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ORIGINAL ARTICLE

Circulating fibrocytes correlate with the asthma control test score

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Abstract
Background: Bronchial asthma is characterised by airway inflammation and remodelling with a decline of lung function. Fibrocytes are bone marrow-derived mesenchymal progenitor cells that play important roles in the pathogenesis of airway remodelling. Several clinical parameters are currently being used in routine clinical practice to assess outcome of therapy in asthma including frequency of rescue with short-acting β2-agonist and the asthma control test. In this study, we hypothesised that asthma control test is associated with circulating levels of fibrocytes in bronchial asthma.
Methods: There were 20 patients with asthma and seven healthy controls. The number of $CD45^{+}$Collagen I^{+} circulating fibrocytes was assessed in the peripheral blood by flow cytometry.
Results: The number of circulating fibrocytes was significantly increased in asthma patients with moderate and severe disease compared to controls, and it was inversely correlated with % forced expiratory volume in one second and % forced vital capacity (%FVC). The frequency of inhalation of short-acting β2 agonist and the asthma control test score was significantly and inversely correlated with the number of circulating fibrocytes.
Conclusion: The results of this study showed that the number of circulating fibrocytes is inversely correlated with clinical asthma control parameters, further supporting the relevance of measuring circulating fibrocytes as a marker of clinical control in bronchial asthma.

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Introduction

The airway of patients with long-term bronchial asthma is characterised by chronic inflammation and structural tissue remodelling.[1–3] Structural remodelling in asthmatic airways includes epithelial detachment, increased airway smooth muscle mass, mucous gland/goblet cell hyperplasia, proliferation of blood vessels, and subepithelial fibrosis.[4] Subepithelial fibrosis is characterised by extensive deposition of extracellular matrix (ECM) components leading to a decline in lung function and irreversible airway obstruction.[5] One of the mechanisms of the enhanced ECM deposition is the accumulation of activated fibroblasts and myofibroblasts.[5] In particular, myofibroblasts are the main players in the pathogenesis of airway wall fibrosis because they produce and secrete collagens and other ECM molecules.[4] The origin of myofibroblasts may be multiple; some of them derive from pre-existing fibroblasts or from airway smooth muscle cells that migrate towards the epithelial basement membrane and differentiate into myofibroblasts under the stimulation of cytokines and growth factors, whereas others originate from fibrocytes that are bone marrow-derived mesenchymal progenitor cells that coexpress markers of haematopoietic and stromal cells and differentiate to fibroblasts and myofibroblasts by transforming growth factor-β1 or endothelin-1.[6–8] Several lines of evidence have shown that fibrocytes significantly accumulate in the asthmatic airway wall not only in patients with progressive, chronic obstructive, untractable and severe asthma but also in patients in early stages of the disease, suggesting their role in the onset of airway tissue remodelling.[9–14] The mainstay of current asthma therapy is the use of inhaled corticosteroids alone or in combination with long- or short- (SABA) acting β2-agonists.[15] Several parameters have been suggested to use for assessing the outcome of therapy in asthma including signs of clinical impairment (symptom frequency, the rescue with SABA, sleep interference) and scoring systems such as the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT)) or the Test for Respiratory and Asthma Control in Kids (TRACK).[16] These asthma control composite tools are being extensively used because of the importance of therapeutic control in asthma.[17–19] Among all parameters, ACT has the largest number of validation data.[16]

No previous study has explored whether circulating fibrocytes are related to asthma control composite scores. In the present investigation, we tested the hypothesis that the number of circulating fibrocytes is correlated with the ACT score in patients with chronic bronchial asthma.

Materials and methods

Patients and measurements

This study comprised 20 stable asthmatic patients that consulted at Mie University Hospital. Among patients, six had mild, nine moderate, and five had severe asthma but without clinical exacerbation. The diagnosis of the disease stage was based on the Guidelines of Japanese Society of Allergology and Global Initiative for Asthma (GINA).[20,21] All patients were being treated with standard doses of inhaled corticosteroids and relievers (short-acting beta-2-agonist) on demand before consultation. Clinical data and pulmonary function tests were obtained from case records. Blood samples for evaluating circulating fibrocytes were obtained from seven healthy controls and from 20 patients on the first day of consultation after obtaining informed consent (Table 1). To score the asthma clinical control on the date of consultation, all patients were asked to complete the ACT questionnaire translated to Japanese language. The research protocol was approved by the Ethics Committee for Clinical Investigation of Mie University, Japan.

Flow cytometry

Circulating fibrocytes were identified as previously described by flow cytometry in blood sampled during the first visit.[22,23] Briefly, after freshly isolated blood was cultured in sodium chloride lysis solution, leukocytes were stained with anti-CD45-PerCP (BD Biosciences), and after permeabilisation using cytofix/cytoperm (BD Biosciences),

Table 1 Characteristics of the subjects.

	Healthy controls	Asthmatic patients		
		Mild	Moderate	Severe
No of subjects	7	6	9	5
Age	54.7 ± 14.0	66.0 ± 12.1	59.2 ± 15.1	52.8 ± 20.5
Male/female	3/3	1/5	3/6	1/4
Disease period (yrs)	–	10.5 ± 4.4	18.3 ± 11.6	11.8 ± 8.2
%FEV1 (%)	ND	92.2 ± 11.3	71.9 ± 8.0	40.5 ± 14.5
FEV1% (%)	ND	73.4 ± 5.6	63.5 ± 8.9	44.8 ± 12.9
%FVC (%)	ND	87.5 ± 11.7	84.3 ± 7.7	52.7 ± 8.6
%Eosin (%)	ND	7.8 ± 5.8	11.2 ± 7.9	8.3 ± 12.6
IgE (U/L)	ND	819 ± 488	355 ± 209	388 ± 430
ICS	–	5/6	9/9	5/5
Oral corticosteroid	–	0/6	2/9	5/5
ACT score	–	23.8 ± 1.0	20.0 ± 1.5	13.2 ± 2.6
SABA inhalation (/wk)	–	0	0 3.2 ± 4.9	19.2 ± 8.4