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Association of interleukin-25 levels with development of aspirin induced respiratory diseases

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ABSTRACT

Background: Aspirin-exacerbated respiratory diseases (AERD) are caused by ingestion of non-steroidal anti-inflammatory drugs and are characterized by acute bronchospasms and marked infiltration of eosinophils, the latter being attributable to altered synthesis of cysteinyl leukotrienes (LT) and prostaglandins (PG). Recently, the innate Th2 response is revealed to induce eosinophil infiltration in allergic inflammation, however the role of the innate Th2 response has not been studies in AERD. Thus, we evaluated the relationship between the innate Th2 cytokines including IL-25, thymic stromal lymphopoietin (TSLP) and IL-33 and the development of AERD.

Methods and materials: Plasma IL-25, IL-33, and TSLP levels were measured before and after aspirin challenge in subjects with AERD ($n = 25$) and aspirin-tolerant asthma (ATA, $n = 25$) by enzyme-linked immunosorbent assay (ELISA). Pre and post-aspirin challenge levels of LTC4 and PGD2 were measured using ELISA.

Results: Basal plasma IL-25 levels were significantly higher in AERD group than in normal controls and in ATA group ($p = 0.025$ and 0.031, respectively). IL-33 and TSLP levels were comparable in the AERD and ATA groups. After the aspirin challenge, the IL-25 levels were markedly decreased in the ATA group ($p = 0.024$), while not changed in the AERD group. The post-challenge IL-25 levels of all asthmatic subjects were significantly correlated with aspirin challenge - induced declines in FEV1 ($r = 0.357$, $p = 0.011$), but not with basal and post challenge LTC4 and PGD2 levels.

Conclusions: IL-25 is associated with bronchospasm after aspirin challenge, possibly via mechanisms other than altered LTC4 and PGD2 production.

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1. Introduction

Aspirin-exacerbated respiratory disease (AERD) refers to the development of non-allergic hypersensitivity reactions by asthmatics following the ingestion of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) [1]. The syndrome is characterized by clinical manifestations of nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma, and non–IgE-mediated respiratory reactions on ingestion of aspirin and other NSAIDs that inhibit cyclooxygenase-1 (COX-1) [2]. AERD is associated with eosinophilic airway inflammation and ongoing activation of mast cells with systemic release of multiple mediators, including leukotrienes, prostaglandins, and tryptase [1]. One of the main underlying mechanisms involves overproduction of cysteinyl leukotrienes (cysLTs) and overexpression of the cysLT receptor by inflammatory cells of the respiratory tract [3]. In addition to the increased levels of cysLTs in various biological fluids, including saliva, induced sputum, blood, and urine [4], dysregulation of arachidonic acid (AA) metabolism reduces prostaglandin E2 (PGE2) synthesis and increases prostaglandin D2 (PGD2) production in patients with AERD compared with those in patients with aspirin-tolerant asthma (ATA) [5].

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Histologically, AERD is characterized by extensive eosinophilic inflammation in the sino-nasal and bronchial mucosae, along with the presence of degranulated mast cells [6]. Infiltration of eosinophils and mast cells is accompanied by elevated levels of the eosinophil-active cytokines IL-5 and eotaxin and activated T-helper type 2 (Th2) cytokines in the airways of AERD patients [7–9]. As in asthma, a shift from a T-helper type 1 (Th1) to a Th2 immune response is the major mechanism of AERD. This results in the overproduction of various cytokines—such as interleukin 4 (IL-4), IL-5, and IL-13—and underproduction of the Th1-type cytokine interferon-gamma (IFN-γ) [10]. Recently, innate Th2 immune response has been well documented in asthma and allergic inflammation [11,12]. However, the role of the innate Th2 has not been studied in AERD up to data.

Epithelial cell-derived cytokines, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 influence innate immunity in several inflammatory diseases, including inflammatory bowel diseases, asthma, and atopic dermatitis [13]. TSLP can activate mast cells to generate type 2 cytokines [14], which stimulate eosinophils [15], basophils [16], type 2 innate lymphoid cells (ILC2s) [17], and CD34-positive hematopoietic progenitor cells [18] in conjunction with IL-1, TNFα, or IL-33 [14,19]. IL-33 alone is capable of acting on mast cells to induce expression of Th2 cytokines as well as of increasing the survival and sensitization of mast cells to TSLP [19]. IL-25 also induces expansion of a non-B, non-T ckit + cell population *in vivo*. Additionally, this presumed mast cell progenitor population expresses Th2 cytokines in response to stimulation by IL-25 [20].

Nasal polyps are outgrowths of inflamed sino-nasal mucosa that occur in patients with chronic rhinosinusitis. They are densely infiltrated by eosinophils, activated mast cells, and large numbers of ILC2s [21,22]. Recently, the TSLP level was reported to be elevated in nasal polyps of AERD patients and to stimulate mast cells to produce a large quantity of PGD2 [23]. PGD2 is the preferred ligand for the chemoattractant receptor homologue expressed by TH2 cells (CRTH2), which is expressed by Th2 cells [24] eosinophils, basophils [24,25], and ILC2s [26]. The IL-33 level is also increased in the nasal polyps of AERD patients, which is driven by cysLTs [27]. Accordingly, IL-33, IL-25, and TSLP may stimulate ILC2 to produce Th2 cytokines in conjunction with PGD2 and cysLTs in AERD. However, the contribution of each cytokine to the development of AERD has not been evaluated to date. In the present study, plasma IL-33, IL-25, and TSLP levels were compared before and after aspirin challenge in subjects with AERD and ATA, and were analyzed in terms of their association with PGD2 and LTE4 levels.

2. Materials and methods

2.1. Study subjects

All patients were diagnosed by physicians and met the criteria for asthma of the Global Initiative for Asthma (GINA) guidelines. All patients had a history of dyspnea and wheezing during the previous 12 months plus one of the following: (1) >15% increase in FEV1 or >12% increase plus 200 mL following inhalation of a short-acting bronchodilator, (2) <10 mg/mL PC20 methacholine, and (3) >20% increase in FEV1 following 2 weeks of treatment with inhaled steroids and long-acting bronchodilators. Current smokers and ex-smokers with more than 10 pack year were excluded. At the baseline visit, demographic information, such as enrollment age, sex, BMI, onset age of asthma, asthma duration, smoking amount, was collected. All patients underwent a standardized assessment, which included analyses of the induced sputum, complete blood cell count with differential counts, total IgE, chest radiography, spirometry, and allergy skin prick tests with 24 common inhalant allergens (Bencard Co., Brentford, UK). Atopy was defined as a wheal reaction equal to or greater than that to histamine or at least 3 mm in diameter over that of saline control. Total IgE was measured using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). The asthma patients had not experienced exacerbations of asthma or respiratory tract infections during the 6 weeks preceding the oral aspirin challenge (OAC). The OAC was carried out using increasing doses of aspirin [28,29]. Briefly, patients with a history of aspirin hypersensitivity were administered 30 mg orally. Respiratory and nasal symptoms, blood pressure, external signs (urticaria and angioedema), and FEV1 were documented at 30-min intervals for a period of 1.5 h. In the absence of any symptom or sign suggesting an adverse reaction after 1.5 h, increasing doses of aspirin (60, 100, 300, and 400 mg) were administered until the patient developed a reaction, and the measurements were repeated at 1 h intervals. Those having no history were started on 100 mg of aspirin, which was gradually increased to 200, 350, and 450 mg until the patient developed a reaction. If no reaction had occurred 4 h after the final dose, the test result was deemed to be negative. Aspirin-induced bronchospasm, reflected by a decline (%) in FEV1, was calculated as the pre-challenge FEV1 minus the post-challenge FEV1 divided by the pre-challenge FEV1. OAC reactions were categorized into the following two groups: (1) 15% or greater decrease in FEV1 or nasal reactions, such as rhinorrhea and nasal congestion (AERD); and (2) less than a 15% decrease in FEV1 without naso-ocular or cutaneous reactions (ATA). Peripheral venous blood was collected before and after the aspirin challenge. None of the study subjects had been treated with the cysteinyl leukotriene (cysLT) 1 receptor blocker montelukastor or the 5-lipoxygenase (5-LO) inhibitor zileuton before the challenge. The patients' spouses and general population were recruited as normal controls (NCs). The NCs had no respiratory symptoms, as determined by a screening questionnaire [30], had a predicted FEV1 and FVC >80%, and had normal chest radiogram results. All study subjects were Korean and provided informed written consent to participate in the study. Plasma from subjects with AERD ($n = 25$), ATA ($n = 25$), and normal controls (NCs) ($n = 20$) was obtained from a biobank at Soonchunhyang University Hospital, Bucheon, Korea, after approval of the protocol by the Ethics Committee of Soonchunhyang University Hospital (approval no. SCHBC 2015-06-018-001, schbc-biobank-2015-011-01).

2.2. Measurement of plasma IL-25, IL-33, TSLP, LTC4 and PGD2 levels

IL-25, IL-33, and TSLP levels were measured using quantitative sandwich enzyme immunoassay kits: IL-25 (Busterbio, CA, USA) and IL-33 and TSLP (R&D Systems, Minneapolis, MN) according to the manufacturer's recommendations. The lower limits of detection were 10 pg/mL (IL-25), 0.52 pg/mL (IL-33), and 3.46 pg/mL (TSLP). Results below these thresholds were assigned a value of 0 pg/mL. Plasma LTC4 and PGD2 levels were measured using an enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, MI) according to the manufacturer's recommendations. The inter- and intra-assay coefficients of variability for all assays were less than 15%.

2.3. Statistical analysis

Data analysis was performed using the statistical software package SPSS ver. 20.0. The normality of the distribution of data was evaluated by means of a Shapiro–Wilk test. Normally distributed data are presented as means (standard errors), and skewed data are presented as medians (interquartile ranges). Comparisons were performed using the Kruskal–Wallis test and a *post hoc* analysis; a Mann–Whitney *U*-test was conducted to evaluate

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