STAT1 and STAT3 in lymphocyte differentiation, STAT3 in anaphylaxis and vascular permeability, and the roles of each of the STATs in discrete, microbe-specific immunity.

THE ROLE OF STAT3 IN B CELLS

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Loss of function mutations in *STAT3* cause autosomal dominant hyper-IgE syndrome (AD-HIES), a primary immunodeficiency characterised by recurrent mucocutaneous infections with *C. albicans* and *S. aureus*, susceptibility to pneumonia due to *S. pneumoniae* and *H. influenzae*, impaired humoral immunity and distinctly elevated levels of serum IgE. STAT3 is a transcription factor that acts downstream of many cytokine receptors that have key roles in lymphocyte differentiation and function including the common gamma chain family (IL-2, IL-7, IL-9, IL-15 and IL-21), IL-23R, IL-6R and IL-10R. It is therefore not surprising that STAT3 has emerged as a key regulator of multiple lymphocyte lineages and that loss of STAT3 function would impair myriad aspects of protective immunity.

Here, I will examine what we know about the role of STAT3 in regulating B cells and how this impacts on establishing a protective antibody response. Further, I will discuss what this reveals about the pathophysiology not only of the loss-of-function mutations in *STAT3* which are associated with AD-HIES but also the more recently described *STAT3* gain-of-function mutations that are associated with early onset autoimmunity and aspects of dysregulated B cell responses.

TIPS, TRICKS AND A QUIZ – HOW TO INTERPRET EQA

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The provision of high quality testing is the foundation of any immunopathology laboratory. This is achieved by ensuring that appropriate quality practices are in place, with robust interpretation and root cause analysis. Proficiency testing allows our laboratories to ensure that their methodology, results and interpretation are comparable to other service providers. Using a series of case studies, this session will focus on the interpretation and troubleshooting of RCPAQAP reports and the statistical analysis included in the end of cycle reports.

AN APPROACH TO THE DIAGNOSIS OF INTERSTITIAL PNEUMONIAS IN ADULTS AND CHILDREN

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In adults with an idiopathic interstitial pneumonia (IIP), an updated classification system was published in 2013. Although

definitions for the seven histological patterns remain essentially unchanged, there has been substantial progress in our understanding. In relation to usual interstitial pneumonia (UIP), updated management recommendations were published in 2011, with the most significant change recommending varying degrees of confidence in diagnosis. A pattern of UIP is also being increasingly recognised in patients with chronic hypersensitivity pneumonitis. Idiopathic non-specific interstitial pneumonia is now better defined as a specific clinico-pathological entity, with the majority cases proving to have secondary associations/causes after multidisciplinary review. Respiratory bronchiolitis–interstitial lung disease is now commonly diagnosed without surgical biopsy, and acute exacerbation of IIPs is now well defined. A group of rare entities, including pleuroparenchymal fibroelastosis and rare histological patterns, is also introduced. There have also been advances in the undertaking of biopsies with most institutions sampling at least two sites, ideally using preoperative targeting. These histological patterns are also recognised in children, although classification is more complex and includes entities specific to a younger age group (e.g., neuroendocrine hyperplasia of infancy, pulmonary interstitial glycogenosis). Surfactant protein gene mutations are also being increasingly identified.

ELISA ASSAYS TO MONITOR MONOCLONAL ANTIBODY THERAPIES

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Monoclonal antibody therapies that inhibit the proinflammatory cytokine TNF alpha are used to treat patients with immune mediated diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis associated uveitis (JIA). A proportion of patients will initially respond but later become unresponsive to the therapy. Inadequate dosing and the formation of antibodies to the drug contribute to treatment failure. Investigation in our laboratory, using an in-house assay demonstrated anti-infliximab antibodies (AIA) in JIA and adult inflammatory bowel disease (IBD) patients. Of 27 adult patients with IBD tested for AIA, 15% ($n=4$) had a detectable AIA response. All of the patients with a detectable AIA level had a trough level of Infliximab less than 1 µg/mL for a least one time point during the evaluation period.

In the children with refractory JIA ($n=14$) 6 patients with high AIA levels and low trough infliximab levels had more breakthrough flares or loss of response over time.

The identification of anti-drug antibodies and trough levels may assist early identification of patients who require altered management and thereby reduce unscheduled outpatient and/or hospital admission.

USE OF FLOW CYTOMETRY TO MONITOR MONOCLONAL ANTIBODY THERAPIES

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