airway smooth muscle cells, suggesting that CD4+ T cells may modulate smooth muscle cell function through paracrine cytokine effects and direct cell-cell interaction. Subsequently, adoptive transfer of CD4+ T cells from sensitized donors induced increased proliferation and inhibition of apoptosis of airway myocytes in naive recipients upon repeated antigen challenge, which resulted in an increase in airway smooth muscle mass. Overall, our data show that activated CD4+ T cells regulate myocyte turnover and induce airway remodeling in experimental asthma. We will now analyze airway responses subsequent to transfer of transduced CD4+ T cells overexpressing IL-13. In addition, transduced CD4+ T cells producing a dominant negative IL-13 mutant will be transferred into sensitized and challenged animals to study their potential to modulate experimental asthma.

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769.23

Role of Interleukin-1 in Toluene Diisocyanate Asthma

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Diisocyanates are the leading cause of occupational asthma. Numerous human studies have implicated the immune system in the pathogenesis of diisocyanate asthma and increased interleukin-1 (IL-1) immunostaining is evident in the submucosa. We and others have demonstrated increased production of IL-1β in the airways of mice with TDI asthma. We hypothesized that IL-1β plays a critical role in the pathogenesis of TDI asthma. C57BL/6 mice were sensitized to TDI by vapor inhalation (20 ppb; 4hrs/day, 5 days/week, 6 weeks) and then challenged 2 weeks later by inhalation of 20 ppb TDI vapor for 1 hr. Sensitized/challenged mice showed increased airway hyperresponsiveness (AHR) to methacholine challenge and a TDI-specific late asthmatic reaction 4-5 hours following challenge. Significant airway inflammation was also evident. Pulmonary expression of IL-1β and IL-4 mRNA was also increased following challenge. Mice deficient in IL-1 receptor type I did not show any increase in AHR, airway inflammation or cytokine expression. Systemic administration of neutralizing antibody to IL-1β 24 hours prior to challenge only partially reduced AHR but blocked leukocyte recruitment and cytokine gene expression in the airways. These results suggest that IL-1 signaling is an important mediator of TDI asthma. IL-1β neutralization effectively prevented inflammation but only partially reduced AHR suggesting a possible role for IL-1α in this disease.

B-CELL DEVELOPMENT/HOMEOSTASIS (770.1-770.15)

770.1

CLIPR-59 regulates NF-kappa B activation mediated by Death Receptor 6 (DR6)

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Death Receptor (DR) family is a group of ligand-regulated transmembrane proteins to induce apoptosis and NF-κB activation. DR6 is a new member of this family including TNF receptor type1, Fas, DR3, DR4 and DR5. In recent studies, it was shown that targeted disruption of DR6 results in enhanced CD4 T cell expansion and Th 2 differentiation. In addition, DR6 deficient B cells exhibited unregulated hyper-proliferation. These findings indicate that DR6 has important roles for regulating peripheral lymphocyte differentiation and activation. However, the intracellular signaling pathways of DR6 are yet to be elucidated. In this study, we attempted to identify DR6-associated proteins by yeast two-hybrid screening for analyzing this signaling pathway. We identified Cytoplasmic Linker Protein-170 related protein (CLIPR-59) as a protein interacting with the cytoplasmic domain of DR6. CLIPR-59 interacted with DR6 in mammalian cells. The cytoplasmic segment, from position 380 to 411, conserved in human and other species DR6, is essential for its association with the CLIPR-59. Interestingly, over-expression of CLIPR-59 inhibits DR6-mediated NF-kappa B activation. Taken together, we demonstrate that CLIPR-59 is a negative regulator of DR6-mediated NF-kappa B activation.

770.2

Lymphoid development in HK-1 transgenic mice

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Hemokinin 1(HK-1) is an 11 amino acid peptide of family. Its predominant expression in lymphoid precu critical role in lymphopoiesis. Our previous studies ha that HK-1 enhanced the proliferation of lymphoid promoted the survival of bone marrow B lineage c Tachykinin antagonists, on the other hand, blocked bo development at specific stages. To further elucidate its r development and function, we generated an Eμ-driven l mouse. Bone marrow B cells from this mouse demons survival with increased bcl-2 levels. While the total r marrow B cells was not significantly altered, the prop remarkably increased. This could be either due to accele or increased survival of maturing B cells. Preliminary da an inceased number of NK1.1+ cells in this mouse, sugg may be involved in the development of natural killer cell

770.3

Activation of PI3-K by CD40 protects B cells from apoptosis

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The death receptor CD95 and the activation molecule necrosis factor receptor (TNFR) superfamily receptors B lymphocyte homeostasis. CD40 signaling increas CD95, sensitizing cells to undergo apoptosis, yet con through CD40 protects B cells from CD95 killing in murine B cells and in transformed B cell lines. Here molecular mechanisms mediating CD40 rescue from We found that a CD40 rescue signal given withi stimulation through CD95 can decrease the amount of by 50%. CD40 rescue is independent of the classic (NF)-kappa B pathway and de novo protein synthesis a formation of the death-inducing signaling complex (DI rafts. However, CD40 signaling does decrease le caspase 8. In order to elucidate which CD40 signal required for rescue, we examined the role of the factors (TRAFs) in protection from apoptosis. Rescue independent of binding to TRAFs 1, 2, 3, or 6, in combinations tested thus far. Interestingly, phosphatidylinositol 3-kinase (PI3K) activation reduc CD95 apoptosis, suggesting a role for the pro-sur

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770.4

In Utero Exposure to Alcohol Adversely Affect Regulation of B cell Progenitors in Neonatal Bone

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Fetal Alcohol Syndrome (FAS) is a spectrum of disor consumption of alcohol during pregnancy. Previ confirm the immuno-suppressive effects of *in utero* The present study examined the role of *in utero* alco regulation of transcription factors (TF) important i $HSA^{lo}CD43^{lo}Lin^-$ B cell progenitors. When grown $HSA^{lo}CD43^{lo}Lin^-$ cells up-regulate both Pax5 (B-c activator protein) and IL-7R transcription, and initiat of B220 and CD19. EBF (early B cell factor) and P message RNA were detected by single cel $HSA^{lo}CD43^{lo}Lin^-$ cells, isolated from 14 days old m to alcohol, express EBF at less than 20% the level o control animals and show a reduced capacity to exp to B lineage cells. When growth in liquid culture t

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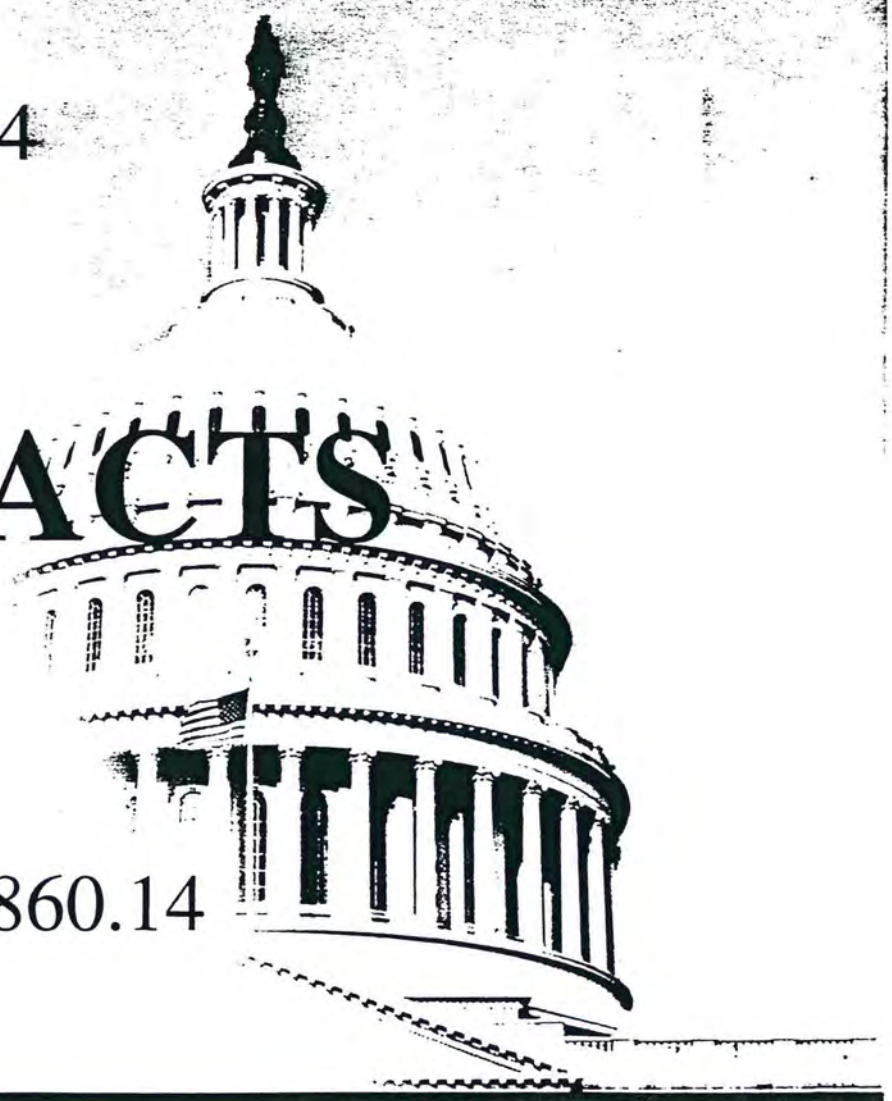

ABSTRACTS

PART II

Abstracts 480.1–860.14

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