



Editorial

Recent discoveries regarding the pathogenesis of chronic rhinosinusitis and their implications for future therapies



The prevalence of chronic rhinosinusitis (CRS) is steadily increasing and becoming an increasing component of our medical practices. Most presentations of CRS with nasal polyps (NP) (CRSwNPs) and close to half of CRS without NPs are associated with eosinophilia and type 2 (T₂) inflammation (interleukin [IL]-4, IL-5, and IL-13).^{1,2} In the current issue of the *Annals of Allergy, Asthma & Immunology*, several state-of-the-art articles update our understanding of the pathogenesis of CRSwNPs and point to future interventions that will ameliorate the adverse impact CRS has on our patients' quality of life.

One of the most striking features of these articles is the extent to which CRS is increasingly recognized as being driven by the innate immune system. These observations suggest that, although perhaps initiated (and exacerbated) by an adaptive—antigen-targeted—immune response, the ongoing misery may persist *without* the presence of an antigen. Historically, the primary source of T₂ cytokines was assumed to be type 2 T-helper (T_H2) lymphocytes. However, the term “type 2 immunity” was adopted recognizing their numerous alternative sources. One of the most important producers of these cytokines is innate lymphoid 2 (ILC2) cells. In this issue, 2 articles address our understanding of ILC2 cells in CRS. Stevens and Kato³ review the role of ILC2s as crucial drivers of T₂ cytokine expression and evaluate several synergistic downstream inflammatory cascades mediated by ILC2-derived IL-4, IL-5, and IL-13. These observations argue for a role of biotherapeutics for CRS through the targeting of ILC2-derived cytokines. The paper by Cavagnero and Doherty⁴ builds on this concept that ILC2s are central drivers of the immune response in CRS and other T₂-associated airway diseases. This paper focuses on the role of lipid mediators, especially cysteinyl leukotrienes and prostaglandin D₂ in promoting ILC2 proliferation, recruitment, and activation, including in particular, the surge in production of these lipid mediators in aspirin-exacerbated respiratory disease (AERD). These lipid pathways suggest additional therapeutic targets to ameliorate CRSwNPs.

A striking feature of ILC2 lymphocytes is their activation by endogenous danger signals, including cytokines IL-25, IL-33, and TSLP. An important—perhaps the most important—source of these cytokines is sinus epithelial cells. Although previously thought to be homogeneous, other tissue types are dispersed among the ciliated cells. Sell et al⁵ discuss the role of the solitary chemosensory cell (SCC) in the pathogenesis of CRSwNPs. SCCs

are “chemosensory” in that they have pathways used by conventional taste cells but used these pathways to “taste” the presence of pathogens, in response to which they promote mucociliary clearance and antimicrobial responses. However, in the context of NPs, they are the primary source of IL-25, a cytokine that is a central mediator driving T_H2 immune deviation and ILC2 activation. Furthermore, SCCs are sources of cysteinyl leukotriene and prostaglandin D₂, lipids that, as noted,⁴ drive ILC2 (and T_H2) recruitment and activation. Their subsequent production of IL-5 underlies the eosinophilic inflammation, whereas IL-13, among its many activities, drives the expansion of SCCs, completing a vicious circle.

Paradoxically, one of the most overlooked cells among allergists in the current era seems to be the mast cells. However, mast cells are undergoing a renaissance reflecting their increasingly recognized role in being engaged in innate immune inflammation, including through pathways not dependent on an interaction with allergen and immunoglobulin E (IgE). This evolving role of mast cells in CRSwNPs is summarized in the article by Martin et al.⁶ Nasal polyps in AERD have a greater number of mast cells relative to those in patients tolerant for aspirin. The authors identified distinct populations of mast cells, most notably a proliferatively active population that was more prevalent in AERD. These findings suggest that local mast cell proliferation could underlie the mast cell hyperplasia found in AERD (and other conditions characterized by increased mast cell burden).

When considering the evolving roles of innate and adaptive immune responses in CRSwNPs, although many patients have disease worsened by IgE, allergy is not necessary or sufficient for disease pathogenesis. However, as discussed by Buchheit and Hulse,⁷ there is compelling evidence for production of IgE *locally* in NP tissues and interventions that target this local IgE can be beneficial. More recent studies have suggested perhaps an even greater role for IgG and IgG4 in CRS. IgG4 is particularly intriguing as, although traditionally associated with anti-inflammatory effects, a proinflammatory role for IgG4 is present in IgG4-related disease. Furthermore, a pathogenic role for IgG4 is increasingly suspected in another eosinophilic inflammatory disorder, eosinophilic esophagitis (and intriguingly, eosinophilic esophagitis develops in up to 10% of patients with AERD⁸).

All this basic immunology is only meaningful if translatable into our clinical armamentarium. Indeed, we have found the first approval of the Food and Drug Administration of a biologic for the treatment of NP,⁹ and biologics targeting other mediators are likely to be approved in the near future. Until now, these clinical trials have focused on targeting the hallmarks of T₂

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inflammation, including IgE, and the T2 cytokines, IL-4, IL-5, and IL-13, interventions that give *moderate* improvement in a *moderate* percent of patients. A common denominator of these articles is their suggestion to consider the broader context of NP pathogenesis, including such inviting targets as epithelial cells (IL-25, IL-33, TSLP, RANKL), B cells (rituximab), and mast cells (imatinib). However, targeting these mediators comes, literally, with a high cost. The final article in this issue¹⁰ provides a critical perspective for how we need to approach clinical decision making regarding the use of biologics for CRSwNPs. In this rapidly evolving world of biologics, it is our role as immunologists to stay abreast of information so we can guide our patients and empower them make the best decisions for their care. For example, although dupilumab is a compelling treatment option for patients with AERD,⁹ aspirin desensitization followed by daily aspirin remains a viable—markedly less expensive—treatment option. In clinical practice, the decision to choose one therapy over another is not always obvious and requires the physician to take into account not only the efficacy, safety, and cost of each treatment but also the patient's personal goals and preferences. Clinicians must realize that the factors behind decision making to pursue biologic therapy are nuanced and must be a patient-centered decision.

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