Workshop/poster session 2: Cytokines in the pathogenesis of inflammatory disease

27 Severe SARS coronavirus infection in aged macaques is associated with reduced expression of anti-inflammatory type-1 interferons
Bart L. Haagmans, Saskia L. Smits, Anna de Lang, Judith M.A. van den Brand, Lonneke M.E. Leijten, Arno Andeweg, Geert van Amerongen, Thijis Kuiken, Albert D.M.E. Osterhaus, Department of Virology, Erasmus Medical Center, PO Box 2040, 3000 CA, Rotterdam, The Netherlands

Advanced age is an independent correlate for adverse outcome of many viral infections, including severe acute respiratory syndrome virus (SARS-CoV) infection that causes respiratory disease in humans. To study the pathogenesis of SARS-CoV in relation to age, six aged (10–18 years old) and four young adult (3–5 years old) cynomolgus macaques were infected with SARS-CoV HKU39849. Aged macaques were more prone to develop severe SARS-CoV-associated clinical symptoms and gross pathology than young adult macaques. Histopathological analysis revealed diffuse alveolar damage in the lungs with pulmonary edema, desquamation of epithelial cells, hyaline membrane formation, and infiltration of inflammatory cells. Comprehensive genomic analysis of the host response indicates that aged macaques have a more zealous response to virus infection than young adult macaques, with a significant increase in the differential expression of genes associated with influx and activation of immune cells whereas the expression of type-1 interferons was reduced. Therapeutic administration of pegylated interferon alpha in aged macaques on the other hand, inhibited gross pathology and expression of pathogenic pathways, including IL-8 levels. Because viral replication in the lungs was similar between the different groups, the intrinsic host response seems to regulate the severity of SARS-CoV induced acute lung injury. We conclude that anti-inflammatory actions of type-1 interferons may determine the outcome of virus induced acute lung injury.


28 Differential roles of IL-6 and IL-11 in inflammation and tumorigenesis
Brendan J. Jenkins1,2, Meri Nadjovska1, Claire Greenhill1, Louise McLeod1, Hazel Tye1, Catherine Kennedy1, Ceri Fielding1, Simon A. Jones2, Matthias Ernst3, Paul J. Hertzog1, 1Monash Institute of Medical Research, Clayton, Vic. 3168, Australia, 2School of Medicine, Cardiff University, Heath Park, Cardiff, UK, 3Ludwig Institute for Cancer Research, Parkville, Vic. 3050, Australia

Deregulated activation of cytokine signaling pathways, especially the latent STAT1 and STAT3 transcription factors, is implicated in various cancers and debilitating inflammatory disorders. However, the mechanisms leading to, as well as the downstream molecular consequences of, their activation in disease remain to be fully elucidated. To provide novel molecular insights into the mechanisms by which deregulated STAT1 and STAT3 activation via IL-6 family cytokines contribute to pathophysiological responses in vivo, we have developed a unique genetic approach based on a mouse strain (gp130Y757F/Y757F) carrying a specific “knock-in” mutation in the IL-6 cytokine family co-receptor gp130 which abolishes a negative feedback mechanism to terminate gp130 signaling, resulting in hyper-activation of STAT1 and STAT3. These mice spontaneously develop a host of pathologies, the most striking of which are gastric tumors and multi-organ inflammation (including gastric), and they are also hyper-sensitive to experimentally-induced endotoxic shock and peritonitis. Monoallelic ablation of STAT3 in gp130Y757F/Y757F mice, thus genetically identifying a pro-inflammatory and oncogenic role for gp130-dependent STAT3 hyper-activation. We also observe that gastritis and gastric tumorigenesis is partially suppressed in gp130Y757F/Y757F mice deficient in STAT1, suggesting functional oncogenic redundancy exists between STAT1 and STAT3 in the inflamed gastric compartment. Furthermore, we identify IL-11 as the primary gp130-using cytokine that is essential for gastritis and gastric tumorigenesis, whereas IL-6 is required to drive the non-gastric hyper-inflammatory responses.


29 Antagonistic role of STAT6 for regulatory T-cells
Svetlana P. Chapoval, Ann E. Kelly-Welch, Elizabeth Smith, Achsah D. Keegan, Department of Microbiology and Immunology, Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, MD, USA

STAT6 plays a critical role in Th2 cell differentiation and in allergic lung inflammation. Using a chimeric mouse model, we observed alternative lung pathology in STAT6 KO mice even when WT bone marrow or Th2 cells were provided. Thus, we hypothesized that STAT6 contributes to inflammation in a complex manner. To detail STAT6 function, WT and STAT6 KO mice were subjected to OVA priming and challenges. Broncho-alveolar lavage (BAL) cell composition, lung histology, and FACS analysis of digested lungs were assessed 48 h after the last challenge. As expected, eosinophils composed a majority of BAL cells in WT mice and less than 2% in STAT6 KO mice. The OVA-induced inflammation in STAT6 KO lungs was composed mainly of macrophages with small fractions of neutrophils and lymphocytes. We found a significantly higher number of CD4+CD25+Foxp3+ T cells in PBS-treated STAT6 KO mouse lungs as compared to WT animals (3.9 ± 0.4% vs 2.7 ± 0.2%, respectively, p < 0.03). The fraction of these cells in OVA-treated STAT6 KO mouse lungs also exceeded that of control WT mice. These results suggest that STAT6 may suppress the development of both naturally occurring and antigen-included Tregs. The requirement of STAT6 in lung resident and inflammatory cells for this effect is currently being investigated. Taken together, our studies demonstrate STAT6-dependent and -independent features of asthma phenotype which may impact treatments targeting STAT6.


30 Inhibition of IL-23 prevents disease in an inducible psoriatic-like mouse model
Jennifer Towne1, Donna Shows1, Huyen Dinh1, Yu Zhang1, Charley Dean2, Esther Trueblood2, Keith Bailey2, John Sims1, Hal Blumberg1, 1Department of Inflammation Research, Amgen, Seattle, WA, USA, 2Department of Pathology, Amgen, Seattle, MA, USA

Psoriasis is a grievous skin illness whose initiating events are poorly understood. Disease development involves the complex interplay between keratinocytes, immune cells, and endothelial cells. Here we describe a mouse transgenic line that exhibits histologic, mechanistic, and pharmacologic similarities to psoriasis. Mice with keratinocyte-driven expression of IL-1β, a member of the IL-1 ligand family, have skin abnormalities as pups which resolve before adulthood. Topical administration of TPA to symptomless adult IL-1F6 mice results in dramatic skin alterations, reminiscent of the Koebner phenomenon in which damage to non-lesional skin in psoriatic patients leads to plaque conversion. Histological similarities of this TPA-inducible skin pathology with psoriasis include acanthosis, parakeratotic hyperkeratosis, intracorneal, and intra-epithelial microabsesses, dilated superficial dermal blood vessels, and a mixed inflammatory infiltrate. Many of the cytokines and chemokines increased in expression in the TPA-treated transgenic mouse skin are also elevated in psoriatic skin. However, mature T cells are not required for the skin pathology as K14/IL-1F6, rag2−/− mice do not have