Regulation of Th9-Type Pulmonary Immune Responses A New Role for COX-2

Prostaglandins (PGs) are ubiquitous products of arachidonic acid metabolism by the cyclooxygenase (COX) enzymes. Five structurally and functionally distinct PGs (PGE₂, PGF₂, PGI₂, PGD₂, and thromboxane A₂) form in a cell- and tissue-specific manner from the COX-derived precursor, PGH₂, which is converted to end products by specific terminal synthases (1). Each PG is implicated in a broad range of homeostatic functions, including thrombosis, maintenance of vascular tone and blood flow, and repair of epithelial surfaces. Most have also been implicated in inflammation; indeed, COX inhibitors are one of the oldest and most successful target-based treatments for inflammatory diseases, and are still used widely to control pain, fever, and swelling. These drugs also impair the synthesis of PGs needed for homeostatic functions of PGs, likely accounting for some of their unwanted side effects.

Although PGs play proinflammatory roles in most organ systems, their role in the lungs is largely protective and antiinflammatory. The most obvious example in humans is the approximately 5–10% of asthmatic individuals who develop bronchoconstriction with the administration of nonselective COX inhibitors (aspirin-exacerbated respiratory disease) (2). These individuals exhibit marked eosinophilic inflammation of the sinonasal and bronchial mucosal surfaces, along with impaired expression of the COX-2 isoenzyme in their sinonasal mucosa (3). In mice, pharmacologic inhibition of COX-1 and/or COX-2 or genetic deletion of either enzyme results in enhanced eosinophilia and bronchovascular pathology after allergen sensitization and challenge (4–6). More recently, the use of mice with targeted deletions in specific PG synthases and receptors for PGs has implicated separate roles for PGE₂ and PGI₂ in regulating pulmonary immune responses to allergen, as well as end-organ responsiveness to the inflammatory state (7, 8). The broad distribution of receptors for these and other PGs on cells of the innate and adaptive immune systems suggests multiple potential immunologic targets and effects of PGs, most of which have not been defined.

T-helper 9 (Th9) cells are a recently described subset of CD4⁺ T cells that generate IL-9 and IL-10 (previously thought to be Th2-type cytokines) (Figure 1) (9). Th9 cells develop from naive T cells as a result of stimulation by IL-4 and transforming growth factor β , and express the type B IL-17 receptor (IL-17RB). The IL-17RB ligand, IL-25, amplifies the production of IL-9 (a potent inducer of mast cell expansion and airway reactivity) (10) by Th9 cells. In this issue of the *Journal*, Li and colleagues (pp. 812–822) demonstrate a marked homeostatic function for COX-2-derived PGE₂ and PGD₂ in the control of Th9 development *in vitro* and *in vivo* (11). Using a traditional model of ovalbumin sensitization and challenge, the authors demonstrate that mice lacking COX-2, but not those lacking COX-1, display increased numbers of Th9 cells in the blood, lung, bronchoalveolar lavage fluid, and lung-draining lymph nodes relative to wild-type controls. The absence of endogenous COX-2 in naive CD4⁺ T cells amplifies their expression of IL-9 and other Th9 lineage markers when polarized under Th9-favoring conditions *in vitro*. Using a combination of

complementary approaches, the authors demonstrated that two PGs, PGE₂ (acting at E prostanoid [EP]₂ and EP₄ receptors) and PGD₂ (acting at D prostanoid [DP]₂ receptors) could suppress Th9-cell development *in vitro* and *in vivo* by suppressing the expression of the IL-17RB (Figure 1). Finally, they showed that PGE₂ and PGD₂ suppressed Th9 development from naive human T cells *in vitro*.

The study by Li and colleagues demonstrates a completely novel role for endogenous COX-2 products in regulating T-helper cell polarization *in vivo*, and translates the findings in mice to human cells. Given the implied role for IL-9 in several allergic diseases, including asthma (12), atopic dermatitis (13), and food allergy (14), the discovery that two COX products control Th9 development has exciting potential implications for pathobiology and treatment of human disease. Inhaled PGE₂ blocks pulmonary late-phase reactions in allergen-challenged atopic individuals (15) and aspirin-challenged subjects with aspirin-exacerbated respiratory disease (16), and it is tempting to speculate that EP₂ and EP₄ receptors on Th9 cells are among the targets responsible for these effects. Like Th9 cells, the recently identified innate helper cell type 2 (ILC2) population (which generates large quantities of IL-5, IL-13, and, interestingly, IL-9 in allergic inflammation) requires expression of IL-17RB and the presence of IL-25, and also expresses DP₂ receptors (17). Whether EP and/or DP receptor signaling controls ILC2 functions by regulating IL-17RB expression as it does in Th9 cells remains to be determined. Lastly, the study further complicates the functions of PGD₂, which is either inductive (18) or suppressive (19) of allergen-induced pulmonary inflammation depending on the model used and the receptor involved. Understanding the full range of relevant receptors and targets of PGs is a necessary step before the application of targeted agonists and antagonists to human allergic disease.

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Figure 1. Naïve CD4 cells differentiate into Th9 cells when activated in the presence of TGF- β and IL-4. (A) Th9 cells produce IL-9. (B) IL-25, signaling through its heterodimeric receptor consisting of IL-17 receptor type A (IL-17RA) and IL-17RB, augments IL-9 production by Th9 cells. (C) Prostaglandin D₂ (PGD₂) and PGE₂ produced by the COX-2 pathway of arachidonic acid metabolism inhibit expression of IL-17RB, thus preventing the IL-25-driven augmentation of IL-9 protein expression by Th9 cells. COX = cyclooxygenase; TGF- β = transforming growth factor β .

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Bronchiectasis with Chronic Obstructive Pulmonary Disease

Association or a Further Phenotype?

When reviewing articles for the *Journal*, one of the questions asked is, "Should an editorial accompany this article?" and a second, "If so, would you be willing to write it?" In general my response is no, but occasionally an article allows a moment's

reflection or in some cases (with age) a 35-year reflection. If you look up Chronic Obstructive Pulmonary Disease (COPD) on PubMed, there are 110 papers identified for 1975. By 1995, it had risen to 433, and by 2012 to 3,196 (Figure 1), and ECLIPSE