macrophages was too low to quantify. The results demonstrate that instilled apoptotic macrophages are rapidly ingested and processed by resident alveolar macrophages while otherwise normal macrophages are not.

1637 APOPTOTIC CELL INSTILLATION RESULTS IN ELEVATED TGF-β AND APOPTOSIS-INDUCED-APOPTOSIS IN RAT LUNG.

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Results from animal inhalation with either high burden or highly toxic particles showed increased apoptosis in the lungs. Previous studies by our group indicated that pulmonary administration of apoptotic lung cells induced inflammatory cell influx and lung fibrosis, indicating a direct linkage between apoptosis and fibrotic lung disorders (Ref.1). In this study, we further characterized the kinetics of pulmonary response to apoptotic cell instillation in rats and investigated the possible role of TGF-β in this process. Rats instilled with apoptotic cells showed a decrease in lung cell apoptosis at 1 week post-treatment, consistent with our previous finding showing the clearance of labeled apoptotic cells in rat lungs after 1 week (Ref.2). However, the level of lung cell apoptosis was higher at 4 and 12 weeks post-treatment compared to the control groups instilled with normal non-apoptotic cells. These results suggest that the apoptotic cells observed at latter time points were not those originally instilled but were subsequently induced after the treatment. Analysis of BAL fluids from treated rats showed an increase in TGF-β expression at 1 and 4 week post-treatment compared to the control groups. TGF-β is a known inducer of apoptosis and a key mediator of lung fibrosis, our results therefore suggest that increased TGF-β by apoptotic cell instillation may be responsible for the increased lung cell death and subsequent development of pulmonary fibrosis. References: 1. Wang L, Antonini J, Rojanasakul Y, Castranova V, Scabilloni JF, Mercer RR. Potential role of apoptotic macrophages in pulmonary inflammation and fibrosis. Am. J. Cell. Physiol. 194:215, 2002 2. Robert R. Mercer James Scabilloni, James Antonini, Vincent Castranova and Liying Wang. The fate of apoptotic macrophages instilled into the lung. American Thoracic Society Annual Meeting, Baltimore, MD, March 2004.

1638 PERTURBATION OF TESTICULAR CELL PROLIFERATION USING SODIUM ARSENITE.

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In this study we report the effects of sodium arsenite exposure on the cell proliferation of the normalized mouse Leydig cell line, TM3. The Leydig cells were grown in culture medium containing 5% horse serum, 2.5% fetal bovine serum. Cell cultures were switched to serum-free medium prior to treatment with test compound. The treatments consisted of 1pg, 10pg, 100pg, 1ng, 10ng, and 100ng per ml sodium arsenite, along with a control. Results indicated a significant ($p \leq 0.05$) increase in cell proliferation in all treatments with growth ranging from 119.79 to 191.80%, with the exception of 100ng/ml when compared to the control. Peak proliferation for sodium arsenite was noted at 10pg/ml (191.80%). The other growth was recorded as follows: 166.88% at 1pg/ml, 163.03% at 100pg/ml, 155.32% at 1ng/ml, 126.80% at 10ng/ml, and 119.79% at 100ng/ml. These results are of concern given that sodium arsenite has previously been reportrd to decrease DNA repair. Hence, when coupled with our findings here, a mechanism for the induction of genomic instability can be postulated. This then may explain the carcinogenic activity of sodium arsenite.

1639 ARSENIC ACTIVATES NADPH OXIDASE THROUGH CDC42 AND THEIR INVOLVEMENT IN ACTIN FILAMENT REMODELING AND CELL MOTILITY IN ENDOTHELIAL CELLS.

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Although arsenic is a human cancinogen, the molecular mechanisms of its action remain to be understood. By stimulating mouse endothelial cell lines (SVEC4-10) with 10 μM arsenic, we found that arsenic induced activation of NADPH oxidase as determined by the nitroblue tetrazolium test. Using confocal microscopy, the generation of $O^{\cdot}_2$ and H_2O_2 was observed to be increased in SVEC4-10 cells after exposure to arsenic. We also found that arsenic activated Small Rho GTPase CDC42. Disruption of CDC42 with a dominant negative CDC42 abolished arsenic-induced activation of NADPH oxidase and subsequent generation of $O^{\cdot}_2$ and H_2O_2, suggesting that CDC42 may mediate the effects of arsenic on NADPH oxidase. Furthermore, it was found that arsenic stimulation induced actin filament remodeling and increased cell motility in SVEC4-10 cells. These changes were abrogated by either disruption of CDC42 or inhibition of NADPH oxidase, indicating that the cell signaling changes induced by arsenic are relevant to these cellular functions. Taken together, the data imply that arsenic may promote motility-dependent metastasis of cancer cells through CDC42, NADPH oxidase and reactive oxygen species.

1640 TRANSGENERATIONAL EFFECTS OF CHROMIUM(III) ON OFFSPRING WEIGHT, SERUM TIIODOTHYRONINE, AND HEPATIC GENE EXPRESSION.

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Exposing male mice to chromium(III) chloride before mating results in increased tumors in offspring. An epigenetic mechanism has been postulated, involving alterations in hormones and in gene expression in the offspring. In pursuit of this hypothesis, male Swiss mice were injected i.p. with 1 mmol/kg chromium(III) chloride, 2 wks before mating. Offspring (10 wks old) were weighed and assessed for serum triiodothyronine (T3)and hepatic gene expression by cDNA microarray analysis. Both male and female offspring of Cr(III)-treated fathers were significantly heavier than those of control fathers: 31.4 +/- 0.4 g (S.E.) (N = 62) vs 30.6 +/- 0.2 (N = 90) (P = 0.035) for males and 24.6 +/- 0.3 (N = 54) vs 23.0 +/- 0.3 (N = 54) (P = 0.0003) for females. Serum T3 levels were also greater in the offspring of Cr(III)-treated fathers: 107.7 +/- 2.0 ng/dl vs 95.6 +/- 3.4 for males (P<0.0001) and 96.4 +/- 2.2 vs 89.3 +/- 2.8 for females (P = 0.054). Microarray analysis was carried out on eight pairs of livers from female offspring of Cr(III)-treated and control fathers, chosen to represent serum T3 ratios over the range 1.04 to 2.68. Linear regression analysis selected for hepatic genes showing microarray ratios correlating with serum T3 ratios with a significance of P <= 0.001. Fifty-eight genes met this criterion, including 25 named genes. Several are known to be regulated by T3, e.g. beta 2 adrenergic receptor and the calcium-regulator phospholamban. Others may pertain to growth: protein tyrosine phosphatase 4a2, pancreatic colipase, and complement component 3a receptor 1. Expressions of several genes associated with tumor suppression were negatively associated with serum T3 ratios: the transcription factors Ikaros, zinc finger protein 161, and Kruppel-like factor 5, as well as single-strand DNA binding protein and natural killer tumor recognition sequence. These results are consistent with hormone-mediated effects of paternal Cr(III)-treatment on offspring physiology, and with an epigenetic mechanism of transgenerational carcinogenesis.

1641 INDUCTION OF THE HYPOXIA MARKERS, CARBONIC ANHYDRASE IX AND Cap43, BY NICKEL OR CELL DENSITY IS RELATED TO ASCORBATE DEPLETION.

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Nickel compounds are known carcinogens and represent potential hazard for environmentally and occupationally exposed people. Mechanisms of nickel-induced carcinogenesis are currently unknown. Recently, we have shown that carcinogenic nickel compounds induced HIF-1 transcription factor and all known hypoxia-inducible genes. HIF-1 activation likely plays important an role in malignant transformation caused by nickel since stimulation of soft agar growth by nickel can be observed in HIF-1 alpha normal but not in knock-out cells. In this study we further investigated mechanisms of nickel-induced activation of hypoxia-inducible genes. We have found that both carbonic anhydrase IX (CAIX) and Cap43, known as intrinsic marker of hypoxia and a tumor marker, are also induced by exposure to soluble nickel compounds in human lung epithelial (HAE) cells. In cells exposed to 0.5 mM nickel(II) sulfate, the induction of both proteins was observed as early as after 2 hrs. The involvement of HIF-1 transcription factor in the induction of these proteins was also confirmed in cells exposed to cobalt(II), desferoxamine and dimethyloxoglycine (DMOG). Additionally, both CAIX and Cap43 were induced in HIF-1 alpha normal but not in knock-out cells. The induction of CAIX and Cap43 by nickel(II), cobalt(II) and desferoxamine, but not by DMOG, can be abolished by 0.1 mM of ascorbic acid added to culture media. These data suggest that nickel exposure may result in depletion of cellular ascorbate, leading to a shift in the iron oxidation status. CAIX and Cap43 could be also induced by high cell culture density. Here we show that the density-dependent induction of Cap43 and CAIX may be associated with the depletion of ascorbate in dense cultures.

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Preface

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