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Phenotype of asthma related with high serum periostin levels

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ABSTRACT

Background: Asthma is a heterogeneous disease composed of various phenotypes. Periostin, a molecule inducible with interleukin (IL)-4 or IL-13 in bronchial epithelial cells, is a biomarker of "TH2-high" asthma. The objective of this study is to examine whether the serum periostin concentrations are correlated with the severity, specific phenotype(s), or comorbidity of asthma.
Methods: Serum concentrations of periostin were measured in 190 Japanese asthmatic patients and 11 healthy controls. The protocol was registered under UMIN 000002980 in the clinical trial registry.
Results: The serum concentrations of periostin were significantly higher ($P = 0.014$) in asthmatics [70.0 (54.0–93.5) ng/ml] than in healthy subjects [57.0 (39.0–63.0) ng/ml], though we found no correlation between serum periostin concentrations and treatment steps required to control asthma. To characterize "high-periostin" phenotype(s), the patients with asthma were divided among tertiles based on the serum concentrations of periostin. The high-periostin group was older at onset of asthma ($P = 0.04$), had a higher prevalence of aspirin intolerance ($P = 0.04$) or concomitant nasal disorders ($P = 0.03$–0.001), higher peripheral eosinophil counts ($P < 0.001$), and lower pulmonary function ($P = 0.02$–0.07). The serum concentrations of periostin were particularly high in asthmatic patients complicated by chronic rhinosinusitis with nasal polyps and olfactory dysfunction. In contrast, neither atopic status, control status of asthma, nor quality of life were related with the "high-periostin" phenotype.
Conclusion: Elevated periostin concentrations in serum were correlated with a specific phenotype of eosinophilic asthma, late-onset and often complicated by obstructive pulmonary dysfunction and nasal disorders.

Introduction

Asthma is an inflammatory disease of the airways characterized by bronchial hyperresponsiveness and reversible airflow limitation, affecting about 300 million people in the world.[1] While

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airway inflammation and respiratory symptoms can be controlled with inhaled corticosteroids in most instances, they remain refractory to the highest tolerable doses of inhaled corticosteroids, long-acting bronchodilators, and leukotriene receptor antagonists in patients with severe asthma.[2] The frequent disease exacerbations suffered by these patients, and multiple emergency department visits and hospitalisations represent a heavy social and economic burden.[3] Furthermore, because the heterogeneous characteristics of severe asthma preclude its control by a single therapeutic agent, relevant phenotyping and individualized treatment are essential.[4]

Interleukin (IL)-13, a TH2 cytokine, plays an important role in the development and persistence of eosinophilic inflammation and hyperresponsiveness in the asthmatic airways.[5] Patients with "TH2-high" asthma have been identified by transcriptome analysis, whose bronchial epithelial cells express excessive amounts of IL-13-inducible genes, such as *Clca1* and *Postn*.[6] These patients present with increased eosinophilic inflammation and airway hyperresponsiveness, thickened basement membranes, and greater responsiveness to corticosteroids.[7] On the other hand, periostin, the product of IL-13-inducible *Postn*, is an extracellular matrix protein of the fasciclin family,[8] and can be measured in serum. Serum periostin concentrations are correlated with a sustained eosinophilic inflammation of the airways[9] and rapid decline of pulmonary function[10] despite treatment with inhaled corticosteroids. Another study has suggested that the concentrations of serum periostin can be used to predict the responsiveness to treatment with anti–IL-13 antibody.[11] Therefore, periostin might be a useful biomarker as a companion diagnostic for severe asthma.[12] However, clinical characteristics or phenotype of asthmatics with elevated serum periostin levels are not well studied. This study examined whether, in asthmatic Japanese, the serum concentrations of periostin are correlated with the disease severity, specific phenotype or comorbidity.

Methods

Patient populations

Between April 1, 2010 and December 31, 2012, we enrolled Japanese patients ≥20 years of age, who presented with difficult-to treat asthma at Keio University Hospital and affiliated hospitals. Asthma was diagnosed on the basis of the Japanese Society of Allergology guideline.[13] Asthma requiring step 4 or 5 treatment actions, defined in the updated version of the 2006 statement by the Global Initiative for Asthma (GINA) to achieve its optimum control was defined as severe asthma.[14] Healthy subjects with no history of allergic diseases and patients with mild to moderate asthma controlled with step 1 to 3 treatment actions of GINA, served as controls. Patients with uncontrolled malignant tumours or widespread lung disease that prominently impaired lung function were excluded from enrolment. The protocol (no 2009-9-5) initially approved by the Institutional Review Board of Keio University School of Medicine, was subsequently approved by the Review Board of each participating institution, and implemented in compliance with the Declaration of Helsinki. All participants granted their written informed consent.

Collection of clinical information

The study participants reported their clinical information at the time of enrolment by means of a self-completed questionnaire. Poor adherence to the treatment was defined as < 5 day-use of inhaled corticosteroids per week. Olfactory dysfunction was defined by the presence of hyposmia/anosmia. The control status of asthma and the disease-specific quality of life were ascertained, using the Japanese versions of the asthma control test[15] and the Juniper's asthma quality of life questionnaire,[16,17] respectively. Laboratory data and information pertaining to medications and disease exacerbations were collected from medical records.

Serum concentrations of periostin and cytokines

The serum periostin concentrations were measured by enzyme-linked immunosorbent assay, as previously reported.[18] The serum concentrations of IL-4, IL-5, and IL-13 were measured, using the Bio-Plex® Suspension Array System (Bio-Rad Laboratories, Hercules, CA, USA). Total and allergen-specific serum immunoglobulin (Ig)E concentrations for house-dust mites, cat dander, fungi, and insects were measured using a fluorescence-enzyme immunoassay (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Atopic asthma was defined as one or more allergen-specific IgE concentrations >0.70 UA/mL.

Pulmonary function tests

Pulmonary function during stable asthma was measured using a CHESTAC-9800 spirometer (Chest, Tokyo, Japan), which met the criteria of the American Thoracic Society. The predicted value of vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) for a Japanese population was calculated using the formula proposed by the Japanese Respiratory Society. The fraction of exhaled nitric oxide was measured with a Sievers nitric oxide analyser (GE Healthcare Japan, Tokyo, Japan) in some participating institutions.

High-resolution computed tomography

Airway wall thickness was measured by high-resolution computed tomography scans, using an Aquilion™ (TOSHIBA Medical Systems Corporation, Tochigi, Japan) or LightSpeed® volume scanner (GE Healthcare). The wall area and % wall area of the apical bronchus of the right upper lobe (RB1) were measured using the AZE VirtualPlace Lexus64® software (AZE, Tokyo, Japan).

Statistical analysis

The data are expressed as means ± SD, median and interquartile range, or percentages. Categorical data were analysed with the chi-square test. Mann–Whitney test or Kruskal–Wallis test, as appropriate. Spearman's rank correlation coefficient was determined between serum levels of periostin, TH2 cytokines, and blood eosinophil counts. A regression analysis was performed to examine the correlations between pulmonary functions and age- and sex-adjusted or unadjusted, log-transformed serum periostin concentration, duration of asthma and smoking history. A statistically significant difference was defined as a two-tailed P value <0.05. All statistical analyses were performed with the SPSS statistical software package for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the study groups

This study enrolled 11 healthy subjects (mean age 39.5 ± 12.1 years, 73% men) and 190 asthmatic patients (mean age 60.2 ± 14.5 years, 44% men), including 22 in the GINA steps 1 and 2, 20 in step 3, 83 in step 4 and 65 patients in step 5. In 58 patients in step 4 (70%) and 58 patients in step 5 (89%), the status corresponded to the definition of severe asthma by international ERS/ATS