Allergology International. 2008;57:187-196
DOI: 10.2332/allergolint.R-08-161

REVIEW ARTICLE

Prostaglandin as a Target Molecule for Pharmacotherapy of Allergic Inflammatory Diseases

Hiroichi Nagai[1]

ABSTRACT

The purpose of this review is to summarize the role of prostaglandins (PGs) in allergic inflammation and to know the value of PGs, as a target molecule for an anti-allergic drug.

PGD_2 is the major PG produced by the cyclooxygenase pathway in mast cells. Our and others findings indicate that PGD_2 is one of the potent allergic inflammatory mediators and must be a target molecule of anti-allergic agent. From our data, one of PGD_2 receptor antagonists show clear inhibition of airway hypersensitivity caused by allergic reaction. Concerning the role of PGE_2 in allergic inflammation, conflicting results have been reported. Many experimental data suggest an individual role of each PGE_2 receptor, EP_1, EP_2, EP_3 and EP_4 in allergic reaction. Our results indicate the protective action of PGE_2 on allergic reaction via EP_3. In addition, one of EP_3 agonists clearly inhibits the allergic airway inflammation. These findings indicate the value of EP_3 agonists as an anti-allergic agent.

In addition, some investigators including us reported that PGI_2 plays an important role for the protection of the onset of allergic reaction. However, the efficacy of PGI_2 analogue as an anti-allergic agent is not yet fully investigated.

Finally, the role of thromboxane A_2 (TxA_2) in allergic reaction is discussed. Our experimental results suggest a different participation of TxA_2 in allergic reaction of airway and skin. In this review, the role of PGs in allergic inflammation is summarized and the value of PGs as a target molecule for developing a new anti-allergic agent will be discussed.

KEY WORDS

allergy, anti-allergic drug, PGD_2, PGI_2, prostaglandin

Lipid mediators including prostaglandin (PG), thromboxane (Tx), leukotriene (LT) and lipoxin (LX) exhibit a wide variety of actions in various cells and tissues to maintain local homeostasis in the body. These substances are released immediately after synthesis and act on the cell surface receptors to elicit their actions. These lipid mediators show strong action on mainly cardiovascular, nerve, reproduction and gastrointestinal systems and inflammatory responses, as shown in Table 1. In addition to above systems, recent extensive investigations indicate that lipid mediators play an important role in immune system.[1-6]

Among the lipid mediators, PGs are the most common autacoid and there is persuasive evidence that some PGs contribute to the signs and symptoms of inflammation and immune system. Most of PGs are commonly considered as potent proinflammatory mediators, actually involved in the pathogenesis of several inflammatory diseases such as rheumatoid arthritis, periodontitis and other inflammatory diseases.[7-10]

Apart from these findings, much attention has been paid to allergy, another inflammatory disease related to immune systems, because the incidence of allergic patients had increased dramatically in recent decades.[11-15] However the precise role of PGs in allergy is not fully understood. Therefore, we have attempted to elucidate the role of PGs in allergy (allergic inflammation) by employing animal models. This review will provide the reader with an introduction to the role of PGs in allergic inflammation and then will discuss the role of PG, as a target molecule for an anti-allergic drug.

[1]Department of Clinical Pharmacology, Gifu Pharmaceutical University, Gifu, Japan.
Correspondence: Hiroichi Nagai, Prof.,Ph.D., Department of Clinical Pharmacology, Gifu Pharmaceutical University, 5−6−1 Mitahora-higashi, Gifu 502−8585, Japan.
Email: nagai@gifu−pu.ac.jp
Received 11 January 2008.

Table 1 Prostaglandins and thromboxane receptors and physiological actions

PGs	Receptor	Cellular signaling	Action
PGD_2	DP	c-AMP ↑	Platelet aggregate ↓ , Allergic inflammation ↑ Sleep ↑
	CRTH2		Eosinophils ↑
PGE_2	EP_1	Ca^{2+}	Smooth muscle ↑ , Stress ↑ , Ovatian follicle ↑
	EP_2	c-AMP ↑	Vasodilation ↑ , Blood pressure ↓
	EP_3	c-AMP ↓	Pyrexia ↑ , Gastric secretion ↓ , Pain sensation ↑
		Ca^{2+} ↓	Smooth muscle ↑
	EP_4	c-AMP ↑	Patent ductus arteriosus ↑ , Ossification ↑ , Immune response ↓
$PGF_{2\alpha}$	FP	IP_3/DG ↑	Labor ↑ , Smooth muscle ↑ , Intraocular pressure ↓
PGI_2	IP	c-AMP ↑	Blood pressure ↓ , Platelet aggregation ↓ , Renal blood flow ↑
TxA_2	TP	IP_3/DGA	Platelet aggregation ↑ , Smooth muscle ↑
		c-AMP ↓	Thrombosis ↑
LTB_4	BLT_1	IP_3/DG ↑	Chemotaxis ↑
	BLT_2	c-AMP ↓	?
LTC_4, D_4, E_4	cys LT_1	Ca^{2+} ↑	Airway smooth muscle ↑ , Eosinophils ↑ , Permeability ↑
	cys LT_2	Ca^{2+} ↑	?

↓, down regulation; ↑, up regulation.

THE ROLE OF PGs IN ALLERGIC INFLAMMATION

Identifying a role of any mediator in pathological state is dependent on the collection of various types of evidence. Often, after the structure of a mediator is identified, and synthesized, the mediator is given to humans or experimental animals, to observe whether it can mimic signs or symptoms of the disease. Then when quantitative assays are available, efforts are made to measure it in the biological fluid, to determine whether it is released during a disease state. In addition, when the specific antagonists or inhibitors to the mediator, suppress the symptoms in animal disease model, the role of mediator is confirmed as a causative component in the disease.

From these points of view, the role of PGs in allergic inflammation has been examined by many researchers, including us, and various results were obtained. Most researchers agree with the production of several types of PGs during allergic reaction in human and experimental animals.[16-20] But each researcher has failed to obtain consensus in terms of the effect of the PG inhibitors on allergic response and the magnitude of allergic response caused by each PG. So, in this review, we focused on the experimental results employing PG synthesis inhibitor, indomethacin, and PG receptor gene manipulated mice on allergic reaction in mice.

EFFECT OF INDOMETHACIN

In the first segment of experiment, in order to know the role of PGs in allergic inflammation, we tried to establish an allergic airway inflammation model in mice.[21-25] Airway allergic inflammation was caused by repeated inhalation of aerosolized antigen into sensitized mice. Antigen provocation result in T helper 2 cell (Th2) polarized immune responses and eosinophilic airway inflammation (Fig. 1). Th2 polarized immune response is characterized by the elevation of serum IgE and the increase of Th2 cytokines, IL-4, 5 and 13 level and decrease of INF-γ level in bronchial alveolar lavage fluid (BALF). In addition, the airway responsiveness to acetylcholine is accelerated by repeated antigen provocation. This symptom is similar to many features of human airway hypersensitivity (AHR), one of typical asthmatic response.

In the next segment of experiment, to discover the role of PGs, the effect of indomethacin on this allergic airway inflammation and AHR was examined. As shown in Figure 2, indomethacin accelerates the production of Th2 cytokines, the accumulation of inflammatory cells in BALF and IgE antibody production (data not shown). The drug also shows the tendency to accelerate the AHR. These data suggest that the inhibition of PG production auguments the allergic inflammation. This means the COX products, probably some PGs, suppress the Th2 dependent allergic inflammatory responses. On the other hand, some other studies so far reported suggest the existence of a pathological role of PGs in allergic inflammation.[26,27] In fact, the existence of some PGs in allergic lesion has been recognized and some of them are able to mimic the symptoms of allergy. Therefore we carried out further experiments to elucidate the role of each PG in allergic reaction by employing each PG receptor gene deficient mice.

PGD_2

PGD_2 is the major PG produced by the COX pathway

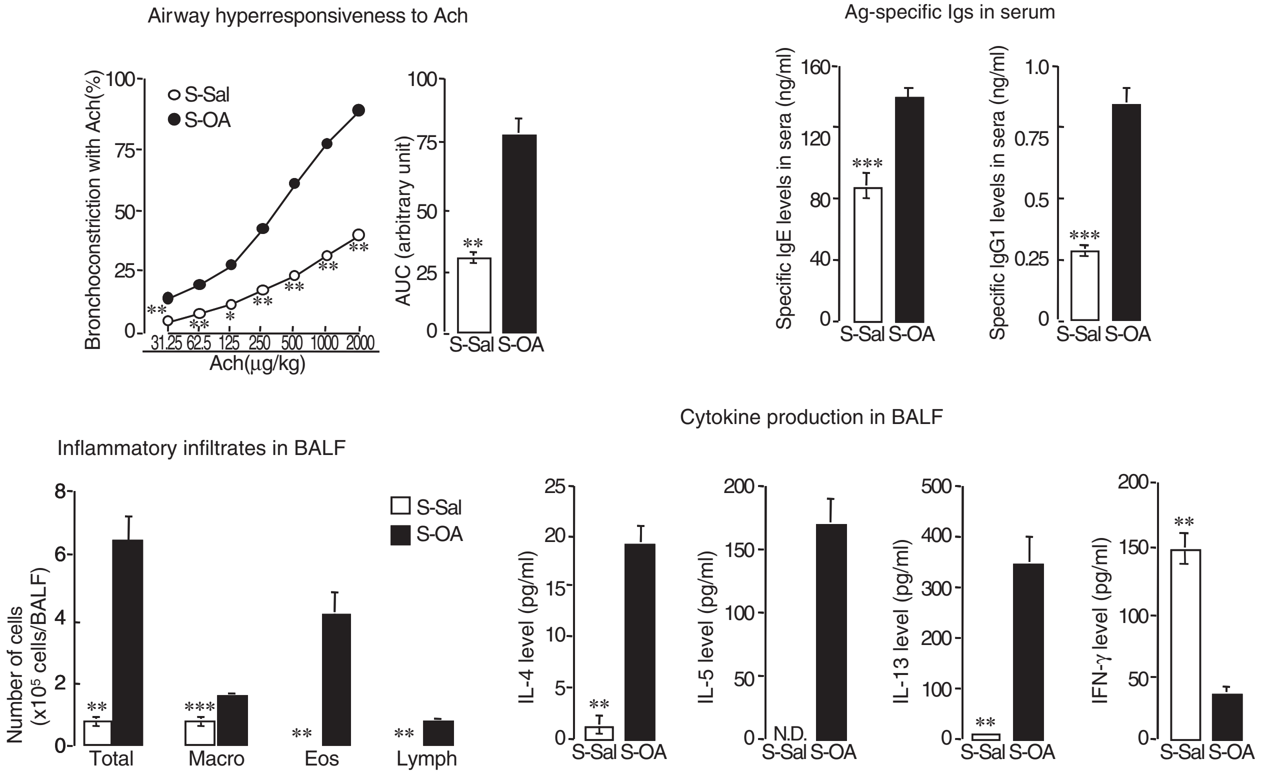

Fig. 1 Changes in airway responsiveness to acetylcholine, immunoglobulin levels in serum, the number of infiltrated cells and cytokine levels in bronchial alveolar lavage fluid (BALF) after repeated allergen provocation in mice. Each value represents the mean ±SEM of 8−12 mice. S-Sal; Injection and inhalation of saline instead of allergen, S-OA; Immunization and inhalation of ovalbumin (allergen).
*, **, *** $p < 0.05$, 0.01 and 0.001, respectively (vs S-OA).

in mast cells.[28] Significant quantities of PGD_2 are not produced by the immunological activation of basophils.[29,30] Generally, PGD_2 is produced by either L-type (lipocalin type) or H-type (hematopoetic type) PGD_2 synthetase. L-type PGD_2 synthetase exists in mainly central nervous system and H-type PGD_2 synthetase exists in peripheral tissues and immune cells including mast cells, antigen-presenting cells and Th2 cells. In addition, recent studies have revealed two G protein-coupled receptor for PGD_2, DP and chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2). [31,32]

Concerning the role of PGD_2 in allergic bronchial asthma, there are some clinical evidence to suggest the patho-physiological role of PGD_2. PGD_2 is detected in BALF from asthmatic patients and it constricts human bronchial smooth muscle in vitro.[33-35] Despite the recognition of the existence and action of PGD_2 during bronchial asthma, basic research about the role of PGD_2 in allergic inflammation is still lagging.

Therefore, we investigated the role of PGD_2 in allergic inflammation by employing DP gene deficient mice. Consequently, we demonstrated that PGD_2 plays a role in an allergic asthma as a mediator.[24] Our results are summarized below briefly. Sensitization and aerosol challenge of the homozygous mutant DP gene deficient mice with ovalbumin induced increases in the serum concentration of IgE similar to those in wild-type mice subjected to this model of allergic asthma. However, the concentration of Th2 cytokines (IL-4 and IL-5) and the extent of lymphocyte accumulation in the antigen challenged lung of DP gene deficient mice significantly decreased compared to those in wild type mice. DP gene deficient mice showed only marginal infiltration of eosinophils and failed to develop AHR. Thus, PGD_2 functions as a mast cell derived mediator, to trigger asthmatic responses. Our results and related evidence regarding the pharmacological action of PGD_2 are summarized in Table 2.

As described in Table 2, Fujitani *et al.*[36] confirmed a role of PGD_2 in allergic inflammation by employing L-type PGD_2 synthetase gene over-expressed mice. The overproduction of PGD_2 causes an increase in the levels of Th2 cytokines and chemokines, accompanied by the enhanced accumulation of eosinophils and lymphocytes in the lung. The findings of Fujitani

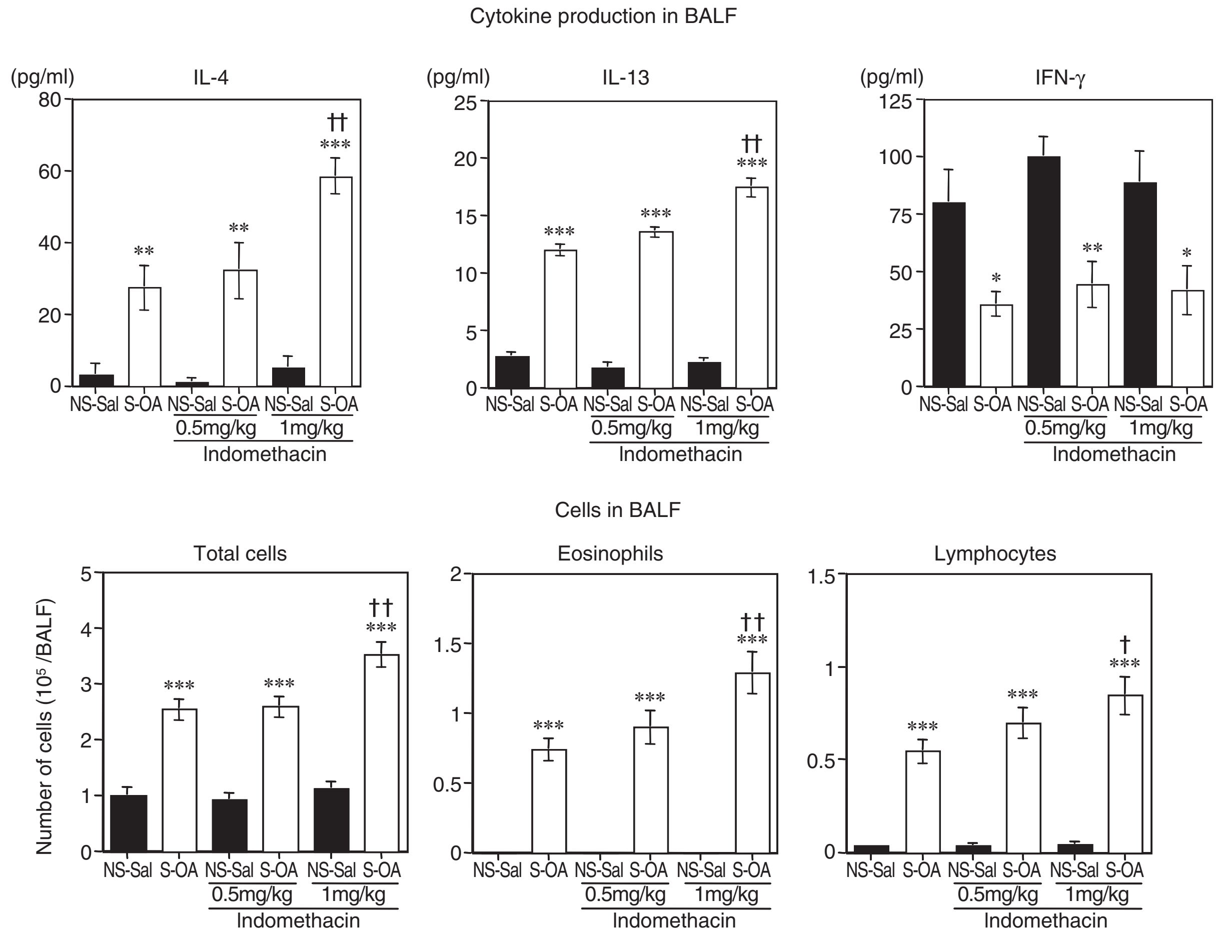

Fig. 2 Effect of indomethacin on antigen-induced cytokine production and leukocytes accumulation in BALF in mice. Each value represents the mean ±SEM of 6 − 11 mice. NS-Sal; Injection and inhalation of saline instead of allergen, S-OA; Immunization and inhalation of ovalbumin (allergen).
** , *** $p < 0.01$ and 0.001, respectively (vs NS-Sal).
† , † † $p < 0.05$ and 0.01, respectively (vs S-OA).

Table 2 The role of PGD_2 in experimental asthmatic responses in mice

Treatment	Eosinophils in BALF	Th2 cytokine in BALF	Chemokine in BALF	AHR
DP gene deficient	↓ ↓	↓ ↓	ND	↓ ↓
L-PGDS gene over expression	↑ ↑	↑ ↑	↑ ↑ (eotaxin)	ND
Inhalation of PGD_2	↑ ↑	↑ ↑	↑ ↑ (MDC)	↑ ↑

↑ ↑, Increase when compared to control; ↓ ↓, Decrease when compared to control; ND, Not done; BALF, Broncho alveolar lavage fluid; AHR, Airway hyperresponsiveness; PGDS, Prostaglandin D_2 synthetase; MDC, Macrophase derived chemokine.

et al.[36] and our studies indicate that PGD_2 plays an important role for the accumulation of eosinophils into allergic lesion. Moreover, Honda *et al.*[37] revealed the mechanism of PGD_2 induced eosinophil infiltration. They have described the mediation of macrophage-derived chemokine from airway epithelial cells for PGD_2 inducing local eosinophilia.

In addition to DP, recent studies suggest the participation of CRTH2 receptor in allergic inflammation.[38,39] Some groups have demonstrated that CRTH2 selective agonists induce eosinophilic airway and skin inflammation in animal models.[40-44] These data support the hypothesis that CRTH2 may play a critical role in allergic inflammation; however, more

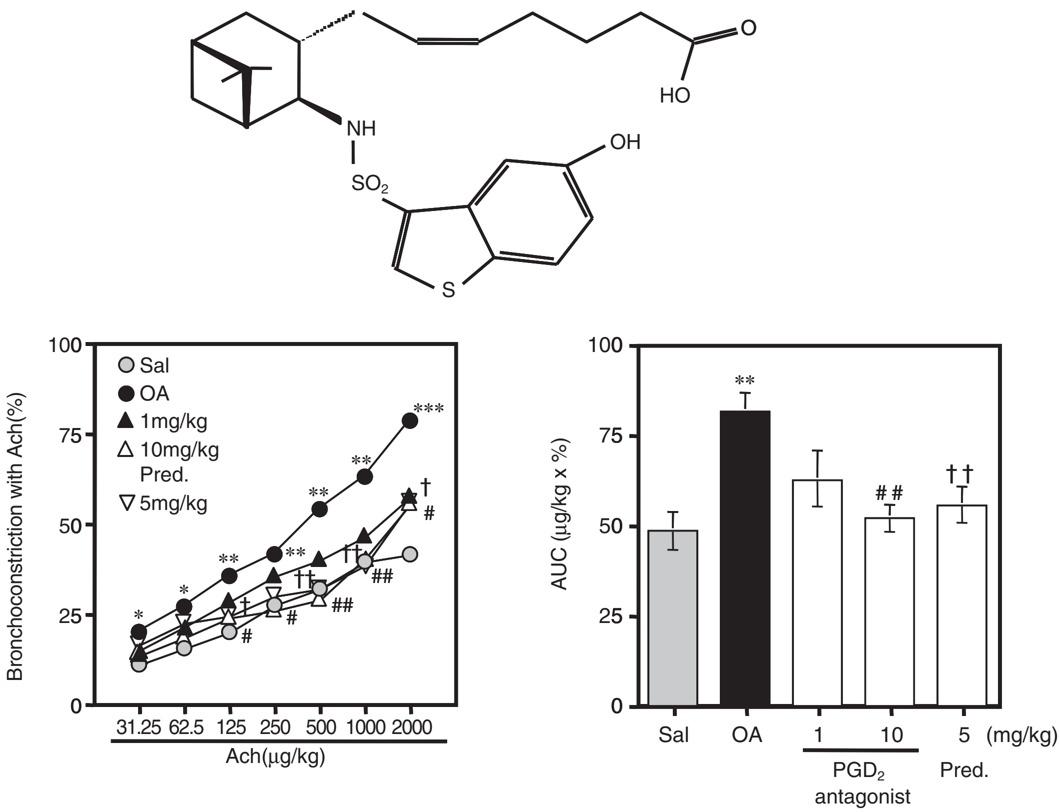

Fig. 3 Chemical structure of PGD_2 receptor (DP) antagonist and the effect of DP antagonist on antigen-induced airway hyperresponsiveness in mice. Each experiment consists of the mean ± SE on 5 − 7 mice. AUC; area under the curve (range; 31.25 − 2000 mg/Kg), Ach; acetylcholine.
* , ** , *** $p < 0.05$, 0.01 and 0.001, respectively (vs Sal; Student's test).
# , ## $p < 0.05$ and 0.01 respectively (vs OA; Student's t-test).
† , †† $p < 0.05$ and 0.01, respectively (vs OA; Dunnett's multiple comparison test).

data are necessary to clarify the precise role of CRTH2 in allergic diseases.

From the clinical point of view, whereas extensive efforts have been made to elucidate the role of PGD_2 in allergic diseases, adequate data are not yet forthcoming. Two of the important references suggest a close relationship between the onset of allergic asthma and polymorphism of haematopoietic PGD_2 synthetase and DP gene.[45,46] These are important findings to investigate the role of PGD_2 in human allergic diseases.

The above-noted clinical and basic researches stimulate the studies to develop a new anti-DP agent as a remedy for allergy. Mitsumori *et al.*[47,48] and Arimura *et al.*[49,50] have reported the efficacy of DP antagonist on allergic diseases, especially triggered by mast cell activation. Using the past findings as a background, we also tried to examine the effect of DP antagonist on the allergic AHR in mice. Figure 3 indicates the chemical structure of one of a potent DP antagonist and the results of the experiments to measure the AHR. The DP antagonist showed a clear inhibition of allergic AHR. The increase of eosinophils in the airway is also inhibited, but the elevation of serum IgE and Th2 cytokine level in BALF are not affected by this agent. In summary, above data suggest that PGD_2 is one of the potent allergic inflammatory mediators and must be a target molecule of anti-allergic agent.

PGE2

PGE_2 is commonly considered to be a potent proinflammatory mediator and is involved in several inflammatory diseases including rheumatoid arthritis (RA). The activity of PGE_2 is mediated by four receptors, termed E prostanoid receptors (EP_{1-4}). Activation of EP_2 and EP_4 increases intracellular cAMP whereas the EP_1 receptor mediates the elevation of intracellular calcium. The different isoforms of the EP_3 receptor couple to multiple G proteins producing either inhibition of adenylate cyclase and calcium mobilization or stimulation of adenylate cyclase activity. These differences are caused by the condition of employed cells and circumstances.

Table 3 Effect of PGE_2 on allergic responses

Anti-allergic actions of PGE_2
1. Inhibition of antigen-induced asthmatic responses (Bronchoconstriction, Airway hyperresponsiveness, Eosinophilia, Edema)
2. Inhibition/augmentation of the immunological release of allergic mediators from mast cells
3. Inhibition of allergic eosinophil recruitment
4. Augmentation of IgE production

Regarding the role of PGE_2 in allergic reaction, conflicting results have been reported by some researchers, as shown in Table 3. Parord *et al.* and other investigators[51-55] have reported that PGE_2 inhibits the antigen-induced allergic asthmatic responses, but other researchers[56,57] have shown an augmentation of IgE production and the enhancement of immunological release of mast cell mediators.

As for the protective effect of PGE_2, when PGE_2 solution is inhaled by the asthmatic patients, it prevents allergen-induced airway response and airway inflammation.[52] Other researchers also reported that PGE_2 prevents the early and late phase antigen-induced bronchoconstriction through the relaxation of airway smooth muscles and inhibition of the release of mast cell mediators including histamine, leukotrienes and PGD_2.[51,53] Moreover, PGE_2 protects the allergen-induced AHR by the reduction of inflammatory cells, especially eosinophils recruitment. In fact, they indicate that the inhalation of PGE_2 by asthmatic patients markedly attenuates the increase of eosinophils and metachromatic cells detectable in sputum.

Despite the accumulation of such data, the mechanism of PGE_2 action and participating receptors still remains to be fully elucidated. While there is little evidence about the role of EP_1 in allergic reaction, Chan *et al.*[53-55] have indicated the relationship between EP_2 and anti-allergic responses including the relaxation of airway smooth muscle and the inhibition of histamine release from mast cells. In addition to EP_2, the role of EP_3 in allergic reaction has been extensively studied.[56-58] Our recent study employing EP_3 gene deficient mice indicates the importance of EP_3 in the recruitment of eosinophils in the lung during antigen-induced airway inflammation.[58] When allergic airway inflammation is caused by repeated allergen inhalation in EP_3 gene deficient mice, allergic airway eosinophilia, IgE antibody production, Th2 cytokines (IL-4, 5 and 13) production are accelerated significantly when compared to those in wild type mice. These data suggest that an EP_3 agonist can be one of the ingredients of a new anti-allergic drug. Then we examined the effect of EP_3 receptor selective agonist, ONO-AE-248, on the allergic airway inflammation in mice. ONO-AE-248 shows an inhibitory effect on antigen-induced airway allergic inflammation as indicated in Table 4. The EP_3 agonist clearly inhibits the elevation of airway sensitivity to methacholine and eosinophilia without affecting IgE antibody production. These data indicate that the lack of EP_3 gene accelerates the allergic responses and the EP_3 agonist suppresses an allergic inflammation. This probably means that PGE_2 has an anti-allergic inflammatory action through EP_3 receptor. Regarding the main target cell for EP_3-induced anti-allergic effect, our further experiments indicate the importance of mast cells. As indicated in Table 4, passive cutaneous anaphylaxis, immunological histamine release and IL-13 release from mast cells are accelerated by the depletion of EP_3 gene. Simultaneously, EP_3 agonist clearly inhibits the antigen induced histamine release from sensitized mast cells. These data suggest that mast cell is an effecter cell for the EP_3 agonist. Finally, while the interest on the role of EP_4 receptor in allergic reaction is increasing, but unfortunately clear evidence is stll lacking.

In conclusion, although PGE_2 has proinflammatory properties, it also possesses a bronchodilating and anti-allergic actions probably through one of four different receptor subtypes. From our data, EP_3 agonist may lead to a new approach for the treatment of allergic diseases.

PGI_2

PGI_2 is mainly produced by vascular endothelial cells and prevents platelet aggregation caused by a variety of stimuli. Some observations indicated the production of PGI_2 by the local tissues and blood vessels through an acute allergic inflammation and anaphylaxis. In the allergic reaction in lung, produced PGI_2 suppresses the generation of leukotrienes and causes the relaxation of airway smooth muscle.[59] These evidences suggest the role of PGI_2 in allergic inflammation and bronchial asthma.

Therefore, we carried out the experiments to trace the role of PGI_2 in allergic reaction by employing allergic airway inflammation model in IP gene lacking mice.[60,61] In IP gene deficient mice, the elevation of airway eosinophilia, Th2 cytokine production and leakage of serum albumin into BALF are significantly augmented by repeated allergen inhalation. These data suggest that PGI_2 may play a suppressive role in an allergic airway inflammation through IP.

To analyze the mechanism of above response to allergic inflammation in IP gene deficient mice, Th1 and Th2 response of isolated splenocytes were compared in gene deficient mice and wild type mice. While the IL-4 production by antigen stimulation is accelerated in the gene deficient mice, IFN-γ production is not altered, when compared to wild type mice. When the anti-CD3 and anti-CD28 induced cytokine production by isolated $CD4^+$ T cells from non-sensitized mice were examined, the production of IL-4 was not altered but IFN-γ production was signifi-

Table 4 Effect of EP_3 gene depletion and EP_3 agonist, ONO-AE-248, on antigen-induced allergic inflammation in mice

	AHR	Eo	Th2 cytokine	IgE	Histamine release
Wild type mice	↑ ↑	↑ ↑	↑ ↑	↑	↑
EP_3 KO mice	↑ ↑	↑ ↑ ↑	↑ ↑ ↑	↑ ↑	↑ ↑
EP_3 agonist ONO-AE-248	↑	↑	↑ ↑	↑ ↑	↑

↑ ↑ ↑, Marked increase; ↑ ↑, Significant Increase; ↑, Increase; ND, Not done.

Table 5 Effect of IP gene depletion and Beraprost on antigen-induced airway inflammation in mice

	AHR	Eo	Th2 cytokine	IgE
Wild type mice	↑ ↑	↑ ↑	↑ ↑	↑ ↑
IP-KO mice	↑ ↑	↑ ↑ ↑	↑ ↑ ↑	↑ ↑ ↑
Beraprost	↑ ↑	↑	↑	↑ ↑

↑ ↑ ↑, Marked increase; ↑ ↑, Significant Increase;
↑, Increase.

cantly decreased in the T cells from IP gene deficient mice. These data suggest the possibility that PGI_2 suppresses the antigen-induced activation of Th2 cells and stimulates the activity of resting Th1 cells. Furthermore, Jaffar *et al.*[62] have reported one potential mechanism supporting our findings. They have inferred that the anti-allergic action of PGI_2 is closely related to the production of T cell derived IL-10 which is known to suppress Th2 immunity. Thus, PGI_2 may show an immunomodulating action through a production of IL-10 via IP.

In addition to above-noted sub-chronic airway inflammation, we conducted another experiment to investigate the role of PGI_2 in the chronic airway allergic inflammation, airway wall remodeling in mice by using IP gene deficient mice.[61] Airway wall remodeling model was produced by daily inhalation of antigen for 3 weeks after the systemic immunization in mice. In this model, apparent airway eosinophilia, goblet cell hypertrophy and fibrosis under airway epithelial cell were observed. These changes are depend on Th2 cells, eosinophils and TGF-β1. By employing this experimental model, we confirmed a suppressive role of PGI_2 in chronic airway inflammation, airway wall remodeling in mice. Regarding to chronic inflammatory responses, Strauon *et al.*[63] have reported that the production of connective tissue growth factor and collagen synthesis by TGF-β1 stimulated fibroblast were clearly inhibited by PGI_2. These data suggest that PGI_2 plays a role in the production of collagen directly.

From these data PGI_2 can be considered as a useful source to tap up a remedy for allergic diseases, we examined the effect of Beraprost, a PGI_2 analogue, on the experimental airway allergic inflammation. As shown in Table 5, Beraprost indicated the suppression of airway allergic eosainophilia and Th2 cytokine production, but did not show the inhibition of AHR and IgE production. Moreover, the inhibition pattern of Beraprost is not dose related. To confirm the effect of PGI_2 agonists, the effect of two other PGI_2 analogues on allergic inflammation were studied, and the results were similar to those of Beraprost. These data indicate the difficulty in developing a new anti-allergic drug from PGI_2 analogues and the necessity of additional studies to confirm the suitability of PGI_2 analogue as a remedy for allergic diseases.

OTHER EICOSANOIDS

TxA_2 is not a PG but an important another cyclooxgenase derived eicosanoid. Many evidences suggest a role of TxA_2 in allergic inflammation.[63-65] Various reports also indicate the release of TxA_2 during allergic reaction and TxA_2 causes a potent bronchoconstriction in vitro and in vivo.[66-68] In addition, the TxA_2 receptor, TP, exists in immune competent organs including thymus and spleen.[69,70] Moreover, recent studies concerning human subject polymorphism in the TP gene are associated with atopic dermatitis.[71] Using such background information as pegs, we investigated the role of TxA_2 in allergic inflammation by employing TP gene deficient mice.[72] Our examination was carried out in two different types of experimental models. An allergic inflammation was caused in the airway and skin by repeated local antigen provocation. Surprisingly, our findings from two experiments indicate a reversal of results in terms of causing an allergic inflammation in the skin and lung. Our data suggest that TxA_2 may play a pathological role in the airway inflammation but it acts as a suppressive factor in the skin. These data indicate the existence of different allergic mechanism in the lung and skin regarding the role of TxA_2, and also suggest a difficulty in developing a new anti-TxA_2 agent as an anti-allergic drug.

CONCLUSION

This review describes the role of PGs in allergic inflammation and the value of PGs as a target molecule for developing a new anti-allergic agent. Several investigators, including us, have shown that some PG and anti-PG agents are effective in the therapy of experimental allergic disease models. Our studies employing PG receptor and TxA_2 receptor gene deficient mice suggest that EP_3 or IP agonists and DP or TP antagonist would be expected to be a remedy for allergic diseases. IP agonist and TP antagonist, however, indicates the partial efficacy in an allergic model. Our data indicate that an EP_3 agonist and DP-antagonist have more possibility as a remedy for allergic airway inflammation. Further studies regarding more effective agent and precise mechanism of PGs in allergic inflammation are needed for discovering a new anti-allergic drug.

ACKNOWLEDGEMENTS

The author would like to thank Professor S. Narumiya (Department of Pharmacology, Faculty of Medicine, Kyoto University) and the members of Department of Pharmacology, Gifu Pharmaceutical University, especially Associate Professor H. Tanaka for their contribution to complete this manuscript.

REFERENCES

1. Chen Y, Perussia B, Campbell KS. Prostaglandin D_2 Suppresses Human NK Cell Function via Signaling through D Prostanoid Receptor. *J Immunol* 2007;**179**:2766-73.
2. Biteman B, Hassan IR, Walker E *et al*. Interdependence of Lipoxin A_4 and heme-oxygenase in counter-regulating inflammation during corneal wound healing. *FASEB J* 2007; **21**:2257-66.
3. Middleton MK, Rubinstein T, Pure E. Cellular and molecular mechanisms of the selective regulation of IL-12 production by 12/15-lipoxygenase. *J Immunol* 2006;**176**: 265-74.
4. Liu W, Kelly KA. Prostaglandin E (2) modulates dendritic cell function during chlamydial genital infection. *Immunology* 2008; **123**: 290-303. Epub 2007 Aug 3.
5. Kontogiorgis CA, Hadjipavlou-Litina DJ. Non steroidal anti-inflammatory and anti-allergy agents. *Curr Med Chem* 2002;**9**:89-98.
6. Auray G, Lacroic-Lamande S, Mancassola R, Dimier-Poisson I, Laurent F. Involovement on intestinal epithelial cells in dendritic cell recruitment during C. parvum infection. *Microbes Infect* 2007;**9**:574-82.
7. Minghetti L, Pocchiari M. Cyclooxygenase-2, prostaglandin E_2, and microglial activation in prion diseases. *Int Rev Neurobiol* 2007;**82**:265-75.
8. Rainsford KD. Anti-inflammatory drugs in the 21st century. *Subcell Biochem* 2007;**42**:3-27.
9. Riccia DN, Bizzini F, Perilli MG *et al*. Anti-inflammatory effects of Lactobacillus brevis (CD2) on periodontal disease. *Oral Dis* 2007;**13**:376-85.
10. Leonard BE, Inflammation, depression and dementia: are they connected? *Neurochem Res* 2007; **32**: 1749-56. Epub 2007 Aug 20.
11. Malo JL, Gautrin D. From asthma in the workplace to occupational asthma. *Lancet* 2007;**370**:295-7.
12. Burns D. Exploring the growing problem of allergy. *Nurs Times* 2007;**103**:44-5.
13. Acton D, McCauley L. Laboratory animal allergy: an occupational hazard. *AAOHN J* 2007;**55**:241-4.
14. Jayawardena S, Eisdorfer J, Indulkar S, Pal SA, Sooriabalan D, Cucco R. Prescription errors and the impact of computerized prescription order entry system in a community-based hospital. *Am J Ther* 2007;**14**:336-40.
15. Shaaban R, Zureik M, Soussan D *et al*. Allergic rhinitis and onset of brochial hyperresponsiveness: a population-based study. *Am J Respir Crit Care Med* 2007; **176**: 659-66. Epub 2007 Jul 5.
16. Mastalerz L, Sanak M, Gawlewicz-Mroczka A, Cmiel A, Gielicz A, Szczeklik A. Prostaglandin E_2 systemic production in patients with asthma with and without aspirin hypersensitivity. *Thorax* 2008; **63**: 27-34. Epub 2007 Jun 21.
17. Okano M, Fujiwara T, Sugata Y *et al*. Presence and characterization of prostaglandin D_2-related molecules in nasal mucosa of patients with allergic rhinitis. *Am J Rhinol* 2006;**20**:342-8.
18. Pinto S, Gallo O, Polli G *et al*. Cyclooxygenase and Lipoxygenase metabolite generation in nasal polyps. *Prostaglandins Leukot Essent Fatty Acids* 1997;**57**:533-7.
19. Dunlap NE, Fulmer JD. Corticosteroid therapy in asthma. *Clin Chest Med* 1984;**5**:669-83.
20. Godard P, Chantreuil J, Clauzel AM, Crastes de Paulet A, Michel FB. Plasma concentrations of prostaglandins E_2 and $F_{2\alpha}$ in asthmatic patients. *Respiration* 1981;**42**:43-51.
21. Iwama T, Nagai H, Suda H, Tsuruoka N, Koda A. Effect of murine recombinant interleukin-5 on the cell population in guinea-pug airways. *Br J Pharmacol* 1992;**105**:19-22.
22. Nagai H, Yamaguchi S, Inagaki N, Tsuruoka N, Hitochi Y, Takatsu K. Effect of anti-IL-5 monoclonal antibody on allergic bronchial eosinophilia and airway hyperresponsiveness in mice. *Life Sci* 1993;**53**:243-7.
23. Nagai H, Yamaguchi S, Tanaka H. The role of interleukin-5 (IL-5) in allergic airway hyperresponsiveness in mice. *Ann N Y Acad Sci* 1996;**796**:91-6.
24. Matsuoka T, Hirata M, Tanaka H *et al*. Prostaglandin D_2 a mediator of allergic asthma. *Science* 2000;**287**:2013-7.
25. Kobayashi T, Miura T, Haba T *et al*. An essential role of mast cells in the development of airway hyperresponsiveness in a murine asthma model. *J Immunol* 2000;**164**: 3855-61.
26. Demoly P, Crampette L, Lebel B, Campbell AM, Mondain M, Bouaquet J. Expression of cyclo-oxygenase 1 and 2 proteins in upper respiratory mucosa. *Clin Exp Allergy* 1998;**28**:278-83.
27. Serrano-Mollar A, Closa D. Arachidonic acid signaling in pathogenesis of allergy: therapeutic implications. *Curr Drug Targets Inflamm Allergy* 2005;**4**:151-5.
28. Shichijo M, Inagali N, Nakai N *et al*. The effects of anti-asthma drugs on mediator release from cultured human mast cells. *Clin Exp Allergy* 1998;**28**:1228-36.
29. Shichijo M, Shimizu Y, Hiramatsu K *et al*. IPD-1151T (suplatast tosilate) inhibits interleukin (IL)-13 release but not IL-4 release from basophils. *Jpn J Pharmacol* 1999;**79**: 501-4.
30. Shimizu Y, Shichijo M, Hiramatsu K, Takeuchi M, Nagai H, Takagi K. Mite antigen-induced IL-4 and IL-13 production by basophils derived from atopic asthma patients. *Clin Exp Allergy* 1998;**28**:497-503.
31. Nagata K, Tanaka K, Ogawa K *et al*. Selective expression of a novel surface molecule by human Th2 cells in vivo. *J Immunol* 1999;**162**:1278-86.
32. Vinall SL, Townsend ER, Pettipher R. A paracrine role for chemoattractant receptor-homologous molecule expressed on T heoper type 2 cells (CRTH2) in mediating chemotactic activation of CRTH2+ CD4+ T helper type 2 lymphocytes. *Immunology* 2007;**121**:577-84.
33. Wenzel SE, Westcott JY, Smith HR, Larsen GL. Spectrum of prostanoid release after bronchoalveolar allergen challenge in atopic asthmatics and in control groups. An alteration in the ratio of bronchoconstrictive to bronchoprotective mediators. *Am Rev Respir Dis* 1989;**139**:450-7.
34. Chiba T, Kanda A, Ueki S *et al*. Possible novel receptor for PGD2 on human bronchial epithelial cells *Int Arch Allergy Immunol* 2007; **143**: 23-7.
35. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD.

Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 2006;**129**:39-49.
36. Fujitani Y, Kanaoka 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**:443-9.
37. Honda K, Arima M, Cheng G *et al*. Prostaglandin D_2 reinforces Th2 type inflammatory responses of airways to low-dose antigen through bronchial expression of macrophage-derived chemokine. *J Exp Med* 2003;**198**:533-43.
38. Ulven T, Kostenis E. Targeting the prostaglandin D_2 receptors DP and CRTH2 for treatment of inflammation. *Curr Top Med Chem* 2006;**6**:1427-44.
39. Okano M, Fujiwara T, Sugata Y *et al*. Presence and characterization of prostaglandin D_2-related molecules in nasal mucosa of patients with allergic rhinitis. *Am J Rhinol* 2006;**20**:342-8.
40. Pettipher R, Hansel TT, Armer R. Antagonism of the prostaglandin D_2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. *Nat Rev Drug Discov* 2007;**6**:313-25.
41. Uller L, Mathiesen JM, Alenmyr L *et al*. Antagonism of the prostaglandin D_2 receptor CRTH2 attenuates asthma pathology in mouse eosinophilic airway inflammation. *Respir Res* 2007;**8**:16.
42. Satoh T, Moroi R, Aritake K *et al*. Prostaglandin D_2 plays an essential role in chronic allergic inflammation of the skin via CRTH2 receptor. *J Immunol* 2006;**177**:2621-9.
43. Ishizuka T, Matsui T, Okamoto Y, Ohta A, Shichijo M. Ramatroban (BAY u 3405): a novel dual antagonist of TXA_2 receptor and CRTH2, a newly identified prostaglandin D_2 receptor. *Cardiovasc Drug Rev* 2004;**22**:71-90.
44. Takeshita K, Yamasaki T, Nagao K *et al*. CRTH2 is a prominent effector in contact hypersensitivity-induced neutrophil inflammation. *Int Immunol* 2004;**16**:947-59.
45. Noguchi E, Shibasaki M, Kamioka M *et al*. New polymorphisms of haematopoietic prostaglandin D synthase and human prostanoid DP receptor genes. *Clin Exp Allergy* 2002;**32**:93-6.
46. Oguma T, Palmer LJ, Birben E, Sonna LA, Asano K, Lilly CM. Role of prostanoid DP receptor variants in susceptibility to asthma. *N Engl J Med* 2004;**351**:1752-63.
47. Mitsumori S, Tsuri T, Honma T *et al*. Synthesis and biological activity of various derivatives of a novel class of potent, selective, and orally active prostaglandin D_2 receptor antagonists. 2.6,6-Dimethylbicyclo[3.1.1] heptane derivatives. *J Med Chem* 2003;**46**:2446-55.
48. Mitsumori S. Recent progress in work on PGD_2 antagonists for drugs targeting allergic diseases. *Curr Pharm Des* 2004;**10**:3533-8.
49. 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**:411-9.
50. Hirano Y, Shichijo M, Deguchi M *et al*. Synergistic effect of PGD_2 via prostanoid DP receptor on TNF-alpha-induced production of MCP-1 and IL-8 in human monocytic THP-1 cells. *Eur J Pharmacol* 2007;**560**:81-8.
51. Pavord ID, Wong CS, Williams J, Tattersfield AE. Effect of inhaled prostaglandin E_2 on allergen-induced asthma. *Am Rev Respir Dis* 1993;**148**:87-90.
52. Gauvreau GM, Watson RM, O'Byrne PM. Protective effects of inhaled PGE2 on allergen-induced airway responses and airway inflammation. *Am J Respir Crit Care Med* 1999;**159**:31-6.
53. Hartert TV, Dworski RT, Mellen BG, Oates JA, Murray JJ. Sheller JR. Prostaglandin E(2) decreases allergen-stimulated release of prostaglandin D(2) in airways of subjects with asthma. *Am J Respir Crit Care Med* 2000;**162**:637-40.
54. Chan CL, Joones RL, Lau HY. Characterization of prostanoid receptors mediating inhibition of histamine release from anti-IgE-activated rat peritoneal mast cells. *Br J Pharmacol* 2000;**129**:589-97.
55. Fedyk ER, Phipps RP. Prostaglandin E_2 receptors of the EP_2 and EP_4 subtypes regulate activation and differentiation of mouse B lymphocytes to IgE-secreting cells. *Proc Natl Acad Sci USA* 1996;**93**:10978-83.
56. Gomi K, Zhu FG, Marshall JS. Prostaglandin E_2 selectively enhances the IgE-mediated production of IL-6 and granulocyte-macrophage colony-stimulating factor by mast cells through an EP_1/EP_3-dependent mechanism. *J Immunol* 2000;**165**:6545-52.
57. Wang XS, Lau HY. Prostaglandin E potentiates the immunologically stimulated histamine release from human peripheral blood-derived mast cells through EP_1/EP_3 receptors. *Allergy* 2006;**61**:503-6.
58. Kunikata T, Yamane H, Segi E *et al*. Suppression of allergic inflammation by the prostaglandin E receptor subtype EP_3. *Nat Immunol* 2005;**6**:524-31.
59. Thien FC, Walters EH. Eicosanoids and asthma: an update. *Prostaglandins Leukot Essent Fatty Acids* 1995;**52**:271-88.
60. Nagao K, Tanaka H, Komai M, Masuda T, Narumiya S, Nagai H. Role of prostaglandin I_2 in airway remodeling induced by repeated allergen challenge in mice. *Am J Respir Cell Mol Biol* 2003;**29**:314-20.
61. Takahashi Y, Tokuoka S, Masuda T *et al*. Augmentation of allergic inflammation in prostanoid IP receptor deficient mice. *Br J Pharmacol* 2002;**137**:315-22.
62. Jaffar Z, Wan KS, Roberts K. A key role for prostaglandin I2 in limiting ling mucosal Th2, but not Th1, responses to inhaled allergen. *J Immunol* 2002;**169**:5997-6004.
63. Huszar E, Szabo Z, Jakab A, Barta I, Herjavecz I, Horvath I. Comparative measurement of thromboxane A_2 metabolites in exhaled breath condensate by different immunoassays. *Inflamm Res* 2005;**54**:350-5.
64. Dogné JM, De Leval S, Benoit P, Delarge J, Masereel B. Thromboxane A_2 inhibition; therapeutic potential in bronchial asthma. *Am J Respir Med* 2002;**1**:11-7.
65. Rolin S, Masereel B, Dogné JM. Prostanoids as pharmacological targets in COPD and asthma. *Eur J Pharmacol* 2006;**533**:89-100.
66. Dogné JM, Hanson J, De Leval X *et al*. From the design to the clinical application of thromboxane modulators. *Curr Pharm Des* 2006;**12**:903-23.
67. Allen IC, Hartney JM, Coffman Tm, Penn RB, Wess J, Koller BH. Thromboxane A_2 induces airway constriction through an M3 muscarinic acetylcholine receptor-dependent mechanism. *Am J Physiol Lung Cell Mol Physiol* 2006;**290**:526-33.
68. Hahnenkamp K, Nollet J, Strumper D *et al*. Bupivacaine inhibits thromboxane A_2-induced vasoconstriction in rat thoracic aorta. *Anesth Analg* 2004;**99**:97-102.
69. Ushikubi F, Aida Y, Nakamura K *et al*. Thromboxane A_2 receptor is highly expressed in mouse immature thymocytes and mediates DNA fragmentation and apoptosis. *J Exp Med* 1993;**178**:1825-30.
70. Ushikubi F, Sugimoto Y, Ichikawa A, Narumiya S. Roles

of prostanoids revealed from studies using mice lacking specific prostanoid receptors. *Jpn J Pharmacol* 2000;**83**: 279-85.
71. Tanaka K, Roberts MH, Tamamoto N *et al*. Genetic variants of the receptors for thromboxane A_2 and IL-4 in atopic dermatitis. *Biochem Biophys Res Commun* 2002; **292**:776-80.
72. Kabashima K, Murata T, Tanaka H *et al*. Thromboxane A_2 modulates interaction of dendritic cells and T cells and regulates acquired immunity. *Nat Immunol* 2003;**4**:694-701.