Toward a More Precise Solution to Asthma Therapy

Asthma is a common and complex disease, clinically defined by compatible symptomatology (wheezing and dyspnea) and reversible airflow obstruction with long-term sequelae of airway remodeling and hyperresponsiveness (1, 2). The pathogenesis of asthma is a combination of environmental and genetic factors that can lead to multiple overlapping aberrations in immune signaling. The classic etiology of asthma is a dysfunctional activation of CD4 T-helper 2 (Th2) cells and production of type 2 cytokines (IL4, IL5, and IL13). This may occur in the setting of a deficiency in CD4 Th1 signaling (3), which has been well supported in human and mouse studies where a lack of early Th1 stimulation leads to a hyperresponsive Th2 lung phenotype (4, 5). The same Th2 phenotype is common in mouse models of airway hyperreactivity and humans with asthma with intact Th1 immune systems. Patients with asthma can be subdivided into multiple overlapping subgroups, such as atopic versus nonatopic, steroid responsive versus nonresponsive, and eosinophilic versus neutrophilic asthma (3). Various non-Th2 cell types participate in the pathology, including epithelial cells, macrophages, type 2 innate lymphocytes (ILC2s) (6, 7), and iNKT cells (8), which are responsible for the cytokines IL25, IL33, and TSLP (3). They express pathogen recognition receptors, particularly TLR3, TLR7, and TLR9 (9), and respond to TLR ligands. Of particular interest are ILC2s, which have been shown to be potent producers of type 2 cytokines in mouse models of asthma (7), and IL27, which is a potent inhibitor of this cytokine production in the lungs (10). Many groups have sought to rebalance Th2 and Th1 activation through skewing Th1 modulation of pathogen recognition receptors as potential therapeutic approaches for asthma (11). Although many of the preclinical trials of TLR-modifying agents have been promising, subsequent clinical trials have not yet supported their use as an asthma or allergy therapeutic. One potential reason for this failure may be the underlying heterogeneity of asthma pathogenesis. It is possible that targeting selected TLR modulation to specific asthma immunophenotypes may lead to more effective therapeutic interventions.

In this issue of the *Journal*, Okuzumi and colleagues (12) (pp. 309–318), building on prior evidence that the TLR7 agonist R848 (commercially available as Resiquimod) induces a strong Th1 response and limits Th2 responses, report on its role in IL33-mediated nonallergic asthma. Specifically, they investigated whether R848 could modulate IL33-induced ILC2 activation. They modeled nonallergic eosinophilic inflammation through repeated airway stimulation of mice with I33 with an intervening treatment dose of R848 after the first dose of IL33. Treatment with R848 protected mice against many aspects of IL33-induced inflammation, reduced alveolar and tissue inflammatory cell infiltration (specifically eosinophils and ILC2s), decreased production of Th2 cytokines IL5 and IL13, and limited goblet cell hyperplasia. Notably, they did not measure airway hyperreactivity. Interestingly, the mechanism of this protection appears to be mediated by remodeling of IL33-activated interstitial macrophages (IMs) from an M2 toward an M1 phenotype rather than a direct effect of R848 on ILC2s. Abrogation of ILC2 activation appeared to be secondary to increased IL27 production by IMs, which did not occur when IL27 receptor knockout mice were treated with IL33 and R848. Taken together, the authors demonstrate a novel and complex inflammatory pathway, whereby IL33-activated IMs with an M2 phenotype can be modulated through TLR7 signaling, leading to upregulation of the antiinflammatory cytokine IL27 and abrogation of ILC2-mediated nonallergic eosinophilic inflammation (Figure 1).

It must be noted that this work, although illuminating, remains very preliminary in regard to future use of R848 as a therapeutic agent for nonallergic eosinophilic asthma. Most importantly, this work was performed in mice, and confirmatory studies in humans will be needed. Second, their model used an IL33 stimulation model, which is less applicable to human asthma exacerbations, where direct viral infection is often the causative stimulus in asthma exacerbation. Additional work needs to be performed to understand whether TLR7 agonism would be helpful in a viral upper respiratory infection trigger of asthma exacerbation. Finally, it is not clear whether the mechanisms presented in this work are specific to IL33 or other cytokines that induce ILC2-driven eosinophilic asthma (such as TSLP).

Ultimately, in this work, the authors present a potentially novel therapeutic approach to asthma that takes advantage of immunophenotyping efforts already in progress (13). One could

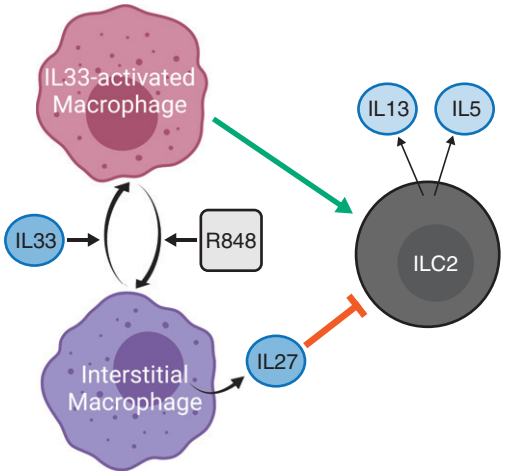

Figure 1. Stimulation of interstitial macrophages by IL33 leads to activation and polarization toward an M2 phenotype. IL33-activated macrophages then stimulate ILC2s to produce the type 2 cytokines IL5 and IL13. Treatment of IL33-activated IMs with R848 drives their polarization away from M2 and induces the production of IL27, which inhibits ILC2 production of type 2 cytokines. Figure created with BioRender.com. ILC2 = type 2 innate lymphocyte; IM = interstitial macrophage; M2 = macrophage type 2.

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imagine a scenario in which patients with asthma have an immunophenotype established by measuring various cytokine levels, and then based on their phenotype (i.e., IL33-dominant, nonallergic), adjunctive therapeutics such as R848 could be added at the time of exacerbation risk or as controller therapy. One advantage of an agent such as R848 is that it is available in intranasal or inhaled formulations rather than injected biologic agents targeting specific cytokines. Ultimately, R848 (or other TLR7 agonists) might be another precise agent for treatment of selected asthma phenotypes as part of an array of immune modulating tools that provide targeted therapy. At the very least, the studies by Okuzumi and colleagues point us toward more precision in diagnosis and treatment of asthma. ■

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