Host defense, inflammation and remodeling in the upper airway
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The Northwestern University (NU) Sinus Research Group is composed of Allergists, ENT surgeons and bench scientists. We have been using clinical, cellular, molecular and bioinformatic approaches to study the pathogenesis of chronic rhinosinusitis (CRS), especially CRS with nasal polyps (CRSwNP), and have made several observations of potential importance. A model has emerged that can briefly be summarized as follows: patients with CRS have impairments in the "immune barrier", i.e. the ability of the mucosal surface to maintain a strong physical barrier and to produce adequate innate host defense molecules. As a consequence, these patients experience frequent colonization of their upper airways and sinuses by bacteria, fungi and perhaps viruses. Possibly as a result of persistent colonization, patients with CRSwNP have substantial numbers of B cells, plasmablasts and plasma cells in nasal polyp tissue, and these cells produce significant quantities of immunoglobulins of most isotypes, including autoantibodies in patients with recalcitrant disease. Associated with this immune response in CRSwNP patients, is a Th2 biased inflammatory response notably characterized by large numbers of eosinophils, basophils and mast cells, as well as alternatively activated macrophages (M2) and type 2 innate lymphoid cells (ILC2). Deposition of fibrin is a recently recognized characteristic of nasal polyp formation. This presentation will be divided into four major topics of recent interest to our group.

I. Relationship of CRS to asthma. Approximately half of our patients with CRSwNP have asthma, and a small percentage of patients have CRSwNP, asthma and aspirin sensitivity (Triad disease that we will refer to as AERD). In the NU cohort, the patients with AERD have a history of sinus surgery approximately 2-3 fold higher than patients with CRSwNP without AERD. Evaluation of nasal polyp tissue from asthmatics compared to non-asthmatics demonstrates much higher levels of plasmablasts in the polyps of asthmatics, suggesting that the upper airway immune response in asthmatics may be qualitatively different than in patients with CRSwNP without comorbid asthma. Preliminary Principal Components Analysis (PCA) and bioinformatic analysis of four independent microarray studies of CRSwNP and four published studies of asthmatic lung biopsies indicate that upper and lower airway tissues have alterations in expression of many of the same genes: (for instance, in a direct comparison of one CRS study and one asthma study, of 6044 genes altered in CRS, 1450 were also altered in lower airway biopsy tissues from asthmatics). Interestingly, many of the shared genes describe common changes in the innate barrier, giving support to the "united airway" hypothesis.

II. The immune barrier. It is now also clear that there are defects in the physical epithelial barrier in bronchial tissues from asthmatics and sinonasal epithelial cells in CRS patients. Our recent studies implicate Oncostatin M (OSM) as a potential mediator of barrier disruption in nasal or sinus epithelial cells. OSM is elevated in nasal polyp tissue and in vitro can cause loss of barrier integrity in differentiated nasal epithelial cells at similar concentrations to those found in vivo. Previous studies from our group and others have shown that epithelium and/or polyp tissue from CRSwNP patients have reduced levels of several host defense molecules, including members of the PLUNC family, S100 molecules, lysozyme and lactoferrin. Our bioinformatics analysis of several CRS gene expression microarray studies has confirmed this impairment of innate immune host defense molecule expression. Interestingly, our PCA analysis has discovered that the nature of the control
tissue used in various transcriptomics studies (e.g. inferior turbinate vs uncinate process vs sphenoid sinus tissue) can dramatically influence the overall result of the genomic analysis due to significant regional variability of expression of host defense molecules within the nasal and sinus cavities.

III. Gender, age, race and disease. Recent studies have suggested that gender and age modify the risk of acquiring CRS significantly and race can influence the manifestation of eosinophilia. Although we find more men with CRSwNP in the NU cohort than women, the women have considerably more severe disease, based on surgical history and comorbidity with asthma and aspirin sensitivity (AERD). The defects in the immune barrier, at least so far as expression of certain innate host defense molecules is concerned, appear to worsen with age. As far as eosinophilia is concerned, we have preliminary data that suggest that patients of Asian descent have less eosinophilia than patients from other regions, even if born in the US.

IV. Inflammation and remodeling in CRSwNP. Using microarray, PCR, Luminex and Western Blotting, we have more extensively explored the expression of inflammatory chemokines and cytokines in CRS. Although we can confirm a strong Th2 bias in CRSwNP (primarily as indicated by IL-13 and STAT6 activated chemokines), we do not detect a Th1 bias in the non-polypoid form of CRS (CRSSNP) (primarily as indicated by lack of elevated expression of members of the interferon family). Among epithelial derived cytokines, TSLP appears to be of potential importance, and recent studies indicate that TSLP is cleaved by specific proteases within nasal polyp tissue that can increase or decrease activity. A number of novel human chemokines are induced that likely play a role in the cellular composition of the inflammatory response in CRSwNP. The deposition of fibrin that we have detected in nasal polyp tissue appears to be driven in part by factors produced by M2 cells and epithelial cells exposed to type 2 cytokines (especially IL-13).

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