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Lipid Mediator Regulation of Group 2 Innate Lymphoid Cells

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Abstract

ILC2s were originally found to be activated by epithelial cell derived cytokines to induce the secretion of Th2 cytokines, IL-5 and IL-13. Recent research has shown that lipid mediators play a large role in the activation and inhibition of ILC2 function. Unlike the traditional epithelial cell derived cytokines IL-33 and IL-25, lipid mediators have been shown to promote ILC2 secretion of not only IL-5 and IL-13, but the secretion of IL-4 as well. Prostaglandin D_2 has been shown to be a potent chemoattractant of ILC2s as well as a potent activator of ILC2s to release Th2 cytokines. In addition to prostaglandin D_2, cysteinyl leukotrienes also activate ILC2s to secrete Th2 cytokines during inflammation. Notably, lipid mediators have been shown to work in concert with epithelial cell derived cytokines to increase IL-5 and IL-13 secretion from ILC2s. On the other hand, lipid meditators prostaglandin I_2 and lipoxin A_4 are the first identified lipid mediator inhibitors of ILC2 function, and thus limit ILC2 contribution to Th2 inflammation. ILC2s play a potential significant role in Th2 mediated inflammation in a variety of allergic disease states, such as asthma, atopic dermatitis, and chronic rhinosinusitis. The identification of lipid mediators as activators and inhibitors of ILC2 function provides additional therapeutic targets for altering ILC2 function during disease states.

Keywords: ILC2; Lipid mediators; Prostaglandin D2; Prostaglandin I2; Prostacyclin; Cysteinyl leukotrienes; Lipoxin A4

Introduction

Group 2 innate lymphoid cells (ILC2) represent a group of cells that lack conventional lineage markers associated with well-established immune and inflammatory cells, such as T and B cells, mast cells, basophils, myeloid cells, and erythroid cells. Despite lacking lineage markers, ILC2s have been shown to express CD127 (IL-7Rα), CD25 (IL-2Rα), inducible T-cell costimulatory (ICOS), Sca-1, and the receptors for IL-25 (IL-17RB) and IL-33 (T1/ST2) [1]. One of the defining characteristics of ILC2s is the production of large amounts of Th2 cytokines upon stimulation. ILC2s have been shown to produce IL-5 and IL-13 in response to IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) and produce IL-4 in response to lipid mediators [2-4]. Specifically, ILC2s have been shown to have a larger capacity to produce Th2 cytokines compared to other cell types on a per cell basis [5]. Compared to other ILC group members, the secretion of Th2 cytokines is specific to ILC2s compared to Th1 cytokines secreted by ILC1, and Th17 cytokines released by ILC3. ILC2s also secrete other inflammatory mediators including IL-9 which can regulate immune cell survival, and amphiregulin which can regulate tissue repair [6-10].

There are increasing numbers of studies demonstrating an association between ILC2s and allergic inflammation, despite ILC2s not directly responding to allergen exposure, as they do not express antigen recognition receptors. Patients with chronic rhinosinusitis (CRS) and atopic dermatitis show increased levels of ILC2s in nasal polyps and skin lesions respectively [11-13]. Recent studies show elevated ILC2 levels in both the sputum and blood of adult severe asthmatics compared to mild asthmatics, as well as in the BAL, induced sputum, and blood of children with severe asthma compared to children without [14,15].

In addition, in mice, ILC2s have been shown to directly influence and contribute to the development of airway hyperresponsiveness (AHR). In the absence of IL-13-producing CD4 T cells, ILC2s are sufficient for induction of AHR and IL-13 production in response to either allergen or glycolipids when wildtype ILC2s are transferred to IL-13 deficient mice [16,17]. Additionally, during influenza infection in mice, ILC2s can induce AHR through the IL-33-IL-13 axis, which is independent of Th2 cells and adaptive immunity [18].

Despite ILC2 involvement in Th2 inflammation, an initial innate stimulation of epithelial cells, mast cells, eosinophils, and/or myeloid cells is required for ILC2 activation. ILC2s do not express antigen recognition receptors and thus do not directly interact with an antigen. However they are activated through either secreted mediators or direct cell contact with activated cells. Initially ILC2s were shown to be activated by IL-25, IL-33, and TSLP, which are epithelial cell-derived cytokines. In the past few years, studies have shown ILC2 activation by tumor necrosis factor (TNF)-like ligand 1A (TL1A) and modulation by prostaglandin and leukotriene lipid mediators [19,20].

Lipid Mediator Activation of ILC2

Several cell types have been known to rapidly produce lipid mediators, such as activated mast cells, macrophages, dendritic cells, and eosinophils [21]. A study by Roediger et al. found that mast cells and ILC2s interact *in vivo* [22]. This study demonstrated that mouse dermal ILC2s migrated closely to resident mast cells and formed stable interactions between the dermal ILC2s and resident mast cells [22]. In patients with CRS, it has been shown that the percentage of ILC2s found in eosinophilic nasal polyps was significantly higher compared to the percentage of ILC2s found in non-eosinophilic nasal polyps, and that an overall positive correlation existed between the percentages of eosinophils and ILC2s in nasal polyps [23]. This was also confirmed by a recent study by Bal et al., which determined that in patients with CRS, ILC2s were present in the majority of nasal polyps with

eosinophils, however in nasal polyps with few or lacking eosinophils ILC2s were not detected [24]. Within the nasal polyps, ILC2s and eosinophils co-localized spatially such that areas with high ILC2 density also had high eosinophil density [24]. In addition, this study showed ILC2 distribution in the nasal polyp was not random but was embedded in areas of the nasal polyp with higher eosinophil density. Together these studies provide evidence of ILC2 interactions with both mast cells and eosinophils *in vivo*, which suggests crosstalk between the cell types and a mechanism by which these cells can lead to ILC2 activation potentially through lipid mediator release from mast cells and/or eosinophils.

Lipid mediators is a broader term for a class of bioactive lipids that includes eicosanoids, such as prostaglandins (PG) and leukotrienes (LT). Eicosanoids have long since been associated with Th2 inflammatory diseases and share a common origin, from arachidonic acid [25-27]. Arachidonic acid can be metabolized into downstream prostaglandins by the cyclooxygenase enzymes, COX-1 and COX-2, and to leukotrienes by the 5-lipoxygenase enzyme. Specifically, prostaglandin D_2 (PGD_2) and cysteinyl leukotrienes (CysLTs) have been shown to promote ILC2 responses [4,28], while PGI_2 and LXA_4 have been shown to dampen ILC2 responses [29,30]. This review focuses on the regulation of ILC2s by these lipid mediators.

Prostaglandin D_2 (PGD_2)

PGD_2 is strongly correlated to a variety of allergic disorders, as it is generated by eosinophils and in large quantities by IgE-activated mast cells [26]. Therefore, it is not surprising that studies have shown the PGD_2 signaling pathway plays a role in allergic rhinitis, asthma [31,32] atopic dermatitis [33,34] CRS and nasal polyposis [35-37], and aspirin exacerbated respiratory disease (AERD) [38]. PGD_2 has also been found to be a more potent bronchoconstrictor than histamine in normal and atopic individuals [39]. This long standing strong correlation between PGD_2 and allergic inflammation makes PGD_2 a potential important mediator in ILC2 activation, especially as ILC2s express CRTH2, a receptor for PGD_2.

PGD_2 binds to two receptors DP1 and CRTH2 (also known as DP2) [40]. CRTH2 is highly expressed on the surface of ILC2s and is a commonly used phenotypic ILC2 marker in humans [41]. CRTH2 is a G protein coupled receptor involved in the chemotaxis of cells toward PGD_2 [40]. PGD_2 induces the chemotaxis of human peripheral blood ILC2s from both allergic and nonallergic individuals, however allergic ILC2s showed enhanced chemotaxis compared to nonallergic [42]. In addition, the chemoattractant effect of PGD_2 was dependent on CRTH2, as incubation of human peripheral blood cells with a pharmacologic CRTH2 antagonist inhibited PGD_2-induced ILC2 chemotaxis [42]. In addition to the chemoattractant effect of PGD_2, PGD_2 has been shown to induce IL-13 secretion from human peripheral blood ILC2s [30]. Notably, PGD_2 induction of IL-13 secretion from ILC2s was significantly reduced when ILC2s were also treated with a CRTH2 receptor antagonist, however the DP1 antagonist diminished PGD_2 induced ILC2, IL-13 secretion but not enough to achieve statistical significance. In addition, the stimulation of peripheral blood ILC2s with a CRTH2 agonist, but not a DP1 agonist, significantly increased IL-13 secretion [30]. This study suggests that while PGD_2 can signal through both the DP1 and CRTH2 receptors, CRTH2 plays a larger role in PGD_2 induced IL-13 secretion from ILC2s.

ILC2s are enriched in nasal polyps of patients with eosinophilic CRS and systemic corticosteroids are associated with reduced ILC2 levels in nasal polyps [23]. Prednisone like other corticosteroids have been shown to inhibit the prostaglandin metabolic pathway. Therefore, it is possible that administration of corticosteroids could influence PGD_2-induced ILC2 responses. A recent study demonstrated that IL-33 and TSLP stimulate mast cells to produce PGD_2, and that TSLP expression in nasal polyps of AERD patients correlates with PGD_2-generating enzymes [43]. The potential of both TSLP and PGD_2 to activate ILC2s and TSLP to further induce PGD_2 generation suggests a network of signals that can occur during Th2 inflammation that results in synergistic ILC2 responses.

Similarly to human blood ILC2s, Tait Wojno et al. showed that murine ILC2s also express CRTH2 and exposure to PGD_2 causes ILC2 accumulation in the mouse lung *in vivo* [28]. Mice infected with *N. brasiliensis* had increased lung inflammation and ILC2 accumulation [28]. However when utilizing mice lacking CRTH2 or using a specific CRTH2 inhibitor, there was decreased ILC2 levels in the airways and decreased inflammation following *N. brasiliensis* infection. Therefore, *N. brasiliensis*-induced lung inflammation and airway ILC2 accumulation is CRTH2 dependent [28]. In addition, another study by Xue et al. showed that CRTH2 mediates the chemotaxis of ILC2s isolated from human skin, as well as peripheral blood, as PGD_2 induced migration of ILC2s was reduced by a CRTH2 specific inhibitor, TM30089 [3]. PGD_2 signaling through CRTH2 induces the activation of human ILC2s and the production of Th2 cytokines IL-4, IL-5, and IL-13 [3]. In addition, stimulation of ILC2s with PGD_2 in combination with IL-33 and IL-25 had increased induction of IL-4, IL-5, IL-13, as well as IL-9, when compared to IL-33 and IL-25 stimulation alone. PGD_2 also upregulates the expression of the IL-33 receptor, while it downregulates CRTH2 expression in human ILC2s [3]. Thus, PGD_2 can potentiate IL-33 and IL-25 responses and increase IL-33/IL-25 induced Th2 cytokine production [3,30]. Together these studies demonstrate the role of PGD_2 not only as a major chemoattractant for ILC2s to the site of inflammation, but also as a potent ILC2 activator to express Th2 cytokines.

Cysteinyl Leukotrienes (CysLTs)

CysLTs comprise of LTC_4, LTD_4, and LTE_4, which are generated by cell types important to allergic inflammation including eosinophils, mast cells, basophils, and macrophages [44]. LTC_4 is the parent LT that is metabolized into LTD_4 and LTE_4 [21]. The main receptors for CysLTs are $CysLT_1R$ and $CysLT_2R$. LTD_4 can bind both receptors, however it binds $CysLT_1R$ with higher affinity than $CysLT_2R$. $CysLT_2R$ binds both LTC_4 and LTD_4 with equal affinity [45]. CysLTs have a variety of proinflammatory activities which are associated with allergic inflammation during innate immune responses, such as increased eosinophil migration, and activation of mast cells, macrophages, dendritic cells, and neutrophils [46]. Due to the proinflammatory nature of CysLTs, CysLTs have been associated with several allergic diseases such as asthma, allergic rhinitis, and AERD, as well as other diseases such as COPD [45-48]. Therefore, it is possible that CysLT production activates ILC2s during allergic inflammation, as CysLTs affect a wide array of cells and are strongly correlated to allergic inflammation.

Mouse lung and bone marrow ILC2s have been shown to express $CysLT_1R$ [4]. Additionally mouse lung ILC2s produce the Th2 cytokines IL-5 and IL-13 after stimulation with LTD_4. Unlike IL-33 and IL-25, LTD_4 has been shown to also induce the secretion of

another Th2 cytokine, IL-4, from ILC2s [4]. LTD_4-induced Th2 cytokine production was dependent on the $CysLT_1R$ receptor, as pretreatment of ILC2s with montelukast, a $CysLT_1R$ antagonist, significantly reduced LTD_4-induced Th2 cytokine production. In addition, this study demonstrated that mice challenged intranasally with LTC_4, LTD_4, and LTE_4 had significantly higher levels of IL-5 producing ILC2s in the lung compared to control challenged mice. This study highlights a significant role of CysLTs in ILC2 activation and more importantly that the profile of ILC2 Th2 cytokine secretion (IL-5 and IL-13 *vs.* IL-4, IL-5, and IL-13) is dependent on the nature of the stimulus of ILC2 activation. Similarly, a recent study, by Pelly et al. also demonstrated that LTD_4 induces IL-4 secretion from mouse ILC2s [49]. Mouse ILC2s produce IL-4 in response to *H. polygyrus* infection and ILC2-derived IL-4 was required for Th2 differentiation during *H. polygyrus* infection [49]. This study demonstrates a potential role for the ILC2-IL-4 axis in Th2 differentiation and provides a previously unidentified role for ILC2s in immunity which may be regulated by leukotrienes.

Prostaglandin I_2 (PGI_2)

Similarly to other prostaglandins, PGI_2 is generated from arachidonic acid metabolism through the cyclooxygenase enzymes, however it also requires downstream conversion by PGI synthase (PGIS) [26]. PGI_2 is also known as prostacylin, and signals through the prostacylin receptor, IP. PGI_2 functions in both the innate and adaptive immune systems as mainly an immunosuppressive mediator. PGI_2-IP activation of downstream protein kinase A leads to several anti-inflammatory actions, such as reduced cell proliferation, relaxation of smooth muscle, and other cellular inhibitory mechanisms (i.e., IL-10 production) [50]. PGI_2 has a well-established correlation to allergic disorders, as several studies in mice have shown that PGI_2 administration diminishes features of allergic and asthmatic airways including airway eosinophilia, Th2 cytokine production, and AHR, while PGI_2 signaling deficiency leads to exaggerated allergic inflammation [51-54]. In addition, it has been shown that PGI_2 levels are elevated in the lungs of individuals during allergic inflammation, which demonstrates that PGI_2 is present during allergic inflammation in humans [26]. Therefore, PGI_2 is considered an important player in the regulation and dampening of Th2 inflammation.

A study by Zhou et al. investigated the role of PGI_2 in ILC2 regulation and found an inhibitory effect of PGI_2 on ILC2 function [29]. This study showed that mouse lung ILC2s express the PGI_2 receptor IP. Isolated wildtype mouse bone marrow ILC2s when treated with a PGI_2 analog, cicaprost, had significantly diminished IL-33-induced IL-13 secretion in culture. Interestingly, cicaprost also inhibited IL-33 induced ILC2 proliferation. The effect of PGI_2 was specific to the IP receptor, as bone marrow ILC2s from mice deficient in IP stimulated with IL-33 and cicaprost maintained similar levels of IL-13 secretion and proliferation to IL-33 treatment alone. Similarly to mouse ILC2s, human blood ILC2s stimulated *in vitro* with IL-2 and IL-33 had diminished IL-5 and IL-13 secretion when treated with cicaprost compared to vehicle treated. These findings were expanded to show that mice deficient in IP had increased ILC2 accumulation in the lungs in response to Alternaria extract treatment compared to wildtype mice also treated with Alternaria. In addition, IP deficient mice had increased Th2 cytokine secretion when treated with Alternaria, while the number of CD4+ cells expressing Th2 cytokines was not altered by IP deficiency. Moreover, when wildtype mice were administered cicaprost together with Alternaria, there was diminished airway inflammation and diminished ILC2 secretion of Th2 cytokines. These findings support a role for PGI_2 as a potent inhibitor of ILC2 secretion of Th2 cytokines, as well as an inhibitor of ILC2 proliferation, which suggests that PGI_2 regulates airway inflammation through inhibition of ILC2 function.

Lipoxin A_4 (LXA_4)

Lipoxins, like leukotrienes and prostaglandins, are derived from arachidonic acid, however they are a product of 5-, 12-, and 15-lipoxygenases [55]. The primary lipoxins found in mammals are LXA_4 and its isomer LXB_4. Lipoxins have a variety of pro-resolution and anti-inflammatory effects on cells. They have been shown to inhibit neutrophil and eosinophil recruitment and activation, stimulate macrophage phagocytosis of apoptotic cells, inhibit TNF secretion from T cells, as well as having effects on dendritic cells and monocytes, and on structural cells, i.e., fibroblasts and epithelial cells [56]. In addition to the active downstream effects of lipoxins, lipoxin generation is inversely related to leukotriene biosynthesis and therefore dampen leukotriene pro-inflammatory effects. Inflammatory mediators, such as IL-4, and IL-13, can enhance 15-lipoxygenase expression and subsequent lipoxin generation [56]. Due to the pro-resolution nature of lipoxins, the dysregulation of lipoxin synthesis has a role in a variety of diseases, including respiratory inflammation, renal diseases, and cancer [55]. Specifically, LXA_4 has a variety of pro-resolution actions that inhibit AHR and pulmonary inflammation, and if unregulated can lead to allergic and asthmatic symptoms [57]. Therefore it is not surprising that several studies have shown lower levels of LXA_4 correlate with the degree of airflow obstruction in asthmatics, and diminished LXA_4 levels are found in patients with asthma [58-61].

A study by Barnig et al. found that human peripheral blood ILC2s from both healthy and asthmatic individuals express the natural receptor for LXA_4, ALX/FPR2, as well as the receptor for an additional pro-resolving mediator, CMKLR1 [30]. In addition, the authors found that PGD_2 potentiates IL-2/IL-25/IL-33 induced IL-13 secretion from ILC2 which is reduced when pretreated with equimolar amounts of LXA_4. This reduction in ILC2 IL-13 production by LXA_4 was dependent on ALX/FPR2, as incubation with the receptor antagonist, WRW4, lowered LXA_4 inhibition of ILC2 secretion of IL-13. These findings are in agreement with the well-established role of lipoxins as anti-inflammatory and pro-resolution mediators.

Summary

While ILC2s were originally characterized as innate lymphoid cells that respond to epithelial-derived cytokines, IL-33, TSLP, and IL-25, an increasing amount of studies are demonstrating lipid mediators as significant regulators of ILC2 function. ILC2s are a significant source of Th2 cytokines, including IL-13, IL-5, and IL-4. In addition, PGD_2 has been shown to promote ILC2 recruitment and amplify ILC2 cytokine responses, as well as work with epithelial cell-derived cytokines to promote a more robust activation of ILC2s. Importantly, PGI_2 and LXA_4 have been shown to dampen ILC2 responses, demonstrating the role of lipid mediators as both positive and negative regulators of ILC2 function. Due to the increasing understanding of the role of ILC2 in Th2 inflammation, targeting of lipid mediators, both activating and inhibiting, provide attractive potential targets for a variety of allergic disorders.

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