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Invited review article

## Prostanoids in allergy

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## ABSTRACT

Prostanoids, which include prostaglandin and thromboxane, are metabolites of arachidonic acid released in various pathophysiological conditions. They induce a range of actions mediated through their respective receptors expressed on target cells. It has been demonstrated that each prostanoid receptor has multiple functions and that the effect of receptor stimulation can vary depending on context; this sometimes results in opposing effects, such as simultaneous excitatory and inhibitory outcomes. The balance between the production of each prostanoid and the expression of its receptors has been shown to be important for maintaining homeostasis but also involved in the development of various pathological conditions such as allergy. Here, we review the recent findings on the roles of prostanoids in allergy, especially focusing on atopic dermatitis and asthma.

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## Introduction

When tissues are exposed to diverse pathophysiological stimuli, arachidonic acid (AA) is released from membrane phospholipids and converted into lipid mediators, such as prostanoids, leukotrienes (LT) and hydroxy-eicosatetraenoic acids (HETEs) via their respective synthases.<sup>1</sup> Prostanoids are formed by the cyclooxygenase (COX) pathway.<sup>1</sup> COX has two isoforms, COX-1 and COX-2. While COX-1 is constitutively expressed in cells, COX-2 requires specific stimulation by substances such as acetone and phorbol ester. The COX reaction results in the formation of an unstable endoperoxide intermediate called prostaglandin (PG) H<sub>2</sub>, which, in turn, is metabolized to PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub>, and thromboxane (TX) A<sub>2</sub> by their specific synthases<sup>1</sup> (Fig. 1).

Prostanoids are released from cells immediately after formation. Since they are chemically and metabolically unstable, they usually function only locally through membrane receptors on target cells.<sup>1</sup> Nine types and subtypes of membrane prostanoid receptors are conserved in mammals from mouse to human: two subtypes of the PGD receptor (DP (DP<sub>1</sub>)) and a chemoattractant receptor homologous-molecule expressed on Th2 cells known as CRTH2 (DP<sub>2</sub>),<sup>2</sup> four subtypes of the PGE receptor (EP1, EP2, EP3, and EP4), the PGF receptor (FP), the PGI receptor (IP), and the TXA receptor

(TP)<sup>1</sup> (Fig. 1). All are G protein-coupled rhodopsin-type receptors with seven transmembrane domains.

Although it has been difficult to analyze the physiological roles of prostanoids because of their instability *in vivo*, recent developments in both the disruption of the respective genes and the creation of receptor-selective compounds have made it possible.<sup>3,4</sup> These genetic and pharmacological approaches have revealed new roles played by prostanoids and their receptors in allergic diseases. In this review, we describe the current state of our knowledge of prostanoids' roles in atopic dermatitis and asthma.

## Prostanoids in atopic dermatitis (allergy, skin barrier functions, pruritus)

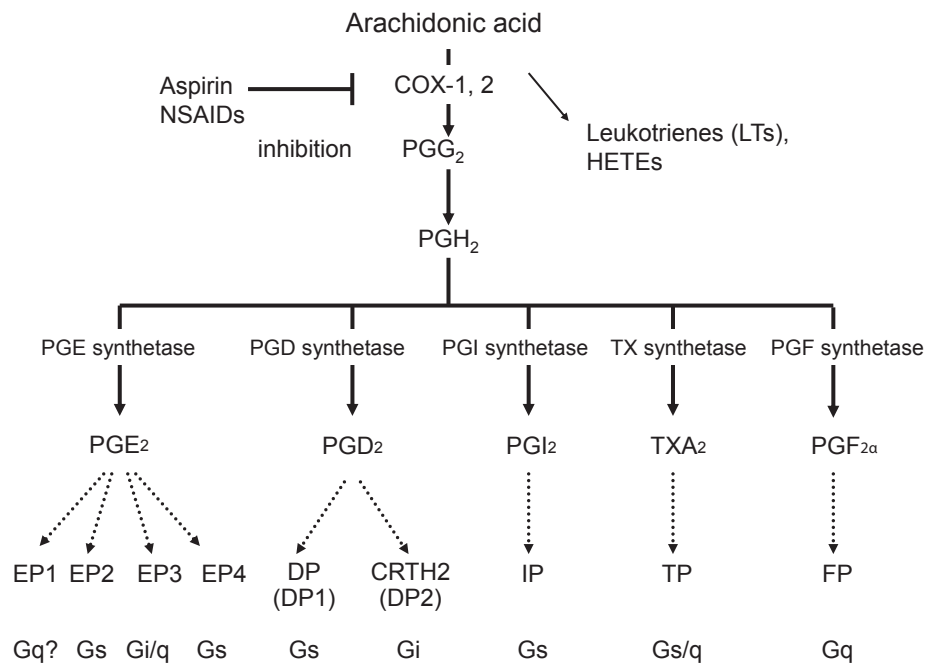
Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by a complex, heterogeneous pathogenesis, including allergy/immunology, skin barrier dysfunction, and pruritus.<sup>5–7</sup> In the dermis, a cellular infiltrate is present consisting of lymphocytes, monocytes and mast cells.

It has been reported that several kinds of prostanoids including PGE<sub>2</sub> and PGD<sub>2</sub> are produced in the skin of AD patients.<sup>8–10</sup> Yet the roles of the various prostanoids in the pathogenesis of AD have not been thoroughly pursued, because treatment with COX inhibitors, which block the production of prostanoids, are not usually effective against AD symptoms, implicating a weaker association of prostanoids with the pathogenesis of AD. However, recent studies have suggested that various prostanoid receptors do play distinct stimulatory and regulatory functions in the pathogenesis of AD.

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**Fig. 1. Prostanoids synthesis and receptors.** Prostanoids synthesis pathways, their respective receptors, and the signal transduction mechanisms from the receptors. Gs is a heterotrimeric G protein subunits that activates adenylate cyclase, which produces cAMP, and activates cAMP-dependent protein kinase. Gi is also a heterotrimeric G protein subunits that inhibits the production of cAMP, and Gq activates phospholipase C and increases the cytosolic calcium concentration. PG, Prostaglandin; COX, cyclooxygenase; NSAIDs, Non-steroidal anti-inflammatory drugs; HETEs, hydroxy-eicosatetraenoic acids.

### Prostanoids in immunology of AD

Recently, several new types of murine AD models have been established,<sup>11</sup> including an ovalbumin (OVA)-induced mouse AD model<sup>12</sup> and a repeated hapten application contact hypersensitivity (CHS) model.<sup>13</sup> In an OVA-induced mouse AD model, COX-2-deficient mice exhibited both enhanced eosinophil infiltration and elevated IL-4 expression in the skin and spleen with elevated serum antigen-specific IgE and IgG1,<sup>14</sup> suggesting the existence of prostanoid receptors that have regulatory functions in AD.

Among the prostanoids, PGD<sub>2</sub> is the major prostanoid produced by activated mast cells. It is detected in the skin of AD patients<sup>9,10,15,16</sup> as well as in the OVA-induced AD model.<sup>17</sup> PGD<sub>2</sub> production in skin can also be stimulated by scratching, however.<sup>18</sup> Because local application of PGD<sub>2</sub> induces peripheral vasodilation, while systemic injection of PGD<sub>2</sub> induces flushing and nasal congestion, it has generally been believed that PGD<sub>2</sub> acts as an inflammatory mediator in AD.<sup>19</sup> However, recent studies have revealed that PGD<sub>2</sub> plays both pro- and anti-inflammatory roles in cutaneous immune responses depending on the receptors.

PGD<sub>2</sub> has two types of receptors, DP<sup>1</sup> and CRTH2.<sup>2</sup> In an OVA-induced AD model, administration of BW245c, a DP agonist, inhibits sensitization with OVA by inhibiting the migration of skin dendritic cells (DC).<sup>20,21</sup> Consistently, DP-deficient mice exhibit enhanced inflammation in the AD model of repeated hapten application and CHS, with increased skin DC migration to draining LNs,<sup>22</sup> suggesting that PGD<sub>2</sub>-DP signaling exerts a regulatory role in the development of AD. Even in a more acute skin inflammation model, it is reported that PGD<sub>2</sub>-DP signaling plays suppressive roles by enhancing vascular endothelial barrier function.<sup>23</sup>

PGD<sub>2</sub>-CRTH2 signaling, on the other hand, generally plays pro-inflammatory roles in skin inflammation. CRTH2 induces chemotaxis in Th2 cells, neutrophils, eosinophils and basophils with enhanced degranulation.<sup>2,24,25</sup> These chemotactic effects have been confirmed in several skin inflammation models. CRTH2-deficient

mice exhibit normal sensitization but reduced eosinophil and CD4<sup>+</sup> T cell infiltration in the OVA-induced AD model.<sup>17</sup> CRTH2-deficient mice also exhibit reduced inflammation in CHS<sup>22,26</sup> as well as the repeated hapten application AD model<sup>26,27</sup> and a croton oil-induced acute skin inflammation model.<sup>23</sup> Basophil infiltration into the skin is significantly impaired in CRTH2-deficient mice in an IgE-mediated chronic allergic skin inflammation model.<sup>26</sup> Consistently, administration of a CRTH2 antagonist inhibits neutrophil infiltration into the skin and attenuates the CHS response<sup>25</sup> and the OVA-induced AD model.<sup>28</sup> In humans, virtually all CRTH2<sup>+</sup> CD4<sup>+</sup> lymphocytes have a pure Th2 phenotype; they constitute not all but a large proportion of circulating Th2 cells in both normal and AD subjects.<sup>29,30</sup> In AD subjects, a preferential increase in CRTH2<sup>+</sup> cells was noted within the disease-related cutaneous lymphocyte-associated antigen-positive CD4<sup>+</sup> T cell compartment.<sup>30</sup> These results suggest the importance of CRTH2 in Th2 cell, neutrophil, eosinophil and basophil infiltration or activation in cutaneous allergic disease including AD.

Recently, the class of innate lymphoid cells (ILCs) known as type 2 ILC (ILC2) has been identified in various tissues such as skin, lung, and intestine.<sup>31</sup> ILC2 are responsive to IL-25 or IL-33, and abundantly produce type 2 cytokines such as IL-5 and IL-13. ILC2 are supposed to play significant roles in the development of allergic diseases such as asthma or atopic dermatitis.<sup>32</sup> Human ILC2 have been shown to express CRTH2.<sup>33</sup> Furthermore, it has recently been reported that PGD<sub>2</sub> induces type 2 cytokine production and chemotaxis of ILC2 via CRTH2.<sup>34,35</sup> Therefore, an antagonist for CRTH2 may inhibit not only Th2 cells and eosinophils but also the recruitment of ILC2 into tissues.

In addition to its direct chemotactic effects, PGD<sub>2</sub> has recently been reported to mediate eosinophil skin infiltration indirectly by inducing eotaxin-3 production from sebocytes.<sup>36</sup>

To summarize, PGD<sub>2</sub> seems to play some pro-inflammatory roles and some anti-inflammatory roles in the pathogenesis of AD, through DP and CRTH2, respectively.

PGE<sub>2</sub> is also detected abundantly in the skin of AD.<sup>8</sup> PGE<sub>2</sub> has four subtypes of receptors; EP1, EP2, EP3, and EP4. Like PGD<sub>2</sub>, PGE<sub>2</sub> has been assumed to be an important mediator in acute skin inflammation. In fact, vasodilation in ultraviolet (UV) B-induced dermatitis is mediated through EP2 and EP4 receptors.<sup>37</sup> In an arachidonic acid-induced dermatitis model, PGE<sub>2</sub>-EP3 signaling mediates this process by inducing mast cell activation and subsequent histamine release and IL-6 production.<sup>38,39</sup> Nevertheless, the role of each PGE receptor in AD remains unclear. It has been reported, however, that PGE<sub>2</sub> receptors exert various important roles in cutaneous immune response, suggesting the importance of PGE<sub>2</sub> receptors in AD. For example, EP1, EP2 and EP4 signaling on CD4 T cells facilitate Th1 and/or Th17 differentiation in CHS.<sup>40,41</sup> EP4 signaling promotes cutaneous DC migration to draining LNs and initiates sensitization in CHS,<sup>42</sup> while EP3 signaling inhibits their migration and regulates sensitization.<sup>43</sup> EP3 also regulates chemokine production from keratinocytes.<sup>44</sup> It has also been reported that EP4 signaling mediates regulatory T cell induction through upregulation of RANKL on keratinocytes in a UV-induced immunosuppression model.<sup>45</sup> In *in-vitro* studies, PGE<sub>2</sub> drives Ig class switching to IgE by acting on EP2 and EP4 on B cells under LPS and IL-4 stimulation.<sup>46</sup> These results suggest that PGE<sub>2</sub> both suppresses and aggravates the development of AD.

PGI<sub>2</sub> and TxA<sub>2</sub> also exert important roles in cutaneous immune response and might play significant roles in AD. PGI<sub>2</sub>-IP signaling on naïve CD4<sup>+</sup> T cells facilitates Th1 differentiation in CHS,<sup>47</sup> although the role of PGI<sub>2</sub> in Th1/2 differentiation is context-dependent.<sup>48</sup> Cutaneous DCs produce abundant TXA<sub>2</sub>, which acts on naïve T cells to impair the DC-T cell interaction and negatively regulates the priming of T cells.<sup>49</sup> TP-deficient mice exhibit enhanced CHS responses as well as elevated serum IgE in the repeated hapten application model,<sup>49</sup> suggesting that TP signaling

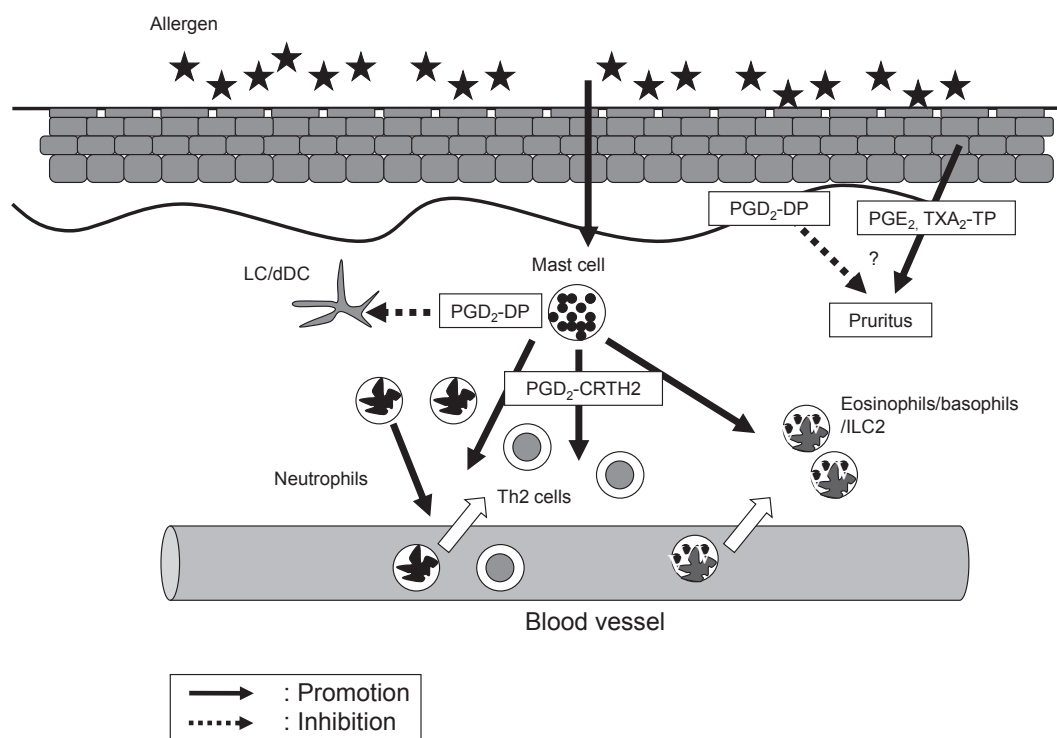
plays regulatory roles in Th2 cell differentiation or proliferation in AD. The possible involvement of the various prostanoid receptors in AD is summarized in Fig. 2.

### Prostanoids in pruritus

Pruritus is an important hallmark of AD. It has been reported that PGE<sub>2</sub> evokes pruritus in AD patients, probably via histamine release.<sup>50,51</sup> On the other hand, topical application of PGE<sub>2</sub> inhibited spontaneous scratching in NC/Nga mice with chronic dermatitis.<sup>51,52</sup> Topical application of PGD<sub>2</sub>, but not a CRTH2 agonist, also reduced scratching behavior in NC/Nga mice, suggesting that DP suppresses pruritic activity.<sup>52</sup> A recent report suggests that, in addition to PGE<sub>2</sub> and PGD<sub>2</sub>, TxB<sub>2</sub> elicits itch through TP on primary afferents and keratinocytes.<sup>53</sup> Although the mechanisms by which prostanoids regulate pruritus remain largely unknown, regulation of these lipid mediators or their receptors may offer potential for a novel antipruritic treatment.

### Prostanoids in skin barrier functions

Skin barrier function is important to avoid desiccation and to protect against foreign insults. Two sets of barriers are involved: the stratum corneum and the tight junction.<sup>5</sup> As barrier dysfunction is thought to be not merely an epiphenomenon of AD but rather the initiator of AD pathogenesis,<sup>5</sup> control of barrier function is important for the treatment of AD. So far, the involvement of prostanoids in skin barrier function remains largely unknown. However, studies using a mechanical scratching-induced cutaneous barrier disruption model suggest a protective role of PGD<sub>2</sub> in skin barrier function.<sup>54,55</sup> Further detailed analysis may reveal novel functions of prostanoids in regulation of skin barrier function.



**Fig. 2. The possible roles of prostanoids in the development of atopic dermatitis.** Schematic summary of the possible roles of prostanoids in the development of atopic dermatitis. PG, Prostaglandin; TX, Thromboxane; CRTH2, chemoattractant receptor homologous-molecule expressed on Th2 cells; ILC2, innate lymphoid cells type 2; LC, Langerhans cell; dDC, dermal dendritic cell.

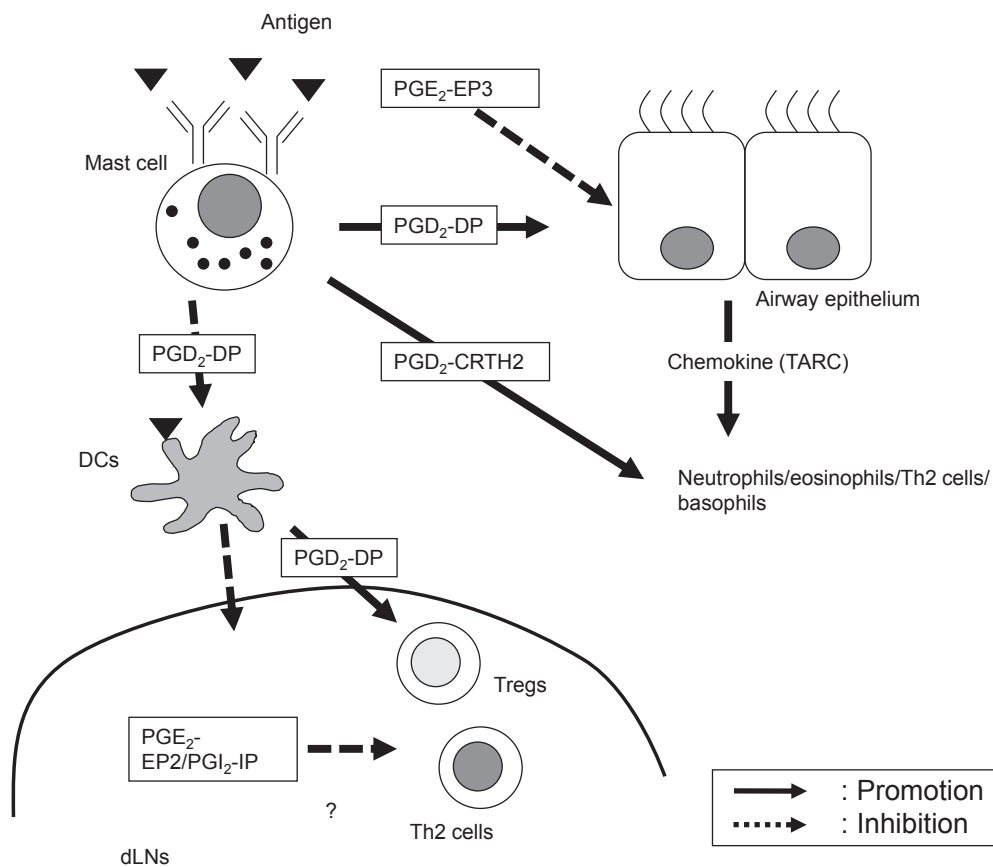
### Prostanoids in asthma

Asthma is a chronic inflammation of the conducting airways, and is characterized by intermittent attacks of breathlessness, wheezing, and cough.<sup>56</sup> Th2 cells, Th2-associated cytokines, eosinophils and basophils mediate the inflammation. Involvement of prostanoids in the pathogenesis of asthma has long been suspected, because it is well known that ingestion of aspirin, an NSAID that blocks prostanoid synthesis, sometimes induces severe bronchoconstriction in a proportion of subjects with asthma,<sup>57,58</sup> and COX-2-deficient mice exhibit augmented airway inflammation in an asthma model.<sup>59</sup> Previously, the pathogenesis of aspirin-induced asthmatic attacks (AIA) were explained by the diversion of arachidonic acid metabolism from the COX pathway to the LO pathway and the subsequent elevation of leukotrienes, such as cysteinyl LTs (CysLT)<sup>60,61,62</sup> because CysLTs are strong inducers of bronchoconstriction<sup>63</sup> and tissue eosinophilia.<sup>63</sup> However, the loss of inhibitory signaling from prostanoid receptors may also be involved in the pathogenesis of AIA.

EP3 receptor is one of the inhibitory receptors that may be involved in allergy.<sup>44,64,65</sup> In an OVA-induced murine asthma model, EP3-deficient mice exhibited similar levels of serum IgE but exaggerated airway inflammation, and administration of an EP3 agonist suppressed the inflammation by inhibiting mast cell activation and chemokine production from airway epithelial cells.<sup>64</sup> EP3 signaling is also reported to play an anti-inflammatory role in experimental allergic conjunctivitis by inhibiting chemokine production from the conjunctival epithelium.<sup>65</sup> These results indicate that PGE<sub>2</sub>-EP3 signaling negatively regulates allergic inflammation

during the effector phase. One recent study suggests that, in addition to EP3, endogenous PGE<sub>2</sub>-EP2 signaling also exerts regulatory effects in the development of asthma.<sup>66</sup> EP2-deficient mice exhibit an exaggerated phenotype with elevated serum IgE levels, and administration of an EP2 agonist during the sensitization phase reduces the IL-4 or IL-13 production from CD4<sup>+</sup> T cells and reduces airway inflammation.<sup>66</sup> In addition, a polymorphism in EP2 gene is reported to be associated with AIA.<sup>67</sup> These results suggest that EP2 plays suppressive roles during the sensitization phase. Intriguingly, it has been reported that IP-deficient mice also exhibit elevated serum IgE levels and exaggerated airway inflammation.<sup>68</sup> Signaling from EP2 and IP facilitates Th1 differentiation through the elevation of cAMP,<sup>40,47,69</sup> which may explain the enhanced Th2 response in EP2-deficient mice and IP-deficient mice.

PGD<sub>2</sub> is a major prostanoid produced by activated mast cells<sup>70</sup> and is released in large amounts during asthmatic attacks in certain patients.<sup>71</sup> Although the role of PGD<sub>2</sub> in allergic asthma long remained unclear, an analysis using DP-deficient mice revealed that PGD<sub>2</sub>-DP signaling stimulates chemokine expression in airway epithelial cells, facilitates Th2 cell and eosinophil accumulation in the lungs, and plays a central role in asthma.<sup>70</sup> On the other hand, it has also been reported that administration of a DP agonist during the sensitization phase suppresses airway inflammation by inhibiting DC migration and induction of regulatory T cells.<sup>72,73</sup> These results suggest that DP signaling plays regulatory roles in the sensitization phase but exerts pro-inflammatory roles in the effector phase of asthma (Fig. 3). The involvement of DP in the pathogenesis of asthma is also suggested by the results of human single nucleotide polymorphism analysis studies.<sup>74</sup>



**Fig. 3. The possible roles of prostanoids in the development of asthma.** Schematic summary on the possible roles of prostanoids in the development of asthma. PG, Prostaglandin; CRTH2, chemoattractant receptor homologous-molecule expressed on Th2 cells; DC, dendritic cell; Treg, regulatory T cell.

PGD<sub>2</sub>-CRTH2 signaling may also contribute to the development of asthma. Administration of a CRTH2 antagonist reduced eosinophil accumulation in a mouse asthma model, and administration of a CRTH2 agonist augmented the infiltration of inflammatory cells into the lungs,<sup>75,76</sup> suggesting that PGD<sub>2</sub>-CRTH2 signaling mediates airway inflammation. However, it has been reported that CRTH2-deficient mice exhibited increased inflammatory cell infiltration and IL-5 production from activated T lymphocytes,<sup>77</sup> suggesting that CRTH2 signaling regulates cytokine production in the development of asthma. Further analyses are needed to clarify whether inhibition of CRTH2 signaling would have an overall beneficial effect.

## Conclusions

In this review, we have summarized current findings on the actions of prostanoid receptors in allergic diseases. Although the role of each lipid mediator is various and complex, selective manipulation of the actions mediated by each receptor may lead to the discovery of a novel therapeutic strategy for allergic disorders.

### Conflict of interest

The authors have no conflict of interest to declare.

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