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HIGHLIGHTS

Clinical

REVIEW

Prostaglandin regulation of type 2 inflammation: From basic biology to therapeutic interventions

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Type 2 immunity is critical for the protective and repair responses that mediate resistance to parasitic helminth infection. This immune response also drives aberrant inflammation during atopic diseases. Prostaglandins are a class of critical lipid mediators that are released during type 2 inflammation and are integral in controlling the initiation, activation, maintenance, effector functions, and resolution of Type 2 inflammation. In this review, we explore the roles of the different prostaglandin family members and the receptors they bind to during allergen- and helminth-induced Type 2 inflammation and the mechanism through which prostaglandins promote or suppress Type 2 inflammation. Furthermore, we discuss the potential role of prostaglandins produced by helminth parasites in the regulation of host–pathogen interactions, and how prostaglandins may regulate the inverse relationship between helminth infection and allergy. Finally, we discuss opportunities to capitalize on our understanding of prostaglandin pathways to develop new therapeutic options for humans experiencing Type 2 inflammatory disorders that have a significant prostaglandin-driven component including allergic rhinitis and asthma.

Keywords: Host-pathogen interactions · Prostaglandins · Therapies · Type 2 inflammation

Introduction

Type 2 immunity is important in the generation of protective immune responses that drive worm clearance during helminth parasite infection as well as for the repair and regenerative process that occurs following infection [1,2]. On the other hand, unnecessary Type 2 immune activation in response to innocuous environmental antigens, such as pollen, food antigens, hair, and animal danders, causes chronic allergic inflammation and tissue damage during allergic diseases such as asthma and atopic dermatitis [2]. Fibrotic Type 2 responses also occur during chronic helminth infection, leading to pathology and loss of tissue function, as seen in chronic infection by Schistosoma species [3]. Furthermore, the antagonistic effect of Type 2 immunity on Type 1 immune activation can decrease the efficacy of protective immune responses against bacterial and protozoan pathogens [4,5] and tumors [2]. More recently, Type 2 immunity has been shown to be important in tissue homeostasis, with key Type 2 immune cells central to barrier maintenance, thermoregulation, tissue adiposity, and metabolism [6–11]. Thus, the Type 2 immune response is integral in steady-state physiology and protection against parasitic worm infection, while aberrant Type 2 responses lead to allergic disease, tissue fibrosis, and increased susceptibility to pathogen exposure and tumor growth. As such, studies that increase our understanding of the factors that regulate Type 2 immune responses have major translational potential.

The Type 2 immune response involves different phases, starting with the sensing of the stimuli and initiation of the immune response via the release of a diverse array of biochemical factors and danger signals [10,12]. These events set the stage for activation and recruitment of cardinal Type 2-associated immune cells and production of Type 2 cytokines and growth factors. This response culminates in the emergence of altered tissue physiology and host–effector responses such as the characteristic "weep and sweep response" [1,2]. Finally, a resolution phase develops that limits the activation of inflammatory cells and helps to promote tissue repair [2]. Lipid mediators such as prostaglandins

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have important functions during the different phases of Type 2 inflammation—initiation, activation and recruitment of cells, the effector phase, and the resolution phase of the response. These factors are enriched in inflamed tissues and are thought to tightly regulate local events that dictate the outcomes of inflammation [13]. While a large body of literature focuses on how cytokines guide Type 2 inflammatory activities [1], in this review, we will turn a spotlight on recent literature that illustrates the critical roles that prostaglandins play in the regulation of Type 2 immune responses.

Basic prostaglandin biology and metabolism

Bioactive lipid mediators include the eicosanoid leukotrienes, lipoxins, and prostaglandins that are released under Type 2 and other inflammatory conditions [14–18]. Studies in both mice and humans have shown that these lipids play a crucial role in all aspects of Type 2 immunity including in the promotion and regulation of Type 2 inflammation [14–19] and associated tissue repair [20,21]. Key among these bioactive lipid mediators are prostanoids, which include prostaglandin (PG)D_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TXA_2). These factors bind to various G-coupled protein receptors to induce a suite of pleiotropic functions that are dictated by the type of inflammation, the timing, the specific receptor engaged, and the disease context [14,22–29].

Production of most eicosanoids starts with cyclic oxidation of polyunsaturated fatty acids such as arachidonic acids (AAs) and linoleic acids, released from membrane phospholipids [14–16,30,31]. Eicosanoid production occurs in response to epithelial cell-derived cytokines, tissue damage, exposure to antigens and crosslinking of Fc receptors in various immune cells including mast cells, macrophages, and Th2 lymphocytes [31–37]. In addition, other cell types, including parenchymal and epithelial cells, such as tuft cells, have also been shown to have enzymes important for the synthesis of PGD_2 [38–44], and a wide array of cell types have been described to produce PGE_2 and other prostanoids [45–48]. Activation of phospholipase (PLA) enzymes (mostly PLA2) is important in the release of free fatty acids including AAs from the membrane phospholipid stores into the cytosol for metabolism [22]. For prostanoid production (prostaglandins and thromboxane), AAs are metabolized through the cyclooxygenase (COX) pathway by COX enzymes, which are bifunctional and act in a successive manner to catalyze the bisoxygenation and cyclization of released AA to form PGG_2 as well as the peroxidation of PGG_2 to PGH_2 [13,26]. There are two main isoforms of COX enzymes, COX-1 and COX-2. COX-1 is constitutively expressed with a housekeeping homeostatic role, and COX-2, the inducible COX, is important in activating processes during inflammation [49]. Formation of active prostanoids then occurs through conversion of PGH_2 by various synthases, such as prostaglandin D synthase (PGDS), prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS), prostaglandin I2 synthase (PGIS), and thromboxane A synthase (TXAS), that synthesize PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (also known as prostacyclin), and TXA_2, respectively [47,50–55] (Fig. 1).

During Type 2 inflammation at mucosal surfaces, the full scope of the roles that individual prostaglandins play is not currently well defined. Indeed, some studies have shown contrasting results when studying the significance of different prostaglandins and their receptors, in some cases dependent upon tissue site and disease state [22,56]. Some studies have utilized manipulation of the COX pathway upstream of the prostanoid synthesis pathways to extrapolate conclusions related to the effects of individual prostanoids, in some cases generating results that are difficult to interpret [57–62]. Therefore, a better understanding of the role of the individual prostaglandins still needs to be developed. To do so, chemical or genetic manipulation of the individual prostaglandin pathways and their associated receptors must be employed. To this end, we focus on and explore the different roles of the individual prostanoid family members during Type 2 inflammation.

Prostaglandin D_2

PGD_2 is one of the products of the prostaglandin synthesis pathway, synthesized as a result of the conversion of the direct precursor PGH_2 to PGD_2 by PGDS. PGD_2 is produced in immune cells, with mast cells proposed as one major source of this eicosanoid [31,63,64]. Other immune cells, like Th2 cells, basophils, macrophages and ILC2s, can also produce PGD_2 [32,37,65–67]. In addition, nonimmune cells, like tuft cells [41–44,68–70], mesenchymal cells [71], and stromal cells [72], are potential sources of PGD_2. PGD_2 binds to the G-protein coupled receptors DP1 and chemoattractant-receptor homologous molecule expressed on Th2 cells (CRTH2, also known as DP2). DP1 was the first receptor identified for PGD_2 and is expressed by vascular smooth muscle, platelets, eosinophils, and DCs [73–75]. DP1 engagement has well-characterized effects in mediating vasodilation, inhibiting platelet aggregation, and modulating production of cytokines in DCs [73]. CRTH2 is expressed preferentially by Th2 lymphocytes, eosinophils, ILC2s, basophils, and small intestinal epithelial cells and binds to PGD_2 and some downstream derivatives[70,76–78] (Table 1).

Studies in both humans and mice have shown that PGD_2 is found in most tissues in the steady state and is involved in regulation of homeostatic functions in the body. These include regulation of sleep pattern, body temperature, hormone release, and modulation of odor and pain responses, among others [124]. However, this eicosanoid also plays an important role in the regulation of immune responses during Type 2 inflammation. For example, most studies have generally shown an increase in PGD_2 levels in various Type 2 inflammatory contexts [70,125–128], although there are few studies, such as during helminth infection of mice with *Brugia malayi* in the lungs, in which PGD_2 levels can also be decreased during Type 2 inflammation [129]. Additionally, one key study has compared the relative production of PGD_2 and other prostanoids in murine models of allergic disease versus helminth infection [67]. Henkel et al. showed that more PGD_2

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Table 1. Prostanoid sources, receptors, and functions in Type 2 inflammation

Lipid	Cellular source	Receptor	Cells expressing the receptor	Effector function
PGD_2	Mast cells [31,63,64] Th2 cells [32] Basophils [65] ILC2s [66] Tuft cells [41–44,68,69] Macrophages [67] Stromal cells [72] Mesenchymal cells [71]	CRTH2 [73]	Eosinophils [76, 77, 79] Basophils [76,77,80] ILC2s [78,81] Th2 helper cells [76,77] Bronchial epithelial cells [82,83]	Chemotaxis [73, 76, 77, 79] Degranulation [80] Type 2 cytokine production [76,77,81] Epithelial cell migration, differentiation and epithelial cell integrity [82,83]
		DP1 [73]	Eosinophils [74] Basophils [80] Platelets [73] Nervous System [84]	Lipid droplet biogenesis [74] Inhibits migration and degranulation [80] Platelet aggregation [85,86] Cognitive function, [84] sensory nerve activation [87]
PGE_2	Endothelial cells, monocytes, macrophages, osteoblasts, and fibroblasts [14] DCs [88,89]	EP1, EP2, EP3 and EP4 [90–94]	Eosinophils [95,96] T lymphocytes [88] Keratinocytes [97,98] Airway epithelial cells [99,100] ILC2s [92,101] Mast cells [102,103] DCs [89,104]	Abrogation of eosinophil migration and accumulation and release of ROS [37,95,96] Suppression of differentiation of Th2 cells [88] Suppression of chemokine production [98] Suppression of release of chemokines [99] and mucin production [100] Decreased ILC2 proliferation and Type 2 cytokine production [92,101] Inhibits degranulation [102,103] Induces priming of Th2 cells [89] Suppression of DC proinflammatory effects [104]
PGI_2	Fibroblasts, follicular DCs, endothelial cells, smooth muscle cells and thymic nurse cells [105]	IP [105]	Th2 cells [106,107] T regulatory cells [107] Platelets [108] Neuronal cells [108] Endothelial cells [108] DCs [109,110] ILC2s [111] Eosinophils [112]	Suppression via IL-10 production [106] Suppresses Type 2 cytokine production, [113–115] Inhibits CD4 T cell proliferation [113] Influences recruitment of Th2 cells [107] Induces T regulatory cell differentiation [116] Antithrombotic role [117] Involved in nociceptive response [117] Regulate vascular permeability/vasodilation [108,117] Induction of production of IL-10 [116,118] Regulation of chemokine production [109] Regulation of migration [109,110] Regulates release of inflammatory mediators [110] Inhibits ILC2 proliferation [111] Inhibits ILC2 Type 2 cytokine production [111] Inhibits recruitment and migration [112,119]
Thromboxane	Activated platelets [120] DCs [121] Macrophages [122]	TP [121] (mice) TPα, $TP\beta^{(26)}$(human)	Platelets [26] T lymphocytes [121]	Prothrombosis [26,120,123] Proinflammatory role [121]

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), dendritic cells (DCs), prostaglandin E_2 receptor (EP), group 2 innate lymphoid cells (ILC2s), PGI_2 receptor (IP), Th2 (T helper type 2), thromboxane receptor (TP).

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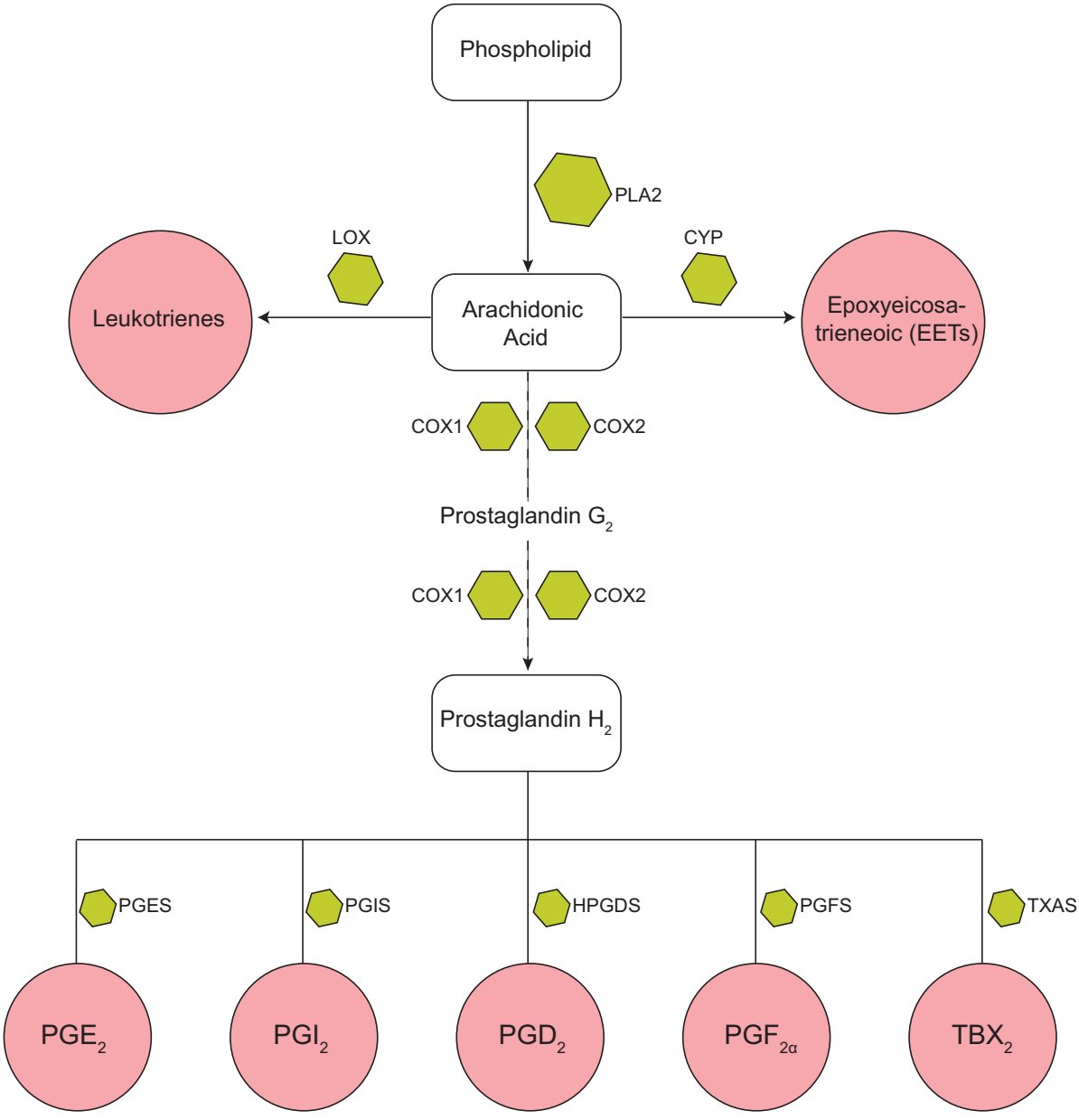

Figure 1. Figure 1. Prostaglandin synthesis cascade. Phospholipase A2 (PLA2) releases free fatty acids, including arachidonic acid (AA), from membrane phospholipid stores. From AA, lipoxygenase enzymes synthesize leukotrienes and cytochrome P450 epoxygenases (CYP) synthesize epoxyeicosatrienoic acids. For prostanoid production, AA is metabolized through the cyclooxygenase (COX) pathway by COX1 and COX2, which catalyze the bisoxygenation and cyclization of released AA to form PGG_2 as well as the peroxidation of PGG_2 to PGH_2. PGH_2 is then converted by prostaglandin D synthase (PGDS), prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS), prostaglandin I_2 synthase (PGIS) and thromboxane A synthase (TXAS) to synthesize PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TXA_2), respectively.

and other prostanoids were released in the acute phase of *Nippostrongylus brasiliensis*-induced Type 2 inflammation than during chronic house dust mite (HDM) exposure in the lungs in mice [67]. Increased PGD_2 production in helminth infection compared to allergic inflammation was attributed to context-specific lung macrophage reprogramming, though the time point in the inflammatory arc that was assessed in these two models [67] and the potential for helminths to be endogenous sources of PGD_2 and other prostanoids [130] may also have contributed.

The increase in PGD_2 levels during Type 2 inflammation has largely been associated with proinflammatory roles for this pathway via effects on immune cells that express CRTH2 [17,78,131,132] (Fig. 2). PGD_2 binds to CRTH2 on eosinophils, ILC2s, basophils, and Th2 cells to induce cellular migration and cytokine production [77,80, 78, 81,131,133]. We have the most understanding about the effects of PGD_2 and CRTH2 on murine and human cells in vitro and in vivo in mouse models of helminth- and allergen-elicited lung inflammation and in

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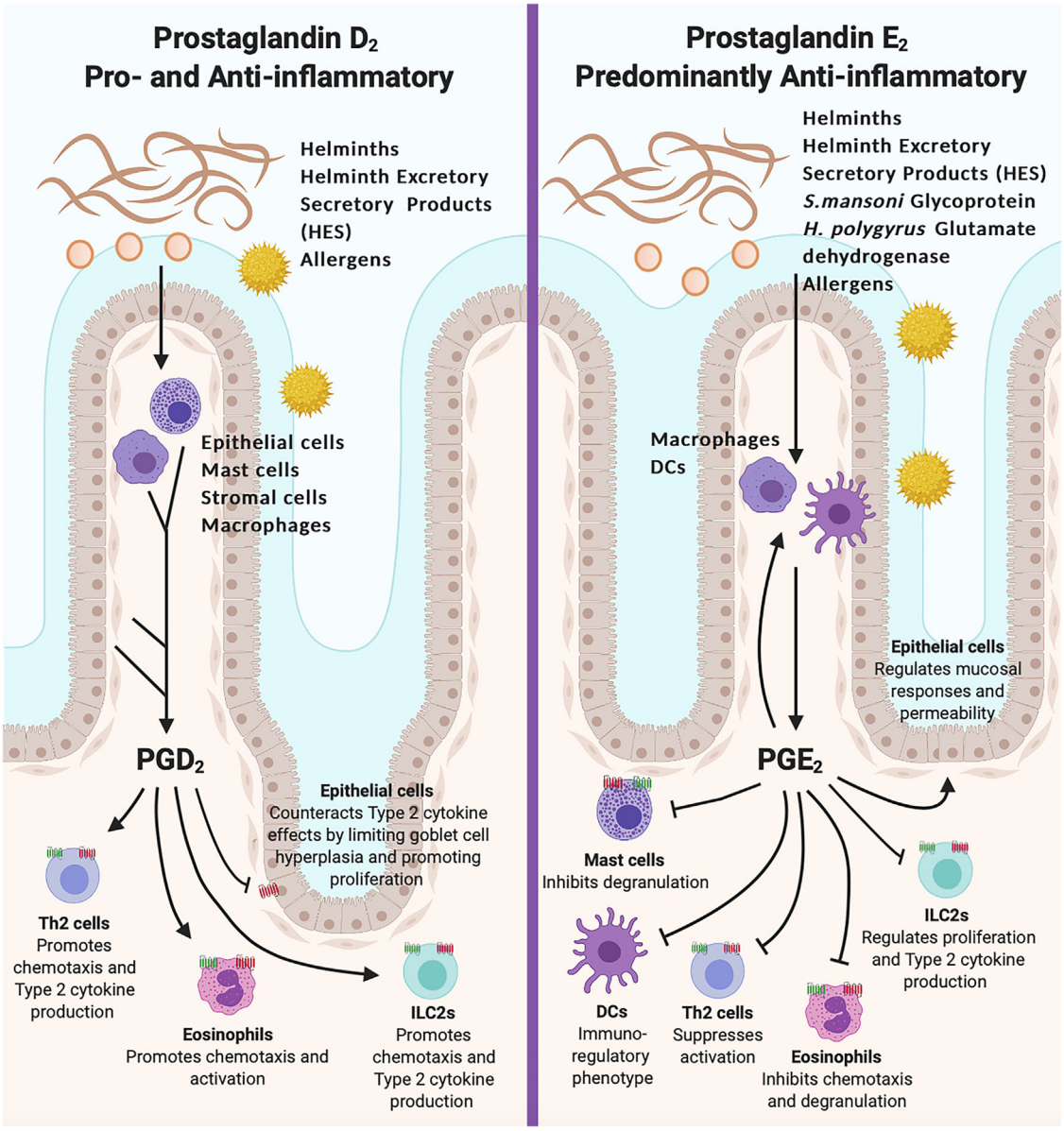

Figure 2. Role of PGD_2 and PGE_2 in regulating Type 2 inflammation at an epithelial barrier. Schematic diagram depicting the role of PGD_2 (pleiotropic) and PGE_2 (mostly anti-inflammatory) at an example epithelial barrier, the small intestine. PGD_2 acts through its receptor CRTH2 on ILC2s, basophils, eosinophils, and Th2 lymphocytes to induce cytokine production and migration of immune cells during helminth- and allergen-induced Type 2 inflammation. It also acts on CRTH2-expressing intestinal epithelial cells to counteract the Type 2 inflammatory program. PGE_2 acts through its receptors EP2 and EP4 on eosinophils, mast cells, Th2 cells, ILC2s, epithelial cells, and DCs. PGE_2 can inhibit eosinophil chemotaxis and degranulation and mast cell degranulation, regulate T-cell activation, regulate ILC2 proliferation and chemotaxis, and induce an immunoregulatory phenotype in DCs. Some studies have also shown the PGE_2 acts on macrophages and DCs and to support the ability of these cells to prime Th2 cells, and thus, the effects of PGE_2 on Th2 responses can be direct or indirect and are context-dependent. PGE_2 can also increase epithelial permeability and secretory function.

allergic lung inflammation in humans. In the lungs, the PGD_2-CRTH2 pathway promotes Type 2 cytokine production and tissue migration or accumulation of ILC2s, during allergic inflammation and in response to helminth migration through the lung tissue in murine models [17,78,131]. Some data in murine models of inflammation show that this pathway might have similar proinflammatory roles in other tissue sites like the skin, for example, during allergic skin inflammation [134,135] and in the gut during intestinal inflammation [136], with clear evidence that PGD_2 production and CRTH2 expression in humans are found in other tissue sites [137,138]. However, recent findings from our group demonstrate that PGD_2 and CRTH2 can also have a suppressive effect during helminth infection, acting on small intestinal epithelial cells to oppose effects of Type 2 cytokines on the epithelium like goblet cell hyperplasia and decreased cell proliferation [70]. Despite this recent finding, there is still a need for further studies

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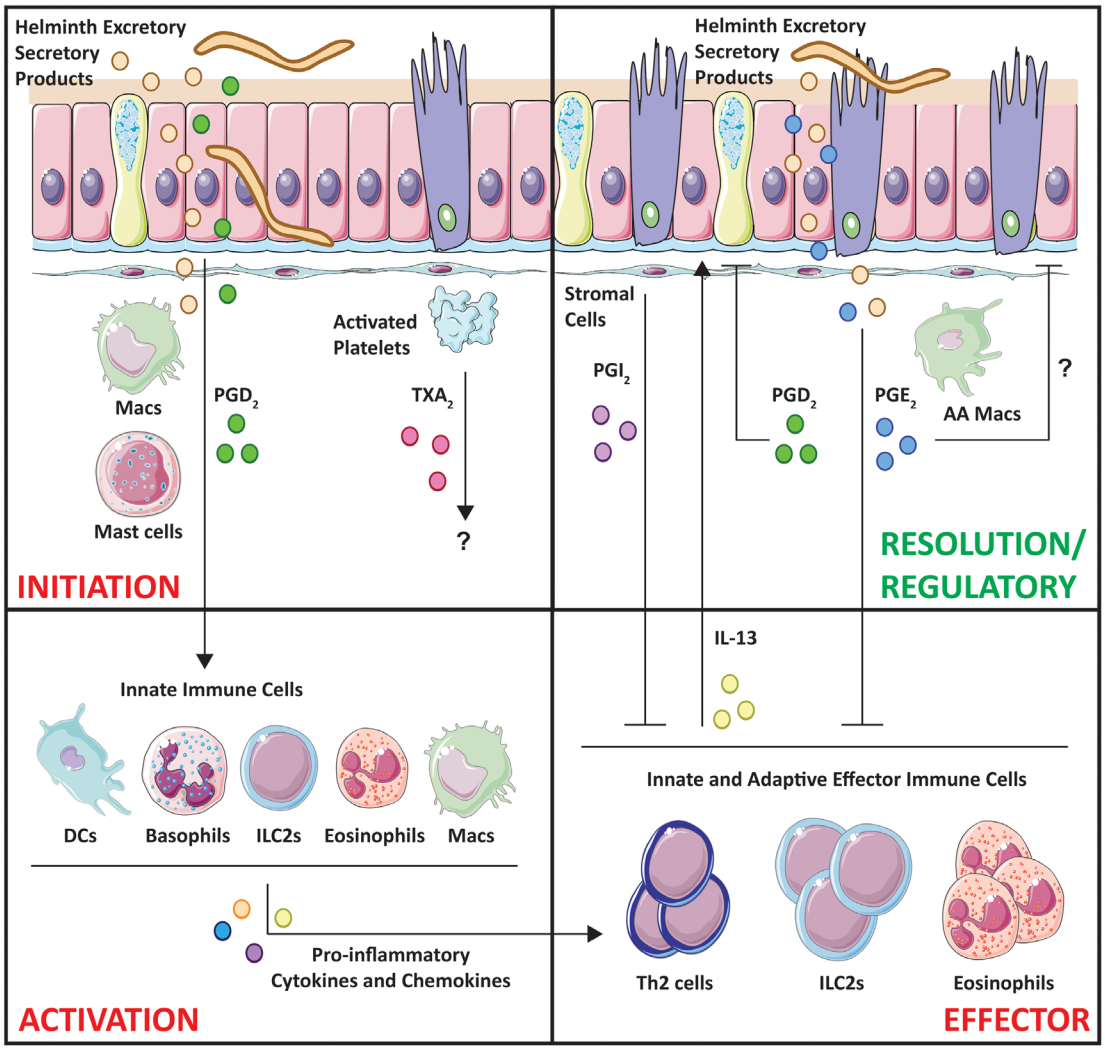

Figure 3. Prostaglandins are involved in different phases of inflammation during helminth infection. Schematic diagram showing the role different prostaglandins play during (A) initiation, (B) activation, (C) effector, and (D) regulatory phases of inflammation. Parasitic helminths and their associated excretory/secretory factors elicit the production of proinflammatory prostanoids like PGD_2 from macrophages (Macs), mast cells, epithelial cells, and other cell types and TXA_2 from activated platelets. The effects of TXA_2 are currently unclear. PGD_2 may also be synthesized by parasites. PGD_2 produced by the host and the parasite is critical during the initiation phase of the inflammatory process (A), activating key innate immune cell types that then release proinflammatory cytokines, chemokines, and in some cases more proinflammatory prostanoids (B). These mediators recruit and activate effector immune cells and promote the production and release of Type 2 cytokines, including IL-13 that acts on the epithelium to promote inflammatory changes (C). Bioactive mediators such as PGE_2 and PGI_2 are immunoregulatory and can restrain or resolve the Type 2 response, though PGE_2 may act on DCs to support their ability to prime Th2 cells (not depicted). Regulatory prostanoids are released in response to helminths and their products, and helminths have been shown to synthesize and release PGE_2. Stromal cell-derived PGI_2 dampens Th2 and ILC2 activation. PGE_2 derived from alternatively activated macrophages (AA Macs) and possibly parasites also restrain Th2, ILC2, and eosinophil responses and may also act on epithelial cells to promote wound healing. PGD_2 can also play a regulatory role depending on the context, acting on small intestine epithelial cells to negatively regulate the epithelial response to helminth infection (D). Figure was made from the Servier Medical Art's image collection and licensed under a Creative Common Attribution 3.0 Unported License.

to fully unravel the roles of PGD_2 and CRTH2 in shaping inflammation in various tissues and the factors that dictate whether this pathway is pro- or anti-inflammatory. In addition, how PGD_2 binding to its other receptor, DP1, which is expressed by a wide array of cell types across tissues [73], affects Type 2 inflammation requires more investigation. Thus, much remains unknown regarding how PGD_2 regulates the initiation and effector phases of Type 2 inflammation, particularly during helminth infection (Fig. 3).

Prostaglandin E_2

PGE_2 is another product of the prostaglandin synthesis pathway, synthesized by the conversion of the direct precursor PGH_2 to PGE_2 by PGES. PGE_2 is produced by various cell types including but not limited to endothelial cells, monocytes/macrophages, osteoblasts, and fibroblasts [14]. This lipid mediator exerts its function by binding to the PGE_2 receptors EP1, EP2, EP3, or EP4, which are expressed by a wide variety of cell types. The role

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of PGE_2 in various contexts, such as during autoimmunity, cancer, and chronic inflammation, has been well documented, with PGE_2 playing both pro- and/or anti-inflammatory roles depending on receptor usage, disease context, and timing of inflammation [56,90–94] (Table 1).

During Type 2 inflammation, the most well-documented role for PGE_2 is anti-inflammatory [92,98,99] (Fig. 2). The study of various models of Type 2 inflammation either in the skin [98,139] or in the lungs [37,99,101,140–145] has demonstrated this effect. For example, Zhou et al. showed that PGE_2 suppressed lung pathology in an IL-33-elicited allergic inflammation model in mice, via binding to the receptor EP4 to induce its response, as EP4-deficient mice displayed exacerbated inflammation in the Alternaria-induced asthma model. EP engagement suppressed expression of the IL-33 receptor, ST2, as well as *Gata3* transcription, both important factors for ILC2 activation and Type 2 inflammatory responses [101]. A suppressive role for PGE_2 was previously reported in an ovalbumin-elicited model of allergic inflammation as well [99].

In the context of helminth infection, some studies have also demonstrated increased production of PGE_2 and have proposed similar immunoregulatory functions. Brattig et al. showed that PGE_2 production can be induced in human macrophages following infection with *Onchocerca volvulus* [146]. While some studies have suggested that PGE_2 has no role in clearance of *N. brasiliensis* from the intestine of mice [147], de los Reyes Jiménez et al. recently showed that production of PGE_2 stimulated by helminth-derived larval products can lead to suppression of eosinophilic airway inflammation and lung pathology in an HDM-induced airway model of Type 2 inflammation [37]. In addition, some other studies have shown that PGE_2 acts through its receptors EP2 and EP4 to regulate proliferation and Type 2 cytokine production from activated ILC2s [92], the migration and release of inflammatory mediators in eosinophils [95,96], degranulation of mast cells [102,103], and immunomodulatory effects in DCs [104]. All of these findings strongly suggest an anti-inflammatory or regulatory role for PGE_2 during Type 2 inflammation (Fig. 3).

Of note, a few studies suggest that PGE_2 can also have a proinflammatory role in the regulation of Type 2 inflammation or can alter the balance of Type 1 versus Type 2 inflammation to allow for the emergence of a Type 2 response [89,140,148]. For example, Kaisar and others showed that PGE_2, a component of *Schistosoma mansoni* soluble egg antigen, could act on DCs to induce expression of OX40 ligand. This effect influenced the dynamics of production of Type 1 and Type 2 cytokines from T cells that consequently allowed for Th2 responses [89]. PGE_2 may also play a key role in skewing toward a Th2 response via suppression of a Th1 response. This can occur through regulation of cytokine production by human DCs [149] and regulation of macrophage responses in genetically Th2-prone inbred mouse strains [150]. Furthermore, Church et al. demonstrated that mice lacking the microsomal PGE_2 synthase-1 (mPGES1), which is important in production of PGE_2, had decreased immune cell infiltration and Type 2 cytokine production in an ovalbumin-induced model of Type 2 inflammation [140]. It is important to keep in mind that in this study, the inflammation observed in the absence of PGE_2 could be due to the loss of direct effects of PGE_2 or to shunting of the prostaglandin synthesis pathway into overproduction of more proinflammatory prostaglandins in the absence of the ability to make PGE_2. Finally, Shea-Donohue and colleagues showed that PGE_2 stimulation of intestinal sections mounted in an Ussing chamber increased mucosal permeability, reduced sodium-linked glucose absorption, and increased secretory responses. These changes were only seen in intestinal sections harvested from mice during secondary but not primary *Heligmosomoides polygrus* infection [151], demonstrating that the proinflammatory role for PGE_2 came into play after the induction of an adaptive Th2 response and in the epithelial effector phase of Type 2 inflammation, as previously reported [140]. Taken together, these studies suggest that the pro- versus anti-inflammatory effects of PGE_2, acting through its various receptors, might be regulated by the timing and stage of inflammation, at least in the context of helminth infection [104]. Therefore, newly developed mouse models [152] that allow for timed deletion of various genes that govern PGE_2 synthesis and function can be used to carefully explore how PGE_2 regulates Type 2 responses at various stages of inflammation.

Prostaglandin I_2

PGI_2 or prostacyclin is another end product of the prostaglandin biosynthesis pathway, synthesized through the sequential metabolism of AAs by the COX enzymes and PGIS. Several cell types, including fibroblasts, DCs, endothelial cells, smooth muscle cells, and thymic nurse cells, have been shown to express enzymes that produce this lipid mediator [105,153–155]. Prostacyclin binds to the G-coupled protein receptor IP to elicit its effect [105]. This receptor is expressed in a variety of cells and tissues including but not limited to neuronal cells, endothelial cells, smooth muscle cells and platelets [108]. PGI_2 acts on platelets to inhibit platelet aggregation, on blood vessels to regulate vascular permeability and on neuronal cells to regulate pain and nociceptive responses [117,156]. Immune cells, such as neutrophils, DCs, eosinophils, and Th2 lymphocytes cells, also express IP [105,106,118] (Table 1).

PGI_2 production is elicited in various Type 2 inflammatory contexts and has been implicated mostly as an immunomodulatory factor, acting at the resolution phase of Type 2 inflammation [106,110,111,118,157–161] (Fig. 3). For example, during allergen-induced Type 2 inflammation in the lungs of mice, PGI_2 binds to IP to suppress Type 2 inflammation through induction of production and release of IL-10 from Th2 cells [106] and DCs [116,118]. In addition, PGI_2 has been shown to suppress production and release of Type 2 cytokines [110,158,159] from ILC2s [159], Th2 lymphocytes [113,114,157], and DCs [110]; potentiate differentiation of Tregs [116]; and regulate production and release of IL-2, a T-cell prosurvival factor [159]. Furthermore, this lipid mediator can influence the accumulation, recruitment, and migration of Type 2 immune cells including ILC2s

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[111], eosinophils [112,119], Th2 lymphocytes [107], and DCs [109,110]. While PGI_2 seems to have a clear regulatory role in the lungs in murine models of allergic inflammation, its role during helminth infection remains less clear. PGI_2 production is dependent on Type 2 cytokines during helminth infection [162], but its effects in this context remain poorly understood.

Thromboxane A_2

TXA_2 is another product of the prostaglandin synthesis pathway produced following direct metabolism of PGH_2 to TXA_2 by TXAS [122]. This prostanoid has a less defined role in the modulation of Type 2 inflammation, possibly due to its short half-life. Most studies of this lipid provide evidence for prothrombotic properties following production by activated platelets, with platelets expressing both TXA_2 and thromboxane receptor (TP) [120,122]. However, DC [121] and macrophage [123] production of TXA_2 can also regulate immune responses in the steady state and in in vitro coculture models [121] (Table 1).

TXA_2 appears to be largely proinflammatory, outside of its platelet effects. Mice deficient in TP had attenuated immune responses following inflammation in a model of tissue injury [163]. Similarly, Yamasaki et al. showed that treatment with either seratrodast, a TXA_2 antagonist, or ozagret, a TXAS inhibitor, significantly reduced vascular permeability, swelling, and intranasal pressure in a guinea pig model of allergic rhinitis [164]. The TP antagonist BAYu 3405 could also alleviate allergen-induced nasal symptoms, total airway resistance, and eosinophil infiltration in guinea pigs [165]. Furthermore, the TXA_2-TP pathway interacts with other prostanoids, such as PGE_2, to control inflammation. For example, a study by Liu et al. showed that during HDM-elicited allergic airway inflammation, exaggerated pulmonary eosinophilia and vascular remodeling seen in PGE_2-deficient mice could be abrogated by deletion of TP [166]. These data suggest that PGE_2 effects might dampen Type 2 immune responses by repressing the inflammatory TXA_2-TP effector circuit [166].

However, much less is known about the role of TXA_2 during helminth infection (Fig. 3). Humans infected with *Dirofilaria immitis* who had pulmonary dirofilariasis had significantly higher TXA_2 levels in the serum than healthy control individuals, although it was not clear whether this was elicited by the helminth parasite or secondary infection with the symbiotic Wolbachia bacteria, which is present in most filarial parasites and is associated with septic shock [167]. Therefore, further studies are necessary to investigate the role of TXA_2 during helminth-induced Type 2 inflammation in various tissue sites.

Prostaglandin $F_{2\alpha}$

$PGF_{2\alpha}$ is the last in this family of prostaglandins. It is synthesized from PGH_2 via PGFS [22,168] and binds to a G-coupled protein receptor, FP [22]. The FP receptor is one of the least selective of the prostanoid receptors, ligating $PGF_{2\alpha}$ and other prostaglandins in the series such as PGD_2 and PGE_2 [169]. $PGF_{2\alpha}$ is produced by various cells and tissues, including adipocytes, renal tissue, and tissues of the reproductive system, and regulates various physiologic processes [22,37,170] (Table 1). Little is known about the role of this prostanoid and its receptor in the regulation of Type 2 inflammation, in mice or humans. A few older studies have suggested that $PGF_{2\alpha}$ is important in regulation of airway conductance [171,172] and also plays a role in regulation of various acute and chronic models of inflammation, but there has been little evidence of a direct influence of this pathway on immune cells [22]. Also, more recent studies have shown that $PGF_{2\alpha}$ was significantly increased in the BALF of mice following infection with *N. brasilensis* at day 5 post-infection but not following exposure to HDM allergen [67]. Furthermore, helminth excretory secretory products (HES) from *H. polygrus* larvae induced $PGF_{2\alpha}$ production from human monocyte-derived macrophages [37]. Together, these data suggest that $PGF_{2\alpha}$ and FP might play a role during Type 2 inflammation, but the specific functions of the $PGF_{2\alpha}$-FP pathway during allergy and helminth infection remain to be fully defined.

Host- and parasite-derived prostanoid networks regulate Type 2 inflammation

Due to their pleiotropic roles in tissues, it is perhaps not surprising that prostaglandins regulate complex networks of responses. As such, these oxylipids are uniquely placed to serve critical functions in balancing immunological interactions. These include but are not limited to interactions between host and pathogen during helminth infection, or known interactions and associations between Type 2 inflammatory responses during allergic disease and helminth infection [173].

In the context of parasite infection, both host- and parasite-derived prostaglandins dictate the outcomes of the host-pathogen interaction, including persistence versus expulsion of the parasite and the extent of collateral damage to the host. Various protozoan parasites, like *Acanthamoeba*, *Entamoeba histolytica*, *Plasmodium*, *Toxoplasma gondii*, and Trypanosomes, among others, can produce prostaglandins (reviewed here [15,23,174]). Other metazoan and parasitic helminthes, like Schistosomes and *Onchocerca* spp., also produce prostaglandins [130,175–179] that have host immunomodulatory roles. For example, *S. mansoni*, a parasitic worm that chronically infects humans, can produce lipid mediators including prostaglandins at various stages of its lifecycle [180–182]. Schistosomes produce PGD_2 that mediates proinflammatory effects in the host, including activation of eosinophils [74], as well as immunomodulatory PGE_2 that can induce production of IL-10 that promotes migration and survival of the parasite [89,176,177,180]. In addition, other helminth parasites, such as microfilaria of *B. malayi*, have also been shown to produce PGE_2, PGD_2, 6-keto-$PGF_{1\alpha}$, $PGF_{2\alpha}$, and TXB_2 [183,184]. These lipids play immunomodulatory roles in the host and influence critical physiological tissue responses to injury, preventing platelet

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Table 2. Parasite-derived prostaglandins and their effects on the host

Metazoan parasite	Prostaglandin	Role and function	References
Schistosoma mansoni	PGD_2 [180]	Impedes TNFα-triggered migration of epidermal Langerhans cells	[130] [74,175]
		Eosinophil activation and lipid biogenesis	
	PGE_2 [180]	Further production of PGE_2 and IL-10 in keratinocytes to support parasite migration through the skin	[176,177] [89,180]
		Further production of PGE_2 in DCs to prime Th2 responses	
Onchocerca volvulus	PGD_2	Unknown	[178]
	PGE_2	Immunomodulation?	[179]
Brugia malayi	PGE_2 [183,185]	Immunomodulation?	[185]
Wuchereria bancrofti	PGE_2 [185]	Immunomodulation?	[185]
Trichuris suis	PGE_2 [104]	Modulates proinflammatory DC responses	[104]
Diphyllobothrium dendriticum	PGE_2 [186]	Immunomodulation?	[186]
Fasciola hepatica	TXB_2, PGI_2, PGE_2 [187]	Immunomodulation?	[187]

aggregation around the parasites as they grow in blood vessels [184,185]. Furthermore, other worms, like *Trichuris suis*, a whipworm, produces PGE_2 that can directly suppress production of cytokines in LPS-stimulated DCs [104] (Table 2).

In some cases, the pathogen-host crosstalk via lipid mediators is indirect, with parasite products directly eliciting host prostaglandin production. HES from parasites, such as *H. polygyrus* and *S. mansoni*, can act on host immune cells to induce production of host-derived lipid mediators [37,89]. As described above, soluble egg antigen from *S. mansoni* can trigger the production and release of PGE_2 from DCs that subsequently license Th2 cells [89]. Similarly, larval products from *H. polygyrus*, dependent on Hpb glutamate dehydrogenase, can condition macrophages and granulocytes to produce PGE_2 that has immunomodulatory roles during chronic Type 2 immune responses [37]. This study has clear implications for our understanding of the inverse relationship between rates of helminth infection and rates of allergic disease across the globe [173]. While it has long been observed that helminth infection may confer protective effects against the development of allergic disease, the molecular mechanisms that underlie this phenomenon are not fully understood. The demonstration that PGE_2 stimulated by helminth-derived larval products can lead to suppression of HDM-induced Type 2 inflammation provides one such mechanism [37]. Another study showed that infection of rats with *Angiostrongylus costaricensis* elicited PGE_2 and lipoxin production that enhanced the resolution of allergic edema in the pleural cavity after allergen challenge [185]. While much remains to be discovered related to how prostaglandins might regulate the interplay between allergic and antihelminth responses, it appears likely that prostanoids are key factors in modulating this relationship.

Thus, either direct prostaglandin production by parasites or parasite product-elicited host prostaglandin production is important for mediating host-helminth interactions as well as immune responses to other stimuli like allergens. This crosstalk may govern the establishment and survival of the parasite, and the initiation, activation, and/or immunomodulation of host immune responses (Fig. 3). Parasite-derived prostanoids can be considered virulence factors that promote chronic infection and/or disease pathogenesis, modulating immune responses in the host to improve the survival of the parasite. However, these could also be considered beneficial products that prevent or limit inappropriate inflammation in response to allergens. These parasite-derived prostanoids may promote tissue repair, supporting epithelial cell proliferation and migration, ECM deposition, tissue remodeling and regeneration of endothelial cells. Thus, parasite-derived prostanoids may be critical for dictating host responses to allergens and helminth infection [21]. Clearly, disentangling the effects of parasite- versus host-derived prostaglandins during infection, and effects on allergic disease, will be complex. Studies that address this important question will require the use of new technologies for genetic manipulation of helminth parasites, such

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Table 3. Selected Drugs for Potential Use during Type 2 inflammation in Humans

Drug name	Target	Model of study	Disease	References
AM156	CRTH2	Mice	Allergic rhinitis, asthma	[205]
BW A868C	DP1	Guinea pigs	Allergic rhinitis, allergic conjunctivitis, asthma	[193]
S-5751	DP1	Guinea pigs	Allergic rhinitis, allergic conjunctivitis, asthma	[193,206]
		Rats		[207]
		Sheep	Asthma	[208]
			Asthma	
Ramatroban (BAY U3405)	CRTH2 and TP	Mice	Allergic rhinitis	[209]
		Humans	Allergic rhinitis	[195]
OC000459	CRTH2	Guinea pigs	Airway eosinophilia	[199]
		Mice	Airway inflammation	[209]
		Humans	Allergic rhinitis, allergic conjunctivitis	[210]
		Humans	Asthma	[211–213]
Vidupiprant (AMG-853, Amgen)	DP1 and CRTH2	Human	Asthma	[200,201]
Fevipiprant (QAW039)	CRTH2	Humans	Eosinophilic airway inflammation	[214]
		Humans	Asthma	[215,216]

as transgenic parasite models, CRISPR-Cas techniques [188,189], and RNA interference [190], coupled with genetic manipulations of host prostaglandin signaling and well-defined models of parasite infection and allergic disease.

Prostaglandin biology in human disease

The synthesis cascades that result in prostaglandin production offer multiple opportunities for therapeutic intervention in human disease. While many of the studies we have discussed thus far involved the use of mouse models, drugs and inhibitors that target specific prostaglandin synthesis pathways or block the different receptors for the individual prostaglandins are being tested for efficacy in treating human diseases. To date, the various complexities associated with interfering in the synthesis of prostaglandins (i.e. the possibility of shunting into different pathways and the pleiotropic effects of individual prostaglandins) have made the use of receptor inhibitors and agonists more attractive. While prostaglandin-targeting drugs are used in a number of contexts, they have been of particular interest in treating signs and symptoms of allergic inflammation in humans.

PGD_2, one of the key prostaglandin mediators produced during Type 2 inflammation, can have both pro- and anti-inflammatory roles during Type 2 inflammation depending on the context and tissue [70,131] or receptor affinity for either CRTH2 or DP1 [191]. Therefore, specific drugs that target these receptors have been used to modulate these responses in human disease, extensively discussed here [75,192], and with selected highlights in Table 3. The DP1 antagonists BW A868C and S-5751 have been used in the treatment of allergic disease to alleviate allergen-induced Type 2-associated symptoms [193]. Also, CRTH2 antagonists like Ramatroban (BAY U3405) that antagonize both CRTH2 and the TXA_2 receptor have been used for the treatment of allergic rhinitis [194–196], blocking chemotaxis of Type 2 immune cells like eosinophils, basophils, Th2 lymphocytes, and ILC2s into inflamed tissues [196–198]. Similarly, OC000459, a CRTH2 competitive antagonist, was shown to have potential for use in cases of airway inflammation, where it can inhibit airway and blood eosinophilia when delivered orally to rats and guinea pigs [199]. Drugs like Vidupiprant (AMG-853, Amgen) that target and block both the DP1 and DP2 receptors [200] appear to have been less successful in the treatment of allergic inflammation [201]; thus, more attention has been paid to CRTH2 inhibition in treating human allergic disease [75,202,203]. Key and foremost among these CRTH2 antagonists [75] is Fevipiprant, an oral, nonsteroidal, highly selective, safe, reversible antagonist of the DP2 receptor that inhibits the binding of all ligands [204]. While Fevipiprant showed great promise in the amelioration of symptoms of eosinophilic airway inflammation in phase II clinical trials [192,203], recent larger scale phase III clinical trials report a marginal improvement in disease activity with the use of this drug over placebo for the treatment of severe airway Type 2 inflammation [202]. Thus, it remains to be seen whether Fevipiprant and other CRTH2 inhibitors are useful in defined endotypes and phenotypes of allergic inflammation. The pleiotropic effects of PGD_2 and CRTH2 on different cell types (epithelial vs. immune) [70] could influence therapeutic efficacy of these drugs, especially considering the importance of the epithelial-immune cell crosstalk during Type 2 inflammation.

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Of note, less specific drugs, like COX inhibitors, including the nonsteroidal anti-inflammatory drugs, can also be used to treat aberrant Type 2 inflammation in humans, though these drugs are less effective in most cases and sometimes result in less desirable outcomes. For example, nonselective COX inhibitors can actually trigger asthma attacks in patients who suffer from aspirin-exacerbated respiratory disease, a chronic Type 2 inflammatory airway disease [217]. Also, mouse studies have demonstrated that use of Cox-1 and Cox-2 inhibitors, like indomethacin and ibuprofen, can reduce immune cell infiltration, production of Type 2 cytokines, and release of antibodies that consequently led to increased number of infective larvae in the lungs and adult worms in the duodenum of mice infected with *Strongyloides venezuelensis* [62]. Therefore, because of current limitations concerning the use of some drugs in the treatment of aberrant Type 2 inflammation, work continues to focus on manipulating the effects of specific prostaglandins or their receptors to achieve defined therapeutic changes in inflammatory immune responses during allergic inflammation. As prostaglandins are highly pleiotropic, it may be necessary to antagonize certain receptors, while stimulating others to achieve maximally beneficial effects. Finally, the use of specific prostaglandin receptor antagonists and agonists to treat deleterious effects of chronic Type 2 inflammation during helminth infection has not been well studied to date.

Conclusions and future directions

Recent work has expanded upon classical literature that demonstrates key roles for prostaglandins in regulating Type 2 inflammation in allergy and helminth infection [37,67,89,92,104,131,145]. The development of specific and powerful prostaglandin receptor inhibitors and agonists has allowed for more granular study of the effects of specific prostaglandins and their receptors during helminth infection, allergic disease, and fibrosis [26,101,145]. Complementarily, new mouse models that allow for the genetic deletion of prostaglandin synthesis ability or specific prostaglandin receptors have been used to reveal the complex biology that prostaglandins control in tissues [22,145,152]. Together, these tools are being leveraged to disentangle the pleiotropic effects of prostaglandins during the steady state and Type 2 inflammation.

Despite these advances, much remains to be explored in the field of prostaglandin biology during Type 2 inflammation. In particular, cell lineage-specific deletion in mice of various components of different prostaglandin pathways is not possible in all cases. Mice that allow for such lineage-specific and inducible deletion of prostaglandin synthases and receptors will be required for building a greater understanding of the effects of individual prostaglandins in various disease states in time and space. Also, currently, in vivo visualization of prostaglandin production in mice is not possible, and tools that make that feasible could revolutionize our understanding of prostaglandin regulation of inflammation in tissues. Such studies in mice will be needed to inform further work in humans that builds understanding of human prostaglandin biology and uses this knowledge to treat diseases that involve a pathologic Type 2 inflammatory component. Of particular interest would be to better understand how host- and parasite-derived prostaglandins modulate host-pathogen interactions and shape host immune responses to impact on the development or progression of allergic responses. Defining the networks of prostaglandins that regulate Type 2 inflammation using mouse models and translational work in human tissue culture has the potential to reveal rich opportunities for therapeutic intervention in Type 2 inflammation-driven allergic disease and fibrosis in humans.

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Abbreviations: **AA**: arachidonic acid · **COX**: chemoattractant receptor-homologous molecule expressed on Th2 cells, CRTH2 cyclooxygenase · **CYP**: cytochrome P450 epoxygenase · **HES**: helminth excretory secretory products · **HDM**: house dust mite · **PLA**: phopholipase · **PG**: prostaglandin · **PGDS**: prostaglandin D synthase · **PGES**: prostaglandin E synthase · **EP**: prostaglandin E2 receptor · **PGFS**: prostaglandin F synthase · **PGIS**: prostaglandin I synthase · **IP**: prostaglandin I2 receptor · **Th2**: T helper type 2 · **TXA^2**: thromboxane A2 · **TXAS**: thromboxane A synthase · **TP**: thromboxane receptor

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