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ORIGINAL ARTICLE

Serum decoy receptor 3 is a biomarker for disease severity in nonatopic asthma patients

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total eosinophil count

Background/Purpose: Decoy receptor 3 (DcR3), a soluble receptor of the tumor necrosis factor receptor superfamily, is a pleiotropic immunomodulator. The aim of this study was to investigate serum DcR3 levels in atopic and nonatopic asthma patients.
Methods: The serum DcR3 levels of 70 adults with asthma and 20 healthy controls were determined by enzyme-linked immunosorbent assay (ELISA). The asthma patients were divided into atopic and nonatopic subgroups, based on the presence or absence of immunoglobulin E (IgE) specific to allergen. Correlations between serum DcR3 levels and blood total-eosinophil counts, forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity (FVC), and Asthma Control Test (ACT) scores were analyzed.
Results: The mean serum DcR3 level was significantly higher in asthma patients than in healthy controls (266.1 $\pm$ 60.6 pg/mL vs. 63.7 $\pm$ 21.9 pg/mL, $p = 0.003$), but there was no significant difference between the mean serum DcR3 level of asthma patients with atopy (37 patients) and patients without atopy (33 patients; 298.7 $\pm$ 111.2 pg/mL vs. 230.6 $\pm$ 38.5 pg/mL, $p = 0.064$). However, the serum DcR3 level was positively correlated with the total eosinophil

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count ($r = 0.448$, $p = 0.012$) and inversely correlated with the percentages of predicted FEV1, FEV1/FVC, and ACT score ($r = 0.409$, $p = 0.018$; $r = -0.399$, $p = 0.021$; and $r = -0.505$, $p = 0.003$, respectively) in nonatopic asthma patients, but not in atopic patients.
Conclusion: High serum DcR3 levels are associated with disease severity in nonatopic asthma patients, which suggests that DcR3 is a potential biomarker that can be used to predict the severity of nonatopic asthma.

Introduction

Asthma is a chronic lung disease characterized by intermittent chest symptoms such as wheezing, dyspnea, chest tightness, and cough. Chronic inflammation in asthma results in airway remodeling such as bronchial smooth muscle contraction, increased airway wall thickness, and hypersecretion of mucus. Asthma was traditionally considered an allergic disease, and allergen-specific immunoglobulin (Ig) E antibodies, mast cells, T helper 2 (Th2) cells, and Th2 cytokines contribute to the pathophysiology of atopic asthma.[1,2] However, some patients with asthma do not appear to be allergic; they experience their first asthma attack in adulthood without preceding allergic diseases and without exhibiting allergen-specific IgE. Several risk factors for nonatopic asthma have been investigated such as a family history of asthma, genetic background, current or past dampness, and lower respiratory tract infections.[3] It has been demonstrated that homozygosity for matrix metalloproteinase-9 variants increases the risk of developing nonatopic asthma[4] and that the interferon-γ levels in allergen-stimulated total peripheral blood mononuclear cells are higher in nonatopic asthma patients.[5] However, serum markers correlated with disease severity in nonatopic asthma patients have not been reported.

Decoy receptor 3 (DcR3), a member of the tumor necrosis factor (TNF) receptor superfamily, is a soluble decoy receptor with a pleiotropic immunomodulatory effect via "decoy" and "nondecoy" functions.[6] In addition to neutralizing the biological effects of Fas ligand, lymphotoxin-like, exhibits inducible expression, and competes with herpes simplex virus glycoprotein D for HVEM, a receptor expressed by T lymphocytes (LIGHT), and TNF-like molecule 1A,[7–9] DcR3 can promote M2 macrophage differentiation via epigenetic regulation, after binding to syndecans and other proteoglycans. Moreover, DcR3 promotes tumorigenesis via the induction of tumor-associated macrophages.[9–12] Accumulating evidence from *in vitro* and *in vivo* studies also indicates that DcR3 can attenuate inflammatory responses,[13–16] which suggests that DcR3 is a pleiotropic immunomodulator in negatively regulating inflammatory responses. A previous study reported elevated levels of DcR3 in the serum of atopic patients.[17] However, only patients aged $<$ 20 years were enrolled in that study, leaving the question unanswered of whether serum DcR3 levels are correlated with disease severity in adult asthma and nonasthma patients. To address this question, we investigated the associations between serum DcR3 levels and clinical parameters of asthma such as laboratory variables, pulmonary function test results, and disease severity.

Patients and methods

Patients

The present study enrolled patients with asthma and healthy controls (HCs) at Taipei Veterans General Hospital (Taipei, Taiwan) and Cheng Hsin Rehabilitation Medical Center (Taipei, Taiwan). All participants were aged $>$ 20 years. All asthma patients had a history of asthma, and the diagnosis was confirmed by evidence of reversibility of airway obstruction [i.e., an increase $>$12% and 200 mL of the initial forced expiratory volume in 1 second (FEV1) with a short-acting bronchodilator or methacholine sensitivity (PC20) $<$ 8 mg/mL]. We also assessed the atopic status of all patients with asthma. Atopy was defined as the presence of IgE antibodies specific to at least one common allergen such as house dust mites (e.g., *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat dander, dog dander, and cockroaches.[18,19] The HCs had no history of, or findings consistent with allergic disease. Patients and HCs with malignancy or chronic inflammation disease were excluded. In addition, study participants with signs and symptoms of infection during the previous 2 weeks were excluded. The Asthma Control Test (ACT) score (range, 5—25) was used to assess asthma control.[20] The ACT is a validated five-question self-administered assessment tool in which higher scores reflect better asthma control. This study was approved by the institutional ethics committees of Taipei Veterans General Hospital (Taipei, Taiwan) and Cheng Hsin Rehabilitation Medical Center (Taipei, Taiwan). Informed consent was obtained from all patients participating in the study.

Laboratory assay and pulmonary function testing

Total serum IgE concentration and serum allergen-specific IgE were measured using the ImmunoCAP system (Pharmacia, Uppsala, Sweden). Blood eosinophils were counted using a Coulter counter (Beckman Coulter, Inc., Fullerton, CA, USA). Serum DcR3 levels were detected in triplicate using an enzyme-linked immunosorbent assay (ELISA) method (Human Soluble DcR3/TNFRSF6B ELISA Kit; BioLegend, San Diego, CA, USA). For patients whose DcR3 level was below the detectable limit, the serum DcR3 level was counted as 0 pg/mL. The average of triplicate results for DcR3 was used in our analysis. The FEV1 and forced vital capacity (FVC) were evaluated on the same day that blood samples were collected. The predicted value of

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