LUNG
Monday, July 6

OR.21. IL-12 Alleviates IL-17-mediated Allergic Lung Inflammation in the Absence of T-bet Regulation

Douglas Durrant, Dennis Metzger
Albany Medical College, Albany, NY

The dysfunction of T-bet, a critical transcription factor in the regulation of Th1 lineage commitment and IFN-γ production, has been implicated in allergic asthma pathogenesis. However, the factors underlying this pathogenesis are unknown. In addition, IL-12 has been shown to suppress the Th2 hyper-response associated with allergic asthma largely through IFN-γ production, yet T-bet-/- mice produce little to no IFN-γ. The therapeutic value of IL-12, in the absence of T-bet, remains unknown. Therefore, to elucidate the causative factor in allergic asthma and the potential mechanism of IL-12 treatment, wild-type and T-bet-/- mice were used in an antigen-induced allergic asthma model. T-bet-/- mice displayed increased inflammatory cellular infiltrates in the bronchiole lining and enhanced airway resistance after methacholine challenge compared to WT mice. However, Th2 cytokine production did not appear to be significantly higher but we did observe a marked increase in IL-17 production. Following IL-17 neutralization, neutrophilic infiltration and airway inflammation were prevented. IL-12 treatment in T-bet-/- mice suppressed IL-17 production, neutrophilic infiltration, bronchoconstriction and airway resistance. In addition, a significant increase in the anti-inflammatory cytokine, IL-10 was observed. However, the suppressive ability of IL-12 was lost in T-bet-/- mice following neutralization of IL-10. Therefore, in the absence of T-bet regulation, the pulmonary immune response is pre-disposed towards IL-17 production which IL-12 treatment suppresses through an IL-10-dependent mechanism. Supported by NIH grant RO1 AI 41715.

OR.22. Synergistic Effects of the Innate and Adaptive Immune System Lead to Immunological Tolerance in the Lung

Marcus Gereke, Harro Frauendorf, Dunja Bruder
Helmholtz Center for Infection Research, Braunschweig, Germany

Background: Although the contribution of alveolar type II epithelial cells (AECII) in respiratory immunity has become increasingly appreciated, their precise function in the induction and regulation of T cell reactivity to self-antigen under non-inflammatory or proinflammatory conditions remains poorly understood. Objectives: To investigate the role of AECII in the initiation of T cell reactivity to alveolar self-antigen and to clarify their function in the peripheral induction of Foxp3(+) regulatory CD4(+) T cells. Methods: To dissect the complex cellular and molecular functions of AECII in lung inflammation and immune regulation, we utilize a transgenic mouse model for CD4(+) T cell mediated pulmonary inflammation. Measurements and Main Results: Here we report that AECII present endogenously expressed antigen to CD4(+) T cells under non inflammatory conditions. Epithelial antigen display was sufficient to induce primary T cell activation and pulmonary inflammation. Upon CD4(+) T cell mediated inflammation AECII induce by a mechanism involving anti-proliferative soluble factors including transforming growth factor-beta (TGF-beta) the differentiation of Foxp3(+) regulatory T cells (Tregs). Conclusion: In the absence of proinflammatory stimuli AECII are capably of priming naive CD4(+) T cells demonstrating an active participation of these cells in respiratory immunity. Moreover, AECII cells display so far unrecognized functions in balancing inflammatory and regulatory T cell responses in the lung by connecting innate and adaptive immune-mechanisms to establish peripheral T cell tolerance to respiratory self-antigen. Nevertheless a beneficial immune response towards pathogens is required. Thus the influence of the immune regulatory effect of AECII under proinflammatory conditions has to be further investigated.

OR.23. CD11c$^+$CD8α$^+$ Dendritic Cells Promote Protective Immunity to Respiratory Infection with *Bordetella Pertussis*

Padraic Dunne[1], Barry Moran[1], Robert Cummins[2], Kingston Mills[1]
[1]Trinity College Dublin, Dublin, Ireland; [2]RCSI Education & Research Centre, Beaumont Hospital, Dublin, Ireland

Here we have used a murine model of infection with Bordetella pertussis to examine the function of dendritic cell (DC) subtypes in protective immunity in the lungs. We found a dramatic increase in the numbers of CD11c$^+$CD8α$^+$ DC in the cervical lymph nodes (CLN) within 4 hours of challenge with *B. pertussis*. CD11c$^+$CD8α$^+$ DC also infiltrated the lung with a peak 7 days post *B. pertussis* challenge. The infiltrating CD11c$^+$CD8α$^+$ DC expressed MHC, co-stimulatory and activation markers, indicative of mature DC. The CD11c$^+$CD8α$^+$ DC in the CLN expressed IL-4 and IL-10, and lower levels of IFN-γ, but in the lungs expressed predominantly IFN-γ. Depletion of CD8α$^+$ cells early in infection attenuated Th1 responses in the lungs and significantly reduced bacterial clearance. Conversely, transfer of FLT3 ligand (FL)-expanded CD11c$^+$CD8α$^+$ DC enhanced bacterial clearance, whereas GM-CSF-expanded conventional DC had no effect. The numbers of CD11c$^+$CD8α$^+$CD103$^+$ cells were also increased during the early phase of infection. Blocking CD103 function caused a significant delay in bacterial clearance and a reduction in cellular infiltration into the lungs. These findings demonstrate that CD11c$^+$CD8α$^+$ and CD103$^+$ DC play a protective role in mediating immunity to *B. pertussis* infection in the respiratory tract.

OR.24. Impaired Immune Responses in the Lungs of Aged Mice Following Infection with Influenza Virus

Franklin Toapanta, Ted Ross
University of Pittsburgh, Pittsburgh, PA

Influenza virus affects both adult and elderly human populations; however, the elderly are more susceptible to infections and complications due to subjacent chronic diseases and senesce of the

immune system. To analyze differences in immunological markers and disease progression aged and adult mice were infected with the mouse adapted influenza virus strain A/PR/8/34 (PR8). Compared to adult mice, aged mice had higher morbidity, lost weight more rapidly, and recovered more slowly from infection. There was also a delay in the accumulation of granulocytic cells and dendritic cells (DCs), but not macrophages in the lungs of aged mice compared to adult ones. The delayed infiltration kinetics of APCs in aged animals correlated with alteration in their activation (CD40 expression), which also correlated with delayed production of APC-primed cytokines and chemokines, resulting in retarded lung infiltration by natural killer (NK), CD4+ and CD8+ T cells. Furthermore, the percentage of activated (CD69+) influenza-specific and IL-12 produced CD8+ T cells was higher in adult mice compared to aged ones. Additionally, activation (CD69+) of adult B-cells was earlier and correlated with a quicker development of neutralizing antibodies in adult animals. Overall, alterations in APC priming and activation lead to delayed production of cytokines and chemokines that ultimately affected the infiltration of immune cells into the lungs following influenza infection. This resulted in delayed activation of the adaptive immune response and subsequent delay in clearance of virus and prolonged illness in aged animals. The elderly is the fastest growing segment of the USA population, a good understanding of the changes that the immune system undergoes with aging is becoming primordial for the development of new vaccines and adjuvants.