

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 D₂ 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 D₂, 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 mediators prostaglandin I₂ and lipoxin A₄ 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-7R α), CD25 (IL-2R α), 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 D₂ (PGD₂) and cysteinyl leukotrienes (CysLTs) have been shown to promote ILC2 responses [4,28], while PGI₂ and LXA₄ have been shown to dampen ILC2 responses [29,30]. This review focuses on the regulation of ILC2s by these lipid mediators.

Prostaglandin D₂ (PGD₂)

PGD₂ 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 PGD₂ 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]. PGD₂ has also been found to be a more potent bronchoconstrictor than histamine in normal and atopic individuals [39]. This long standing strong correlation between PGD₂ and allergic inflammation makes PGD₂ a potential important mediator in ILC2 activation, especially as ILC2s express CRTH2, a receptor for PGD₂.

PGD₂ 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 PGD₂ [40]. PGD₂ 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 PGD₂ was dependent on CRTH2, as incubation of human peripheral blood cells with a pharmacologic CRTH2 antagonist inhibited PGD₂-induced ILC2 chemotaxis [42]. In addition to the chemoattractant effect of PGD₂, PGD₂ has been shown to induce IL-13 secretion from human peripheral blood ILC2s [30]. Notably, PGD₂ 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 PGD₂ 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 PGD₂ can signal through both the DP1 and CRTH2 receptors, CRTH2 plays a larger role in PGD₂ 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 PGD₂-induced ILC2 responses. A recent study demonstrated that IL-33 and TSLP stimulate mast cells to produce PGD₂, and that TSLP expression in nasal polyps of AERD patients correlates with PGD₂-generating enzymes [43]. The potential of both TSLP and PGD₂ to activate ILC2s and TSLP to further induce PGD₂ 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 PGD₂ 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 PGD₂ induced migration of ILC2s was reduced by a CRTH2 specific inhibitor, TM30089 [3]. PGD₂ 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 PGD₂ 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. PGD₂ also upregulates the expression of the IL-33 receptor, while it downregulates CRTH2 expression in human ILC2s [3]. Thus, PGD₂ 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 PGD₂ 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 LTC₄, LTD₄, and LTE₄, which are generated by cell types important to allergic inflammation including eosinophils, mast cells, basophils, and macrophages [44]. LTC₄ is the parent LT that is metabolized into LTD₄ and LTE₄ [21]. The main receptors for CysLTs are CysLT₁R and CysLT₂R. LTD₄ can bind both receptors, however it binds CysLT₁R with higher affinity than CysLT₂R. CysLT₂R binds both LTC₄ and LTD₄ 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 CysLT₁R [4]. Additionally mouse lung ILC2s produce the Th2 cytokines IL-5 and IL-13 after stimulation with LTD₄. Unlike IL-33 and IL-25, LTD₄ has been shown to also induce the secretion of

another Th2 cytokine, IL-4, from ILC2s [4]. LTD₄-induced Th2 cytokine production was dependent on the CysLT₁R receptor, as pretreatment of ILC2s with montelukast, a CysLT₁R antagonist, significantly reduced LTD₄-induced Th2 cytokine production. In addition, this study demonstrated that mice challenged intranasally with LTC₄, LTD₄, and LTE₄ 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 LTD₄ 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 I₂ (PGI₂)

Similarly to other prostaglandins, PGI₂ is generated from arachidonic acid metabolism through the cyclooxygenase enzymes, however it also requires downstream conversion by PGI synthase (PGIS) [26]. PGI₂ is also known as prostacyclin, and signals through the prostacyclin receptor, IP. PGI₂ functions in both the innate and adaptive immune systems as mainly an immunosuppressive mediator. PGI₂-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]. PGI₂ has a well-established correlation to allergic disorders, as several studies in mice have shown that PGI₂ administration diminishes features of allergic and asthmatic airways including airway eosinophilia, Th2 cytokine production, and AHR, while PGI₂ signaling deficiency leads to exaggerated allergic inflammation [51-54]. In addition, it has been shown that PGI₂ levels are elevated in the lungs of individuals during allergic inflammation, which demonstrates that PGI₂ is present during allergic inflammation in humans [26]. Therefore, PGI₂ is considered an important player in the regulation and dampening of Th2 inflammation.

A study by Zhou et al. investigated the role of PGI₂ in ILC2 regulation and found an inhibitory effect of PGI₂ on ILC2 function [29]. This study showed that mouse lung ILC2s express the PGI₂ receptor IP. Isolated wildtype mouse bone marrow ILC2s when treated with a PGI₂ 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 PGI₂ 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 PGI₂ as a potent inhibitor of ILC2 secretion of Th2 cytokines, as well as an inhibitor of ILC2 proliferation, which suggests that PGI₂ regulates airway inflammation through inhibition of ILC2 function.

Lipoxin A₄ (LXA₄)

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 LXA₄ and its isomer LXB₄. 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, LXA₄ 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 LXA₄ correlate with the degree of airflow obstruction in asthmatics, and diminished LXA₄ 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 LXA₄, ALX/FPR2, as well as the receptor for an additional pro-resolving mediator, CMKLR1 [30]. In addition, the authors found that PGD₂ potentiates IL-2/IL-25/IL-33 induced IL-13 secretion from ILC2 which is reduced when pretreated with equimolar amounts of LXA₄. This reduction in ILC2 IL-13 production by LXA₄ was dependent on ALX/FPR2, as incubation with the receptor antagonist, WRW4, lowered LXA₄ 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, PGD₂ 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, PGI₂ and LXA₄ 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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References

- Walker JA, McKenzie AN (2013) Development and function of group 2 innate lymphoid cells. *Curr Opin Immunol* 25: 148-155.
- Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eislely CJ, et al. (2010) Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci USA* 107: 11489-11494.
- Xue L, Salimi M, Panse I, Mjosberg JM, McKenzie AN, et al. (2014) Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy Clin Immunol* 133: 1184-1194.
- Doherty TA, Khorram N, Lund S, Mehta AK, Croft M, et al. (2013) Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. *J Allergy Clin Immunol* 132: 205-213.
- Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, et al. (2010) Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature* 463: 540-544.
- Wilhelm C, Hirota K, Stieglitz B, Van Snick J, Tolaini M, et al. (2011) An IL-9 fate reporter demonstrates the induction of an innate IL-9 response in lung inflammation. *Nat Immunol* 12: 1071-1077.
- Turner JE, Morrison PJ, Wilhelm C, Wilson M, Ahlfors H, et al. (2013) IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med* 210: 2951-2965.
- Wilhelm C, Turner JE, Van Snick J, Stockinger B (2012) The many lives of IL-9: a question of survival? *Nat Immunol* 13: 637-641.
- Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, et al. (2013) A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 210: 2939-2950.
- Zaiss DM, Gause WC, Osborne LC, Artis D (2015) Emerging functions of amphiregulin in orchestrating immunity, inflammation, and tissue repair. *Immunity* 42: 216-226.
- Ho J, Bailey M, Zaunders J, Mrad N, Sacks R, et al. (2015) Group 2 innate lymphoid cells (ILC2s) are increased in chronic rhinosinusitis with nasal polyps or eosinophilia. *Clin Exp Allergy* 45: 394-403.
- Miljkovic D, Bassiouni A, Cooksley C, Ou J, Hauben E, et al. (2014) Association between group 2 innate lymphoid cells enrichment, nasal polyps and allergy in chronic rhinosinusitis. *Allergy* 69: 1154-1161.
- Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, et al. (2013) TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci Transl Med* 5: 170ra16.
- Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, et al. (2016) Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. *J Allergy Clin Immunol* 137: 75-86.
- Nagakumar P, Denney L, Fleming L, Bush A, Lloyd CM, et al. (2016) Type 2 innate lymphoid cells in induced sputum from children with severe asthma. *J Allergy Clin Immunol* 137: 624-626.
- Barlow JL, Bellosi A, Hardman CS, Drynan LF, Wong SH, et al. (2012) Innate IL-13-producing nuocytes arise during allergic lung inflammation and contribute to airways hyperreactivity. *J Allergy Clin Immunol* 129: 191-198.
- Kim HY, Chang YJ, Subramanian S, Lee HH, Albacker LA, et al. (2012) Innate lymphoid cells responding to IL-33 mediate airway hyperreactivity independently of adaptive immunity. *J Allergy Clin Immunol* 129: 216-227.
- Chang YJ, Kim HY, Albacker LA, Baumgarth N, McKenzie AN, et al. (2011) Innate lymphoid cells mediate influenza-induced airway hyperreactivity independently of adaptive immunity. *Nat Immunol* 12: 631-638.
- Islam SA, Luster AD (2012) T cell homing to epithelial barriers in allergic disease. *Nat Med* 18: 705-715.
- Yu X, Pappu R, Ramirez-Carrozzi V, Ota N, Caplazi P, et al. (2014) TNF superfamily member TL1A elicits type 2 innate lymphoid cells at mucosal barriers. *Mucosal Immunol* 7: 730-740.
- Boyce JA (2007) Mast cells and eicosanoid mediators: a system of reciprocal paracrine and autocrine regulation. *Immunol Rev* 217: 168-185.
- Roediger B, Kyle R, Yip KH, Sumaria N, Guy TV, et al. (2013) Cutaneous immunosurveillance and regulation of inflammation by group 2 innate lymphoid cells. *Nat Immunol* 14: 564-573.
- Walford HH, Lund SJ, Baum RE, White AA, Bergeron CM, et al. (2014) Increased ILC2s in the eosinophilic nasal polyp endotype are associated with corticosteroid responsiveness. *Clin Immunol* 155: 126-135.
- Bal SM, Bernink JH, Nagasawa M, Groot J, Shikhagaie MM, et al. (2016) IL-1 β , IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs. *Nat Immunol* 17: 636-645.
- Wenzel SE (1997) Arachidonic acid metabolites: mediators of inflammation in asthma. *Pharmacotherapy* 17: 3S-12S.
- Claar D, Hartert TV, Peebles RS (2015) The role of prostaglandins in allergic lung inflammation and asthma. *Expert Rev Respir Med* 9: 55-72.
- Peters-Golden M (2008) Expanding roles for leukotrienes in airway inflammation. *Curr Allergy Asthma Rep* 8: 367-373.
- Wojno ED, Monticelli LA, Tran SV, Alenghat T, Osborne LC, et al. (2015) The prostaglandin D $_2$ receptor CRTH2 regulates accumulation of group 2 innate lymphoid cells in the inflamed lung. *Mucosal Immunol* 8: 1313-1323.
- Zhou W, Toki S, Zhang J, Goleniewska K, Newcomb DC, et al. (2016) Prostaglandin I2 Signaling and Inhibition of Group 2 Innate Lymphoid Cell Responses. *Am J Respir Crit Care Med* 193: 31-42.
- Barnig C, Cernadas M, Dutile S, Liu X, Perrella MA, et al. (2013) Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. *Sci Transl Med* 5: 174ra26.
- Fajt ML, Gelhaus SL, Freeman B, Uvalle CE, Trudeau JB, et al. (2013) Prostaglandin D $_2$ pathway upregulation: relation to asthma severity, control, and TH2 inflammation. *J Allergy Clin Immunol* 131: 1504-1512.
- Murray JJ, Tonnel AB, Brash AR, Roberts LJ, Gosset P, et al. (1986) Release of prostaglandin D2 into human airways during acute antigen challenge. *N Engl J Med* 315: 800-804.
- He R, Oyoshi MK, Wang JY, Hodge MR, Jin H, et al. (2010) The prostaglandin D(2) receptor CRTH2 is important for allergic skin inflammation after epicutaneous antigen challenge. *J Allergy Clin Immunol* 126: 784-790.
- Satoh T, Moroi R, Aritake K, Urade Y, Kanai Y, et al. (2006) Prostaglandin D2 plays an essential role in chronic allergic inflammation of the skin via CRTH2 receptor. *J Immunol* 177: 2621-2629.
- Okano M, Fujiwara T, Yamamoto M, Sugata Y, Matsumoto R, et al. (2006) Role of prostaglandin D2 and E2 terminal synthases in chronic rhinosinusitis. *Clin Exp Allergy* 36: 1028-1038.
- Yamamoto M, Okano M, Fujiwara T, Kariya S, Higaki T, et al. (2009) Expression and characterization of PGD2 receptors in chronic rhinosinusitis: modulation of DP and CRTH2 by PGD2. *Int Arch Allergy Immunol* 148: 127-136.
- Perez-Novo CA, Holtappels G, Vinnall SL, Xue L, Zhang N, et al. (2010) CRTH2 mediates the activation of human Th2 cells in response to PGD(2) released from IgE/anti-IgE treated nasal polyp tissue. *Allergy* 65: 304-310.
- Cahill KN, Bensek JC, Boyce JA, Laidlaw TM (2015) Prostaglandin D(2): a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 135: 245-252.
- Sampson SE, Sampson AP, Costello JF (1997) Effect of inhaled prostaglandin D2 in normal and atopic subjects, and of pretreatment with leukotriene D4. *Thorax* 52: 513-518.

40. Smith WL, Urade Y, Jakobsson PJ (2011) Enzymes of the cyclooxygenase pathways of prostanoid biosynthesis. *Chem Rev* 111: 5821-5865.
41. Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, et al. (2011) Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CCR4 and CD161. *Nat Immunol* 12: 1055-1062.
42. Chang JE, Doherty TA, Baum R, Broide D (2014) Prostaglandin D2 regulates human type 2 innate lymphoid cell chemotaxis. *J Allergy Clin Immunol* 133: 899-901.
43. Buchheit KM, Cahill KN, Katz HR, Murphy KC, Feng C, et al. (2016) Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 137: 1566-1576.
44. Peters-Golden M, Henderson WR (2007) Leukotrienes. *N Engl J Med* 357: 1841-1854.
45. Kanaoka Y, Boyce JA (2014) Cysteinyl leukotrienes and their receptors; emerging concepts. *Allergy Asthma Immunol Res* 6: 288-295.
46. Theron AJ, Steel HC, Tintinger GR, Gravett CM, Anderson R, et al. (2014) Cysteinyl leukotriene receptor-1 antagonists as modulators of innate immune cell function. *J Immunol Res* 2014: 608930.
47. Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, et al. (2003) Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin Exp Allergy* 33: 1380-1388.
48. Laidlaw TM, Boyce JA (2012) Cysteinyl leukotriene receptors, old and new; implications for asthma. *Clin Exp Allergy* 42: 1313-1320.
49. Pelly VS, Kannan Y, Coomes SM, Entwistle LJ, Ruckerl D, et al. (2016) IL-4-producing ILC2s are required for the differentiation of T2 cells following *Heligmosomoides polygyrus* infection. *Mucosal Immunol*.
50. Dorris SL, Peebles RS (2012) PGI2 as a regulator of inflammatory diseases. *Mediators Inflamm* 2012: 926968.
51. Idzko M, Hammad H, van Nimwegen M, Kool M, Vos N, et al. (2007) Inhaled iloprost suppresses the cardinal features of asthma via inhibition of airway dendritic cell function. *J Clin Invest* 117: 464-472.
52. Jaffar Z, Ferrini ME, Buford MC, Fitzgerald GA, Roberts K (2007) Prostaglandin I2-IP signaling blocks allergic pulmonary inflammation by preventing recruitment of CD4+ Th2 cells into the airways in a mouse model of asthma. *J Immunol* 179: 6193-6203.
53. Takahashi Y, Tokuoka S, Masuda T, Hirano Y, Nagao M, et al. (2002) Augmentation of allergic inflammation in prostanoid IP receptor deficient mice. *Br J Pharmacol* 137: 315-322.
54. Nagao K, Tanaka H, Komai M, Masuda T, Narumiya S, et al. (2003) Role of prostaglandin I2 in airway remodeling induced by repeated allergen challenge in mice. *Am J Respir Cell Mol Biol* 29: 314-320.
55. Chandrasekharan JA, Sharma-Walia N (2015) Lipoxins: nature's way to resolve inflammation. *J Inflamm Res* 8: 181-192.
56. Maderna P, Godson C (2009) Lipoxins: revolutionary road. *Br J Pharmacol* 158: 947-959.
57. Barnig C, Levy BD (2015) Innate immunity is a key factor for the resolution of inflammation in asthma. *Eur Respir Rev* 24: 141-153.
58. Levy BD, Bonnans C, Silverman ES, Palmer LJ, Marigowda G, et al. (2005) Diminished lipoxin biosynthesis in severe asthma. *Am J Respir Crit Care Med* 172: 824-830.
59. Planagumà A, Kazani S, Marigowda G, Haworth O, Mariani TJ, et al. (2008) Airway lipoxin A4 generation and lipoxin A4 receptor expression are decreased in severe asthma. *Am J Respir Crit Care Med* 178: 574-582.
60. Kazani S, Planaguma A, Ono E, Bonini M, Zahid M, et al. (2013) Exhaled breath condensate eicosanoid levels associate with asthma and its severity. *J Allergy Clin Immunol* 132: 547-553.
61. Eke Gungor H, Tahan F, Gokahmetoglu S, Saraymen B (2014) Decreased levels of lipoxin A4 and annexin A1 in wheezy infants. *Int Arch Allergy Immunol* 163: 193-197.