIC TRIOXIDE INHIBITS NUCLEAR RECEPTOR SIGNALING BY PHOSPHORYLATION OF RXR.

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Arsenic is a wide spread environmental contaminant, but arsenic trioxide (ATO) is also used to treat patients with acute promyelocytic leukemia (APL). We have previously published that ATO inhibits APL cell differentiation induced by retinoic acid, the other common treatment for APL, complicating the development of combination therapy using these two effective agents. Upon further investigation, we have found that ATO inhibits the transcriptional activation in transient transfections not only of retinoic acid receptor, but also several other nuclear receptors, all of which heterodimerize with the retinoid X receptor (RXR). ATO does not inhibit transactivation of the estrogen receptor, which acts as a homodimer. Previously published data show that phosphorylation of RXR can inhibit nuclear receptor signaling. Indeed, we find that ATO phosphorylates RXR in the N-terminal ABC region exclusively on serine residues, as assessed by *in vivo* labeling and phosphoamino acid experiments. We have previously identified JNK as a kinase activated by ATO and therefore, sought to determine if RXR is a target of JNK-mediated phosphorylation. When JNK activation is impaired through pharmacologic inhibition or by genetic deletion of the upstream regulator, SEK1, the ability of ATO to inhibit transactivation of the RXR/vitamin D receptor heterodimer is abrogated. Inhibition of JNK activity also decreases the level of ATO-induced RXR phosphorylation. These data suggest ATO-induced JNK activation leads to RXR phosphorylation and the inhibition of transcription by RXR heterodimers. This suggests that consecutive use of retinoic acid and ATO in the treatment of patients with APL may be preferred. In addition, consideration of this interaction between ATO and nuclear receptor function may give some insight into molecular mechanisms of arsenic-induced carcinogenesis resulting from environmental exposure.

1147 EFFECT OF LOW DOSE AS(III) IN THE DRINKING WATER OF MICE ON TUMOR GROWTH AND ANGIOGENESIS.

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Arsenite (As(III)), a major drinking water contaminant, is associated with many vascular abnormalities in contaminated populations. We have previously shown that As(III) at levels approaching the current US drinking water standard (10 PPB) stimulates angiogenesis and As(III) injected into tumor-bearing mice at levels below those used to treat cancer can actually stimulate tumor growth. We now show that B16-F10 melanoma tumor-bearing mice exposed to 10, 50, and 200 PPB As(III) in their drinking water for 10 weeks prior to tumor implantation show considerably higher tumor growth rates versus mice given nanopure water. Additionally, we show by immunohistochemistry that levels of HIF-1α and two of its regulated proteins, VEGF and PAI-1, are substantially increased in mice receiving 10 and 50 PPB As(III)), but not in mice receiving 200 PPB As (III). Interestingly, tumor blood vessel counts were substantially higher in animals given all doses of As(III). In isolated B16 cells, a 4 hr exposure to high dose (75 and 750 PPB) As(III) stimulated HIF-1α protein levels by immunoblot analysis. In contrast, a 72 hr exposure to low dose (0.75 and 7.5 PPB) As(III) caused comparable HIF-1α protein induction. Using the CAM angiogenesis assay, the VEGFR kinase inhibitor SU5416 (10μM) and an inhibitor of HIF-1α, YC-1 (10μM), abrogated the angiogenic effects of As(III). Finally, the antioxidants tocopherol (100μM), NAC (1mM), DMSO (0.5 percent) and TEMPOL (1mM) all reduced As(III)-mediated vessel formation in the CAM assay. These results indicate that the angiogenic effects of low dose As(III) can enhance tumor growth and the angiogenic stimulation by low dose As(III) likely involves reactive oxygen species (ROS) and HIF signaling.

1148 PANCREATIC OXIDATIVE DAMAGE AND ENDOCRINE FUNCTION IN RATS SUBCHRONICALLY EXPOSED TO ARSENITE.

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Chronic exposure to inorganic arsenic (iAs) contributes to oxidative stress in several organs and systems through production of reactive oxygen species. Since the pancreas is a susceptible organ to the oxidative stress and target of the toxic action of iAs exposure, our study evaluated the presence of oxidative stress and endocrine function of pancreas in rats subchronically exposed to iAs. The oral glucose tolerance test (OGTT) was performed in male Wistar rats after 60 days of treatment with sodium arsenite at 1.7mgAs3+/kg/12h. The effect of subchronic iAs administration on blood glucose, serum insulin, lipid peroxidation (LPO), levels of glutathione (GSH) and As species in pancreas were evaluated after 90 days of iAs treatment in other group of male Wistar rats exposed with sodium arsenite at 1.7mgAs3+/kg/12h. The OGTT shown an impaired glucose tolerance. Hyperinsulinemia (2.7±0.9 vs 1.4±0.6 ng/ml of control group) and hyperglycemia (9.3± 0.7 vs 7.1 ±0.8 mmol/l) was observed at the end of iAs treatment. On the other hand the pancreatic LPO and glutathione levels increased significantly in iAs exposed rats. Dimethylated arsenic (DMA) was the main specie present in the pancreas. The results of this study suggest that subchronic iAs exposure causes oxidative damage and pancreatic beta cell dysfunction related to insulin resistance and hyperglycemia. These results may be related with the presence of pre-diabetes status.

1149 HEAT SHOCK PROTEIN 70 AS AN INDICATOR OF EARLY LUNG INJURY CAUSED BY EXPOSURE TO ARSENIC.

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Heat shock proteins (HSPs) are a family of highly conserved proteins that are induced by stress, temperature, redox status, heavy metals, and inflammation. HSPs play a major role within a cell from folding of synthesized proteins or its degradation by proteosome. Intracellular transport and defects in folding can cause accumulation of these proteins resulting in several disease processes. HSP expression can be interpreted as an early and sensitive biomarker of cells in stress. Arsenic (As) is a naturally occurring metal that is distributed widely in the environment and is used in several industries. Exposure to As is associated with the development of pulmonary and skin cancers. The present study was undertaken to evaluate the expression levels of Hsp70 protein and mRNA induced by exposure to As which could be a sensitive and early biomarker. In addition, the cellular and molecular mechanisms of Hsp70 expression by As were investigated in the human bronchial cell line BEAS-2B. Cytotoxicity, lipid peroxidation and hydrogen peroxide generation were measured as indicators of cell injury and perturbed oxidative metabolism by As. Exposure of BEAS-2B cells to As(III) was associated with increased expression of Hsp70 protein and mRNA in a time and dose dependent manner. Hsp70 protein expression showed a significant five-fold increase by Western blot analysis and was increased 20-fold using an ELISA assay at a 50 uM As(III) concentration with a 6 hr exposure and an 8 hr recovery time. Hsp70 mRNA expression showed a 28% increase compared to controls. Cytotoxicity resulting from As(III) increased with a longer exposure time (48 hr). Lipid peroxidation increased six-fold at a concentration of 20 uM As(III) for 24 hr exposure, while H2O2 generation showed a two-fold increase. These results suggest that the induction of Hsp70 was the most sensitive indicator of cell injury by As(III), and Hsp70 may be a valuable indicator of oxygen free radical-induced lung cell injury.

1150 ROLE OF CALCIUM AND MITOGEN-ACTIVATED PROTEIN KINASES ON CADMIUM-MEDIATED GROWTH ARREST AND CASPASE-3 ACTIVATION IN MURINE MACROPHAGES.

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Cadmium (Cd) is a well-known carcinogen and immunotoxic metal commonly found in cigarette smoke. Proliferation and apoptosis is regulated to provide appropriate cell number and to avoid tumor growth. Present study was designed to deter-

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Preface

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