121.2

**IL-4 is not required to generate antigen-specific Th2 response but is critical to expand Th2 response in murine model of allergic airway inflammation**

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IL-4 plays important roles in asthma pathogenesis. It has been shown to upregulate VCAM-1 expression selectively and to induce chemokine expression, such as MDC/CCL22, TCA3/CCL1 and eotaxin/CCL11. Interestingly, IL-4 also upregulate CCR3, CCR4 and CCR8 expression. Recent evidence indicates that IL-4 can cause AHR directly. More importantly, IL-4 is a critical factor in Th2 cell development. However, the role of IL-4 in the initiation and expansion of Th2 response remains unclear. Using GFP/IL-4 reporter mice, we found that in the absence of IL-4 GFP homozygous mice can generate an antigen specific Th2 immune response. The number of CD4+GFP− T cells increased in the airway and the lung. They were antigen specific. When stimulated with OVA, but not cytochrome c peptides, these cells produced IL-5 and IL-13. The IL-4-independent CD4+GFP+ cells expressed predominantly Vβ8, Vβ3 and Vβ14. Although few of CD4−GFP+ cells expressed γδ or NK1.1 in the peripheral lymphoid organs, we failed to detect NK T GFP+ cells in the airway and the lung. However, IL-4 is critical in expanding CD4+ Th2 effector cells in the airway and the lung. The percentage and total number of CD4+GFP+ cells significantly increase in GFP heterozygous mice compared to GFP homozygous mice. These results suggest that IL-4 is not required to generate an antigen specific Th2 response but it is critical in expanding the number of CD4+Th2 effector cells in allergic airway information.

121.3

**Examination of the role of Natural Killer cells in allergic airway inflammation**

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Asthma is a T cell mediated inflammatory disease consisting of reversible airway obstruction, nonspecific airway hyperresponsiveness, and eosinophilic airway inflammation. We show that natural killer (NK) cells, hitherto considered an innate immune effector cell, also play a role in the induction and progression of asthma in a murine model. We injected C57BL/6 (B6) mice three times with ovalbumin (OVA) intraperitoneally, and then rechallenged intranasally daily for a week. Mice receiving the challenge dose develop significant airway inflammation by day 7, and exhibit many of the characteristics of human asthma. Here we show that NK cells migrate to the airways of challenged mice along with T, B and innate cells, and thus may contribute to the observed effects in asthma. Moreover mice lacking NK cells (NK-Deficient mice) show a significant suppression of airway eosinophilia, IL-4, IL-5 and IL-13 secretion in comparison with normal B6 mice, indicating that NK cells may also modulate T cell responses during allergic asthma. Presence of eosinophilia in _eta 2-microglobulin, CD1d KO, and Perforin KO mice suggests that this suppression is not dependent on MHC Class I interactions, NKT cells, or perforin mediated NK cell cytotoxicity. We propose that NK cells may participate in asthma induction and progression during both the 'priming' and 'challenge' phases using an as yet unidentified mechanism.

Supported by a grant from the Sandler Program for Asthma Research (to H.L.A.)

121.4

**Development and characterization of an Immune Mouse Model for Toluene Diisocyanate (TDI) Asthma**

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Isocyanate-induced asthma, which is the most common type of occupational asthma, has been difficult to diagnose and control, in part, because the biological mechanisms responsible for the disease and the determinants of exposure have not been well defined. To address these issues, a murine model was established and characterized that reflects exposure conditions that occur in the workplace. C57BL/6J mice were sensitized to toluene diisocyanate (TDI) by inhalation for 6 weeks (20ppb, 4hrs/day, 5 days/week) and challenged 14 days later by inhalation with TDI (20ppb, 1hr). Mice demonstrated allergic asthma evidenced by marked increases in airway inflammation, lung eosinophilia, goblet cell metaplasia, epithelial cell thickening, airway hyper-reactivity, Th2 cytokine expression, and serum IgE levels as well as TDI-specific IgG antibodies. Adoptive transfer with T and B lymphocytes from sensitized mice indicated that both cellular and humoral immunity played a role in the asthma response. Additional studies involving passive transfer and the use of transgenic FcERIg knockout mice, which lack IgE and IgG Fc receptors, established the importance of reagenic antibodies. Taken together, these results suggest that in subchronic model, with a dose reflective of the current permissible workplace exposure level, that sensitization to TDI can occur under these conditions and demonstrates the importance of both a cellular and humoral response in the manifestation of TDI-induced asthma.

121.5

**DC Phenotype in Airway Tolerance and Inflammation**

**Timothy B Oriss**[1], Carole Devaux[2], Grace Olshansky[1], Barbara Dixon-McCarthy[2], Anuradha Ray[2]. [1]Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, 3459 Fifth Avenue, Pittsburgh, PA 15213, [2]Internal Medicine; Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, [3]Internal Medicine; Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA

The role of dendritic cells (DC) in the initial stages of asthma development has not been described in great detail. We show that DCs isolated from murine lung-draining lymph nodes following intranasal administration of ovalbumin (OVA) with or without the Th2 adjuvant cholera toxin (CT), treatments that induce tolerance and airway inflammation, are phenotypically different. Whereas surface phehotype as determined by flow cytometry is only marginally different between the two groups, analysis by RNase protection assay (RPA) reveals altered DC cytokine expression profiles in the presence of CT. Most importantly, DCs isolated after each treatment are functionally different in terms of their ability to stimulate naïve T-cells. OVA DCs were very poor inducers of cytokine production in naïve T cells, as would be expected from a tolerogenic condition. In contrast, OVA/CT DCs are potent inducers of T- cell cytokines, particularly those associated with a Th2 phenotype such as that found in the asthmatic lung. Further characterization of these DC populations should lead to better understanding of the breaking of tolerance in conditions such as asthma, and may lead to clues to help establish effective biological-based therapies for this ailment.

121.6

**Airway inflammation and cytokine responses in mouse models of peanut allergy**

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Appropriate animal models of food allergy and food-induced airway inflammation are needed. Further, it remains unclear how these processes are influenced by the oral or nasal route of initial sensitization. We have developed mouse models of peanut allergy by oral or nasal immunization with whole peanut extract and cholera toxin as adjuvant. Airway inflammation and cytokine responses were evaluated after nasal challenge with peanut or legumes (i.e., pea, soybean, or lupine). Oral immunization induced higher levels of peanut-specific IgE while nasal immunization promoted low IgE but significant IgG2a Abs. Nasal peanut challenge triggered lung inflammation in both groups of mice; however, eosinophilia was significantly higher in orally immunized mice. The latter group also exhibited higher lung IL-5 and IL-13 mRNA in response to the nasal peanut challenge. Only minimal lung inflammation and no IL-4, IL-5 or IL-13 responses were induced

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# ABSTRACTS 29.1 – 162.31

## Indexes
### Key Word
### Author

The American Association of Immunologists

American Association of Veterinary Immunologists
American Society of Transplantation
Association of Medical Laboratory Immunologists
Canadian Society for Immunology
Clinical Immunology Society
International Society for Interferon and Cytokine Research
International Society for NeuroImmunoModulation
International Society of Neuroimmunology
PsychoNeuroImmunology Research Society
Society for Leukoctye Biology
Society for Mucosal Immunology
Society for Natural Immunity

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# ABSTRACTS

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THURSDAY
May 8, 2003



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