Prostaglandin D₂ and TH2 Inflammation in the Pathogenesis of Bronchial Asthma

Masafumi Arima¹ and Takeshi Fukuda²

¹Department of Developmental Genetics (H2), Chiba University Graduate School of Medicine, Chiba; ²Department of Pulmonary Medicine and Clinical Immunology, Dokkyo University School of Medicine, Tochigi, Japan

INTRODUCTION

Asthma is characterized by chronic inflammation of the airways, associated with inflammatory cells, including eosinophils, mast cells, basophils, macrophages, and T helper (Th1) cells. These cells are involved in development of airway hyperresponsiveness (AHR), bronchoconstriction, mucus secretion, and remodeling by releasing inflammatory mediators, such as chemokines, growth factors, lipid mediators, and chemical mediators. Then, the complex pathogenesis of asthma is contributed to by various cellular responses, based on the dysregulated interaction between the innate and adaptive immune systems.

Recent evidence suggests that prostaglandin D₂ (PGD₂) is a major prostanoid, produced mainly by mast cells, in allergic diseases, including bronchial asthma. PGD₂-induced vasodilatation and increased permeability are well-known classical effects that may be involved in allergic inflammation. Recently, novel functions of PGD₂ have been identified. To date, D prostanoid receptor (DP) and chemoattractant receptor homologous molecule expressed on TH2 cells (CRTH2) have been shown to be major PGD₂-related receptors. These two receptors have pivotal roles mediating allergic diseases by regulating the functions of various cell types, such as Th2 cells, eosinophils, basophils, mast cells, dendritic cells, and epithelial cells. This review will focus on the current understanding of the roles of PGD₂ and its metabolites in TH2 inflammation and the pathogenesis of bronchial asthma. (Korean J Intern Med 2011;26:8-18)

Keywords: Basophils; Asthma; Eosinophils; Mast cells; Prostaglandins; TH₂ cells

T_H2 immune response in asthma

Allergic diseases are characterized by elevated serum immunoglobulin (Ig) E levels and hypersensitivity to normally innocuous antigens as allergens. A particular allergen first encounters antigen-processing cells (APC), such as dendritic cells or macrophages, directly. The allergen captured by the APC is processed and presented to CD4⁺ T cells. CD4⁺ T cells are polarized into distinct types of TH cells. Major TH cell subsets include TH1, TH2, and TH17, and also recently discovered TH9 and TFH cells. Each TH cell subset expresses a characteristic cytokine profile that generates a characteristic inflammatory response in allergic diseases, such as bronchial asthma. Among these TH cells, TH2 cells are believed to play a critical pathogenic role in allergic inflammation. TH2 cells produce cytokines, interleukin (IL)-4, IL-5, IL-6, IL-9, and IL-13, although they may also result from other cell types. Patients with allergic asthma have eosinophilic inflammation in the lung, in parallel with increased TH2 cytokines, as well as elevated serum IgE. IL-4 and IL-13 are representative TH2-type cytokines that play a crucial role in human allergic disease. IL-4 promotes differentiation and proliferation in TH2 cells, whereas IL-13 mediates AHR and mucus hyperproduction [1,2]. IL-5 is a cytokine that is highly specific to eosinophil activation and recruitment and con-
tributes to eosinophilic inflammation, a prominent pathological feature in most asthma. Th2 cytokines also trigger the production of chemokines, including CCL11/eotaxin, CCL17/TARC, and CCL22/macrophage-derived chemokine (MDC), in tissue fibroblasts or epithelial cells, promoting the infiltration of inflammatory cells, such as eosinophils and Th2 cells into sites exposed to allergens. Importantly, IL-4 and IL-13 stimulate immunoglobulin class switching, leading to IgE production, which binds to its high-affinity receptor (FceRI) on the surface of mast cells or basophils. The association of captured allergens with IgE bound to FceRI on the cell surface activates signal transduction in these cells and rapidly leads to the release of inflammatory cytokines and chemical mediators, such as histamine and leukotrienes in mast cells and basophils and PGD, in mast cells. Furthermore, particular interest has been generated in novel epithelial cell-derived cytokines including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which have all been implicated in promoting Th2 cytokine responses, and their ability to influence innate and adaptive immune responses associated with Th2 cytokine-mediated inflammation in airways. Recent evidence suggests that coordinated expression and cross-regulation between TSLP, IL-25, and IL-33 are crucial events for developing Th2 cell-mediated airway immune responses in asthma. In contrast, PGD modulates airway physiology by causing bronchoconstriction, vasodilation, increases in capillary permeability, and mucous production in asthma. These functions are well-known effects that may facilitate transendothelial migration of inflammatory cells, such as eosinophils, mast cells, lymphocytes, and monocytes, during allergic inflammation. In addition to such classical effects, novel properties of PGD include Th2 inflammation in allergic diseases (Fig. 1).

PGD, and its metabolites

PG production begins with the liberation of arachidonic acid from membrane phospholipids by phospholipase A2 in response to inflammatory stimuli. Arachidonic acid is converted to PGH2 by the cyclooxygenase enzymes COX-1 and COX-2. PGH2 is a common precursor of several PGs, including PGD2, which is generated by the actions of two PG synthases, known as the lipocalin-type PGD synthase (L-PGDS), primarily expressed in brain, heart, and adipose tissue, and the hematopoietic PGD synthase (H-PGDS), mainly expressed in mast cells, macrophages, dendritic cells (DCs), and Th2 cells. It is generally thought that COX-1 is expressed constitutively in most tissues of the body and functions to maintain homeostatic processes, such as mucus secretion. In contrast, COX-2 is primarily an inducible enzyme, involved mainly in the regulation of inflammation [3]. PGD2 is a major product from COX-catalyzed reactions in a variety of tissues and cells, including those of the immune system, such as T cells, DCs, macrophages, mast cells, and platelets.

PGD production in asthma

Fujitani et al. [4] generated transgenic mice overexpressing lipocalin-like PGD synthetase in the lung and subjected them to ovalbumin (OVA)-induced pulmonary allergic inflammation. They found elevated IL-4 and IL-5 concentrations and increased eosinophilic infiltration in bronchoalveolar-lavage fluid (BALF) in these mice. Mandal et al. [5] reported that a reduction in PGD2 synthesis, induced by uteroglobin, an anti-inflammatory protein, was associated with reduced allergic inflammation. Furthermore, PGD2 nebulization before aerosol Ag challenge enhanced Th2 inflammatory responses, including eosinophilia, and leads to the development of AHR [6]. Collectively, these findings appear to substantiate the proposal that PGD acts as an important mediator in allergic asthma.

Activated mast cells contribute to asthmatic pulmonary inflammation by producing a variety of chemical mediators and cytokines. During allergic responses, PGD2 is released in large amounts by mast cells during asthmatic attacks in humans. DCs [7] and Th2 cells [8] also produce PGD2. Furthermore, fibroblasts, bronchial smooth muscle cells, and airway epithelial cells are also thought to produce PGD2, precipitating pulmonary inflammation. It is well established that the presence of an allergen triggers PGD2 production in sensitized individuals. In individuals with asthma, a bronchial allergen challenge leads to rapid PGD2 production, which can be detected in the BALF within minutes, reaching biologically active levels at least 150-fold higher than pre-allergen levels [9]. A local antigen challenge also stimulates PGD2 production in the nasal mucosa of patients with allergic rhinitis [10] and in the skin of patients with atopic dermatitis (AD) [11]. Several lines of evidence support the view that mast cells are the principal sources of PGD2 at allergic inflammation sites. Cell fractionation studies have shown that PGD2 is produced predominantly by mast cells [12], and mast cell...
activation is a requirement for PGD2 generation in chopped human lung parenchyma [13]. Thus, mast cells are responsible for the bulk of PGD2 production in the allergic setting. PGD2 produced by mast cells may provide an essential link between early-phase and late-phase allergic responses by initiating cellular processes that lead to the recruitment and activation of TH2 cells and eosinophils with associated pathophysiological effects.

PGD2-related receptors

Among PG receptors, D prostanoid receptor (DP)/DP1, DP2/chemoattractant receptor homologous molecule expressed on TH2 cells (CRTH2), and thromboxane A2 receptor (TP) belong to a family of seven-transmembrane G-protein-coupled receptors (GPCRs), mediating the biological effects of both PGD2 and its metabolites. In contrast, peroxisome proliferator-activated receptor (PPAR)-γ is a nuclear receptor for PGD2 metabolites. DP, TP, and PPAR-γ are present in various types of hematological and non-hematological cells [14,15]. In contrast, human CRTH2 has been specifically identified on hematological cells [16], although the tissue expression pattern of CRTH2 in humans differs from that in rodents [17].

DP is the most studied PGD2 receptor and its activation leads to Gs-mediated elevation in cAMP. DP is activated by PGD2 and its metabolites, including ∆12-PGD2 and PGJ2. Such activation by DP-selective agonists, such as BW245C, promotes relaxation of both vascular and airway smooth muscle, leading to vasodilatation and bronchodilatation, respectively [18]. DP is also expressed by platelets, in which its activation is linked to an anti-aggregatory function [19]. DP plays both anti-inflammatory and proinflammatory roles. Accumulation of cAMP is generally associated with the inhibition of effector cell function in lymphocytes, such as TH1 cells and natural killer cells, and other immune cells, [20]. Consistent with this, DP-mediated signals also suppress cell migration and/or the activation of eosinophils, basophils, neutrophils, DCs, and fibroblasts [16,21-24]. Inhalation of a selective DP agonist suppresses
CRTH2 are mediated through a Goi-dependent increase in intracellular calcium levels and a reduction in intracellular cAMP levels, indicating that CRTH2-mediated signals are predominantly proinflammatory. Unlike the prostanoid DP receptor, CRTH2 is a member of the chemoattractant receptor family, sharing higher sequence homology to the fMLP and C5a receptors than to the prostanoid receptor family [16]. The PGD2 metabolites, 13, 14-dihydro-15-keto PGD2 (DK-PGD2), $\Delta^\alpha$ PGD2, PGJ2, $\Delta^\alpha$-PGJ2, 15d-PGJ2, and $\alpha$, $\beta$-PGF2 bind to CRTH2 [16,17,36] and activate eosinophils [36-38]. PGF2 is a stereoisomer of $\alpha$, $\beta$-PGF2, produced from PGH2 by the action of PGF synthase and from PGE2 by the action of PGE2-ketoreductase, independently of PGD synthetase. PGF2 is also implicated in CRTH2 signaling in the presence or absence of PGD2 production [39]. CRTH2 can also be activated by the thromboxane A, metabolite, 11-dehydro-TBX2 [40]. The existence of these CRTH2 agonists suggests that this receptor may be of physiological importance even in the absence of basal PGD2 production. Ramatroban (BAYu3405) is an effective CRTH2 antagonist [41]. Ramatroban was originally identified as a TP antagonist, but it has been discovered that this drug binds to the CRTH2 receptor with moderate affinity (its antagonistic activity against CRTH2 is about 10-fold lower than that against TP) and blocks responses to the selective CRTH2 agonist DK-PGD2, in vitro and in vivo [41,42]. Uller et al. [43] studied the specificity of CRTH2 antagonism by TM30089, which is closely related structurally to dual TP/CROT2 antagonists in mice. They assessed the inhibition of asthma-like pathological characteristics. Studies with these antagonists suggest that CRTH2 plays an important role mediating airway inflammation in response to an allergic challenge in both the guinea pig nasal mucosa [44] and mouse airway [45]. In humans, CRTH2 activation is responsible, at least in part, for the implications of PGD2 in asthma and inflammatory diseases [46,47] as well as allergic rhinitis [48] Thus, CRTH2 is considered to play an important role in allergic inflammation, similar to DP.

PGD2 enhances or suppresses inflammation by acting on different receptors expressed by hematopoietic and non-hematopoietic cells. Several cells of the immune system express both DP and CRTH2, which are coupled to apparently opposing signaling pathways. Because DP activation is often associated with inhibition of immune cell function [20], whereas CRTH2 activation leads to immune cell activation [20], it is tempting to hypothesize...
that these two PGD2 receptors collaborate to regulate inflammatory cell functions by different mechanisms. Although many immune cells coexpress DP and CRTH2, CRTH2-mediated signals often predominate over DP-mediated signals when cells are exposed to the non-selective agonist PGD2 [17,21,49], which binds to CRTH2 and DP with equal affinity [23,50]. One possible explanation for this observation may be the lower expression level of DP compared with that of CRTH2. Indeed, attempts to quantify DP and CRTH2 transcripts in immune cells, such as basophils, eosinophils, and TH1/2 cells, and in human airway smooth muscle cells have revealed significantly lower DP expression [4,21,24,28,51,52]. Because both DP and CRTH2 expression levels can be upregulated and downregulated by inflammatory stimuli [4,53,54], it is conceivable that the overall effect of PGD2 depends on the expression level of PGD2 receptors in a given cell.

**Role of PGD2 in TH2 cell functions**

TH2 cells, particularly those of the TH1/2 cell-related inflammatory response, have a crucial role in asthma pathogenesis. The TH1/2 type response is coordinated by TH2 cell differentiation and a modification of TH2 cell functions, such as cytokine production, recruitment, proliferation, survival, and apoptosis. Differentiation into each TH cell subset is delicately controlled in vivo by interactions with DCs. Airway DCs [25-27] express both CRTH2 and DP. The role of CRTH2 in DC function remains unclear, whereas DP-mediated regulation of DCs has been demonstrated in several studies. PGD2 suppresses the activation of DCs and prevents their migration into the T cell areas of draining lymph nodes [25]. This effect is mediated by DP. Indeed, it is mimicked by the DP-selective agonist BW 245C, but not by the CRTH2-selective agonist DK-PGD2 [25]. This suppressive mechanism by DP may underlie the inhibition of TH1/2 cell differentiation. Furthermore, inhaling a selective DP agonist suppresses the cardinal features of asthma by targeting the functions of lung DCs [55]. Interestingly, an increase in Foxp3+ CD4+ regulatory T cells was observed in mice treated with a DP agonist or DP-agonist-treated DCs, which suppressed inflammation in an IL-10-dependent manner. In contrast, it has been proposed that the DP-mediated inhibition of the production of TH1-inducing cytokines, such as IL-12 [26], by DCs favors T-cell development towards the TH12 phenotype [27]. This effect has been observed in preclinical models, such as TH1-dependent delayed-type hypersensitivity reactions [56], although additional mechanisms involving PPAR activation have been proposed in some cases.

Interestingly, DCs can themselves produce PGD2, which has been suggested to be involved in PGD2-mediated synthesis of CCL22/MDC, a chemoattractant for TH1/2 cells, in interferon (IFN)-γ-treated human keratinocytes [57]. DCs not only function as target of PGD2, but also may play an important role in modulating local immunity and inflammation through self-producing PGD2.

Among human TH cell subsets, CRTH2 is preferentially expressed on TH1/2 cells, and is the most reliable marker to identify human CD4+ TH1/2 memory cells [32,58]. In contrast, DP is expressed on both TH1 and TH2 cells. Importantly, CRTH2 mediates the migration of TH1/2 cells towards PGD2 [16] and delays TH2 cell apoptosis. Recently, human CRTH2+ TH1/2 memory cells were reported to be maintained by TSLP-activated DC. Furthermore, CRTH2+CD4+ TH1/2 memory cells activated by TSLP-DCs undergo further TH1/2 polarization and express prostaglandin PGD2 synthase. Thus, in cooperation with DC-derived PGD2, TH1/2 cell-derived PGD2 may promote further accumulation of TH1/2 cells to the inflamed tissue [59] by positive feedback mechanisms, causing persistent inflammation and damage to the asthma airways.

Another notable role of PGD2 is regulating the production of proinflammatory cytokines in TH1/2 cells [28,51]. Tanaka et al. have shown that human CD4+ and CD8+ T cells producing IFN-γ and IL-2 are reduced in number by DP-mediated signals [28], whereas CRTH2-mediated signals enhance the ability of human TH1/2 cells to produce IL-2, IL-4, IL-5, and IL-13, an effect that was inhibited by ramatroban [51]. This PGD2-mediated effect on cytokine production by TH1/2 cells is mimicked by the selective CRTH2 agonist DK-PGD2 [51]. CRTH2-mediated PGD2 effects were dominantly observed on CRTH2+ TH1/2 cells, compared with DP-mediated effects after treatment with BW 245C, resulting in the attenuated production of cytokines by TH1/2 cells [28]. Furthermore, activation of TH1/2 cells in response to supernatants from immunologically activated human mast cells is mediated by PGD2, through an action on CRTH2 [60]. Together, these findings suggest that PGD2 favors TH1/2 functions through CRTH2 for recruiting TH1/2 cells to sites of allergic inflammation and for driving TH1/2-cytokine production, while restraining TH1 functions via DP, which may contribute to the development of TH1/2-dominated status during allergic inflammation. However, CRTH2 expression in mice is not
biased towards T_{H2} cells, unlike humans \[61\], and the functions of CRTH2 may differ between mice and humans. Indeed, IL-4 and IFN-γ production was not affected in CRTH2-deficient mice. These results do suggest that the cytokines and chemokines regulated by CRTH2 differ between mice and humans. Furthermore, Chevalier et al. \[62\] found that CRTH2-deficient mice show enhanced eosinophil recruitment into the lung, compared with their wild-type littermates, and showed that CRTH2-deficient T cells produced significantly higher amounts of IL-5 and IL-3 in vitro. These results suggest a non-redundant role for CRTH2 in restricting eosinophilia and allergic responses in vivo. The authors suggested that one possible explanation for their findings was that CRTH2 promoted IL-5 production early on, and that the inhibitory pathway was subsequently turned on. In contrast, Satoh et al. \[63\] reported that allergic skin inflammation and IgE production were significantly diminished in CRTH2-deficient mice, consistent with the results of the pharmacological studies with human cells discussed above. Studies of allergic responses in mice in which CRTH2 has been genetically deleted have so far produced conflicting results. The CRTH2-mediated effects of PGD₂ may interact in a complex fashion, with redundant roles and non-redundant roles, in stimulating cytokine production and allergic inflammation. These findings suggest that CRTH2 might be a highly promising therapeutic target, because CRTH2 blockade by small-molecule antagonists is likely to attenuate T_{H2} activity with respect to accumulation at sites of inflammation, cytokine release, and survival in tissue (Fig. 2).

**Role of PGD₂ in nonhematopoietic-cell functions**

Although minimal expression of DP was detected in the lungs of non-immunized mice, an airway OVA challenge markedly enhanced DP receptor expression \[30\]. Immunoelectron microscopy, using an antibody to mouse DP, revealed that the DP receptor is highly expressed on ciliated and non-ciliated epithelial cells of the bronchioles.

---

**Figure 2.** Hypothetical mechanism for developing asthmatic airway inflammation promoted by prostaglandin D₂ (PGD₂). PGD₂ has been recognized as an important mediator of asthmatic airway inflammation. Critical effects of receptors, in particular the D-prostanoid receptor (DP) and chemoattractant receptor homologous molecule expressed on T_{H2} cells (CRTH2), are immune and inflammatory regulators of various immune cells, particularly T cells, basophil, eosinophils, mast cells, dendritic cells, and bronchial epithelial cells. CRTH2 signaling is involved in accelerating allergic inflammation by promoting chemotaxis and upregulating cytokine production. In contrast, the effect of DP signaling is mainly as an immune suppressor. MDC, macrophage-derived chemokine; TSLP, thymic stromal lymphopoietin; IL, interleukin.
and type II alveolar epithelial cells. Moderate expression was also found in type I alveolar epithelial cells and inflammatory white blood cells [30]. Airway epithelium has been proposed to be a source of proinflammatory cytokines and chemokines during asthma pathogenesis [64]. These findings suggest the following model for PGD2 in asthma: mast cell-derived PGD2 acts at DP receptors in the epithelium and stimulates the production and release of cytokines and chemokines to induce airway inflammation, obstruction, and hyper-reactivity. Chiba et al. reported that PGD2 induced IL-8 and granulocyte-macrophage colony-stimulating factor by bronchial epithelial cells, Honda et al. [6] established a novel experimental model of asthma that permitted the direct assessment of the role of PGD2 in airway inflammation. Antigen-sensitized mice were exposed to aerosolized PGD2 1 day before challenge with low-dose aerosolized antigen. The results showed that not only the numbers of eosinophils, lymphocytes, and macrophages, but also the levels of IL-4 and IL-5 in BALF were higher in PGD2-pretreated mice than in control mice. Moreover, the expression of MDC, a TH2 cell chemoattractant, was higher in PGD2-pretreated mice than in controls. Furthermore, the authors showed that injecting anti-MDC antibody into PGD2-pretreated mice markedly inhibited inflammatory cell infiltration as well as TH2 cytokine production after antigen challenge. These results indicate that PGD2 accelerates TH2 type inflammation by inducing MDC. However, unfortunately, the PGD2 receptor required for the epithelial induction of MDC expression has yet to be identified, although DP is a candidate receptor for the initiation of MDC production in epithelial cells.

Recently, a novel aspect of DP in airway epithelial cells was shown by Mandal et al. [5]. They demonstrated that uteroglobin (UG)-deficient mice had elevated levels of PGD2 in BALF and increased COX-2 gene expression in epithelial cells. They also found that DP signaling was mediated via p38 MAP kinase (MAPK), p44/42 MAPK, and protein kinase C (PKC) pathways in a cell type-specific manner, leading to the activation of nuclear factor (NF)-κB, which then stimulated COX-2 expression. UG as also found to bind PGD2, block DP signaling, inhibit NF-κB activation, and, consequently, suppress COX-2 gene expression. These studies demonstrated that DP signaling mediated allergic inflammatory responses by activating NF-κB, which stimulated COX-2 expression. This phenomenon is also observed in fibroblasts and smooth muscle cells. Thus, in asthma, DP augments the production of COX-2 metabolites of arachidonic acid, including PGD2, in airway epithelial cells by an autocrine mechanism, resulting in their local accumulation and further production of chemokines. UG thus appears to be a key component of an innate homeostatic mechanism, acting to prevent stimulation of an allergen-induced, DP-mediated inflammatory response (Fig. 2).

Role of PGD2 in inflammatory cell functions (mast cells, eosinophils, and basophils)

TH2 cells play an important role in allergic disease by organizing the characteristic inflammatory response, involving mast cells, basophils, and eosinophils. These inflammatory cells also produce TH2 type cytokines, indicating that these cells and TH2 cells interact to promote TH2 type inflammation in asthma. While the above studies suggest an important role for PGD2 in asthma pathogenesis, DP suppresses mast cell activation. Chan et al. [66] collected rat peritoneal mast cells and examined the effects on anti-IgE-induced histamine release of agonists specific to various types of prostanoid receptors. They found that several prostanoid agonists inhibited histamine release; BW 245C and ZK 118182 were the most potent. Based on these findings, they suggested that developing highly specific agonists for the mast cell DP receptor might improve the management of allergic diseases, such as asthma. In contrast, Matsuoka et al. [30] showed that the net action of DP in allergic asthma appears to be facilitative, given that DP is present. Strong evidence supporting a role for CRTH2 in mast cells is lacking, although the receptor is expressed. In contrast, activating CRTH2 induces migration of murine mast cells, based on the upregulation of CD23 and CD30 on the cell surface.

Eosinophils express both DP and CRTH2, which interact to regulate cellular responses to PGD2. Previous studies have revealed that CRTH2 mediates eosinophil chemotaxis induced by mast cell products [34]. The receptor directly responsible for stimulating eosinophil migration appears to be CRTH2, not DP [16]. Gervais et al. [21] found that DK PGD2, a CRTH2 agonist, stimulated chemokinesis and degranulation of eosinophils, whereas BW 245C did not. CRTH2 activation also leads to changes in the shape of eosinophils, chemotaxis, enhanced chemotactic responsiveness to other chemoattractants, and
degranulation [21,22,38,39], whereas DP activation is linked to eosinophil apoptosis [21], which is delayed by BW 245C but not DK-PGD2. However, inhibiting DP with the selective antagonist BW A868C resulted in markedly enhanced CRTH2-mediated activation, as assessed by an increase in CD11b expression on exposure to PGD2 [22]. Novel effects of PGD2 on eosinophils have been reported by Mesquita-Santos et al. [67]. They showed that administering PGD2 to mice enhanced leukotrienes (LT) C4 production by inducing lipid body-driven LTC4 synthesis, dependent on the synergistic activity of endogenous eotaxin, acting via the CCR3 receptor.

Opposing effects of DP and CRTH2 on cell function have also been observed in basophils, circulating leukocytes that are particularly relevant during the late phase of the allergic response and for asthmatic inflammation [24]. CRTH2 signaling is responsible for mobilizing intracellular Ca2+ in basophils, upregulating CD11b and CD203c expression, and enhancing IgE-mediated basophil degranulation [68]. Conversely, DP activation inhibits basophil migration and IgE-mediated degranulation. Thus, it seems that activating basophils and eosinophils, balanced by PGD2 via the dual receptor system, plays an important role in asthma.

According to CRTH2 and DP studies, these two receptor subtypes may collaborate in the activation and accumulation of inflammatory cells, such as mast cells, eosinophils, and basophils, at sites of allergic inflammation (Fig. 2).

Role of the PGD2 receptor in allergic disease pathogenesis

Recent studies have shown an accumulation of CRTH2-positive leukocytes, including Th2 cells, eosinophils, basophils, and mast cells, in human allergic inflammatory regions. Furthermore, CRTH2 mRNA and protein levels are higher in eosinophils from atopic subjects than in those from healthy controls [69]. Consistent with the increased number of CRTH2 receptors in eosinophils from atopic individuals, PGD2-induced chemotaxis is significantly higher in these cells. Increased levels of CRTH2 expression and an enhanced sensitivity of eosinophils to PGD2 might explain the tissue eosinophilia in atopic patients. Furthermore, the percentage of CD4+ T cells expressing CRTH2 in patients with AD correlates with disease severity [70-72]. Additionally, available evidence indicates that genetic alterations in CRTH2 are related to allergic asthma. Genetic variants of CRTH2 predispose individuals to develop asthma. CRTH2 is associated with severe asthma in African-American and Chinese populations [70]. Associated polymorphisms in the 3′-untranslated region of CRTH2 lead to increased mRNA stability, suggesting that CRTH2 variants are associated with higher degrees of bronchial hyperresponsiveness and are causally linked to asthma [70]. These findings indicate that higher CRTH2 expression levels and increased responsiveness to its PGD2 ligand may be the biological basis for the association of this receptor with asthma. In contrast, variants of PTGDR (the gene encoding DP) with reduced transcriptional activity have been detected in patients with asthma [73]. Studies in a small cohort of patients with asthma provided evidence that these putative loss-of-function variants protect against asthma development.

CONCLUSION

PGD2 has been recognized as an important mediator of allergic responses. It is becoming clear that PGD2 and its metabolites may play important roles in the pathogenesis of allergic diseases, including asthma. Although the potential clinical benefits of modifying PGD2-related receptor function remain unsubstantiated, many studies have provided promising evidence that these receptors are immune and inflammatory regulators in various immune cells. The roles of DP and CRTH2 are diverse and complex in the allergic system. Thus, future studies into the function(s) of these receptors will likely lead to new approaches for the treatment and, perhaps, prevention of allergic diseases, including asthma.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

We thank Emiko Ohta for help in preparing the manuscript.
REFERENCES

1. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest 2008;118:3546-3556.

2. Wills-Karp M, Finkelman FD. Untangling the complex web of IL-4- and IL-13-mediated signaling pathways. Sci Signal 2008;1:pe55.

3. Smith WI, Meade EA, Devitt DL. Pharmacology of prostaglandin endoperoxide synthase isozymes-1 and -2. Ann N Y Acad Sci 1994;714:136-142.

4. Fujitani Y, Kanoaka Y, Aritake K, Uodome N, Okazaki-Hatake K, Urade Y. Pronounced eosinophilic lung inflammation and Th2 cytokine release in human lipocalin-type prostaglandin D synthase transgenic mice. J Immunol 2002;168:443-449.

5. Mandal AK, Zhang Z, Ray R, et al. Uteroglobin represses allergen-induced inflammatory response by blocking PGD2 receptor-mediated functions. J Exp Med 2004;199:1317-1330.

6. Honda K, Arima M, Cheng G, et al. Prostaglandin D2 reinforces Th2 type inflammatory responses of airways to low-dose antigen through bronchial expression of macrophage-derived chemokine. J Exp Med 2003;198:333-354.

7. Urade Y, Uijihara M, Horiuchi Y, Iki K, Hayashi O. The major source of endogenous prostaglandin D2 production is likely antigen-presenting cells. Localization of glutathione-requiring prostaglandin D synthetase in histiocytes, dendritic, and Kupffer cells in various rat tissues. J Immunol 1989;143:2982-2989.

8. Tanaka K, Ogawa K, Sugamura K, Nakamura M, Takano S, Nagata K. Cutting edge: differential production of prostaglandin D2 by human helper T cell subsets. J Immunol 2000;164:2277-2280.

9. Murray JJ, Tonnel AB, Brash AR, et al. Release of prostaglandin D2 into human airways during acute antigen challenge. N Engl J Med 1986;315:800-804.

10. Nacero RM, Meier HL, Kagey-Sobotka A, et al. Mediator release after nasal airway challenge with allergen. Am Rev Respir Dis 1983;128:597-602.

11. Charlesworth EN, Kagey-Sobotka A, Schleimer RP, Norman PS, Lichtenstein LM. Prednisone inhibits the appearance of inflammatory mediators and the influx of eosinophils and basophils associated with the cutaneous late-phase response to allergen. J Immunol 1991;146:671-676.

12. Benyon RC, Robinson C, Church MK. Differential release of histamine and eicosanoids from human skin mast cells activated by IgE-dependent and non-immunological stimuli. Br J Pharmacol 1989;97:898-904.

13. Schumman ES, Newhall HH, Demers LM, Fitzpatrick FA, Adkinson NF Jr. Anaphylactic release of thromboxane A2, prostaglandin D2, and prostaclin from human lung parenchyma. Am Rev Respir Dis 1981;124:402-406.

14. Hirata M, Kazikawa A, Aizawa M, Ushikubi F, Narumiya S. Molecular characterization of a mouse prostaglandin D receptor and functional expression of the cloned gene. Proc Natl Acad Sci USA 1994;91:11192-11196.

15. Boie Y, Sawyer N, Slipetz DM, Metters KM, Abramovitz M. Molecular cloning and characterization of the human prostanoid DP receptor. J Biol Chem 1995;270:18910-18916.

16. Hirai H, Tanaka K, Yoshiie O, et al. Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. J Exp Med 2001;193:255-261.

17. Sawyer N, Cauchon E, Chateauneuf A, et al. Molecular pharmacology of the human prostaglandin D2 receptor, CRTH2. Br J Pharmacol 2002;137:1163-1172.

18. Giles H, Leff P, Bolofo ML, Kelly MG, Robertson AD. The classification of prostaglandin DP-receptors in platelets and vasculature using BW A868C, a novel, selective and potent competitive antagonist. Br J Pharmacol 1989;96:291-300.

19. Whittle BJ, Hamid S, Lidbury P, Rosam AC. Specificity between the anti-aggregatory actions of prostacyclin, prostaglandin E1 and D2 on platelets. Adv Exp Med Biol 1985;192:109-125.

20. Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J Clin Invest 2001;108:15-23.

21. Gervais FG, Cruz RP, Chateauneuf A, et al. Selective modulation of chemokinesis, degranulation, and apoptosis in eosinophils through the PGD2 receptors CRTH2 and DP. J Allergy Clin Immunol 2001;108:982-988.

22. Monneret G, Gravel S, Diamond M, Rokach J, Powell WS. Prostaglandin D2 is a potent chemoattractant for human eosinophils that acts via a novel DP receptor. Blood 2001;98:1942-1948.

23. Angeli V, Staumont D, Charbonnier AS, et al. Activation of the D prostanoid receptor 1 regulates immune and skin allergic responses. J Immunol 2004;172:3822-3829.

24. Yoshimura-Uchiyama C, Ikura M, Yamaguchi M, et al. Differential modulation of human basophil functions through prostaglandin D2 receptors DP and chemoattractant receptor-homologous molecule expressed on Th2 cells/DP2. Clin Exp Allergy 2004;34:1283-1290.

25. Hammad H, de Heer HJ, Soullie T, Hoogsteden HC, Trottle F, Lambrecht BN. Prostaglandin D2 inhibits airway dendritic cell migration and function in steady state conditions by selective activation of the D prostanoid receptor 1. J Immunol 2003;171:3936-3940.

26. Faveeuw C, Gosset P, Bureau F, et al. Prostaglandin D2 inhibits the production of interleukin-12 in murine dendritic cells through multiple signaling pathways. Eur J Immunol 2003;33:889-898.
27. Gosset P, Pichavant M, Faveveu C, Buref F, Tonnel AB, Trottein F. Prostaglandin D2 affects the differentiation and functions of human dendritic cells: impact on the T cell response. Eur J Immunol 2003;35:1491-1500.

28. Tanaka K, Hirai H, Takano S, Nakamura M, Nagata K. Effects of prostaglandin D2 on helper T cell functions. Biochem Biophys Res Commun 2004;316:1009-1014.

29. Hirano Y, Shichijo M, Deguchi M, et al. Synergistic effect of PGD2 via prostanoxin DP receptor on TNF-alpha-induced production of MCP-1 and IL-8 in human monocytic THP-1 cells. Eur J Pharmacol 2007;560:81-88.

30. Matsuoka T, Hirata M, Tanaka H, et al. Prostaglandin D2 as a mediator of allergic asthma. Science 2000;287:2013-2017.

31. Arimura A, Yasui K, Kishino J, et al. Prevention of allergic inflammation by a novel prostaglandin receptor antagonist, S-5751. J Pharmacol Exp Ther 2001;298:411-419.

32. Zhu G, Vestbo J, Lenney W, et al. Association of PTGDR gene polymorphisms with asthma in two Caucasian populations. Genes Immun 2007;8:398-403.

33. Cosmi L, Anmuznati F, Iwasaki M, et al. CRTH2 is the most reliable marker for the detection of circulating human type 2 Th and type 2 T cytotoxic cells in health and disease. Eur J Immunol 2000;30:2972-2979.

34. Nagata K, Hirai H, Tanaka K, et al. CRTH2, an orphan receptor of T-helper-2-cells, is expressed on basophils and eosinophils and responds to mast cell-derived factor(s). FEBS Lett 1999;459:195-199.

35. Gosset P, Buref F, Angeli V, et al. Prostaglandin D2 affects the maturation of human monocyte-derived dendritic cells: consequence on the polarization of naive Th cells. J Immunol 2003;170:4943-4952.

36. Gazi L, Gyles S, Rose J, et al. Delta12-prostaglandin D2 is a potent and selective CRTH2 receptor agonist and causes activation of human eosinophils and Th2 lymphocytes. Prostaglandins Other Lipid Mediat 2005;75:153-167.

37. Monneret G, Li H, Vasilescu J, Rokach J, Powell WS. 15-Deoxy-delta 12,14-prostaglandins D2 and J2 are potent activators of human eosinophils and Th2 lymphocytes. Prostaglandins Other Lipid Mediat 2005;75:153-167.

38. Heinemann A, Schuligoi R, Sabroe I, Hartnell A, Peskar BA. Delta 12-prostaglandin J2, a plasma metabolite of prostaglandin D2, causes eosinophil mobilization from the bone marrow and primes eosinophils for chemotaxis. J Immunol 2003;170:4752-4758.

39. Schmidt G, Goehring UM, Schirmer J, et al. Lysine and polyamines are substrates for transglutamination of Rho by the Bordetella dermonecrotic toxin. Infect Immun 2001;69:7663-7670.

40. Bohn E, Sturm GJ, Weighfhofer I, et al. 11-Dehydro-thromboxane B2, a stable thromboxane metabolite, is a full agonist of chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2) in human eosinophils and basophils. J Biol Chem 2004;279:7663-7670.

41. Sugimoto H, Shichijo M, Ino T, et al. An orally bioavailable small molecule antagonist of CRTH2, ramatroban (BAY u 3405), inhibits prostaglandin D2-induced eosinophil migration in vitro. J Pharmacol Exp Ther 2003;305:347-352.

42. Shichijo M, Sugimoto H, Nagao K, et al. Chemoattractant receptor-homologous molecule expressed on Th2 cells activation in vivo increases blood leukocyte counts and its blockade abrogates 13,14-dihydro-15-keto-prostaglandin D2-induced eosinophilia in rats. J Pharmacol Exp Ther 2003;307:518-525.

43. Uller L, Mathiesen JM, Alenmyr L, et al. Antagonism of the prostaglandin D2 receptor CRTH2 attenuates asthma pathology in mouse eosinophilic airway inflammation. Respir Res 2007;8:16-25.

44. Narita S, Asakura K, Kataura A. Effects of thromboxane A2 receptor antagonist (Bay u 3405) on nasal symptoms after antigen challenge in sensitized guinea pigs. Int Arch Allergy Immunol 1996;109:161-166.

45. Nagai H, Takeda H, Yamaguchi S, Tanaka H, Matsuo A, Inagaki N. The effect of a thromboxane A2 receptor antagonist BAY-u-3405 on experimental allergic reactions. Prostaglandins 1995;50:75-87.

46. Kabashima K, Narumiya S. The DP receptor, allergic inflammation and asthma. Prostaglandins Leukot Essent Fatty Acids 2003;69:187-194.

47. Nagata K, Hirai H. The second PGD(2) receptor CRTH2: structure, properties, and functions in leukocytes. Prostaglandins Leukot Essent Fatty Acids 2003;69:169-177.

48. Nantel F, Fong C, Lamontagne S, et al. Expression of prostaglandin D synthase and the prostaglandin D2 receptors DP and CRTH2 in human nasal mucosa. Prostaglandins Other Lipid Mediat 2004;73:87-101.

49. Gallant MA, Samadifam R, Hackett JA, Antoniou J, Parent JL, de Brum-Fernandes AJ. Production of prostaglandin D(2) by human osteoblasts and modulation of osteoprotegerin, RANKL, and cellular migration by DP and CRTH2 receptors. J Bone Miner Res 2005;20:672-681.

50. Hirai H, Abe H, Tanaka K, et al. Gene structure and functional properties of mouse CRTH2, a prostaglandin D2 receptor. Biochem Biophys Res Commun 2003;307:797-802.

51. Xue L, Gyles SL, Wettey FR, et al. Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemoattractant receptor-like molecule expressed on Th2 cells. J Immunol 2005;175:6531-6536.

52. Clarke DL, Belvisi MG, Smith SJ, et al. Prostanoid receptor expression by human airway smooth muscle cells and regulation
of the secretion of granulocyte colony-stimulating factor. Am J Physiol Lung Cell Mol Physiol 2005;288:L238-L250.

53. Venet F, Lepape A, Debard AL, Bienvenu J, Bohé J, Monneret G. The Th2 response as monitored by CRTH2 or CCR3 expression is severely decreased during septic shock. Clin Immunol 2004;113:278-284.

54. Hamada K, Yamada Y, Kamada Y, et al. Prostaglandin D and interleukin-5 reduce CRTH2 surface expression on human eosinophils. Allergol Int 2004;53:179-184.

55. Hammad H, Kool M, Soullié T, et al. Activation of the D prostanoïd 1 receptor suppresses asthma by modulation of lung dendritic cell function and induction of regulatory T cells. J Exp Med 2007;204:357-367.

56. Trivedi SG, Newson J, Rajakariar R, et al. Essential role for hematopoietic prostaglandin D2 synthase in the control of delayed type hypersensitivity. Proc Natl Acad Sci U S A 2006;103:5179-5184.

57. Shimura C, Satoh T, Igawa K, et al. Dendritic cells express hematopoietic prostaglandin D synthase and function as a source of prostaglandin D2 in the skin. Am J Pathol 2010;176:227-237.

58. Wang YH, Ito T, Wang YH, et al. Maintenance and polarization of human TH2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells. Immunity 2006;24:827-838.

59. Vinall SL, Townsend ER, Pettipher R. A paracrine role for chemoattractant receptor-homologous molecule expressed on T helper type 2 cells (CRTH2) in mediating chemotactic activation of CRTH2+ CD4+ T helper type 2 lymphocytes. Immunology 2007;121:577-584.

60. Gyles SL, Xu L, Townsend ER, Wettey F, Pettipher R. A dominant role for chemoattractant receptor-homologous molecule expressed on T helper type 2 (Th2) cells (CRTH2) in mediating chemotaxis of CRTH2+ CD4+ Th2 lymphocytes in response to mast cell supernatants. Immunology 2006;119:362-368.

61. Abe H, Takeshita T, Nagata K, et al. Molecular cloning, chromosome mapping and characterization of the mouse CRTH2 gene, a putative member of the leukocyte chemoattractant receptor family. Gene 1999;237:71-77.

62. Chevalier E, Stock J, Fisher T, et al. Cutting edge: chemoattractant receptor-homologous molecule expressed on Th2 cells plays a restricting role on IL-5 production and eosinophil recruitment. J Immunol 2005;175:2056-2060.

63. Satoh T, Moroi R, Aritake K, et al. Prostaglandin D2 plays an essential role in chronic allergic inflammation of the skin via CRTH2 receptor. J Immunol 2006;177:2621-2629.

64. Holgate ST. The inflammation-repair cycle in asthma: the pivotal role of the airway epithelium. Clin Exp Allergy 1998;28 Suppl 5:97-103.

65. Chiba T, Kanda A, Ueki S, et al. Prostaglandin D2 induces IL-8 and GM-CSF by bronchial epithelial cells in a CRTH2-independent pathway. Int Arch Allergy Immunol 2006;141:300-307.

66. Chan CL, Jones RL, Lau HY. Characterization of prostaglandin receptors mediating inhibition of histamine release from anti-IgE-activated rat peritoneal mast cells. Br J Pharmacol 2000;129:589-597.

67. Mesquita-Santos FP, Vieira-de-Abreu A, Calheiros AS, et al. Cutting edge: prostaglandin D2 enhances leukotriene C4 synthesis by eosinophils during allergic inflammation: synergistic in vivo role of endogenous eotaxin. J Immunol 2006;176:1326-1330.

68. Monneret G, Boumiza R, Gravel S, et al. Effects of prostaglandin D(2) and 5-lipoxygenase products on the expression of CD203c and CD11b by basophils. J Pharmacol Exp Ther 2005;312:627-634.

69. Okada N, Fukagawa K, Tanaka M, et al. CRTH2 expression on eosinophils from atopic patients. Invest Ophthalmol Vis Sci 2004;45:4853-B177.

70. Huang JL, Gao PS, Mathias RA, et al. Sequence variants of the gene encoding chemoattractant receptor expressed on Th2 cells (CRTH2) are associated with asthma and differentially influence mRNA stability. Hum Mol Genet 2004;13:2691-2697.

71. Luster AD, Tager AM. T-cell trafficking in asthma: lipid mediators grease the way. Nat Rev Immunol 2004;4:711-724.

72. Hata AN, Breyer RM. Pharmacology and signaling of prostaglandin receptors: multiple roles in inflammation and immune modulation. Pharmacol Ther 2004;103:147-166.

73. Oguma T, Palmer LJ, Birben E, Sonna LA, Asano K, Lilly CM. Role of prostanoïd DP receptor variants in susceptibility to asthma. N Engl J Med 2004;351:1752-1763.