

sensitization. In response to various antigens, including influenza and lipopolysaccharide (LPS), CB1/CB2 null mice also produced more IgM. It has been demonstrated that NE engagement of $\beta 2$ adrenergic receptor ($\beta 2$ AR) on B cells is part of the normal physiological mechanism that contributes to antibody production, and in fact, splenic NE concentration and $\beta 2$ AR expression on B cells were higher in CB1/CB2 null mice as compared to wild type mice. These results provide a correlation between splenic NE concentration and antibody production, suggesting the possibility that cannabinoid-mediated suppression of NE release from splenic sympathetic neurons contributes to cannabinoid-induced inhibition of antibody responses. (Supported in part by NIH DA007908).

PS 421 Differential Effects of Delta(9)-Tetrahydrocannabinol on NF κ B Activation in T Cell-Dependent Humoral Immune Response in Humans.

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Delta(9)-Tetrahydrocannabinol (THC), a major psychoactive constituent found in marijuana, modulates immune function. Previously, our laboratory demonstrated that THC inhibits humoral immune responses to T cell-dependent antigens in mice by suppressing sheep erythrocyte or CD40 ligand (CD40L)-induced immunoglobulin M (IgM) secretion and antibody forming cell (AFC) response. CD40 is constitutively expressed on B cells, whereas CD40L is induced in activated T cells. Thus, the objective of this study was to investigate the role of the CD40-CD40L interaction in THC-mediated suppression of the T cell-dependent humoral immune response in humans. These studies show that THC suppressed the anti-CD3/CD28-induced DNA binding activity of NFAT and NF κ B, two transcription factors critical in the upregulation of CD40L in activated human CD4⁺ T cells. An assessment of the effect of THC on proximal T cell-receptor signaling induced by anti-CD3/CD28 revealed modest impairment of sustained elevation in intracellular calcium, but no significant effect on the phosphorylation of Zap70, PLC γ , Akt, and Gsk3 β . Additional findings, using an in vitro T cell-dependent antibody response model, which employs cell surface-expressed CD40L and recombinant cytokines [interleukin (IL)-2, IL-6, and IL-10], to induce B cell responses demonstrated that THC suppressed STAT3, but not NF κ B activation in B cells. Moreover, THC impaired B cell activation and proliferation, ultimately resulting in suppression of IgM AFC response. Collectively, these findings suggest that THC exhibits stimulation- and/or cell type-specific selectivity in NF κ B inhibition, and identifies many aspects of the multi-faceted mechanism by which THC suppresses T cell-dependent humoral immunity in humans. Supported in part by DA07908 and Royal Thai Government Scholarships.

PS 422 Phenotypic Comparison of Leukocyte Populations between Wild Type and Aryl Hydrocarbon Receptor (AhR) Null Rat in the Developing and Mature Spleen and Thymus.

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The immunotoxic effects produced by dioxin and dioxin-like polycyclic aromatic hydrocarbons are mediated through the AhR; however, little is known concerning the role of the AhR in the development or functionality of the immune system. The objective of the present study was to investigate whether targeted deletion of the AhR in the Sprague-Dawley rat altered the leukocyte composition within the developing (3 weeks) and/or mature (8 weeks) thymus or spleen of male and female rats. No significant differences were observed between AhR null and wild type rats in the spleen or thymus body to organ weight ratios or cellularity of the thymus or spleen at 3 or 8 weeks of age. Similarly, leukocyte populations as characterized by comprehensive phenotyping using multiple panels of antibodies directed against specific cell surface proteins (i.e., B cells, T cell subtypes, monocyte-derived lineages, neutrophils and NK cells) using flow cytometry showed no significant differences in the cellular composition of the thymus between the wild type and AhR null rat. Similar analysis of the spleen showed an increase in the CD8⁺NK⁺ (NKT) population at week 3 in the AhR null rat. A trend toward an increase in NKT cells was also present at week 8 but this difference was not statistically significant. These studies show that targeted deletion of the AhR in the Sprague-Dawley rat has minimal effects on the leukocyte composition of the developing and mature rat thymus and spleen. (Supported in part by the Dow Chemical Company)

PS 423 Differential Expression Kinetics of miRNA Involved in Allergic Chemical Sensitization following Dermal Exposure in a Murine Model.

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Allergic disease is an important occupational health concern with work related asthma and allergic contact dermatitis among the most frequently diagnosed occupational illnesses. The development of rapid and sensitive methods for hazard identification of the responsible agents is critical. MicroRNAs (miRNAs) are small non-coding RNAs 20-22 nucleotides long whose primary function is to regulate gene expression by functioning as endogenous inhibitors of protein translation. Allergic disease is characterized by an imbalance between Th1 and Th2 cytokines; however the role of posttranscriptional mechanisms like the ones regulated by miRNAs is just starting to be explored. These studies describe the kinetics of miRNA expression during the sensitization phase of an allergic response following dermal exposure to prototypical chemical sensitizers in a mouse model. Using microarray and other data, six miRNAs were identified for further analysis with RT-PCR including mi-21, 22, 210, 155, 133a, and 27b. These data demonstrate that miRNAs may have a central role early in the allergic response focused on establishing the fine balance of Th1 versus Th2 responses to chemical sensitizers. Identification of unique miRNA expression profiles may help to elicit the mechanisms by which exposure to sensitizing chemicals induce immune cell activation and can potentially help to identify biomarkers for new treatments and preventions.

PS 424 Potential for Immune Sensitization following Dermal Exposure to Indium Tin Oxide.

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Pulmonary disease including pulmonary fibrosis, emphysema and pulmonary alveolar proteinosis has been observed in workers in the indium industry. The mechanisms underlying this disease and its natural history have not been fully elucidated. Among other findings, following inhalation exposure to Indium-tin Oxide (ITO) animal studies have revealed hyperplasia of mediastinal lymph nodes and granulomas of mediastinal nodes and bronchus-associated lymphoid tissue. These studies were undertaken to investigate the potential for ITO to induce immune sensitization using the mouse Local Lymph Node Assay. Furthermore studies were conducted following exposure to both intact and abraded skin to begin to evaluate the potential for dermal penetration of the nanoparticles. BALB/c mice (5 animals/per group for both intact and abraded skin groups) were exposed to either vehicle (dimethyl sulfoxide), increasing concentrations 2.5%-10% ITO (90:10 indium oxide/tin oxide, particle size <50 nm) or positive control (30% alpha-hexylcinnamaldehyde). A dose response was observed in both groups reaching statistical significance and a SI of 4 in the 5% intact dose group (EC3 value of 2.6). Students t-test showed no statistical differences when responses were compared between intact and breach skin exposures at the same dose levels. These studies demonstrate the potential for ITO to induce sensitization following dermal exposure and suggest that the particles may have similar bioavailability through intact and abraded skin.

PS 425 Rat Bioassay of Diisocyanate Asthma: Comparison of Thresholds of the Asthmagenic Response and Pulmonary Irritation.

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Occupational exposure to polymeric diphenylmethane-diisocyanate (MDI) and the more volatile toluene-diisocyanate (TDI), known human asthmagens, can be attributed to two potential routes: the skin and the respiratory tract. Both routes were systematically compared in the Brown Norway (BN) rat MDI asthma model. Induction utilized either 2 topical exposure sessions or inhalation exposures on 5 consecutive days at concentration x exposure time (C x t) relationships of 1000, 5000, and 10000 mg MDI/m³ x min using exposure durations of either 10- or 360-min. This was followed by four 30-min inhalation challenges to 40 mg MDI/m³ on every alternate follow-up week. This comparison revealed that a 'high dose' dermal exposure is markedly more efficacious to produce 'asthmatic rats' than a repeated high-dose/high-concentration inhalation protocol. Therefore, further testing was focusing solely on the topical route for induction. Under otherwise similar conditions, rats were challenged to 80 mg TDI/m³. This overcomes the loss of dose due to the vapor retention in the upper airways of rats and associated drop in

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 52nd Annual Meeting of the Society of Toxicology, held at the Henry B. Gonzalez Convention Center, March 10-14, 2013.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 536.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 561.

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



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