CRTH2 and D-Type Prostanoid Receptor Antagonists as Novel Therapeutic Agents for Inflammatory Diseases

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Abstract
Accumulation of type 2 T helper (Th2) lymphocytes and eosinophils is a hallmark of bronchial asthma and other allergic diseases, and it is believed that these cells play a crucial pathogenic role in allergic inflammation. Thus, Th2 cells and eosinophils are currently considered a major therapeutic target in allergic diseases and asthma. However, drugs that selectively target the accumulation and activation of Th2 cells and eosinophils in tissues are unavailable so far. Prostaglandin (PG)D2 is a key mediator in various inflammatory diseases including allergy and asthma. It is generated by activated mast cells after allergen exposure and subsequently orchestrates the recruitment of inflammatory cells to the tissue. PGD2 induces the chemotaxis of Th2 cells, basophils and eosinophils, stimulates cytokine release from these cells and prolongs their survival, and might hence indirectly promote IgE production. PGD2 mediates its biologic functions via 2 distinct G protein-coupled receptors, D-type prostanoid receptor (DP), and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). DP and CRTH2 receptors are currently being considered as highly promising therapeutic targets for combating allergic diseases and asthma. Here, we revisit the roles of PGD2 receptors in the regulation of eosinophil and Th2 cell function and the efforts towards developing candidate compounds for clinical evaluation.

Introduction
Atopy is one of the most prevalent diseases in the developed world. The prevalence of allergic rhinitis, conjunctivitis, bronchial asthma and dermatitis among others is as high as 20% in the populations of Western countries. Atopy is a genetically determined disorder which results in characteristic inflammatory responses to antigens that are innocuous per se. Many forms of atopy such as asthma are associated with a major reduction in quality of life and life expectancy. In addition, some diseases such as intrinsic asthma, aspirin sensitivity, nasal polyps, adenoid hyperplasia or chronic idiopathic urticaria share several clinical and pathophysiological features of allergy, but with less clear ties to allergens. The pathogenic basis of atopy and related disorders is still only partially understood and no causal therapy, except for specific immunotherapy in selected cases, is available to date. Currently employed symptomatic regimens are...
frequently ineffective or, like corticosteroids, might have serious side effects [1, 2]. Therefore, demand persists for additional treatments of allergic diseases, particularly for those patients who need to avoid corticosteroids (e.g., children), and those who are insufficiently treated by standard therapeutic regimens. In the case of bronchial asthma, these patients rely mainly on bronchodilator therapy and are at risk of suffering both from side effects of these drugs and uncontrolled pulmonary inflammation leading to airway remodeling [3]. The discovery of the orphan G protein-coupled receptor GPR44, its expression pattern (basophils, eosinophils and type 2 T helper, Th2, cells) [4] and its ensuing deorphanization as a receptor for the mast cell-derived mediator prostaglandin (PG)D2 [5] has fueled additional research in the field. This novel receptor, meanwhile termed 'chemoattractant receptor-homologous molecule expressed on Th2 cells' (CRTH2), has thus provided an innovative and promising target for antiinflammatory drug development.

Role of PGD2 in Allergic Inflammation

Like other prostanoids, PGD2 is synthesized by phospholipase A2, cyclooxygenase and specific terminal synthases upon activation of cells by different stimuli such as allergens, oxidative stress or cytokines. PGD2 is the major mast cell product that is released during anaphylaxis [6, 7] and substantial evidence has accumulated in the last few years that PGD2 might be involved in the initiation and perpetuation of allergic inflammation. However, PGD2 is produced in significant amounts also by dendritic cells, macrophages, eosinophils, Th2 cells and endothelial cells [8–14]. A prominent contribution of PGD2 to the late-phase allergic reaction is, on the one hand, suggested by enhanced eosinophilic lung inflammation and cytokine release in transgenic mice overexpressing PGD synthase [15]. Moreover, PGD2 enhances leukotriene (LT) C4 synthesis by eosinophils during allergic inflammation [16]. Conversely, an inhibitor of hematopoietic PGD synthase attenuates the antigen-induced production of PGD2 and ameliorates airway inflammation in vivo in mice [17]. Interestingly, the biosynthesis of PGD2 increases after the intake of cyclooxygenase inhibitors in aspirin-intolerant patients [18–20]. The resulting imbalance between PGD2 and PGE2 has been suggested to favor the development of asthma and nasal polyposis [21]. On the other hand, PGD2 has been suggested to play a beneficial role in the resolution phase of inflammation by controlling Th1-mediated mechanisms [22, 23].

Receptors for PGD2

The biological effects of PGD2 are, in principle, mediated by two distinct G protein-coupled receptors, D-type prostanoid receptor (DP) and CRTH2. Moreover, at higher concentrations, PGD2 is a ligand for the thromboxane (TX) receptor, which mediates the bronchoconstrictor effect of PGD2 [24, 25].

Chemoattractant Receptor-Homologous Molecule Expressed on Th2 Cells

CRTH2, also known as DP2, GPR44 or CD294, has initially been found on Th2 cells, eosinophils and basophils [4], and mediates their chemotaxis towards PGD2 [5, 26]. However, the CRTH2 receptor is activated not only by PGD2 but also by several PGD2 metabolites – including 13,14-dihydro-15-keto-PGD2, PGJ2, Δ12PGJ2, Δ12PGD2, 9α,11β-PGF2 and 15-deoxy-PGJ2 [27–30] –, by PGF2α [30], a thromboxane metabolite, 11-dehydro-TXB2 [31], and also by the precursor of all 2-series PG and TX, PGH2 [32]. In animal models, exogenously administered CRTH2 agonists can induce eosinophil infiltration into the lungs and skin, and aggravate the pathology of allergic responses [33–35]. Moreover, several experimental studies in mice have shown that CRTH2 antagonists can ameliorate allergen-induced cutaneous, pulmonary and upper respiratory inflammation [36–41]. In humans, sequence variants of the gene encoding CRTH2 are associated with asthma and allergic phenotypes [42]. In addition, recent data suggest that CRTH2 is also expressed on monocytes [43] and macrophages, and mediates their migration induced by PGD2 and endotoxin [8, 44]. Strikingly, PGD2 levels in bronchoalveolar lavage fluid of patients with chronic obstructive pulmonary disease correlate inversely with lung function [45]. Therefore, using CRTH2 antagonists is currently being considered as a highly promising approach to the treatment of allergic diseases and asthma. Interestingly, a CRTH2 antagonist is currently being evaluated in phase II trials in patients with chronic obstructive pulmonary disease (clinical trial registration No. NCT00690482, NCT00766415).

CRTH2 signals through G0, proteins, leading to inhibition of cAMP formation and increases in intracellular Ca2+ [5]. In eosinophils, however, we observed that CRTH2 stimulation leads to pertussis-toxin-insensitive activation of phosphatidylinositol 3-kinase (PI3K), phospholipase C, p38 mitogen-activated protein kinase (MAPK) and mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) pathways that mediate eosinophil shape change, actin polymerization

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and CD11b upregulation [26, 46]. The migration and survival of Th2 cells in response to PGD2-induced stimulation of CRTH2 depend on PI3K, while PGD2-evoked cytokine release involves PI3K, calcineurin and nuclear factor of activated T cells [47]. On the other hand, preactivation of p38 MAPK and glycogen synthase kinase-3β restrain the CRTH2-mediated migration of eosinophils and the cytokine section of Th2 cells, respectively [47, 48]. A recent study revealed that, unexpectedly, CRTH2 is not phosphorylated upon agonist stimulation, a mechanism by which the activity of most G protein-coupled receptors is typically regulated. Instead, the C terminus of CRTH2 inhibits Gαi signaling, which may compensate for the absence of the classical phosphorylation-dependent signal attenuation [49].

D-Type Prostanoid Receptor

DP, also referred to as DP1, is expressed more widely than CRTH2, including platelets, several types of leukocytes, the vasculature, the central nervous system, retina, nasal mucosa, lungs and intestine [5, 50–54]. Activation of the DP receptor results in cutaneous and pulmonary venous vasodilatation, arterial hypotension, mucin secretion, inhibition of platelet aggregation and lowering of intraocular pressure [54–60]. DP has been described to play both antiinflammatory and proinflammatory roles: on the one hand, DP activation inhibits the function of neutrophils, basophils, dendritic cells, Langerhans cells, Th1 cells and natural killer cells [43, 61–67]. In vivo, inhalation of a selective DP agonist suppresses asthma in a murine model by downmodulation of lung dendritic cell function and induction of regulatory T cells [68]. In addition, PGD2 but not CRTH2 agonists inhibit the scratching response of mice with atopic dermatitis [69]. Stimulation of DP enhances the barrier function of endothelial cells [70] and confers protection to neurons [71]. On the other hand, PGD2 and DP receptors contribute to astrogliosis and demyelination in the twitcher mouse model [72]. PGD2 synergizes with tumor necrosis factor via DP receptors to promote the production of monocyte chemoattractant protein-1 and interleukin (IL)-8 in monocytic cells [73]. In vivo, a DP antagonist blocks antigen-induced rhinitis, conjunctivitis and eosinophil infiltration into the lung of the guinea pig [74, 75] and experimental asthma in sheep [76]. DP-deficient mice exhibit reduced pulmonary inflammation in response to allergens [77]. The DP receptor is expressed on bronchiolar epithelial cells in antigen-challenged mice [77], as well as nasal epithelial goblet cells in normal human volunteers [52], suggesting that DP might stimulate mucus secretion in allergy. However, an association of polymorphisms of the DP promoter and gene with asthma has been detected in humans [78]. These findings hence point to a proinflammatory role of DP, but are difficult to reconcile with the known functional responses to DP receptor activation.

Despite the fact that it has comparable avidity for PGD2, the DP receptor shows little similarity with the CRTH2 receptor. In addition to PGD2, Δ12-PGD2, PGJ2 and PGH2 are also potent DP agonists, while other metabolites of PGD2 such as 13,14-dihydro-15-keto-PGD2 and 15-deoxy-PGJ2 are selective for CRTH2 [5, 27, 29, 32, 79]. DP receptor activation leads to Gαi-mediated increases in intracellular CAMP although an agonist-evoked Ca2+ flux has also been observed in heterologous expression systems [50, 80]. The effects exerted by PGD2 on dendritic cells are associated with the phosphorylation of CAMK response element-binding protein, but do not parallel with a deactivation of nuclear factor-κB and MAPK pathways [43]. So far, further downstream signaling pathways subsequent to DP activation have received very little attention. Interestingly, PGD2 stimulation of fibroblast repair in an in vitro collagen contraction assay is mediated by DP and Ca2+-independent protein kinase C, but it is independent of CAMP and protein kinase A [81].

Regulation of Eosinophil Responses by PGD2

Eosinophils play important roles in late-phase reactions by releasing bronchoconstrictor mediators such as LTC4 and other chemotactants which cause further influx of inflammatory cells into the tissue [82]. Like Th2 cells, eosinophils produce and release proinflammatory cytokines and growth factors including the immunoregulatory type 2 cytokines IL-4, IL-5, IL-10 and IL-13 [83]. Mucosal damage in chronic asthma is associated with cytotoxic and proinflammatory mediators that are released by activated eosinophils. Consequently, eosinophils also play a role in airway remodeling and angiogenesis in chronically inflamed tissue [84]. Importantly, it was shown that asthmatic patients who receive treatment based on eosinophil counts in sputum have significantly fewer severe asthma exacerbations than patients treated according to standard management therapy [85]. Moreover, animal studies also demonstrated that genetically modified mice lacking eosinophils are protected against allergen-induced lung injury and asthma [86, 87]. Therefore, eosinophils are currently considered a major therapeutic target in allergic diseases and asthma [88], but they...
might also play pathogenic roles in several other diseases such as eosinophilic esophagitis [89], colitis ulcerosa [90], hypereosinophilic syndrome [91] or renal disease [92].

In many eosinophilic inflammatory diseases, eosinophilia has been attributed to reduced eosinophil apoptosis [93]. The Th2 cytokine IL-5 augments eosinophil recruitment and survival in experimental models of allergic inflammation. However, the limited clinical efficacy of antibodies against IL-5 in ameliorating asthma symptoms [94] suggests that additional mediators are also involved, such as granulocyte-macrophage colony-stimulating factor or a plethora of chemoattractants that can stimulate the locomotion of eosinophils. In particular, these chemoattractants comprise the ligands of the chemokine receptor CCR3 [95] including eotaxin-1, -2 and -3, RANTES and the monocyte chemotactic peptides monocyte chemotactic protein-3 and -4. Moreover, activated complement factors such as C5a, and lipid mediators such as LTB4 [96], platelet activation factor [97] and 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) are also potent chemoattractants for eosinophils [98–100].

As mentioned above, PGD₂ and several of its metabolites are potent chemoattractants for eosinophils and this effect mainly relies on CRTH2 activation [5, 28, 32]. Moreover, we observed that PGD₂ and its metabolites are capable of stimulating the release of mature eosinophils from bone marrow [28, 101]. However, PGD₂ not only stimulates eosinophil trafficking but also activates eosinophils with respect to the respiratory burst and release of eosinophil cationic protein, and delays their apoptosis [28, 53]. While most PGD₂ effects in eosinophils are mediated by CRTH2, we could demonstrate that DP receptors are also involved in eosinophil chemotaxis, respiratory burst and mobilization from bone marrow [101, 102]. In contrast, the antiapoptotic effect of PGD₂ in eosinophils is solely mediated by DP receptors [53]. In addition to directly stimulating eosinophil migration, we also demonstrated that PGD₂ very efficiently primes eosinophils for other chemoattractants like eotaxin, 5-oxo-ETE or C5a [28, 48]. The priming effect of PGD₂ is exclusively mediated via CRTH2 receptors. In contrast, eosinophil migration towards PGD₂ is strikingly decreased by other chemoattractants such as eotaxin or 5-oxo-ETE, and P13K as well as p38 MAPK are involved in these inhibitory effects. Conversely, the priming effect of PGD₂ is not reversed by inhibition of P13K, p38 MAPK or peroxisome proliferator-activated receptor-γ, which has been described to mediate the priming effect of the PGD₂ metabolite 15-deoxy-Δ12,14-PGJ₂ [103].

Interestingly, available data also suggest that PGD₂ might inhibit eosinophil degranulation, as investigated by the C5a-induced upregulation of the granule-associated marker CD63 on eosinophils and the release of eosinophil peroxidase [32, 48, 101]. This effect is likewise mediated exclusively by CRTH2 receptors. From these studies we inferred that there is a hierarchy among eosinophil chemoattractants: PGD₂ might be an initial chemoattractant since it maintains its potency also in whole blood [48] and augments the responsiveness of eosinophils to other chemoattractants, but restrains eosinophil degranulation. In contrast, eotaxin seems to be an end point chemoattractant since it has a reduced efficacy in blood, is capable of downmodulating eosinophil responsiveness to other chemoattractants and stimulates eosinophil degranulation [48, 104]. CRTH2 expression levels are likely to be elevated in eosinophils from patients with allergic diseases, as suggested by observations in atopic dermatitis [105].

**Role of PGD₂ Receptors in Regulation of Th2 Lymphocyte Function**

Ligation of the T cell receptor by the antigen-major histocompatibility complex class II induces the clonal expansion of naïve Th lymphocytes and their differentiation into at least four subtypes of effector cells: Th1, Th2, Th17 and regulatory T (T_reg) cells. Th cells can be divided into two subsets, Th1 and Th2, based on their cytokine expression profile. Th1 lymphocytes are characterized by the production of interferon (IFN)-γ and IL-2, whereas Th2 lymphocytes produce IL-4, IL-5, IL-6, IL-10 and IL-13 [106]. The cytokines produced by the Th1 lymphocytes, in particular IFN-γ, activate macrophages and are essentially responsible for cell-mediated immunity against intracellular pathogens [106]. In contrast, Th2 cytokines are responsible for humoral immune responses as well as the growth and differentiation of mast cells and eosinophils, and are involved in antibody-mediated responses to extracellular parasites [107]. Recently identified Th17 cells mainly express IL-17 and are crucial in certain autoimmune diseases [108]. T_reg cells are known to suppress various immune responses including autoimmune responsiveness [109]. An imbalance in the relative proportion and function of Th cell populations, as determined by the complex interaction of the genetic background with environmental factors such as exposure to certain infectious agents, has been implicated in the development of abnormal immune re-
CRTH2-positive cells in peripheral blood is elevated in PGD2, which may constitute an autocrine mechanism to wards PGD2 above, CRTH2 mediates the migration of Th2 cells to-wards Th1 lymphocytes, whereas CCR4, CCR8 and CCR3 are selectively expressed on in-vitro-derived Th2 cells. For example, the chemokine receptors CXCR3 reported to be differentially expressed between Th1 and strain Th2 overactivity.

As mentioned above, CRTH2 mediates the migration of Th2 cells towards PGD2 [5]. Furthermore, activation of the CRTH2 receptor induces the production of proinflammatory cytokines in Th2 cells [65, 123], upregulates the expression of CD40L on Th2 cells [65], and delays their apoptosis [124]. Interestingly, Th2 cells can themselves produce PGD2, which may constitute an autocrine mechanism to recruit further Th2 cells to the inflamed tissue [11]. In vitro studies have revealed that CRTH2 expression increases during Th2 polarization [125] and the number of CRTH2-positive cells in peripheral blood is elevated in patients with atopic dermatitis or HIV infection [122, 126]. These findings suggest that CRTH2 might be a highly promising therapeutic target as the blockade of CRTH2 by means of small-molecule antagonists is likely to attenuate Th2 activity with respect to their accumula-tion at sites of inflammation, cytokine release and sur-vival in tissue.

Further Inflammatory Cells Expressing CRTH2

Basophils were among the first cells that were shown to express CRTH2 and to migrate towards PGD2 [5, 127]. Moreover, CRTH2 activation was found to enhance basophil expression of the adhesion molecule CD11b and histamine release, while activation of the DP receptor was found to have opposing effects in basophils [62, 128]. CRTH2 is also detectable in human monocytes and mu-rine macrophages and mediates their migration towards PGD2 and endotoxin, respectively [8, 43]. Similarly, PGD2 is chemotactic for murine bone marrow-derived mast cells and this response is ablated by a CRTH2 antagonist [129]. Correspondingly, elevated numbers of CRTH2-positive macrophages and mast cells are present in nasal mucosa of allergic patients [44].

Antagonists of PGD2 Receptors as Novel Therapeutic Agents

CRTH2 Receptor Antagonists

Our laboratory and others have simultaneously dis-covered that the cyclooxygenase inhibitor indomethacin is a potent CRTH2 agonist [46, 130], which has thus pro-vided a useful pharmacophore for small-molecule antag-onists to CRTH2 [131–134]. Consecutively, it was shown that ramatroban, formerly used as a TX receptor antagonist, was also a potent CRTH2 antagonist in cell lines transfected with CRTH2 and in human eosinophils [31, 131]. Mathiesen et al. described three novel ramatroban analogs that differ chemically from ramatroban by either (i) a single additional methyl group, or (ii) an acetic acid instead of a propionic acid side chain, or (iii) a combination of both [133]. Each of the three compounds acted as a potent CRTH2 antagonist, yet the nature of their an-tagonism differed markedly, either decreasing the affini-ty of PGD2 to CRTH2, or depressing the ligand-binding capacity causing functional insurmountability. One of these compounds (now referred to as TM30089 or Cay10471) proved to be one of the most potent CRTH2
antagonists described so far. Currently, three chemical classes of CRTH2 antagonists have been reported: (i) indole-acetic acids and ramatroban derivatives [127, 135–139]; (ii) phenylacetic acids [140–142], and (iii) tetrahydroquinolines [143, 144]. Although several phase II trials have been conducted with CRTH2 antagonists, only one study has been presented so far: when compared with placebo, oral treatment with a CRTH2 antagonist for 28 days of moderate persistent asthmatics free of inhaled steroids showed significant beneficial effects with respect to forced expiratory volume, peak flow, circulating IgE levels, nighttime asthma symptoms and quality of life [145].

**DP Receptor Antagonists**

The hydantoin derivative, BWA868c, was the first selective DP antagonist available [25]. Subsequently, a class of bicycloheptane-derivative DP antagonists, including S-5751, has been developed that block the actions of PGD₂ in experimental models of inflammation [74, 75]. In addition to being a starting point for the synthesis of CRTH2 antagonists, indomethacin was also a useful pharmacophore for a number of DP antagonists including laropiprant [146–148]. Although recent phase II studies in asthmatics and patients with allergic rhinitis failed to confirm the promising results obtained from animal models [149], DP antagonisms might be useful in other forms of inflammatory disease. In addition, laropiprant is currently being marketed in combination with niacin as Treximet® to prevent niacin-induced flush that is partially mediated by PGD₂ [150].

**Bivalent CRTH2/DP Receptor Antagonists**

Considering the multiple roles that DP and CRTH2 receptors play in allergic disease, a hybrid antagonist may exert clinically relevant, beneficial effects that are not achieved when just one PGD₂ receptor is blocked. For instance, DP antagonism would prevent IL-12 generation by dendritic cells and the ensuing polarization of Th2 cells, while CRTH2 antagonism could prevent the recruitment of eosinophils, basophils and Th2 cells to inflammatory sites [151]. Dual CRTH2/DP antagonists derived from phenylacetic acid have recently been presented [152].

**Conclusion**

For a long time, PGD₂ has been disregarded as a by-product of mast cells with unclear biological relevance. The discovery of its novel receptor, CRTH₂, has fueled extensive research into the biology and pharmacology of PGD₂ and has attracted enormous attention from the pharmaceutical industry. Currently, PGD₂ receptor antagonists are being developed for the treatment of allergic diseases and asthma, but they might also be useful in other diseases that involve eosinophils, or even in chronic obstructive pulmonary disease. Small-molecule antagonists of CRTH2 and DP have already been demonstrated to be efficacious in a variety of animal models and their clinical usefulness in human disease will be unveiled in the near future.

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