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Invited review article

Prostanoids in allergy

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ABSTRACT

Prostanoids, which include prostaglandin and thromboxane, are metabolites of arachidonic acid released in various pathophysiological conditions. They induce a range of actions mediated through their respective receptors expressed on target cells. It has been demonstrated that each prostanoid receptor has multiple functions and that the effect of receptor stimulation can vary depending on context; this sometimes results in opposing effects, such as simultaneous excitatory and inhibitory outcomes. The balance between the production of each prostanoid and the expression of its receptors has been shown to be important for maintaining homeostasis but also involved in the development of various pathological conditions such as allergy. Here, we review the recent findings on the roles of prostanoids in allergy, especially focusing on atopic dermatitis and asthma.

Introduction

When tissues are exposed to diverse pathophysiological stimuli, arachidonic acid (AA) is released from membrane phospholipids and converted into lipid mediators, such as prostanoids, leukotrienes (LT) and hydroxy-eicosatetraenoic acids (HETEs) via their respective synthases.[1] Prostanoids are formed by the cyclooxygenase (COX) pathway.[1] 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 phorbol ester. The COX reaction results in the formation of an unstable endoperoxide intermediate called prostaglandin (PG) H_2, which, in turn, is metabolized to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane (TX) A_2 by their specific synthases[1] (Fig. 1).

Prostanoids are released from cells immediately after formation. Since they are chemically and metabolically unstable, they usually function only locally through membrane receptors on target cells.[1] Nine types and subtypes of membrane prostanoid receptors are conserved in mammals from mouse to human: two subtypes of the PGD receptor (DP (DP_1) and a chemoattractant receptor homologous-molecule expressed on Th2 cells known as CRTH2 (DP_2)),[2] four subtypes of the PGE receptor (EP1, EP2, EP3, and EP4), the PGF receptor (FP), the PGI receptor (IP), and the TXA receptor (TP)[1] (Fig. 1). All are G protein–coupled rhodopsin-type receptors with seven transmembrane domains.

Although it has been difficult to analyze the physiological roles of prostanoids because of their instability *in vivo*, recent developments in both the disruption of the respective genes and the creation of receptor-selective compounds have made it possible.[3,4] These genetic and pharmacological approaches have revealed new roles played by prostanoids and their receptors in allergic diseases. In this review, we describe the current state of our knowledge of prostanoids' roles in atopic dermatitis and asthma.

Prostanoids in atopic dermatitis (allergy, skin barrier functions, pruritus)

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by a complex, heterogeneous pathogenesis, including allergy/immunology, skin barrier dysfunction, and pruritus.[5–7] In the dermis, a cellular infiltrate is present consisting of lymphocytes, monocytes and mast cells.

It has been reported that several kinds of prostanoids including PGE_2 and PGD_2 are produced in the skin of AD patients.[8–10] Yet the roles of the various prostanoids in the pathogenesis of AD have not been thoroughly pursued, because treatment with COX inhibitors, which block the production of prostanoids, are not usually effective against AD symptoms, implicating a weaker association of prostanoids with the pathogenesis of AD. However, recent studies have suggested that various prostanoid receptors do play distinct stimulatory and regulatory functions in the pathogenesis of AD.

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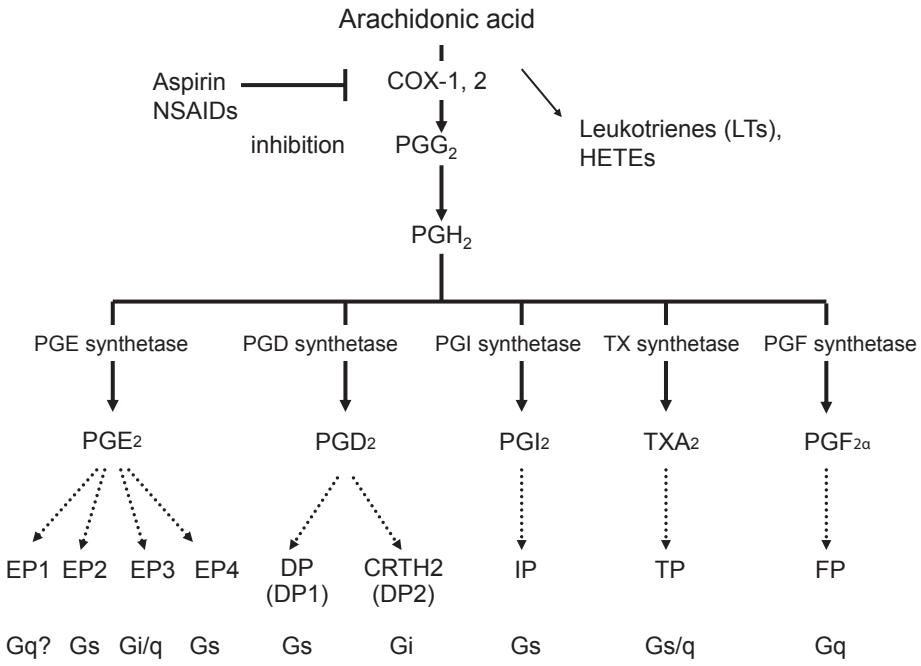

Fig. 1. Prostanoids synthesis and receptors. Prostanoids synthesis pathways, their respective receptors, and the signal transduction mechanisms from the receptors. Gs is a heterotrimeric G protein subunits that activates adenylate cyclase, which produces cAMP, and activates cAMP-dependent protein kinase. Gi is also a heterotrimeric G protein subunits that inhibits the production of cAMP, and Gq activates phospholipase C and increases the cytosolic calcium concentration. PG, Prostaglandin; COX, cyclooxygenase; NSAIDs, Non-steroidal anti-inflammatory drugs; HETEs, hydroxy-eicosatetraenoic acids.

Prostanoids in immunology of AD

Recently, several new types of murine AD models have been established,[11] including an ovalbumin (OVA)-induced mouse AD model[12] and a repeated hapten application contact hypersensitivity (CHS) model.[13] In an OVA-induced mouse AD model, COX-2-deficient mice exhibited both enhanced eosinophil infiltration and elevated IL-4 expression in the skin and spleen with elevated serum antigen-specific IgE and IgG1,[14] suggesting the existence of prostanoid receptors that have regulatory functions in AD.

Among the prostanoids, PGD_2 is the major prostanoid produced by activated mast cells. It is detected in the skin of AD patients[9,10,15,16] as well as in the OVA-induced AD model.[17] PGD_2 production in skin can also be stimulated by scratching, however.[18] Because local application of PGD_2 induces peripheral vasodilation, while systemic injection of PGD_2 induces flushing and nasal congestion, it has generally been believed that PGD_2 acts as an inflammatory mediator in AD.[19] However, recent studies have revealed that PGD_2 plays both pro- and anti-inflammatory roles in cutaneous immune responses depending on the receptors.

PGD_2 has two types of receptors, DP[1] and CRTH2.[2] In an OVA-induced AD model, administration of BW245c, a DP agonist, inhibits sensitization with OVA by inhibiting the migration of skin dendritic cells (DC).[20,21] Consistently, DP-deficient mice exhibit enhanced inflammation in the AD model of repeated hapten application and CHS, with increased skin DC migration to draining LNs,[22] suggesting that PGD_2-DP signaling exerts a regulatory role in the development of AD. Even in a more acute skin inflammation model, it is reported that PGD_2-DP signaling plays suppressive roles by enhancing vascular endothelial barrier function.[23]

PGD_2-CRTH2 signaling, on the other hand, generally plays pro-inflammatory roles in skin inflammation. CRTH2 induces chemotaxis in Th2 cells, neutrophils, eosinophils and basophils with enhanced degranulation.[2,24,25] These chemotactic effects have been confirmed in several skin inflammation models. CRTH2-deficient mice exhibit normal sensitization but reduced eosinophil and $CD4^+$ T cell infiltration in the OVA-induced AD model.[17] CRTH2-deficient mice also exhibit reduced inflammation in CHS[22,26] as well as the repeated hapten application AD model[26,27] and a croton oil-induced acute skin inflammation model.[23] Basophil infiltration into the skin is significantly impaired in CRTH2-deficient mice in an IgE-mediated chronic allergic skin inflammation model.[26] Consistently, administration of a CRTH2 antagonist inhibits neutrophil infiltration into the skin and attenuates the CHS response[25] and the OVA-induced AD model.[28] In humans, virtually all $CRTH2^+$ $CD4^+$ lymphocytes have a pure Th2 phenotype; they constitute not all but a large proportion of circulating Th2 cells in both normal and AD subjects.[29,30] In AD subjects, a preferential increase in $CRTH2^+$ cells was noted within the disease-related cutaneous lymphocyte-associated antigen-positive $CD4^+$ T cell compartment.[30] These results suggest the importance of CRTH2 in Th2 cell, neutrophil, eosinophil and basophil infiltration or activation in cutaneous allergic disease including AD.

Recently, the class of innate lymphoid cells (ILCs) known as type 2 ILC (ILC2) has been identified in various tissues such as skin, lung, and intestine.[31] ILC2 are responsive to IL-25 or IL-33, and abundantly produce type 2 cytokines such as IL-5 and IL-13. ILC2 are supposed to play significant roles in the development of allergic diseases such as asthma or atopic dermatitis.[32] Human ILC2 have been shown to express CRTH2.[33] Furthermore, it has recently been reported that PGD_2 induces type 2 cytokine production and chemotaxis of ILC2 via CRTH2.[34,35] Therefore, an antagonist for CRTH2 may inhibit not only Th2 cells and eosinophils but also the recruitment of ILC2 into tissues.

In addition to its direct chemotactic effects, PGD_2 has recently been reported to mediate eosinophil skin infiltration indirectly by inducing eotaxin-3 production from sebocytes.[36]

To summarize, PGD_2 seems to play some pro-inflammatory roles and some anti-inflammatory roles in the pathogenesis of AD, through DP and CRTH2, respectively.