J Mol Med (2009) 87:1015–1022
DOI 10.1007/s00109-009-0500-1

REVIEW

Prostanoids and inflammation: a new concept arising from receptor knockout mice

Shuh Narumiya

Received: 7 May 2009 / Revised: 24 June 2009 / Accepted: 25 June 2009 / Published online: 17 July 2009

Abstract Prostanoids including various types of prostaglandins and thromboxanes are arachidonate metabolites produced and released in response to a variety of physiological and pathological stimuli and function to maintain the body homeostasis. Since cyclooxygenase, the enzyme initiating their biosynthesis, is inhibited by aspirin-like antipyretic, anti-inflammatory, and analgesic drugs, contribution of prostanoids to acute inflammation such as fever generation, pain sensitization, and inflammatory swelling has been recognized very early. On the other hand, since aspirin-like drugs generally show little effects on allergy and immunity, it has been believed that prostanoids play little roles in these processes. Prostanoids act on a family of G-protein-coupled receptors designated PGD receptor, PGE receptor subtypes EP1–EP4, PGF receptor, PGI receptor, and TX receptor to elicit their actions. Studies using mice deficient in each of these receptors have revealed that prostanoids indeed function in the above aspirin-sensitive processes. However, these studies have also revealed that prostanoids exert both pro-inflammatory and anti-inflammatory actions not only by acting as mediators of acute inflammation but also by regulating gene expression in mesenchymal and epithelial cells at inflammatory site. Such dual actions of prostanoids are frequently seen in immune and allergic reactions, where different type of prostanoids and their receptors often exert opposite actions in a single process. Thus, a new concept on the role of prostanoids in inflammation has arisen from studies using the receptor knockout mice.

S. Narumiya (✉)
Department of Pharmacology, Graduate School of Medicine,
Kyoto University,
Kyoto 606-8501, Japan
e-mail: snaru@mfour.med.kyoto-u.ac.jp

Keywords Prostaglandin · Prostaglandin receptor · Inflammation · Immunity · Allergy

Introduction

Prostanoids including prostaglandin (PG) D_2, prostaglandin E2 (PGE_2), prostaglandin F2alpha ($PGF_{2\alpha}$), prostacyclin (PGI_2), and thromboxane (TX) A_2 are produced from arachidonic acid by the sequential actions of cyclooxygenase (COX) and respective synthases. They are formed and released in response to various, often noxious, stimuli, function in a paracrine and autocrine fashion in the vicinity of their production, and serve to maintain local homeostasis in the body. They act on their cognate receptors on the surface of target cells to exert their actions. There are eight types and subtypes of receptor for prostanoids designated PGD receptor (DP), EP1, EP2, EP3, and EP4 subtype of PGE receptor, PGF receptor (FP), PGI receptor (IP), and TX receptor (TP) [1]. All of them are G-protein-coupled receptors (GPCRs) and constitute a prostanoid receptor family in the superfamily of GPCRs. In addition, there is another GPCR termed chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) that responds to PGD_2 but belongs to the family of chemokine receptors. Main signal transduction of each of these receptors is a rise in intracellular cyclic adenosine monophosphate (cAMP) concentration via Gs in DP, EP2, EP4, and IP, a rise in intracellular free calcium ion concentration via Gq or other G protein in EP1, FP, and TP and a decrease in intracellular cAMP concentration via Gi in EP3 and CRTH2, though most of them couple to more than one G protein and more than one signaling pathway. Mice deficient in each of these receptors individually were generated and subjected to various

analyses. Furthermore, these receptors have been used as a panel in screening of chemical library, and agonists and antagonists highly selective to each member have been developed. Analyses using these knockout mice and applying selective compounds to wild-type mice have revealed roles that each receptor plays in various physiological and pathophysiological processes. Here, I focus mainly on findings my own group have obtained through such studies (Table 1) and discuss new concepts of prostanoids in inflammatory processes arising from these findings. The findings on the knockout mice reviewed were those on the mice that were backcrossed for more than five generations onto the C57BL/6 background except for EP4-deficient mice, which were in the mixed genetic background of 129SV and C57BL/6, or unless specified in the text. For other aspects of the prostanoid receptor actions, please refer to a more comprehensive review [1].

Prostanoid receptors as mediators of classic signs of acute inflammation

Local reddening, heat generation, and swelling are classic signs of acute inflammation, which are caused by increased blood flow and vascular permeability. Inhibitory effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on these signs and vasodilatory action of prostanoids such as PGI_2 and PGE_2 implicated prostanoids as mediators of the vascular responses in acute inflammation. Indeed, using knockout mice deficient in each of prostanoid receptors individually, Murata et al. found the ~50% reduction in carrageenin-induced paw swelling in IP-deficient mice, a reduction similar in magnitude to that achieved by treatment with NSAIDs in wild-type mice [2]. Yuhki et al. showed that EP2 and EP3 as well as IP mediate pleural exudation in carrageenin-induced mouse pleurisy at 1–5 h after the carrageenin injection [3]. Yuhki et al. further showed that the PGI_2–IP pathway is the main prostanoid signaling for exudate formation in zymosan-induced pleurisy [4]. These results are consistent with the role of prostanoids as mediators of acute inflammation and suggest that PGE_2 and PGI_2 elicit inflammatory responses in a context-dependent manner, that is, dependent on the type of stimulus and the site of the body. As for other signs of acute inflammation, EP3 was identified as the receptor mediating febrile response [5], and the neural pathway from pyrogen stimulation to fever generation has been elucidated in detail (Fig. 1; [6] and references therein). In pain sensation, various types of prostanoid receptors, IP, EP1, EP3, and EP4, are involved in peripheral hyperalgesia in a context-dependent manner [2, 7–9], one mechanism being lowering the threshold of TRPV1 cation channel by EP1 and IP [8]. In addition, EP2 inhibits glycinergic inhibitory neurotransmission in the spinal cord and causes central hyperalgesia [10, 11].

Table 1 Summary of actions of prostanoids and their receptors in inflammatory processes discussed in this review

PGD2/DP: facilitates allergic inflammation [18], suppresses Langerhans cell mobilization and migration [46]
PGD_2/CRTH2: facilitates allergic inflammation [28], negatively regulate IL-5 production [29]
PGE_2/EP1: facilitates Th1 differentiation [48], peripheral hyperalgesia [8]
PGE_2/EP2: mediates pleural exudation [3] and central hyperalgesia [10], facilitates progression of arthritis [12], facilitates Th1 differentiation and Th17 expansion [37]
PGE_2/EP3: mediates pleural exudation [3], fever generation [5], and peripheral hyperalgesia [7], negatively regulates allergic inflammation [22–24]
PGE_2/EP4: mediates peripheral hyperalgesia [9], facilitates progression of arthritis [12], suppresses intestinal inflammation [13], facilitates Th1 differentiation and Th17 expansion [37], promotes Langerhans cell mobilization and migration [45]
PGI_2/IP: mediates inflammatory swelling [2], peripheral hyperalgesia [2, 8], and pleural exudation [3, 4], facilitates progression of arthritis [12], attenuates IgE production [30]
TXA_2/TP: negatively regulates interaction of dendritic cells and T cells [47]

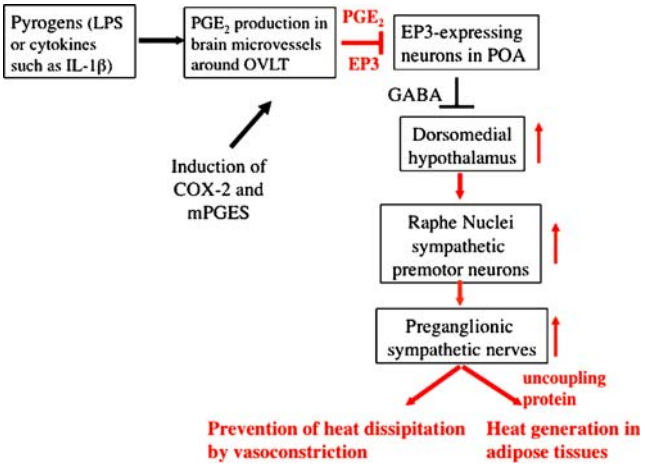

Fig. 1 A current model for the neural pathway of fever generation. When PGE_2 is formed in brain microvessels in the organum vasculosum laminae terminalis (*OVLT*), it enters the brain and acts on the EP3-expressing neurons in the preoptic area (*POA*). The EP3 stimulation inhibits the GABAergic inhibitory transmission of these POA neurons and liberates the downstream neural pathway, ultimately leading to sympathetic stimulation in peripheral tissues (shown in *red*)

Gene expression-dependent pro-inflammatory actions of prostanoids

The above studies thus substantiated the role of prostanoids in acute inflammation. However, one novel and important

message obtained by knockout mouse studies is that prostanoids exert both pro-inflammatory and anti-inflammatory actions through regulation of gene expression in relevant tissues. Honda et al. subjected mice deficient in prostanoid receptors in the DBA/1J background to collagen-induced arthritis, an animal model of rheumatoid arthritis [12]. Whereas the incidence was unaffected, the extent and progression of arthritis were markedly suppressed in IP-deficient mice as well as in EP2-deficient mice treated with an EP4 antagonist, indicating that PGI_2–IP signaling and PGE_2 signaling through EP2 and EP4 mediate joint inflammation in this model. Further analysis revealed that both PGI_2 and PGE_2 pathways function in conjunction with interleukin (IL)-1β and enhance expression of arthritis-related genes, including those for IL-6, vascular endothelial growth factor-A, and receptor activator of NF-kappa B ligand, in synovial fibroblasts and thereby contribute to arthritic inflammation, bone destruction, and pannus formation (Fig. 2). Collagen-induced arthritis thus represents an example in which prostanoids elicit pro-inflammatory actions through expression of pro-inflammatory genes.

Gene expression-dependent anti-inflammatory actions of prostanoids

An example of the prostanoid action contrary to the above was obtained by analysis of the knockout mice subjected to dextran sodium sulfate (DSS)-induced colitis, an animal model of ulcerative colitis [13]. Ulcerative colitis is one of inflammatory bowel diseases (IBD) and is characterized by inflammation in the large intestine associated with diarrhea,

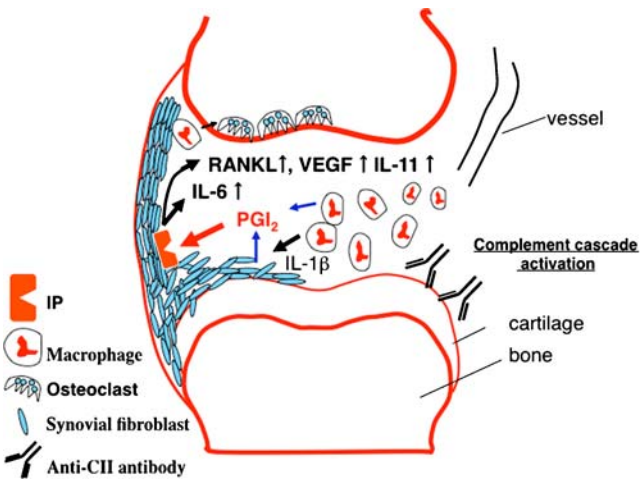

Fig. 2 A model of prostanoid actions in the inflammatory cascade of collagen-induced arthritis. In the arthritic joint, PGI_2 acts on IP in synovial fibroblasts and facilitates the IL-1β-induced expression of genes such as IL-6, RNAKL, VEGF, and IL-11. PGE_2 functions similarly by acting on EP2 and EP4

occult blood, abdominal pain, weight loss, anemia, and leukocytosis. Studies in humans have implicated impaired mucosal barrier function, pronounced innate immunity, production of pro-inflammatory cytokines, and the activation of $CD4^+$ T cells in the pathogenesis. Administration of NSAIDs often triggers or worsens the colitis [14], which was confirmed experimentally by studies on COX-deficient mice subjected to DSS-induced colitis [15], indicating that COX-derived prostanoids contribute to the defense against intestinal inflammation. Based on these findings, Kabashima et al. examined the susceptibility of mice deficient in each of prostanoid receptors to DSS treatment [13]. They found that only EP4-deficient mice developed severe colitis in response to treatment with 3% DSS. They then reproduced this phenotype in wild-type mice by administration of an EP4-selective antagonist and confirmed this finding pharmacologically. EP4 deficiency was shown to result in impairment of mucosal barrier function that was associated with epithelial loss, crypt damage, and accumulation of neutrophils and $CD4^+$ T cells in the colon. DNA microarray analysis revealed increased expression of genes associated with immune responses and reduced expression of genes associated with mucosal repair and remodeling in the colon of EP4-deficient mice. Thus, the PGE_2–EP4 signaling appears to maintain intestinal homeostasis by preserving mucosal integrity and downregulating immune responses through regulation of gene expression. It is intriguing that the same receptor, EP4, exerts an anti-inflammatory action in intestinal inflammation and a pro-inflammatory action in arthritis, emphasizing the context-dependent roles of prostanoid signaling.

Prostanoid receptors in allergic inflammation

Pro-inflammatory and anti-inflammatory actions of prostanoids sometimes operate in a single disease process. One example is allergic inflammation, where the PGD_2–DP signaling and the PGE_2–EP3 signaling exert antagonistic actions. The type I allergic reaction underlies the pathogenesis of bronchial asthma, atopic dermatitis, and anaphylactic shock. Affected individuals produce immunoglobulin (Ig) E antibodies to allergens such as those derived from house dust mites and plant pollen. Exposure to those allergens results in cross-linking of IgE receptors on the surface of mast cells, the consequent activation of these cells, and the development of an allergic reaction. The Th2 subset of T lymphocytes and their cytokines are important mediators of IgE production as well as the development of allergic disease. Various prostanoids are produced during the initial activation of mast cells and subsequent disease development. PGD_2 is a major prostanoid produced by activated mast cells [16] and is released in large amounts

during asthmatic attacks in certain patients [17]. The role of PGD_2 in allergic asthma long remained unclear, however. Matsuoka et al. examined this issue by applying the ovalbumin (OVA)-induced asthma model to DP-deficient mice [18]. Sensitization and aerosol challenge of $DP^{-/-}$ mice with OVA induced increases in the serum concentration of IgE similar to those observed in wild-type mice. However, the DP-deficient animals developed substantially reduced asthmatic responses in this model; the concentrations of Th2 cytokines and the extents of lymphocyte accumulation and eosinophil infiltration in the lungs after OVA challenge were greatly reduced in the mutant animals compared with those apparent in the wild type. These observations thus indicate that PGD_2 is a mast cell-derived mediator that serves to mediate asthmatic responses. This conclusion is supported by single nucleotide polymorphism (SNP) analysis of the DP gene (*PTGDR*) in humans. This gene is located at chromosome 14q22.1, a region that has been associated with asthma and atopy. Oguma et al. [19] examined SNPs of *PTGDR* in Caucasian and black individuals with asthma and control subjects. They identified three haplotypes consisting of four SNPs in the promoter region of the gene. They further found that these haplotypes show a different promoter activity and that the promoter activity of these haplotypes is significantly correlated with susceptibility to asthma.

The above observations suggest that PGD_2 signaling facilitates allergic responses not only in mice but also in humans. However, if PGD_2 is the only prostanoid that functions in allergic asthma, administration of NSAIDs would be expected to ameliorate asthmatic symptoms. Instead, NSAIDs are either without effect or induce severe attacks in certain asthmatic patients, a syndrome known as aspirin-induced asthma [20]. This discrepancy might be explained by the existence of a prostanoid other than PGD_2 that negatively modulates allergic reactions. The most likely candidate for such a prostanoid is PGE_2, given that PGE_2 has been known for some time to exert anti-allergy effects in some contexts [21]. Kunikata et al. subjected mice deficient in each EP subtype individually to the OVA-induced asthma model and examined their responses [22]. Among the four knockout mouse strains, only EP3-deficient mice exhibited substantially exaggerated airway inflammation compared with that observed in their wild-type counterparts while showing similar plasma concentrations of anti-OVA IgE. The EP3-deficient animals also manifested an enhanced passive cutaneous anaphylaxis reaction. These results thus implicated PGE_2–EP3 signaling in suppression of mast cell activation. Consistent with this conclusion, an EP3-selective agonist was found to inhibit the antigen-induced release of histamine and leukotrienes from sensitized lung tissue in vitro and to suppress airway inflammation in OVA-challenged mice in vivo. Previously, aspirin-induced asthmatic attack was explained by diversion of arachidonic acid metabolism from the COX pathway to the lipoxygenase pathway [20]. Our findings indicate that this is not simple diversion of the substrate from one pathway to the other, but due to enhancement of the lipoxygenase pathway by aspirin-mediated suppression of the PGE_2-mediated mast cell inactivation. Thus, the PGE_2–EP3 pathway acts though mast cell inactivation. However, the mast cell inactivation is not the only mechanism of the EP3-mediated inhibition of allergic inflammation. The EP3 agonist was most effective when administered subcutaneously 3 h after OVA challenge, indicating that the major site of EP3 action is at a step (or steps) downstream of mast cell activation. Further analysis revealed that administration of the EP3 agonist suppressed induction of the expression of various asthma-related genes, including those for chemokines and tissue remodeling factors, in the lung, and that EP3 is co-expressed with some of these molecules in the airway epithelium. On the basis of these findings, Kunikata et al. suggested that PGE_2 produced during allergy acts at EP3 on both mast cells and airway epithelial cells, thereby blunting activation of mast cells and impeding progression of the allergic reaction by inducing downregulation of the expression of relevant genes in the airway epithelium. DP is also expressed in the airway epithelium, and given its opposing mechanism of signal transduction relative to that of EP3, it possibly facilitates the asthmatic reaction by increasing expression of these genes. Recently, suppression of allergic response by EP3 has also been found in mouse models of allergic conjunctivitis and contact hypersensitivity of the skin [23, 24], where expression of EP3 is found in epithelial cells of the conjunctiva and keratinocytes of the skin, respectively. The roles of the PGD_2–DP and the PGE_2–EP3 pathways in allergic reactions suggested by these studies are depicted in Fig. 3.

In addition to the above actions of DP and EP3, there are other actions in allergy in which prostanoids and their receptors are involved. For example, PGD_2 may also function in allergy by acting at the receptor CRTH2. CRTH2 can bind PGD_2 and is expressed in cells important in allergy such as Th2 lymphocytes, eosinophils, and basophils [25]. Given that stimulation of CRTH2 induces chemotaxis of these cells in vitro, it has been suggested that CRTH2 facilitates allergic inflammation. Indeed, administration of selective agonists for CRTH2 to the airway or painting of these substances on the skin of sensitized animals was found to augment infiltration of inflammatory cells into the lungs and skin, respectively [26, 27]. The generation of CRTH2 knockout mice allowed further examination of the importance of the PGD_2–CRTH2 pathway in the natural course of allergy. Satoh et al. [28] used CRTH2-deficient mice that were backcrossed more

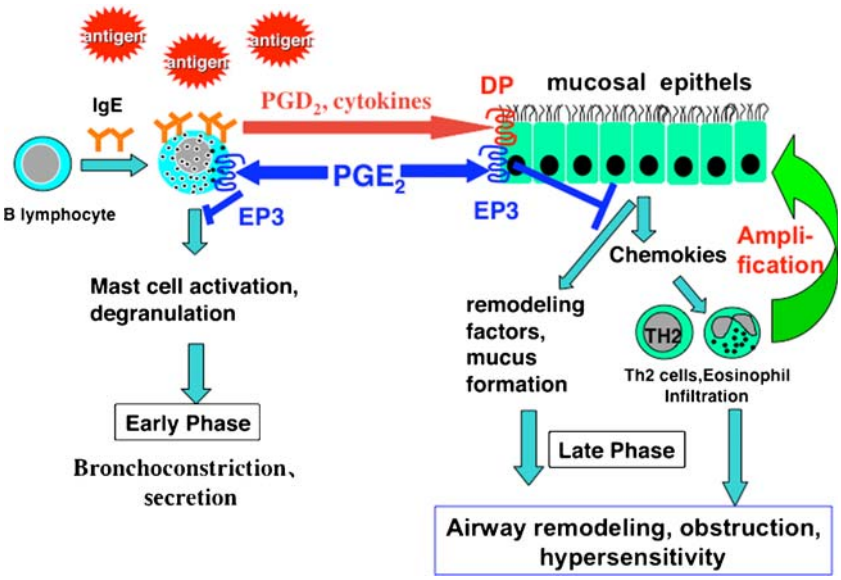

Fig. 3 Antagonism of the PGD_2–DP signaling and the PGE_2–EP3 signaling in allergic inflammation. In the ovalbumin-induced bronchial asthma model, the PGD_2–DP pathway, together with various cytokines stimulates and the PGE_2–EP3 pathway, suppresses the late phase of allergic inflammation through up- and downregulation of expression of inflammation-related gees in the airway epithelial cells, respectively. The PGE_2–EP3 pathway also acts on mast cells and suppresses their activation

than ten generations to the Balb/cJ background and found that allergic inflammation associated with IgE-induced dermatitis was suppressed in these mice. On the other hand, Chevalier et al. [29] subjected to the OVA-induced asthma model the CRTH2 knockout mice they generated in the mixed genetic background of 129SV and C57BL/6 and found that airway inflammation and eosinophil infiltration were augmented in the knockout mice. The latter study also showed that IL-5 production by activated T cells from CRTH2-deficient mice in vitro was increased compared with that observed with wild-type cells. These results indicated that CRTH2 indeed functions to facilitate allergy in situ at the site of inflammation but that this receptor also regulates cytokine production in the early phase of allergy development, raising the question as to whether suppression of this pathway would result in an overall beneficial effect in patients. Application of the OVA-induced asthma model to mice deficient in other prostanoid receptors revealed that airway inflammation was also augmented in IP-deficient mice. In contrast to EP3-deficient mice, however, $IP^{-/-}$ mice exhibited substantially higher plasma concentrations of antigen-specific and total IgE, indicating that PGI_2–IP signaling functions in sensitization to IgE production [30]. Thus, prostanoids and their receptors function at various steps of allergic inflammation.

Prostanoid receptors in immune inflammation

Inflammation can be caused by a variety of stimuli, one of which is immune stimulus. It is known that autoaggressive helper T (T_H) cells induce tissue damage and cause inflammation, and these actions are believed to play roles in pathogenesis of immune diseases such as multiple sclerosis and rheumatoid arthritis [31–33]. Among three effector T_H subsets, T_H17 cells or both T_H1 and T_H17 cells mediate tissue damage, inflammation, and autoimmunity [31–33]. T_H1 and T_H17 cells are characterized by their expression of interferon-γ and IL-17, respectively. T_H1 differentiation is induced by IL-12 and T_H17 differentiation is induced by transforming growth factor-β and IL-6 and expanded by IL-23. Notably, IL-12 and IL-23 shares the common p40 subunit. Recent reports indicate that PGE_2 is involved in differentiation and expansion of these TH subsets and therefore in elicitation and progression of immune diseases. It is known from 1980s that PGE_2 suppresses T_H1 differentiation through a rise in cAMP, and the receptors mediating this action have been identified as EP2 and EP4 [34–36]. However, T cell suppression by PGE_2 generally requires high concentration of this PG and has been shown mostly, if not exclusively, in in vitro culture systems and is rarely seen in vivo in intact animals, raising a possibility that PGE_2 acts differently in in vivo immune responses. Yao et al. [37] reexamined this issue and found that, on the contrary to the previous findings, PGE_2 can induce T_H1 differentiation through EP2 and EP4 under the strengthened TCR stimulation, and this action is dependent on phosphatidyl inositol (PI)-3 kinase activation and not cAMP. They also found that PGE_2 facilitates T_H17 expansion by IL-23 through the receptors, EP2 and EP4, but this action is mediated by cAMP and not PI-3 kinase. The same group further found that production of IL-23 by activated dendritic cells (DCs) requires PGE_2 and this action is also dependent on cAMP. It is now known that some GPCRs transduce signals not only through hetero-trimeric G proteins but also through β-arrestin, which recruits c-Src and signals to PI-3 kinase, and EP4 is one of such GPCRs [38]. Thus, PGE_2 utilizes different signaling

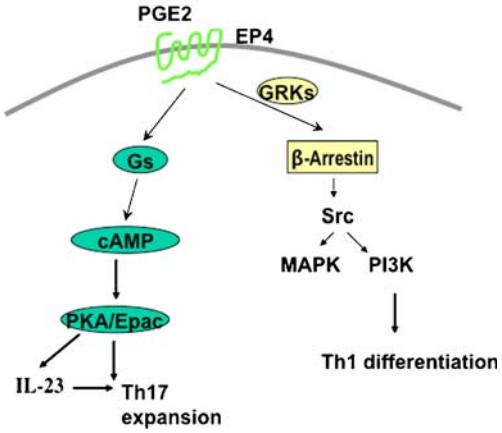

Fig. 4 EP4 signaling in Th1 differentiation and Th17 expansion. The PGE_2–EP4 signaling facilitates Th1 differentiation and Th17 expansion through utilizing the PI-3 kinase pathway in T cells and the cyclic AMP pathway in T cells and DCs, respectively. See the text for details

modules of EP2/4 and facilitates T_H1 differentiation and T_H17 expansion (Fig. 4). To verify that these actions of EP4 operate in vivo in immune disorders, Yao et al. [37] used mouse models of allergic skin disease and multiple sclerosis, that is, contact hypersensitivity (CHS) and experimental autoimmune encephalomyelitis. They subjected mice to these models and examined effects of an EP4 antagonist. The antagonist administration suppressed disease progression in both experiments, which was accompanied by reduced T_H1 and T_H17 cell accumulation in lymph nodes, confirming that the EP4-dependnet step or steps are critical in differentiation or expansion of T_H1 and T_H17 cells and elicitation of diseases. Consistent with the findings by Yao et al., Ganea and collaborators activated bone marrow-derived $CD11c^+$ DCs with lipopolysaccharide in the presence of exogenously added PGE_2 and found that PGE_2 can augment IL-23 production by DCs by about two times [39, 40]. Stimulatory action of PGE_2 on T_H17 differentiation or expansion in vitro has been reported also in human peripheral blood mononuclear cells [41]. It is therefore likely that the PGE2–EP4 signaling operates in immune diseases of humans. It is noted in this context that human EP4 was assigned as a susceptibility gene of Crohn's disease [42, 43], in which involvement of IL-23 and T_H17 is indicated [44]. These findings appear contradictory with the EP4 actions to prevent DSS-induced colitis described above, because ulcerative colitis and Crohn's disease are both IBD. However, intestinal inflammation in the DSS model is initiated by damage of intestinal epithelial cells, and EP4 functions to enhance growth of the epithelial cells to augment their barrier function

In addition to these actions in immune inflammation, the receptor knockout studies have revealed that prostanoids and their receptors work at various steps of immunization, exert actions often opposing each other, and regulate immune response and that general inability of NSAIDs to affect immune response can be due to suppression of these actions altogether. For example, EP4 facilitates [45] and DP suppresses [46] DC mobilization and migration, TP regulates interaction of DCs and naïve T cells to regulate the extent of immune response [47], and EP1 regulates the balance of T_H1 and T_H2 [48] (Fig. 5).

Concluding remarks

Studies using mice deficient in each of the prostanoid receptors have not only substantiated the role of prostanoids and their mechanisms in acute inflammation including fever generation and pain sensation but also have

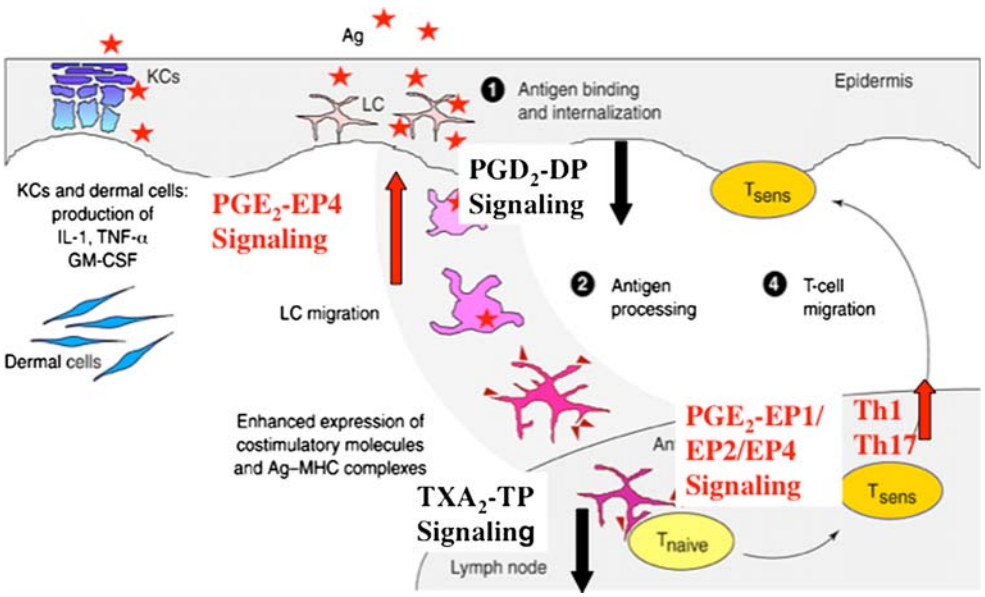

Fig. 5 Prostanoid signaling in the sensitization phase of immune response. Actions of various prostanoid signaling pathways in immune response have been examined using the contact hypersensitivity (CHS) model or other form of skin immune response [37, 44–46], and their presumed sites of action are depicted in the hypothetical scheme of the sensitization phase of CHS illustrated by Grabbe and Schwarz [49]. See the text for details

revealed that prostanoids exert both pro-inflammatory and anti-inflammatory actions through regulation of gene expression in relevant tissues and that such actions are often seen in allergic and immune inflammations. The fact that prostanoids and their receptors exert these actions in a context-dependent manner and regulate various steps of inflammation indicates that context-dependent selective manipulation of each receptor signaling may beneficially control inflammatory responses of certain diseases better than current anti-inflammatory drugs.

Conflict of interest statement The author declares that his research on prostanoid receptors has been supported in part by Ono Pharmaceuticals Co. Ltd. through collaboration with Kyoto University. Ono Pharmaceuticals Co. Ltd. has developed compounds discussed in this manuscript.

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