Prostaglandin D₂ and TH2 Inflammation in the Pathogenesis of Bronchial Asthma

Masafumi Arima¹ and Takeshi Fukuda²

¹Department of Developmental Genetics (H2), Chiba University Graduate School of Medicine, Chiba; ²Department of Pulmonary Medicine and Clinical Immunology, Dokkyo University School of Medicine, Tochigi, Japan

INTRODUCTION

Asthma is characterized by chronic inflammation of the airways, associated with inflammatory cells, including eosinophils, mast cells, basophils, macrophages, and T helper (TH1) cells. These cells are involved in development of airway hyperresponsiveness (AHR), bronchoconstriction, mucus secretion, and remodeling by releasing inflammatory mediators, such as chemokines, growth factors, lipid mediators, and chemical mediators. Then, the complex pathogenesis of asthma is contributed to by various cellular responses, based on the dysregulated interaction between the innate and adaptive immune systems.

Recent evidence suggests that prostaglandin D₂ (PGD₂) is a major prostanoïd, produced mainly by mast cells, in allergic diseases, including bronchial asthma. PGD₂-induced vasodilatation and increased permeability are well-known classical effects that may be involved in allergic inflammation. Recently, novel functions of PGD₂ have been identified. To date, D prostanoid receptor (DP) and chemoattractant receptor homologous molecule expressed on T H2 cells (CRTH2) have been shown to be major PGD₂-related receptors. These two receptors have pivotal roles mediating allergic diseases by regulating the functions of various cell types, such as TH2 cells, eosinophils, basophils, mast cells, dendritic cells, and epithelial cells. This review will focus on the current understanding of the roles of PGD₂ and its metabolites in TH2 inflammation and the pathogenesis of bronchial asthma. (Korean J Intern Med 2011;26:8-18)

Keywords: Basophils; Asthma; Eosinophils; Mast cells; Prostaglandins; TH2 cells

Prostaglandin D₂ and TH₂ Inflammation in the Pathogenesis of Bronchial Asthma

Asthma is characterized by chronic inflammation of the airways, associated with inflammatory cells, including eosinophils, mast cells, basophils, macrophages, and TH1 helper cells. These cells are involved in development of airway hyperresponsiveness (AHR), bronchoconstriction, mucus secretion, and remodeling by releasing inflammatory mediators, such as chemokines, growth factors, lipid mediators, and chemical mediators. Then, the complex pathogenesis of asthma is contributed to by various cellular responses, based on the dysregulated interaction between the innate and adaptive immune systems.

Recent evidence suggests that prostaglandin D₂ (PGD₂), a major prostanoïd, may play an important role in orchestrating interactions between mast cells, TH2 cells, eosinophils, and dendritic cells.

TH₂ immune response in asthma

Allergic diseases are characterized by elevated serum immunoglobulin (Ig) E levels and hypersensitivity to normally innocuous antigens as allergens. A particular allergen first encounters antigen-processing cells (APC), such as dendritic cells or macrophages, directly. The allergen captured by the APC is processed and presented to CD4⁺ T cells. CD4⁺ T cells are polarized into distinct types of TH cells. Major TH cell subsets include TH1, TH2, and TH17, and also recently discovered TH9 and TFH cells. Each TH cell subset expresses a characteristic cytokine profile that generates a characteristic inflammatory response in allergic diseases, such as bronchial asthma. Among these TH cells, TH2 cells are believed to play a critical pathogenic role in allergic inflammation. TH2 cells produce cytokines, interleukin (IL)-4, IL-5, IL-6, IL-9, and IL-13, although they may also result from other cell types. Patients with allergic asthma have eosinophilic inflammation in the lung, in parallel with increased TH2 cytokines, as well as elevated serum IgE. IL-4 and IL-13 are representative TH2-type cytokines that play a crucial role in human allergic disease. IL-4 promotes differentiation and proliferation in TH2 cells, whereas IL-13 mediates AHR and mucus hyperproduction [1,2]. IL-5 is a cytokine that is highly specific to eosinophil activation and recruitment and con-
Arima M and Fukuda T. Role of prostaglandin D2 in asthma

Prostaglandin D2 (PGD2) is a prominent mediator in asthma, contributing to eosinophilic inflammation, a prominent pathological feature in most asthma. TH2 cytokines also trigger the production of chemokines, including CCL11/eotaxin, CCL17/TARC, and CCL22/macrophage-derived chemokine (MDC), in tissue fibroblasts or epithelial cells, promoting the infiltration of inflammatory cells, such as eosinophils and TH2 cells into sites exposed to allergens. Importantly, IL-4 and IL-13 stimulate immunoglobulin class switching, leading to IgE production, which binds to its high-affinity receptor (FcεRI) on the surface of mast cells or basophils. The association of captured allergens with IgE bound to FcεRI on the cell surface activates signal transduction in these cells and rapidly leads to the release of inflammatory cytokines and chemical mediators, such as histamine and leukotrienes in mast cells and basophils and PGD2 in mast cells. Furthermore, particular interest has been generated in novel epithelial cell-derived cytokines including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which have all been implicated in promoting TH2 cytokine responses, and their ability to influence innate and adaptive immune responses associated with TH2 cytokine-mediated inflammation in airways. Recent evidence suggests that coordinated expression and cross-regulation between TSLP, IL-25, and IL-33 are crucial events for developing TH2 cell-mediated airway immune responses in asthma. In contrast, PGD2 modulates airway physiology by causing bronchoconstriction, vasodilation, increases in capillary permeability, and mucous production in asthma. These functions are well-known effects that may facilitate transendothelial migration of inflammatory cells, such as eosinophils, mast cells, lymphocytes, and monocytes, during allergic inflammation. In addition to such classical effects, novel properties of PGD2 include TH2 inflammation in allergic diseases (Fig. 1).

**PGD2 production in asthma**

Fujitani et al. [4] generated transgenic mice overexpressing lipocalin-like PGD synthetase in the lung and subjected them to ovalbumin (OVA)-induced pulmonary allergic inflammation. They found elevated IL-4 and IL-5 concentrations and increased eosinophilic infiltration in bronchoalveolar-lavage fluid (BALF) in these mice. Mandal et al. [5] reported that a reduction in PGD2 synthesis, induced by uteroglobin, an anti-inflammatory protein, was associated with reduced allergic inflammation. Furthermore, PGD2 nebulization before aerosol Ag challenge enhanced TH2 inflammatory responses, including eosinophilia, and leads to the development of AHR [6]. Collectively, these findings appear to substantiate the proposal that PGD2 acts as an important mediator in allergic asthma.

Activated mast cells contribute to asthmatic pulmonary inflammation by producing a variety of chemical mediators and cytokines. During allergic responses, PGD2 is released in large amounts by mast cells during asthmatic attacks in humans. DCS [7] and TH2 cells [8] also produce PGD2. Furthermore, fibroblasts, bronchial smooth muscle cells, and airway epithelial cells are also thought to produce PGD2, precipitating pulmonary inflammation. It is well established that the presence of an allergen triggers PGD2 production in sensitized individuals. In individuals with asthma, a bronchial allergen challenge leads to rapid PGD2 production, which can be detected in the BALF within minutes, reaching biologically active levels at least 150-fold higher than pre-allergen levels [9]. A local antigen challenge also stimulates PGD2 production in the nasal mucosa of patients with allergic rhinitis [10] and in the skin of patients with atopic dermatitis (AD) [11]. Several lines of evidence support the view that mast cells are the principal sources of PGD2 at allergic inflammation sites. Cell fractionation studies have shown that PGD2 is produced predominantly by mast cells [12], and mast cell

**PGD2 and its metabolites**

PG production begins with the liberation of arachidonic acid from membrane phospholipids by phospholipase A2 in response to inflammatory stimuli. Arachidonic acid is converted to PGH2 by the cyclooxygenase enzymes COX-1 and COX-2. PGH2 is a common precursor of several PGs, including PGD2, which is generated by the actions of two PG synthases, known as the lipocalin-type PGD synthase (L-PGDS), primarily expressed in brain, heart, and adipose tissue, and the hematopoietic PGD synthase (H-PGDS), mainly expressed in mast cells, macrophages, dendritic cells (DCs), and TH2 cells. It is generally thought that COX-1 is expressed constitutively in most tissues of the body and functions to maintain homeostatic processes, such as mucus secretion. In contrast, COX-2 is primarily an inducible enzyme, involved mainly in the regulation of inflammation [3]. PGD2 is a major product from COX-catalyzed reactions in a variety of tissues and cells, including those of the immune system, such as T cells, DCs, macrophages, mast cells, and platelets.