486 POSSIBLE ROLE OF ANGIOTENSIN II (ANG II) INDUCED CONNECTIVE TISSUE GROWTH FACTOR (CTGF) MEDIATED ELEVATION IN ELASTIN AND COLLAGEN LEVELS IN RAT PLEURAL MESOTHELIAL CELLS (RPMCS, CCL 216).

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Perturbation in extracellular matrix homeostasis is the hallmark of tissue fibrosis. While many mechanisms are involved in regulation of matrix alteration, studies carried out with antagonists of Renin Angiotensin System (RAS) have implicated a role for Ang II, an effector peptide of RAS, in several fibrotic disorders. Ang II mediated increase in collagen production has been shown to occur via a peptide, CTGF, in renal and cardiac fibrosis. However, in the lung a direct link between Ang II and CTGF expression has not been established with respect to extracellular matrix perturbation. The current study in RPMC was undertaken to examine a possible link between Ang II mediated increase in elastin and collagen levels and CTGF. Cells were grown in supplemented F-12-Nutrient Mix (Ham)-media containing 50µg/ml ascorbic acid or without ascorbic acid and 5% CO2. Cell viability was assessed by MTT assay. Sirus-red assay, ELISA and western blot analysis were carried out to measure collagen, elastin and CTGF levels respectively. Cultures were challenged with various concentrations of Ang II (10nM-1µM) for 24 hrs, following which the cells were either used for MTT assay or allowed to synthesize matrix for 7 days and then used for estimation of protein levels. At concentrations used Ang II did not show any toxicity. Ang II induced a 40 % increase in elastin and 47.1 % increase in collagen ($p<0.01$) levels at a concentration of 1µM by day 7 as compared to control. In western blot analysis, Ang II treatment at 1µM concentration caused an increase of CTGF as measured at day 7. These data indicate that a treatment of RPMC with 1µM concentration of Ang II causes CTGF increase between 0-7 days of treatment. Further, due to such increases the levels of collagen and elastin are elevated by day 7. These data suggest a positive correlationship between Ang II, CTGF and matrix proteins synthesis.

487 LUNG PROTEIN EXPRESSION FOLLOWING ACUTE FORMALIN EXPOSURE – EFFECT OF THE SUBSTANCE P DERIVATIVE SAR^9, $MET(O_2)^{11}$-SUBSTANCE P.

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Previous studies suggest that Sar^9,$Met(O_2)^{11}$-Substance P (SPa) may attenuate lung injury by blocking the action of endogenous substance P at the neurokinin-1 receptor (NK1r) on pulmonary alveolar macrophages and other potential lung cell receptor sites. We sought to determine if SPa pretreatment would attenuate protein alterations associated with formalin-induced acute lung injury. F344 male rats [control; formalin-only (F); or SPa/formalin] were exposed to 67 mg/m^3 (67 ppm) aerosolized formalin or air for 1.5 min while others were administered 35 ppm aerosolized 10 µM SPa over a 10 minute period just before formalin exposure. At ~42 minutes post-formalin or air exposure, rat lungs were removed for protein analysis. Replicate rats were administered pulmonary function and lung permeability tests. The F rats demonstrated a 33-fold increase in inspiratory dynamic lung compliance compared to the SPa rats. Increased compliance was matched by a 6-fold increase in F rat lung permeability versus the SPa group. Two-dimensional gel electrophoresis revealed altered abundance of 71 proteins whose formalin-mediated changes were attenuated in the SPa rats. Given the brief exposure period, the low abundance of the detected proteins (potential charge variants), and their identities, we hypothesize that this formalin effect relates to altered protein posttranslational modification and not protein synthetic/catabolic mechanisms. Conversely, imunoblotting suggests a limited set of proteins may be up- or down-regulated. Though the exact nature of the observed expression changes remains debatable, this study clearly demonstrates the protective effect of SPa against some aspects of acute formalin toxicity. Supported by AFOSR Grants FA9550-06-1-0083 & FA9550-05-1-0216 to FAW and FA9550-04-1-0231 to MLW.

488 MOUSE MODELS OF BERYLLIUM-INDUCED SENSITIZATION AND GRANULOMATOUS LUNG DISEASE.

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Exposure to beryllium (Be) is an occupational hazard that can cause chronic beryllium disease (CBD), an irreversible, debilitating granulomatous lung disease, in as many as 3-5% of exposed workers. CBD begins as an MHC Class II-restricted, Th1 hypersensitivity. CBD can be viewed as a biphasic disease: first peripheral sensitization occurs, and then, in some, there is progression to pulmonary granuloma formation. In order to look at both aspects of the disease, we performed a mouse ear-swelling test (MEST) to correlate with the sensitization process and a 5-month oropharyngeal aspiration study to look at granuloma development in mice. In the MEST, 21 different inbred mouse strains were utilized to see if they would exhibit varying hypersensitivity responses to Be. In two separate experiments, mice were placed into either group: C/C group (sensitized with vehicle, challenged with vehicle) or Be/Be group (sensitized with beryllium sulfate, challenged with beryllium sulfate). The SJL/J strain appeared to exhibit one of the greatest hypersensitivity responses with a 37.7% increase over the baseline ear thickness in the Be/Be group compared with a 2.6% increase in the control group. The FVB/N strain, in contrast, had statistically insignificant, increases in ear thickness. The results for the hypersensitivity MEST response were as follows: SJL/J, AKR, DBA/2J>>PL/J, LG/J, MRL/MpJ>> FVB/N, 129/SvlmJ, SWR/J. The data have been analyzed by haplotype mapping to uncover genes associated with sensitization to beryllium. In the aspiration study, seven inbred strains aspirated either 20µg, 35µg, or 50µg of beryllium metal powder or water vehicle monthly. Clear dose and strain differences in beryllium-induced lymphogranulomatus nodules were observed. Uncovering the genes responsible for the hypersensitive phenotype and granuloma formation in mice may prove useful in learning more about the mechanisms involved in CBD.

489 BINDING OF THE MACROCYCLIC TRICHOTHECENE SATRATOXIN G TO RIBOSOMES IN RAW 264.7 MACROPHAGES AND PC-12 NEURONAL CELLS.

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Satratoxin G (SG), a macrocyclic trichothecene produced by the black indoor air mold Stachybotrys chartarum, causes both inflammation and neurotoxicity in the murine intranasal lavage model suggesting its potential to adversely affect human health. The molecular mode of action for SG and other trichothecenes is believed to involve ribosomal binding and intracellular kinase activation followed by inflammatory and apoptotic gene expression. The purpose of this research was to characterize both concentration-response and kinetics of SG binding to ribosomes in RAW 264.7 macrophage and PC-12 neuronal cell models. Following exposure of the cells to SG at various concentrations over different time intervals, ribosomal fractions were separated from cytoplasmic proteins using a sucrose gradient system. Each fraction was then measured by a competitive ELISA using anti-SG antibodies. SG was preferentially found in the monosome fraction with smaller and negligible concentrations found in the polysome and cytoplasmic fractions, respectively. When SG was incubated at 0, 2.5, 5, 10, 50, 100 ng/ml with the cells for 30 minutes, SG binding to ribosomal fractions increased in a concentration-dependent fashion up to 10 ng/ml with saturation of a single ribosomal binding site. SG binding was largely unaffected by boiling and isopropanol precipitation of the ribosomal fractions. Furthermore, exhaustive RNase treatment for removal of ribosomal RNA, failed to reduce SG content in the ribosomal protein fraction. Taken together, SG has the capacity to rapidly and tightly bind to macrophage and neuronal ribosomal proteins. Both the concentration-dependence and kinetics of this interaction were consistent with previously observed kinetics of SG-induced intracellular kinase cascade activation as well as downstream inflammatory and apoptotic sequelae.

490 ACTIVATION OF RAT ALVEOLAR MACROPHAGES AND TYPE II EPITHELIAL CELLS FOLLOWING OZONE INHALATION.

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Ozone (O_3) inhalation is associated with an inflammatory response, characterized by macrophage (AM) and neutrophil accumulation in the alveolar regions of the lung. These cells release mediators important in the pathophysiology of O_3-induced injury. We speculated that Type II alveolar epithelial cells also participate in inflammatory responses to O_3 and this was investigated. Female Wistar rats (200-225 g; 8-10 weeks) were exposed to air or O_3 (2 ppm) for 3 h. Animals were sacrificed 3-72 h later. Following O_3 inhalation, greater numbers of inflammatory leukocytes were recovered in BAL fluid 6-12 h post-exposure. This was correlated with an increase in BAL protein demonstrating that O_3 induces alveolar epithelial injury. Exposure of animals to O_3 also resulted in an increase in mRNA for the inflammatory cytokine, TNF-α, in AM and Type II cells which was evident after 3 h. Expression of COX-2, the enzyme mediating prostaglandin production, was also increased after O_3. Whereas a rapid and persistent induction of COX-2 was noted in Type II cells, increases in expression of this enzyme were delayed for 72 h in AM. Antioxidant production in the lung is critical in limiting oxidant-induced damage.

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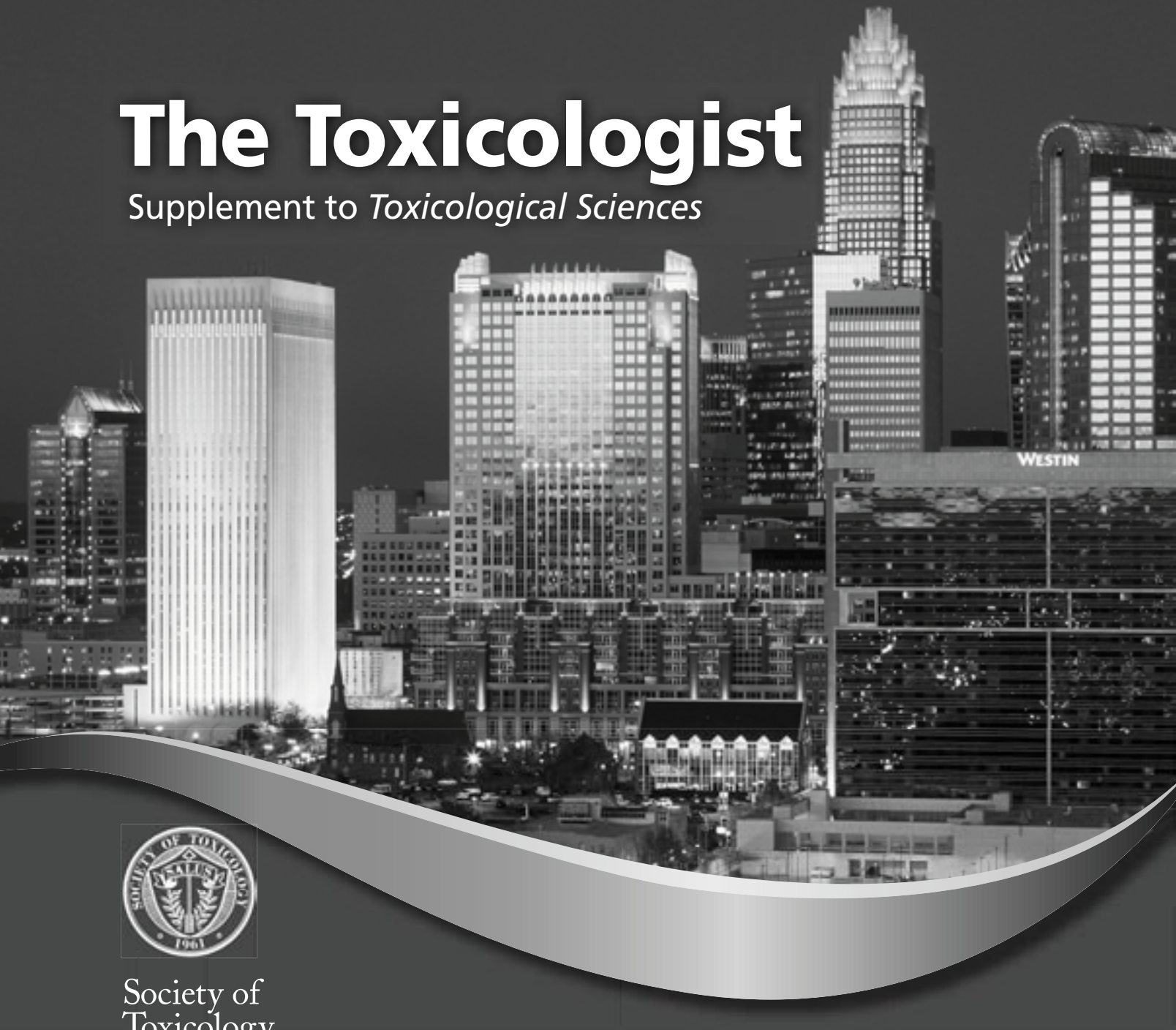

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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