NIH Award from the National Institute of Allergy And Infectious Diseases

Principal investigator: Robert P. Schleimer, medicine: allergy, Feinberg School of Medicine

- **Project:** Epithelial BAFF and APRIL in Airway Inflammation, Immunity and Disease
- **Start Date:** September 12, 2009
- **Total Award Amount:** $281,225

**How the results of this project will benefit society:**
These studies will test new ideas about how our lungs and nose protect us from infections. We will also study what causes sinus disease, emphysema and asthma. We are testing the importance of two new tumor necrosis factors (TNF) called BAFF and APRIL in immunity and disease.

**The problem the project is trying to solve:**
The goal of the project is to test the hypothesis that expression of the TNF family members BAFF and APRIL is important in the local immune and inflammatory responses that occur in the airways in health and disease. These factors are known to cause the proliferation, differentiation and immunoglobulin class switch recombination (CSR) of B lymphocytes. While it has been known for decades that B lymphocytes secrete immunoglobulins locally in the mucosa, until recently it was believed that the process of differentiation and CSR occurred in lymphoid tissues prior to B cell migration to the tissue. Several recent studies support the concept that these events occur extensively in the airways, although the local mechanism is not known. We have made the exciting finding that epithelial cells produce large quantities of BAFF and APRIL, and that BAFF is expressed in chronic rhinosinusitis (CRS) and allergen challenge models in humans, raising the hypothesis that epithelium plays a role in regulation of B cell responses in the airways.

**How the project will work:**
We propose experiments to test this hypothesis, using in vivo and in vitro approaches. Studies in Aim 1 will use an explant model to study the production and source of BAFF and APRIL by antigen-challenged human mucosal tissue and will analyze the furin proteases involved in their expression. Studies in Aim 2 will test the role of BAFF and APRIL in human diseases, including rhinitis (in collaboration with Dr. Stephen Durham), COPD (in collaboration with Dr. James Hogg), asthma and CRS (in collaboration with investigators at Northwestern), using assays for the presence of these cytokines as well as assays to detect the local presence of B cells and the process of CSR (germline, circle and mature immunoglobulin transcripts and the necessary enzyme activation induced cytidine deaminase). In collaboration with Drs. Charles and Fabienne Mackay, studies in Aim 3 will use mouse models of systemic and airway sensitization and challenge with antigen, and challenge with RSV, to test the role of BAFF and APRIL in B cell responses in the airways. These studies will utilize assays for local B cell responses and inflammatory responses. Studies with knockout and transgenic mice will help pinpoint the cytokine and receptors responsible for important findings. We believe that the proposed studies have direct relevance in the mechanisms of host defense to pathogens and inflammatory airways diseases.

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