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# The Role of Prostanoids in Atopic Dermatitis

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## 1. Introduction

Atopic dermatitis (AD) is a common pruritic and chronic inflammatory skin disease, with a prevalence of up to 3% among adults and up to 25% among children (Bieber; Guttman-Yassky et al.; Odhiambo et al., 2009). The clinical features of AD are varied, with patients generally having dry skin, but wet eczematous lesions in the acute stage and lichenification lesions in the chronic stage (Guttman-Yassky et al., 2011). In terms of histology, an increased number of lymphocytes, eosinophils, and mast cells in the dermis are detected. A barrier defect with decreased cornification and epidermal hyperplasia are also characteristic features of AD (Elias and Schmuth, 2009; Guttman-Yassky et al., 2009).

AD is a multi-factorial disease that arises from complex interaction between genetic and environmental factors. As for its pathogenesis, two models have been proposed: the outside-in model and the inside-out model (Bieber, 2008). In the outside-in model, the decreased skin barrier function caused by genetic defects, such as mutations in filaggrin, allows for the penetration of large immunogenic proteins, which subsequently cause T helper type 2 (Th2) deviated immune activation (Elias et al., 2008; Elias and Schmuth, 2009). In the inside-out model, activation of Th2 cells results in reactive epidermal hyperplasia (Nogales et al.; Ong and Leung, 2006). It has been proposed that the lack of environmental antigens during childhood lead to reduced T helper type 1 (Th1) cell-mediated immunity and increased activation of Th2 cells (hygiene hypothesis). In recent reports, involvements of T helper type 17 (Th17) cells and T helper type 22 (Th22) cells have also been proposed (Koga et al., 2008; Nogales et al., 2009).

As for the treatment of AD, various therapies have been employed, and the use of topical steroids plays a major role in therapies (Guttman-Yassky et al.). Although the use of topical corticosteroids is the first-line therapy and provides rapid relief of symptoms, prolonged use can cause severe side effects such as skin atrophy. Therefore, alternative therapies with fewer and less extreme side effects are needed.

## 2. Characteristics of prostanoids

When tissues are exposed to diverse pathophysiological stimuli, arachidonic acid (AA) is released from membrane phospholipids and converted to lipid mediators, such as prostanoids, leukotrienes (LTs) and hydroxy-eicosatetraenoic acids (HETEs). Prostanoids, including prostaglandins (PG) and thromboxane (TX), are formed by the cyclooxygenase (COX) pathway, whereas LTs and HETEs are formed by the 5-, 12- and 15-lipoxygenase (LO) pathways. COX has two isoforms, COX-1 and COX-2. While COX-1 is constitutively

expressed in cells, COX-2 requires specific stimulation by substances such as acetone and the phorbol ester TPA (Narumiya et al., 1999; Scholz et al., 1995). This reaction results in the formation of an unstable endoperoxide intermediate  $\text{PGH}_2$ , which, in turn, is metabolized to  $\text{PGD}_2$ ,  $\text{PGE}_2$ ,  $\text{PGF}_{2\alpha}$ ,  $\text{PGI}_2$ , and thromboxane  $\text{TXA}_2$  by specific synthases.

Prostanoids are released from cells immediately after their formation. Because they are chemically and metabolically unstable, they usually function only locally through their specific membrane receptors on target cells (Narumiya et al., 1999). Nine types and subtypes of membrane prostanoid receptors are conserved in mammals from mouse to human: two subtypes of the  $\text{PGD}$  receptor (DP (DP1) and the chemoattractant receptor homologous-molecule expressed on Th2 cells, CRTH2 (DP2)), four subtypes of the  $\text{PGE}$  receptor (EP1, EP2, EP3, and EP4), the  $\text{PGF}$  receptor (FP), the  $\text{PGI}$  receptor (IP), and the  $\text{TXA}$  receptor (TP) (Figure 1). All are G protein-coupled rhodopsin-type receptors with seven transmembrane domains (Figure 1). The main signal transduction mechanisms of these prostanoid receptors are through the regulation of intracellular cyclic adenosine monophosphate (cAMP) concentration and intracellular free calcium concentration. DP, EP2, EP4 and IP are Gs-coupled receptors and elevate intracellular cAMP concentration, while EP3 and CRTH2 are Gi-coupled receptors and decrease intracellular cAMP. EP1, FP and TP are Gq and other G protein-coupled receptors, which increase intracellular calcium concentration (Narumiya et al., 1999). However, most prostanoid receptors may bind with more than one G protein-coupled receptors via their specific signaling pathway. Recently, individual prostanoid receptor gene-deficient mice have been used as models to dissect out the respective roles of each receptor in combination with the use of compounds that selectively bind to prostanoid

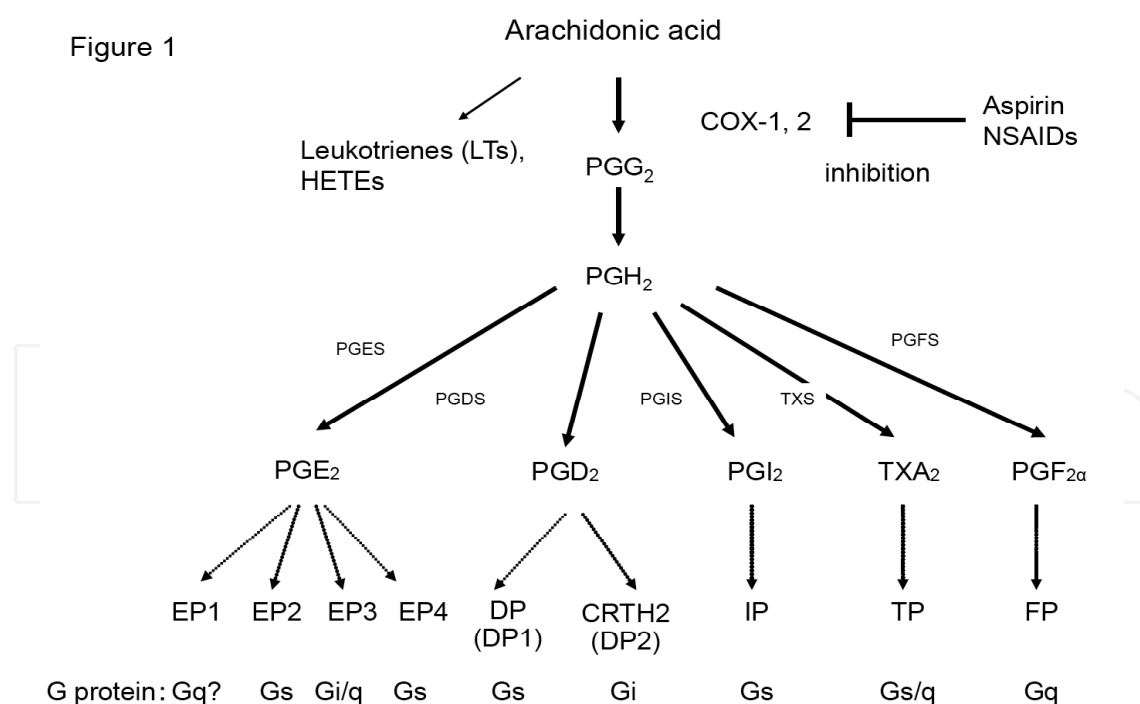


Fig. 1. Biosynthetic pathways of prostanoids. The formation of  $\text{PGD}_2$ ,  $\text{PGE}_2$ ,  $\text{PGF}_{2\alpha}$ ,  $\text{PGG}_2$ ,  $\text{PGH}_2$ , and  $\text{PGI}_2$ , and  $\text{TXA}_2$  from arachidonic acid is shown. The first two steps of the pathway (i.e., conversion of arachidonic acid to  $\text{PGG}_2$  and then to  $\text{PGH}_2$ ) are catalyzed by COX, and the subsequent conversion of  $\text{PGH}_2$  to each prostanoid is catalyzed by the respective synthase as shown. All are G protein-coupled rhodopsin-type receptors.

receptors as agonists or antagonists (Narumiya and FitzGerald, 2001). These genetic and pharmacological approaches have revealed new roles for prostanoids and their receptors in allergic and immune diseases (Honda et al., 2010).

In this chapter, we will discuss the recent findings regarding the role of prostanoids in skin immunity, and discuss the possible involvement of prostanoids in the pathogenesis of AD, and also the clinical potential of receptor-selective drugs as a new therapeutic target for AD.

### 3. Production of prostanoids in skin

Human bodies are exposed to external stimuli continuously. The skin plays an important role in self-defense during exposure to foreign antigens and consists of a vast array of immune cells, such as keratinocytes (KCs), T cells, B cells, mast cells, eosinophils, fibroblasts, and two types of cutaneous dendritic cells (DCs) including epidermal Langerhans cells (LCs) and dermal DCs (dDCs). In the normal human skin, immunohistochemical examinations have revealed that COX-1 is observed throughout the epidermis, whereas COX-2 exists in more differentiated suprabasilar KCs and outer root sheath cells of hair follicles (Leong et al., 1996; Torii et al., 2002). Among prostanoids, PGE<sub>2</sub> is the main COX product in human epidermal homogenates (Hammarstrom et al., 1979). PGD<sub>2</sub> has been detected in human skin (Hammarstrom et al., 1979), and PGD synthase is present predominantly in LCs, dDCs, dermal macrophages and mast cells, but not in KCs (Ruzicka and Aubock, 1987; Ujihara et al., 1988). Among these, mast cells have been found to be one of the major cellular sources of PGD<sub>2</sub>. TX synthase activity has been found in keratinocytes (Andoh et al., 2007) and high levels of TXB<sub>2</sub>, as a metabolite of TXA<sub>2</sub>, were detected in the cultured supernatant of LCs and DCs (Kabashima et al., 2003a). PGI<sub>2</sub> was detected in the skin of the murine AD model (Sugimoto et al., 2006). PGF<sub>2α</sub> was observed in skin exudates of nickel allergy patients (Lerche et al., 1989). In biopsy specimens from patients with AD, PGE<sub>2</sub> has been determined in biologically active amounts in both lesional and perilesional skin (Fogh et al., 1989). In contrast, normal levels of eicosanoids were found in the uninvolved skin of these patients. The above findings on the synthesis of prostanoids are summarized in Table 1.

### 4. Prostanoid receptor expression in skin

Adult human KCs express mRNA for all subtypes of PGE<sub>2</sub> receptors (Konger et al., 1998; Tober et al., 2006) and the expression of all PGE<sub>2</sub> receptors has been detected in mouse KCs by immunohistochemistry (Tober et al., 2007). Mouse LCs and DCs express DP (Angeli et al., 2001), EP1, 2, 3, 4 (Kabashima et al., 2003b), and IP (Huang et al., 2001), and T cells express EP1, 2, 3, 4 (Tilley et al., 2001), IP (Takahashi et al., 2002) and TP (Nataraj et al., 2001). PGE<sub>2</sub> suppresses T cell proliferation and differentiation in the thymus, and interleukin (IL)-1 production by acting at EP2 and EP4 *in vitro* (Nataraj et al., 2001). Mast cells express EP1, 2, 3, 4, DP, and IP (Fedyk and Phipps, 1996; Tilley et al., 2001), and PGE<sub>2</sub> acts at EP3 to suppress their degranulation (Kunikata et al., 2005). Human eosinophils express EP2, EP4, DP, CRTH2 and TP (Nguyen et al., 2002; Schratl et al., 2007), and PGE<sub>2</sub> seems to prolong eosinophil survival (Mita et al., 2002; Peacock et al., 1999). PGE<sub>2</sub> suppresses TNF-α production and enhances IL-6 production from neutrophils stimulated by lipopolysaccharide (LPS) through EP2 and EP4 (Nguyen et al., 2002; Yamane et al., 2000). As summarized in Table 1, prostanoids and their receptors are produced and expressed by a wide variety of cells in the skin. This varied expression pattern of prostanoids maintains the homeostasis of the human body.

	PGDS	PGES	PGFS	PGIS	TXS	DP	CRTH2	EP1	EP2	EP3	EP4	FP	IP	TP
Keratinocytes	m	m, h			m			m, h	m, h	m, h	m, h			m, h
hLangerhans cells	h	m, h			m	m, h		m	m	m	m			
Dendritic cells	h	m, h		m	m, h				m, h		m, h		m	
T cells							m, h(Th2)	m	m	m	m, h		m	m
B cells								m, h	m, h	m, h	m, h		m	
Macrophages	h	m, h		m	m, h		m	m	m	m	m, h			
Eosinophils	h	h	h		h	m	m, h		m, h		h			h
Mast cells, basophils	m, h				h	m, h	m, h	m	m	m	m			
Neutrophils		h			h	h	m		m, h		m			
Blood vessels		h	h	h				m, h	m, h	m, h	m, h		m, h	m, h

PG; prostaglandin, S; synthase, m; mouse, h; human

Modified from the reference by Tilley et al.

Table 1. Expression of prostanoid synthases and prostanoid receptors in the skin

## 5. Involvement of prostanoids in the pathogenesis of AD: Analysis based on animal models of AD

As mentioned above, there are multiple pathogenetic factors of AD, but the skin barrier dysfunction and Th2 mediated immune response are its general characteristic features.

Mouse ovalbumin (OVA)-induced dermatitis is one of the most frequently used AD models (He et al.; Spergel et al., 1998). In a typical mouse OVA-induced AD model, mice are first sensitized with an OVA patch using a transparent bio-occlusive dressing on a shaved and tape-stripped area of skin for one week. This sensitization to OVA is repeated in two-week intervals. After three to four sensitization cycles, the mice show elevated serum IgE and significant eosinophil and Th2-deviated lymphocyte infiltration in the skin, which is similar to the pathology of AD. In this model, COX-2 deficient mice and the administration of COX-2 inhibitor both showed enhanced eosinophil infiltration and elevated IL-4 expression in the skin lesion with elevated serum IgE and IgG1 (Laouini et al., 2005). These results suggest that COX-2-derived prostanoids play regulatory roles in the development of AD, such as Th differentiation and inflammatory cell infiltration in the skin. In the following sections, we will discuss how prostanoids are involved in Th differentiation, DC function, and inflammatory cell infiltration in skin immunity.

## 6. Prostanoids as regulatory factors of Th differentiation

In older *in vitro* studies, PGE<sub>2</sub> has been regarded as a suppressant of Th1 cells, because of its suppressive effect on cell proliferation, differentiation and cytokine production from Th1 cells (Betz and Fox, 1991; Goodwin and Ceuppens, 1983). However, recent reports indicate that several PGE<sub>2</sub> receptors are involved in the regulation of Th differentiation in skin immunity via multiple pathways and different directions (Figure 2).

For example, PGE<sub>2</sub>-EP1 signaling has been reported to facilitate Th1 differentiation in the sensitization process through the skin (Nagamachi et al., 2007). PGE<sub>2</sub> produced by DCs in draining lymph nodes (dLNs) stimulates EP1 receptors on naïve CD4<sup>+</sup> and CD8<sup>+</sup> T cells and promotes Th1 and Tc1 differentiation (Nagamachi et al., 2007). PGI<sub>2</sub>-IP signaling promotes Th1 and Tc1 differentiation through a cAMP dependent mechanism (Nakajima et al., 2010). Intriguingly, IP deficient mice showed enhanced Th2 response such as elevated IgE concentration in serum in the mouse OVA-induced asthma model (Nagao et al., 2003), suggesting that lack of PGI<sub>2</sub>-IP signaling might result in a Th2 biased immune response through the inhibition of Th1 differentiation.

The regulatory mechanism of prostanoid signaling on Th differentiation is complex, because it depends on the context of immune system. For example, PGE<sub>2</sub>-EP2/EP4 signaling regulates Th1 and Th17 differentiation (Yao et al., 2009). In a weaker co-stimulation signaling through CD28, PGE<sub>2</sub> suppresses the Th1 differentiation via EP2 and EP4 receptors. In the case of strong co-stimulation signaling, however, stimulation of EP2 and EP4 signaling conversely facilitates the Th1 differentiation through a PI3-kinase-dependent mechanism (Yao et al., 2009). These results suggest that the action of prostanoid receptor signaling can be changed in a context-dependent manner. EP2 and EP4 signaling also regulates the Th17 differentiation. Th17 is a recently identified Th subset, and can be detected in a number of diseases, including AD (Guttman-Yassky et al., 2011; Koga et al., 2008). *In vitro*, Th17 differentiation is induced from naïve T cells in the presence of IL-6 and TGF- $\beta$ . In this condition, PGE<sub>2</sub> acts on naïve T cells through EP2/EP4 signaling and suppress the Th17 differentiation in a cAMP-dependent manner. However, PGE<sub>2</sub>-EP2/EP4 signaling also acts on DCs and increases the IL-23 production from the DCs. Thus, PGE<sub>2</sub> facilitates the expansion of Th17 (Yao et al., 2009). The blockade of EP4 signaling consistently ameliorated the disease progression in a CHS model and an EAE model, which are mediated by Th1 and Th17 cells, respectively (Yao et al., 2009). These results clearly indicate the importance of prostanoid signaling in Th differentiation *in vivo*. The facilitation effect of PGE<sub>2</sub> on Th17 is also reported in human T cells (Boniface et al., 2009).

## 7. Prostanoids as regulatory factors of DC function

In the initial step of sensitization in AD, allergens which enter the skin are captured by skin DCs and presented to the naïve T cells in the dLNs. Prostanoids can regulate this step by affecting the migration ability or antigen presentation ability of the skin DCs (Figure 2). PGE<sub>2</sub>, which is produced by KCs, acts on EP4 on LCs, and stimulates the migration of LCs (Kabashima et al., 2003b). Conversely, stimulation of DP on DCs inhibits the migration of skin DCs. Topical administration of DP inhibits the migration of DCs to dLNs and significantly suppresses the development of the mouse AD model (Angeli et al., 2001; Angeli et al., 2004). Prostanoids also regulate DC-T cell interaction in the priming of naïve T cells (Kabashima et al., 2003a). Cutaneous DCs produce abundant TXA<sub>2</sub>, which acts on naïve T cells and increases the motility of T cells, which impairs the stable DC-T cell interaction (Kabashima et al., 2003a). TP-deficient mice or wild-type mice treated with a TP antagonist during the sensitization period show enhanced CHS responses, indicating that TP signaling negatively regulates the priming of T cells *in vivo*.

Although the role of IgE in AD is still controversial (Guttman-Yassky et al., 2011), high serum IgE is one of the hallmarks of AD. Compared to the analysis of T cells and DCs, the reports about the role of prostanoids on B cells are relatively scarce. From the *in vivo* data using COX-2 deficient mice or IP deficient mice, which show increased IgE production in OVA sensitization

(Laouini et al., 2005), it might be possible that some prostanoid signaling regulates the antibody production. *In vitro*, PGE<sub>2</sub> drives Ig class switching to IgE by acting at EP2 and EP4 on B cells under LPS and IL-4 stimulation *in vitro* (Fedyk and Phipps, 1996). Whether such actions occur *in vivo* remains unknown, and this should be clarified in future studies.

## 8. Prostanoids and Treg induction

T regulatory cells (Treg) make up one of the T cell subsets which has potent suppressive functions in various disease models. There are several reports that analyzed Treg number and function in AD patients, but those results are not necessarily consistent (Brandt et al., 2009; Ou et al., 2004; Schnopp et al., 2007; Verhagen et al., 2006). However, considering the fact that loss of Treg in skin can lead to AD-like skin lesions in both human (Ochs et al., 2005) and mouse (Brunkow et al., 2001), it is very likely that Treg play important roles in the pathogenesis of AD.

It has been well known that ultraviolet (UV) radiation causes immunosuppression, and it is one of the effective treatment options for AD. Although multiple suppression mechanisms have been proposed, induction of Treg is considered one of the central factors for the suppression mechanism. As blocking of prostanoid production by treatment with non-steroidal anti-inflammatory drugs (NSAIDs) treatment can abolish the immunosuppressive effect through UV (Chung et al., 1986; Hart et al., 2002; Walterscheid et al., 2002), it has been suspected that prostanoids play important roles in the UV-induced immunosuppression, especially in Treg induction. By UV radiation, various prostanoids are produced in the skin, with PGE<sub>2</sub> being the most abundant prostanoids (Kuwamoto et al., 2000; Ruzicka et al., 1983; Soontrapa et al., 2011). Recently, it has been revealed that PGE<sub>2</sub>-EP4 signaling mediates the induction of Treg by UV irradiation, and regulates UV-induced immunosuppression (Soontrapa et al.). Blockade of EP4 signaling suppresses the increase of Treg in dLNs and abolishes the immunosuppressive effect of UV. Blockade of EP4 signaling also diminishes the RANKL expression on KCs after UV irradiation (Soontrapa et al., 2011). It is known that RANKL expression on UV-irradiated KCs activates LCs, and the RANKL-activated LCs function to induce Treg in dLNs (Loser et al., 2006). These results indicate that PGE<sub>2</sub>-EP4 signaling regulates RANKL expression on KCs and controls Treg induction from UV.

Other than PGE<sub>2</sub>, it has been reported that PGD<sub>2</sub> induces Treg differentiation through DP in a mouse asthma model (Hammad et al., 2007). Inhalation of a selective DP1 agonist suppressed the cardinal features of asthma by targeting the function of lung DCs. In mice treated with a DP1 agonist or receiving DP1 agonist-treated DCs, there was an increase in Tregs that suppressed inflammation in an IL-10-dependent way (Hammad et al., 2007). These effects of a DP1 agonist on DCs were mediated by cyclic AMP-dependent protein kinase A. Taken together, control of EP4 and/or DP1 signaling could represent a novel immunosuppressive approach.

## 9. Prostanoids as inflammatory mediators

In an established AD lesion, numerous inflammatory mediators such as cytokines (e.g., IL-4, IL-5, IL-13) and chemokines (e.g., CCL5, CCL11, CCL17) contribute to the development of AD (Guttman-Yassky et al.).

As for the inflammatory mediators in AD lesions, the role of PGD<sub>2</sub>-CRTH2 signaling has been the most frequently investigated. In the skin, PGD<sub>2</sub> is the major prostanoid produced

by activated mast cells.  $\text{PGD}_2$  has two types of receptors, DP and CRTH2. CRTH2 induces chemotaxis in Th2 cells, eosinophils and basophils with enhanced degranulation *in vitro* (Hirai et al., 2001; Yoshimura-Uchiyama et al., 2004). CRTH2 amplifies Th2 responses by preventing apoptosis of Th2 cells and enhancing their capacity to secrete cytokines (Nomiya et al., 2008; Xue et al., 2009). CRTH2 also amplifies eosinophil functions by mobilizing them from the bone marrow, preventing their apoptosis, and promoting their chemokinesis and degranulation (Gervais et al., 2001). CRTH2 mRNA expression is high in peripheral blood mononuclear cells of patients with AD (Hijnen et al., 2005), and circulating eosinophils and T cells in patients with AD have an increased surface expression of CRTH2 (Iwasaki et al., 2002), suggesting the role of CRTH2 in AD.

He et al. have recently reported that lack of CRTH2 signaling ameliorates the inflammation only in newly-challenged skin, while loss of this signaling in chronic challenged areas did not affect the inflammation (He et al., 2011). They used CRTH2 knockout mice in two types of AD models: one that was repeatedly sensitized with OVA for a total of seven weeks, which mimicked the chronic lesions of AD; and one that was challenged with OVA after the repeated sensitization of other skin areas for a total of seven weeks, which was supposed to mimic the acute lesions of AD. In the chronic lesions, the inflammatory cell infiltration and cytokine concentration was similar between wild-type and CRTH2 knockout mice, while in the acute lesions, such factors were significantly decreased in CRTH2 knockout mice compared with wild-type mice (He et al.). Consistently, the concentration of  $\text{PGD}_2$  increased significantly in the acute lesions, while the concentration of  $\text{PGD}_2$  in the chronic lesions was similar compared with that of non-affected skin. CRTH2 knockout mice also showed comparable levels of IgE production, indicating that CRTH2 signaling had little effect much on the antibody production process. Boehme et al. have previously reported that administration of a CRTH2 antagonist inhibited the development of chronic AD lesions in the same model (Boehme et al., 2009), but the CRTH2 antagonist-treated group also showed reduced IgE production, suggesting the possibility that administration of the CRTH2 antagonist affected the extent of sensitization non-specifically and thus lead to the reduced inflammatory cell infiltration in the skin. Collectively, blockage of  $\text{PGD}_2$ -CRTH2 signaling might inhibit allergic skin inflammation elicited in patients with AD by re-exposure to antigens to which they have been sensitized (Figure 3).

In contrast, stimulation of EP3-signaling in KCs is reported to play an anti-inflammatory role in skin inflammation by inhibiting chemokine production from KCs (Honda et al., 2009). Administration of an EP3 specific agonist suppressed a CHS response, and EP3 knockout mice showed an enhanced CHS response, suggesting that  $\text{PGE}_2$ -EP3 signaling works as a negative regulator of allergic cutaneous inflammation. An anti-inflammatory role of EP3 signaling is also reported in other allergic diseases such as mouse asthma and the allergic conjunctivitis model (Kunikata et al., 2005; Ueta et al., 2009).

## 10. Prostanoids as itch mediators

It is reported that some prostanoids can modulate pruritus, a significant hallmark of AD. In human studies,  $\text{PGE}_2$  is a weak pruritogen and prolongs experimentally-induced itch (Hagermark and Strandberg, 1977; Neisius et al., 2002), although injection of  $\text{PGE}_2$  alone does not elicit itch-associated response in animal experiments (Andoh and Kuraishi, 1998).  $\text{TXA}_2$  is also reported as a mediator of itch (Andoh et al., 2007). Injection of a TP agonist alone elicited itch-associated responses. TP was expressed in both KCs and nerve fibers in



skin (Andoh et al., 2007). TX synthase was also expressed in KCs. In some studies, the association of genetic polymorphisms in the TP gene with asthma and atopy has been reported (Shin et al., 2003). TXA<sub>2</sub> may be involved in the pathogenesis of atopic disease not only as an airway constriction factor but also as an itch mediator.

On the other hand, PGD<sub>2</sub> is reported to play anti-pruritic roles in the mouse AD model (Arai et al., 2004). Administration of PGD<sub>2</sub> and a DP1 agonist reduced scratching behaviors in an AD model using NC/Nga mice, while administration of a DP2 agonist did not reduce such behavior (Arai et al., 2004). Inhibition of histamine release from mast cells is proposed as a possible suppression mechanism of the DP signaling (Hashimoto et al., 2005). Blockade of TP signaling or stimulation of DP1 signaling may lead to a new target for the treatment of pruritic disease, including AD.

Figure 2

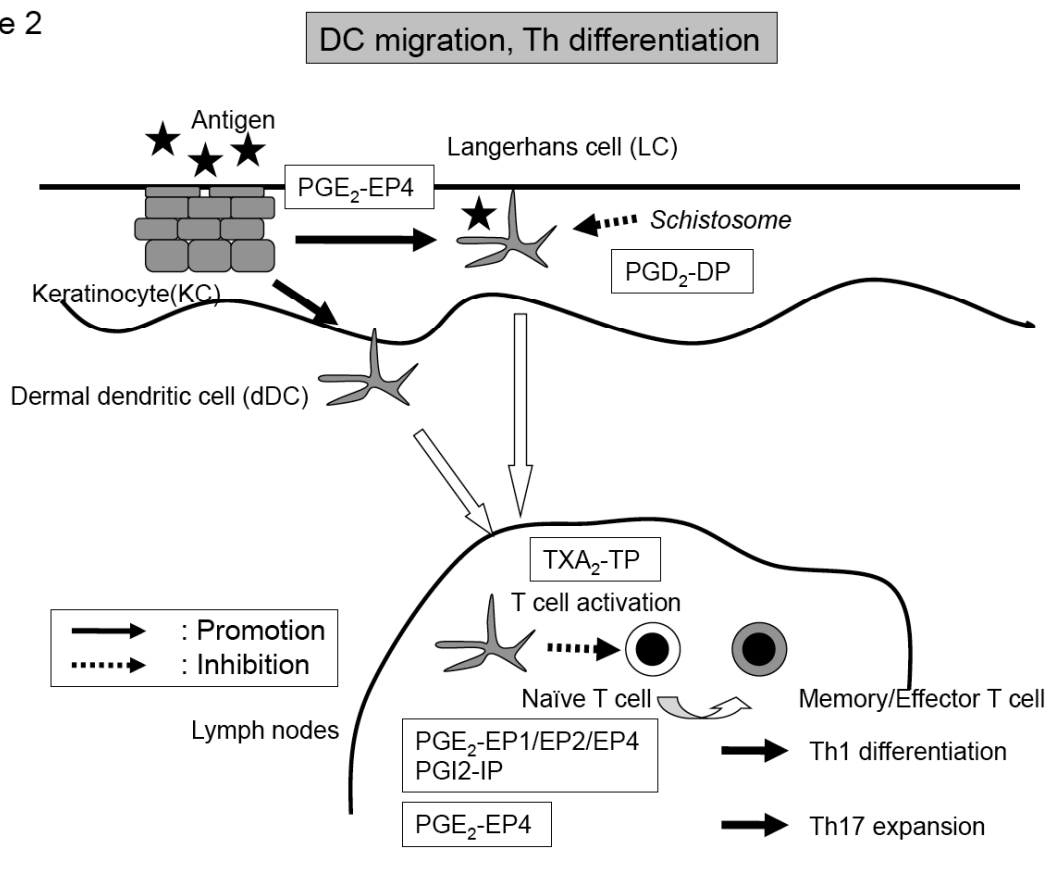


Fig. 2. Regulation of DC migration and Th differentiation by prostanoids

During the sensitization period, antigens induce pro-inflammatory cytokine secretion by KCs, which enhances cutaneous DC (LCs and dDCs) activation and migration to dLNs. In the LNs, cutaneous DCs activate naïve T cells that differentiate into mature memory T cells. During antigen exposure to the skin, KCs produce PGE<sub>2</sub> and mast cells produce PGD<sub>2</sub>. Moreover, *schistosomes* produce PGD<sub>2</sub> during a helminthic infection. The PGE<sub>2</sub>-EP4 pathway promotes, but PGD<sub>2</sub>-DP and PGI<sub>2</sub>-IP pathways inhibit cutaneous DC migration and maturation. TXA<sub>2</sub> produced by activated cutaneous DCs seems to act on naïve T cells to disrupt DC-T cell interaction. The PGE<sub>2</sub>-EP1/EP2/EP4 pathways promote Th1 cell differentiation, and the PGE<sub>2</sub>-EP4 pathway also promotes Th17 cell expansion.

Figure 3

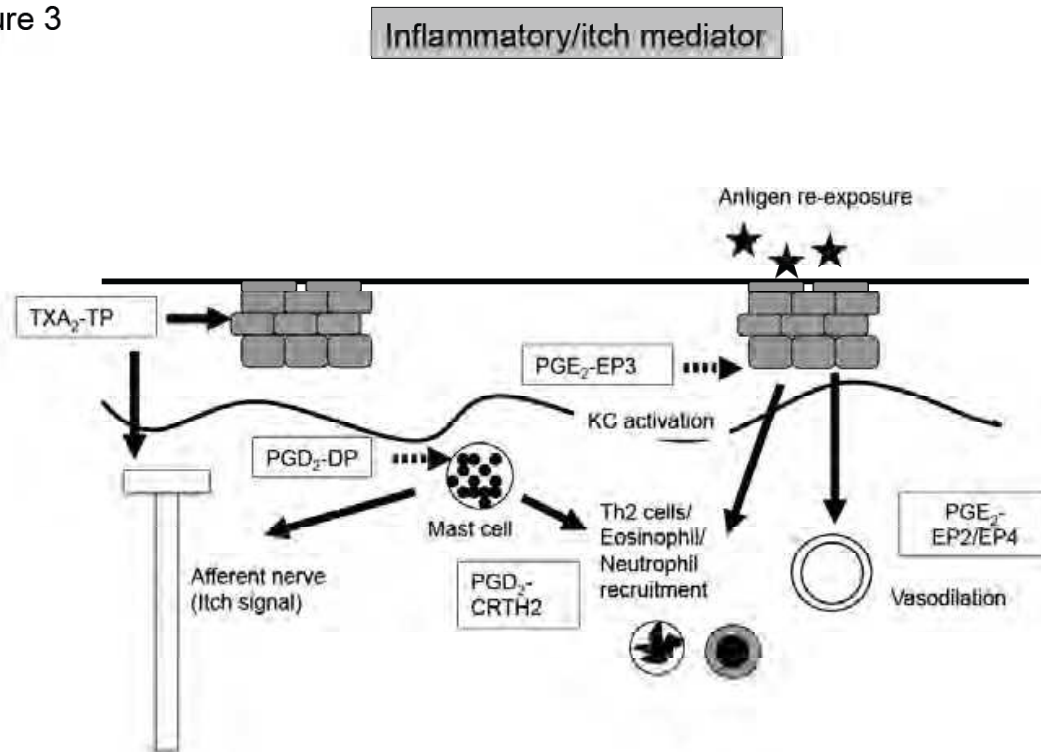


Fig. 3. Prostanoids as inflammatory/itch mediators

Repeated antigen exposure to the skin stimulates KCs to secrete pro-inflammatory cytokines, chemokines and other mediators, which activate the endothelial activation of blood vessels. This activation attracts memory T cell infiltration into the skin.  $PGE_2$  dilates blood vessels possibly through EP2 and EP4. The  $PGD_2-CRTH2$  signaling promotes Th2 cells/eosinophils/neutrophils infiltration in skin. The  $PGE_2-EP3$  signaling inhibits KC activation and plays an anti-inflammatory role in CHS. The TP signaling mediates itch signaling through afferent nerves, while stimulation of DP signaling inhibits itch-associated responses.

## 11. Summary and future direction

NSAIDs, which block the production of all prostanoids, usually have limited effects on AD (Kabashima and Miyachi, 2004) and therefore have not been given so much attention as a potential therapeutic agent. However, the analysis using the receptor knockout mice and receptor specific drugs has revealed new unexpected roles of prostanoids in the immune systems. In addition, signaling from even the same receptor can produce the opposite effect depending on the context, such as the Th1 modulating effect generated through EP2/EP4 signaling (Yao et al., 2009). Therefore, it would be necessary to reconsider the role of prostanoids in the development of AD. It is also important to correlate these immunomodulatory actions of prostanoids found in mice to their actions in immune diseases of humans. Currently, CRTH2 antagonists are on their way to being used in clinical applications for AD or asthma (Ulven and Kostenis., 2010). Further analysis of the role of each prostanoid receptor has great potential in leading to a new therapeutic target for AD.

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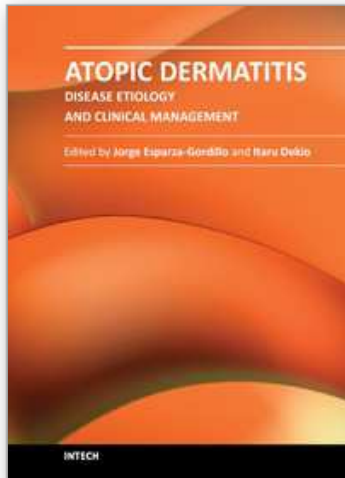


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## **Atopic Dermatitis - Disease Etiology and Clinical Management**

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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