cmA2 silica or the relatively innocuous dust, titanium dioxide, in the presence or absence of hydroxyl radical scavengers. After 6h of exposure, expression of MIP-2 or the gene for a related cytokine, CINC, was assessed using RT-PCR techniques. In addition, nuclear proteins were isolated from the exposed cells and gel mobility shift assays run to characterize NFκB binding activity. *In vitro* silica exposure resulted in dose-related increases in MIP-2 and CINC gene expression; treatment with titanium dioxide had minimal or no effect. Concurrent with increases in MIP-2 expression were increases in nuclear NFκkB binding activity. Addition of the hydroxyl radical scavengers DMSO, TMTU, ethanol or mannitol attenuated the silica-induced increases in MIP-2, CINC and nuclear NFκkB activity in a dose-related manner. These results support a role for oxygen radicals in silica-induced activation of MIP-2 and CINC gene expression. In addition, they suggest that induction of MIP-2/CINC may depend on an oxidant sensitive, NFkB mediated pathway.

708 QUINONE-INDUCED ELEVATION OF MACROPHAGE INFLAMMATORY PROTEIN-2 mRNA IN ALVEOLAR MACROPHAGES

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Neutrophil influx and activation are involved in the pathogenesis of inflammatory lung diseases, including adult respiratory distress syndrome, asthma and chronic bronchitis. Recruitment of neutrophils into the lung is a complex process that depends, in part, upon the local expression of appropriate pro-inflammatory chemokines. Our previous work demonstrated that macrophage inflammatory protein-2 (MIP-2), a member of the CXC subfamily of chemokines, contributes to neutrophil chemotaxis and activation and is induced by bacterial endotoxin in macrophages. The objective of this study was to test the hypothesis that an oxidative stress triggers expression of MIP-2 mRNA and thus, contributes to early inflammation. A rat alveolar macrophage cell line (NR8383) was exposed to menadione (2-methyl-1, 4-naphthoquinone), a quinone compound which undergoes redox cycling and generates reactive oxygen species continuously. Steady state mRNA levels encoding MIP-2 were markedly increased in these cells after 1 h exposure to menadione (25 or 50 μM), remained higher than control levels after 4 h and decreased after 6 h. Menadione-induced up-regulation of MIP-2 mRNA was suppressed by co-treatment with N-acetylcysteine, a synthetic antioxidant. Co-treatment with actinomycin D abolished the induction of MIP-2 mRNA, suggesting that the elevation of mRNA in response to quinone induced oxidative stress was through transcriptional activation of the MIP-2 gene. (Supported by ES05703, ES05947, ES00002 and HL19170)

709 NUCLEAR TRANSCRIPTION FACTORS IN ASBESTOS-MEDIATED LUNG INFLAMMATION

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Studies on the pathophysiology of asbestos - related diseases have indicated the importance of proinflammatory cytokines, chemotactic peptides and certain growth factors, released from asbestos target pulmonary cells. Cytokine gene expression is regulated at several levels, but general control is accomplished by sequence-specific DNA binding proteins, referred to as transcription factors, to the gene promoter or enhancer regions. We studied asbestos-induced modulation of transcription factors activity in lung epithelial cells using in vitro model system. Pulmonary type II-like epithelial cells (A549) following asbestos exposure produced IL-8 and IL6. Coordinated expression of these cytokines, often observed in various inflammatory conditions has been related to common molecular regulation. The binding sites for NF-kB, NF-IL-6 in the both promoters need to be occupied for optimal expression. Asbestos strongly stimulated binding activity of NF-kB and NF-IL-6 to their binding sites in IL-8 promoter. The binding activity to IL-8 promoter required cooperative interactions between NF-kB and NF-IL-6. Asbestos induced binding activity to NF-IL-6 consensus binding site and to NF-kB-like binding sites in IL-6 promoter. Both transcription factors NF-kB and NF-IL-6 respond to oxidative stress, since hydrogen peroxide and hypoxanthine-xanthine oxidase, generating hydrogen peroxide and superoxide anion, upregulated binding activity to NF-kB and NF-IL-6 binding sites in IL-8 and IL-6 promoters. The results demonstrated that asbestos fibers are strong activator of transcription factors and asbestos-induced oxidative stress is involved in transcription factors stimulation. This may be the basis for asbestos affecting the inflammatory cytokine network in the lung.

710 MOLECULAR MECHANISMS OF IMMUNOLOGICAL ACTIVATION OF TYPE II PNEUMOCYTES BY OZONE

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In response to ozone inhalation, pulmonary type II cells become immunologically activated. Our laboratory has been interested in examining the role of activated type II cells in inflammation. In particular, we are investigating molecular mechanisms regulating nitric oxide production by type II cells during lung inflammation. We found that type II cells isolated from control rats readily respond to inflammatory cytokines such as interferon-γ by expressing nitric oxide synthase, a response that is markedly enhanced in cells isolated from rats treated by inhalation of ozone (2 ppm, 3 hr). Type II cells isolated from ozone-treated, but not control rats, were also stimulated to produce nitric oxide following treatment with interferon-γ *in vitro*. The promoter region for the nitric oxide synthase gene is known to contain consensus sequences for several *cis*-acting regulatory factors including NfkB and STAT-1. We found that interferon-γ treatment of type II cells from both control and ozone-treated animals stimulated nitric oxide production by the cells. Treatment with pyrollidine dithiocarbamate, an inhibitor of NfkB activity prevented this response indicating that activation of this factor is important in nitric oxide production by type II cells. Interferon-γ treatment of type II cells isolated from control animals was found to activate STAT-1. Unexpectedly, this transcription factor was found to be constitutively activated in type II cells isolated from ozone-treated rats. Based on these observations, we speculate that both NfkB and STAT-1 transcription factors are important for induction of nitric oxide synthase in type II pneumocytes, and that irritant-induced activation of STAT proteins may, in part, result in enhanced nitric oxide production by type II cells following ozone exposure. (Supported by ALA-NJ and ESO4738.)

711 EFFECTS OF TETRANDRINE ON MACROPHAGE PRODUCTION OF CYTOKINES RESULTING FROM SILICA OR BLEOMYCIN EXPOSURE

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Alveolar macrophage (AM) derived cytokines including interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) play an important role in the development of pulmonary fibrosis. Tetrandrine (TT) has been shown previously to reduce silica-induced pulmonary cell damage and collagen formation. The present objective was to investigate the effects of TT on AM production of IL-1 and TNF-α in response to silica or bleomycin (BLM). AM exposed to silica in vitro exhibited increased release of IL-1 and TNF-α. This increase was effectively reduced in the presence of TT. For in vivo studies, rats were intratracheally instilled with saline as control, 20 mg silica, or 1 mg/kg BLM. TT was administered orally (18 mg/kg) twice before exposure and 3 times/week after exposure for desired time periods. These studies showed that in vivo exposure to silica or BLM yielded AM which produced elevated levels of IL-1 and TNF-α in culture. This production was inhibited by oral treatment with TT. These results indicate that TT treatment inhibits the silica- or BLM-stimulated production of IL-1 and TNF-α. These effects may explain in part the ability of TT to decrease silica induced fibrosis.

712 EARLY INFLAMMATORY RESPONSES TO ADENOVIRAL VECTORS FOR PULMONARY GENE THERAPY

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Cystic Fibrosis (CF) is the most common lethal inherited disease of Caucasians and leads to death from chronic respiratory disease in early adult life in 95% of patients. CF patients suffer from persistent bacterial pulmonary infections and inflammation. The discovery of the CF gene and recognition that the cellular defect can be corrected has opened the door for CF gene therapy. Recombinant adenoviral vectors (Ad) have shown promise for pulmonary gene transfer for CF. However, cellular and humoral immune 2responses to Ad have been problematic and there is evidence inactivated Ad may be proinflammatory. Further, the lipopolysaccharide (LPS) present in the lungs of CF patients may contribute to this inflammation. C3H/HeJ mice (RES) that are hyporesponsive to LPS and normo-responsive C3H/HeBFEJ mice (SEN) were studied to characterize early inflammatory events following Ad intratracheal instillation with or without pretreatment with inhaled-LPS (0.1–8 μg/m^3, MMAD = 1.2 μm, σ_g = 1.8). Dose-response and

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Preface

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An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 351.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 375.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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