

Role of Prostaglandin D₂ and Its Receptors in the Pathophysiology of Asthma

Tsuyoshi Oguma^{1,2}, Koichiro Asano^{1,2} and Akitoshi Ishizaka^{1,2}

ABSTRACT

Prostaglandin D₂ (PGD₂) is one of the most abundant lipid mediators present in the airways of asthmatics. However, little was known of the role it plays in the pathophysiology of asthma, until the identification of DP (DP1, PTGDR) and CRTH2 (DP2), two PGD₂-specific transmembrane receptors with different distribution and intracellular signaling. Pharmacological tools, such as receptor-specific agonists and antagonists, and genetically-engineered mice, which lack either DP or CRTH2, have helped understand the complex effects of PGD₂ in allergic inflammation of the airways. Furthermore, genetic association studies have shown a positive linkage of the genetic polymorphisms in DP and CRTH2, with asthma phenotypes from specific ethnic backgrounds, further highlighting the importance of PGD₂ and its receptors in the pathophysiology of asthma.

KEY WORDS

asthma, CRTH2, DP, eosinophils, lipid mediators, single nucleotide polymorphisms

ROLE OF PROSTAGLANDIN D₂ IN ASTHMA

Prostaglandin D₂ (PGD₂) is a major lipid mediator synthesized from arachidonic acid via the catalytic activities of cyclooxygenases (COX) and PGD₂ synthases (PGDS) in mast cells, macrophages, and other cellular sources. In patients suffering from allergic diseases, such as asthma, the *de novo* production of PGD₂ is increased during allergen exposure.^{1,2} In asthmatics, after an allergen challenge, the concentrations of PGD₂ are increased in the bronchoalveolar lavage (BAL) fluid,³ and the concentrations of 9 α , 11 β -PGF₂, its main metabolite, are increased in plasma and urine.⁴ An increase in the urinary excretion of 9 α , 11 β -PGF₂ has also been observed after aspirin challenge in patients with aspirin-induced asthma.⁵

It is generally believed that, in asthmatics, PGD₂ modulates the physiology of the airways by causing bronchoconstriction,⁶ vasodilation,⁷ increases in capillary permeability⁸ or mucous production.⁹ In addition, the recent identification of new isoforms of PGD₂ receptors, the development of isoform-specific receptor agonists and antagonists, and the creation of

genetic mouse models, which lack the specific isoform of PGD₂ receptors, have helped clarifying the important roles played by PGD₂ and its receptors in the pathophysiology of asthma, especially its role in the airway inflammation and bronchial hyperresponsiveness. Besides observations made in animal models, genetic association studies of PGD₂-related molecules in humans have also revealed a significant link between PGD₂ and asthma. This review updates our understanding of the role played by PGD₂ in asthma gathered from animal models and genetic association studies.

PGD₂ METABOLISM

The first step in the production of PGD₂, is the liberation of arachidonic acid from phospholipids in cellular membranes, via the activities of phospholipases, followed by its conversion to cyclic endoperoxide PGG₂ by COXs.¹⁰ Two isoforms of COXs are present in the airways: COX-1, also known as prostaglandin H synthase 1 (PGHS1) is constitutively expressed and functions as a house keeping gene, while COX-2 (PGHS2) is induced during inflammation. The peroxidase activity of these enzymes transforms PGG₂ to PGH₂, an

¹Division of Pulmonary Medicine, Department of Medicine and
²Shinanomachi Research Park, Keio University School of Medicine, Tokyo, Japan.

Correspondence: Koichiro Asano, M.D., Division of Pulmonary Medicine, Department of Medicine, Keio University School of

Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

Email: ko-asano@qa2.so-net.ne.jp

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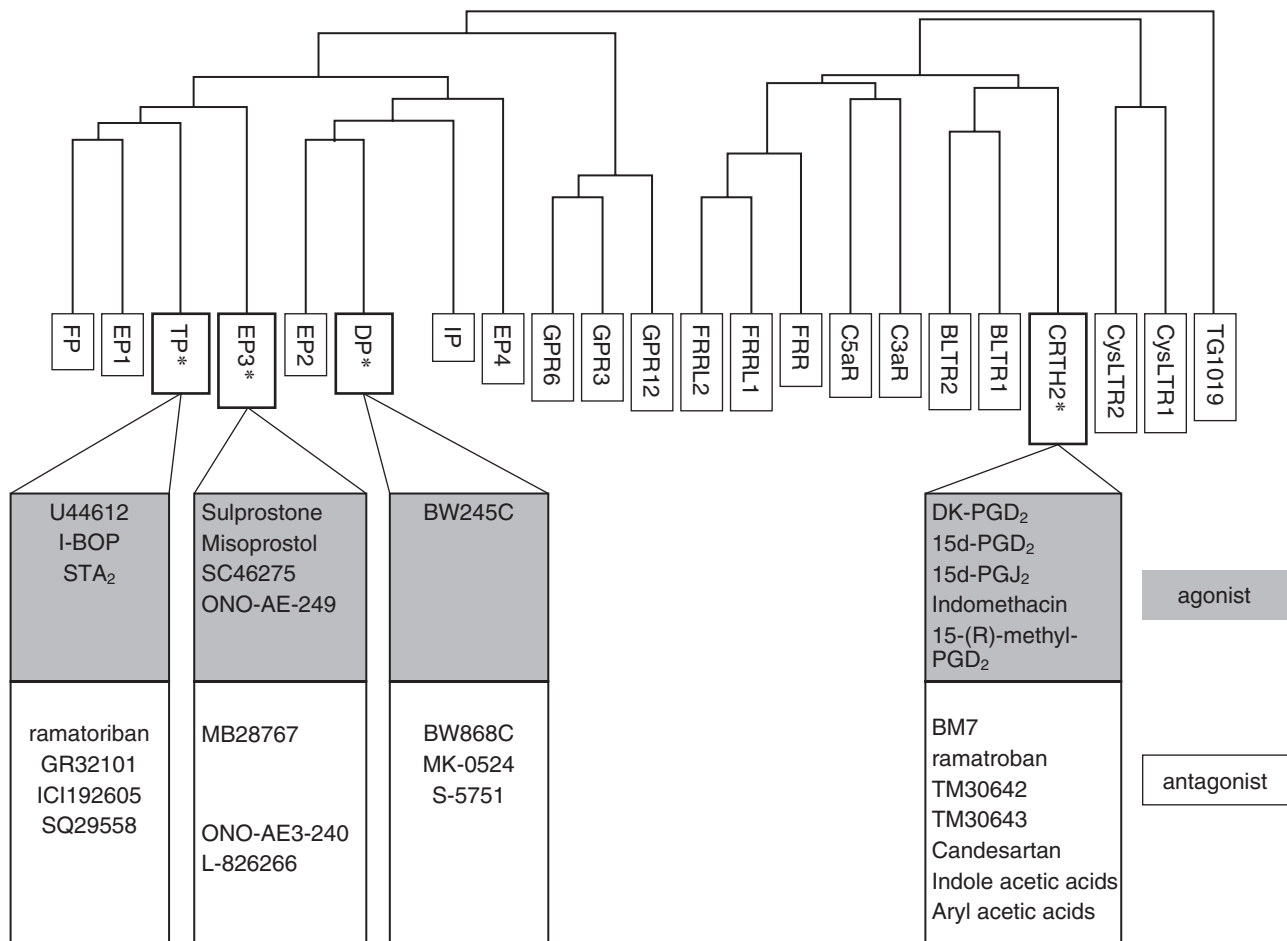


Fig. 1 Phylogenetic tree of prostanoid receptors and other GPCR for chemoattractants and lipid mediators. The asterisk marks the receptors for PGD₂ with their selective agonists and antagonists.

unstable intermediate endoperoxide, which is immediately converted to PGD₂ by PGDS.

These are also 2 isoforms of PGDS.¹¹ Hematopoietic PGDS (H-PGDS) is present in mast cells, macrophages, and dendritic cells, while lipocalin-type PGDS (L-PGDS) is mostly expressed in the central nervous system. Once synthesized, PGD₂ is rapidly metabolized non-enzymatically to 15-deoxy- $\Delta^{12,14}$ -PGJ₂ (15dPGJ₂) or Δ^{12} -PGJ₂ depending on the presence of serum albumin.

PGD₂ RECEPTORS ON EOSINOPHILS AND OTHER INFLAMMATORY CELLS

Recent studies have identified 2 types of transmembrane receptors specific for PGD₂ expressed on inflammatory cells, such as eosinophils, basophils, and lymphocytes. The first, D prostanoid receptor (DP) is a classic PGD₂ receptor also known as PTGDR or DP1^{12,13}; the second is chemoattractant receptor-homologous molecule expressed on Th2 (CRTH2), also known as DP2.¹⁴ Both are members of the seven-transmembrane-domain, G-protein-coupled

receptor (GPCR) superfamily. DP, which is expressed ubiquitously, belongs to a GPCR cluster that includes other prostanoid receptors (Fig. 1),¹⁵ and is coupled with a Gs α protein, which increases the concentration of intracellular cAMP.¹³ In contrast, CRTH2 is genetically closer to chemotactic receptors, such as chemokine receptors and the leukotriene B₄ receptor (Fig. 1), coupled with Gi α protein, which causes an increase in calcium and a decrease in concentrations of cAMP. The expression of CRTH2 is limited to eosinophils, basophils, and Th2 lymphocytes.¹⁴

Whether the DP receptor acts as a pro- versus an anti-inflammatory molecule during allergic inflammation remains controversial. PGD₂ or DP-specific agonists inhibit apoptosis and prolong the survival of eosinophils. These compounds also block the production of interleukin-12 (IL-12) in dendritic cells, biasing the development of naive T lymphocytes to cells producing type 2 cytokines.^{16,17} PGD₂, by the suppressing functions of NK cells, including the production of Th1 cytokine via DP, can promote the Th2-mediated

immune response.¹⁸ Conversely, DP-specific agonists inhibit the migration and degranulation of basophils.¹⁹

In contrast to DP, the activities of CRTH2 observed *in vitro* strongly suggest that CRTH2 acts as a molecule that exacerbates allergic inflammation. CRTH2 agonists induce a marked increase in cell mobility and degranulation, and increase the expression of adhesion molecules in eosinophils and basophils.^{14,19-21} PGD₂ also increases in a CRTH2-dependent manner the lymphocytic production of Th2 cytokines, including IL-4, -5, and -13.²²

Besides DP and CRTH2, PGD₂ binds to the thromboxan A₂ receptor, TP, and one of the PGE₂ receptors, EP3. Figure 1 shows the selective agonists and antagonists identified for these receptors. PGD₂ and its cyclopentenone-type metabolites, such as 15dPGJ₂, also exert an anti-inflammatory activity, partially via a peroxisome proliferator-activated receptor- γ (PPAR- γ).²³ In low concentrations, 15dPGJ₂ promotes the eotaxin-induced chemotaxis of eosinophils in a PPAR- γ -dependent manner, while, in higher concentrations,²⁴ 15dPGJ₂ directly acts as a ligand for CRTH2 and activates the eosinophils.²³

ROLE OF PGD₂ AND ITS RECEPTORS ON ALLERGIC INFLAMMATION OF THE AIRWAYS

We have previously described the COX-2-dependent synthesis of PGD₂ in the lungs of ovalbumin-sensitized and challenged guinea pigs.²⁵ NS-398, a COX-2-specific inhibitor, blocked this synthesis, and inhibited the recruitment of eosinophils into the lungs. Conversely, others have reported that increased concentrations of PGD₂ exacerbated eosinophilic inflammation of the airways. The intra-tracheal administration of PGD₂ intensified the allergen-induced eosinophilic inflammation in mice.²⁶ The over-expression of lipocalin-type PGDS also increased the concentration of Th2 cytokines, and promoted the accumulation of eosinophils in the lungs.²⁷ These observations suggest that PGD₂ plays important roles in allergic inflammation of the airways.

ROLE OF DP

In an allergen-induced asthma model of genetically-engineered DP-deficient mice, the phenotypes, such as airway eosinophilia, bronchial hyperresponsiveness, and Th2 cytokine responses were all attenuated.²⁸ Furthermore, the expression of DP receptors were significantly enhanced in the allergen-stimulated epithelial cells of the airways. The pro-inflammatory role of DP was further supported by the inhibition of the accumulation of eosinophils by a DP-specific antagonist, in sensitized guinea-pig lungs.²⁹ DP receptor antagonists also partially blocked the PGD₂-induced mobilization of eosinophils from the bone marrow in a perfused, guinea pig hind-limb

preparation.³⁰ However, in recent experiments, the intratracheal administration of a DP-selective agonist activated the DP receptors on dendritic cells, increased the number of Foxp3⁺ CD4⁺ regulatory T cells, and suppressed airway inflammation in a IL-10-dependent manner.³¹ The infusion of DP agonist-stimulated dendritic cells similarly suppressed the inflammation, while dendritic cells from DP-deficient mice lacked this activity.

ROLE OF CRTH2

We have observed the induction of airway eosinophilia in IL-5- or allergen-exposed rodents by the intra-tracheal administration of PGD₂ or CRTH2 agonists, however not by a DP agonist.^{32,33} This chemotactic activity of CRTH2 agonists on eosinophils *in vivo* was confirmed by other investigators.^{34,35} Furthermore, we and others have shown that ramatroban, a dual receptor blocker for CRTH2 and TP, but not DP- or TP-specific antagonists, suppressed the eosinophilia induced by PGD₂ or CRTH2 agonists in the blood and airways.^{32,33,36} TM30089, a highly CRTH2-selective antagonist, also inhibited airway eosinophilia and goblet cell hyperplasia after allergen challenge.³⁷ It is, thus, surprising that, after allergen exposure, the eosinophilic inflammation was not attenuated in the airways of CRTH2-deficient mice.^{33,38} Furthermore, the eosinophilia in allergen-exposed, CRTH2-deficient mice with a Balb/c background was as pronounced as that observed in wild-type mice.³³ It is particularly noteworthy that, compared with wild-type mice, CRTH2-deficient mice with a C57BL/6 background developed more severe inflammation of the airways, along with an over-production of IL-3 and IL-5.³⁸ The observations made with respect to murine CRTH2 must be interpreted cautiously. Whereas, in humans, the expression of CRTH2 on T lymphocytes is limited to Th2 subpopulation and does not include Th1, murine Th1 and Th2 lymphocytes both express CRTH2 mRNA.^{38,39}

We have shown, however, that the exacerbation of airway inflammation induced by the instillation of double-stranded RNA (which mimics the exacerbation of asthma induced by RNA virus infection), does not occur in CRTH2-deficient mice.³³ A similar suppression of the exacerbation of allergic inflammation and bronchial hyperresponsiveness induced by double-stranded RNA was observed with pharmacological blockade of CRTH2, which was conserved among different animal species.³³ These observations point to the discovery of a new role played by the PGD₂-CRTH2 axis in the innate immune response to viral infection, and to the potential therapeutic application of CRTH2 antagonists in the prevention of asthmatic exacerbations.

Table 1 Genetic association studies of PGD₂-related genes

Gene name	Acronym	Gene locus	Mutation(s)	Ethnic origin	Outcome	Reference
Hematopoietic prostaglandin D synthase	PGDS	4q21-q22	IVS2 + 11 A > C)	Asian (Japanese)	Positive	40
Prostanoid DP receptor	DP DP1 PTGDR	14q22.1	T-197C, C-2T	Asian (Japanese)	Negative	40
			T-197C, T-549C, C-441T	European-American African-American	Positive	43
			T-197C, T-549C, C-441T	Puerto-Rican; Mexican African	Negative	47
			A-731G, G-338A, C6541T, C6651T	European (UK and Danish) American	Positive	45
			T-197C, T-549C, C-441T	Asian (Chinese-Han)	Negative	46
			T-197C, T-549C, C-441T	European; Spanish-American	Positive	44
Chemoattractant receptor-homologous molecule expressed on Th2	CRTH2 ex-GPR44	11q12-q13.3	G1544C, G1651A, T11336C, G12375T	African-American, Asian (Chinese)	Positive	48
			G1544C, G1651A, T11336C, G12375T	Asian (Japanese)	Negative	49

Table 2 Haplotypes frequencies of polymorphisms in the promoter lesion of DP

Ethnic origin	European-American			African-American			Hispanic		Asian
	Oguma <i>et al.</i> ⁴³ Sanz <i>et al.</i> ⁴⁴ Combined			Oguma <i>et al.</i> ⁴³ Tsai <i>et al.</i> ⁴⁷ Combined			Tsai <i>et al.</i> ⁴⁷		Li <i>et al.</i> ⁴⁶
Control									
<i>n</i>	175	79	254	45	176	221			99
Haplotype							Mexican Puerto-Rican		
CCT	36	39	37	37	43	42	NA	NA	31
TTT	24	27	25	28	30	30	NA	NA	68
TCT	32	22	29	30	15	18	NA	NA	0
CCC	9	9	9	6	12	11	NA	NA	1
Asthmatic									
<i>n</i>	518	118	636	80	176	256	273	336	99
Haplotype									
CCT	39	43	40	43	42	42	24	36	28
TTT	27	25	27	33	32	32	58	32	71
TCT	22 *	19	21 *	13 *	16	15	11	20	0
CCC	12 #	12 *	12	11	10	10	7	12	1

* $p < 0.05$; # $p = 0.08$; NA = not applicable.

GENETIC ASSOCIATION STUDIES OF PGD₂-RELATED MOLECULES WITH ASTHMA

Several noteworthy associations have been reported between the genotypes of PGD₂-related molecules, such as PGDS, DP, and CRTH2, and the phenotype of asthma (Table 1). The hematopoietic PGDS gene is located on chromosome 4q22.3. In Japanese children, a single nucleotide polymorphism (SNP) in the second intron of this gene predicted a risk of asthma.⁴⁰

The human DP gene is located on chromosome 14q21, where multiple whole-genome linkage analyses have suggested the presence of an asthma-related

region.^{41,42} Sequencing of the DP gene revealed three variants (T-549C, C-441T, and T-197C) in the 5'-flanking region, as well as three variants (C+367A, G+894A, and G+1044A) in the coding region. We found that, in both Europeans and African-Americans, carriers of the C allele of T-549C, or of the T allele of C-441T, were at higher risk of asthma.⁴³ Furthermore, there was a significant association between promoter haplotypes of three SNPs in the 5'-flanking region and susceptibility to asthma. The carriers of the haplotype with lower promoter activity were less susceptible to asthma. Our observations were reproduced in three different Caucasian populations, in Spain, the UK, and the Netherlands,^{44,45} however not

in Japanese, Han Chinese, or Hispanics, suggesting the existence of marked differences among ethnic groups (Table 2).⁴⁶

The haplotype frequency measured in two studies of Caucasian populations has been consistent (Table 2). The haplotype frequency observed in African-Americans and Puerto-Ricans was the same as that found in Caucasians, though significantly different from that measured in Asians and Mexicans (Table 2). The absence of a Hispanic control population limits the validity of that study.^{46,47}

The human CRTH2 gene is located on chromosome 11q13. In a case-control study of 2 SNPs, G1544C and G1651A, in the 3'-untranslated region of the CRTH2, the allele of 1651G and the haplotype of 1544G-1651G were both significantly associated with the development of asthma in African-Americans and in Chinese.⁴⁸ A functional analysis of experiments made *in vitro* suggested that the haplotype of 1544G-1651G was associated with a higher stability of CRTH2 mRNA than the 1544C-1651A haplotype.⁴⁸ The association between CRTH2 gene polymorphism and asthma was, however, not confirmed in a Japanese population.⁴⁹

CONCLUSIONS

PGD₂ is abundantly present in the airways of asthmatics. However, its role in the pathophysiology of asthma remains mysterious because of its multidimensional activity, both pro- and anti-inflammatory. While the identification of isoforms of the PGD₂ receptors, DP and CRTH2, has solved some of the enigmas of the PGD₂ story, several issues need to be clarified before the pharmacological modification of PGD₂ signaling can be applied in therapeutics.

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