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ORIGINAL ARTICLE

FIZZ1 Plays a Crucial Role in Early Stage Airway Remodeling of OVA-Induced Asthma

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The aim of this study was to elucidate the role of Found in Inflammatory Zone 1 (FIZZ1, also known as RELM- α or resistin-like molecule- α) in airway remodeling in asthma. We used a rat model of ovalbumin (OVA) sensitization and challenge to induce lung inflammation and remodeling. Expression of α -SMA in the lungs of OVA-treated rats was significantly elevated in the peribronchial regions compared with control saline-treated animals. Expression of FIZZ1 mRNA in alveolar epithelial type II cells (AECII) isolated from OVA-treated animals was higher than in control animals. Forced expression of recombinant FIZZ1 in rat-1 lung fibroblast cell line enhanced production of collagen type I and α -SMA compared with control transfected cells. These results suggest that FIZZ1 can induce fibroblasts to express markers of myofibroblast differentiation such as α -SMA and collagen type I, which are characteristic of early stages of airway remodeling seen in asthma.

Keywords FIZZ1, found in inflammatory zone 1, asthma, α -smooth muscle actin, type I collagen, airway remodeling

ABBREVIATIONS

FIZZ1	=	found in inflammatory zone 1
AECII	=	alveolar epithelial type II cell
α -SMA	=	α -smooth muscle actin
pEGFP-FIZZ1	=	green fluorescent protein-FIZZ1 expressing plasmid
OVA	=	ovalbumin
AHR	=	hyperresponsiveness
RT-PCR	=	reverse transcription-polymerase chain reaction
ELISA	=	enzyme-linked immunoassay
SDS-PAGE	=	sodium dodecyl sulfate polyacrylamide gel electrophoresis
HE	=	hematoxylin-eosin
IDV	=	Integrated Density Value
IOD	=	Integrated Optical Density
PI3K	=	phosphatidylinositol 3-kinase
DMEM	=	Dulbecco's Modified Eagle's Medium

INTRODUCTION

Asthma is a chronic lung disease characterized by airway inflammation, hyperresponsiveness (AHR), structural changes within the smooth muscle layer, and deposition of extracellular matrix (1). These latter features of airway remodeling are observed in severe asthma but also in mild and moderate asthmatics and at early stages of the disease (2). It is conceivable that airway remodeling in asthma contributes to asthma exacerbations and even death from airway obstruction

caused by smooth muscle contraction, airway edema, and mucus plugging.

Previous studies demonstrated an association between early-stage airway remodeling in asthma and pulmonary myofibroblast differentiation, with increased expression of α -smooth muscle actin (α -SMA) (3). Bronchial biopsies of asthmatic patients showed thickening of the subepithelial layer due to deposition of fibrillar collagen, mainly collagen I and collagen III (4, 5). Thus, alterations in the expression of α -SMA and type I collagen are main features observed in asthmatic remodeled airways (6). Although much has been learned in the past years about the presence of airway remodeling in asthma, the natural history of this process is not fully understood. Recent studies had revealed that inflammatory zone 1 (FIZZ1) expression is markedly increased in hypertrophic, hyperplastic bronchial epithelium and is induced in alveolar epithelial type II cells during allergic pulmonary inflammation, such as asthma (7). FIZZ1 was actually discovered during lung allergic inflammation and belongs to a novel class of cysteine-rich secreted proteins, also known as resistin-like molecules (RELMs) (8). Normally, these proteins are expressed in the lung, white adipose tissue, mammary gland, tongue, and heart (9, 10). The role of FIZZ1 in lung pathologies has been described. In a mouse model of chronic hypoxia with pulmonary hypertension, expression of FIZZ1 correlated with its ability to stimulate proliferation of pulmonary vascular smooth muscle cells, and thus, it was suggested that FIZZ1 exhibits angiogenic properties (11). Conversely, Liu et al. reported that FIZZ1 was highly inducible during bleomycin (BLM)-induced lung fibrosis and localized primarily to alveolar epithelial cells as assessed by cDNA microarray analysis and in situ hybridization (12). Functionally, FIZZ1 can induce myofibroblast differentiation in cultured lung fibroblast, as manifested by increased

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expression of α -smooth muscle actin (α -SMA) and collagen type I (13). This suggests the potential involvement of FIZZ1 in the fibrotic response in BLM-induced lung injury model. These observations led to speculate that lung fibrosis may share some aspects with the pathogenesis of early airway remodeling of asthma.

The role of FIZZ1 in airway remodeling in asthma is still not clear. In this study we examined whether FIZZ1 participates in the process of airway remodeling in asthma using a rat model of airway inflammation. In addition, we demonstrated that FIZZ1 is associated with myofibroblast differentiation, resulting in augmented expression of α -SMA and collagen type I in early stage airway remodeling.

MATERIALS AND METHODS

Animal Model

Forty pathogen-free wistar rats (8- to 12-week-old, 200 $\pm$ 20g) purchased from the Animal Experiment Center of Shandong University were randomly divided into an ovalbumin (OVA) group and a control group. Rats in the OVA group were sensitized with OVA as follows (14): 100 mg/mL OVA (Sigma, St. Louis, Montana, USA) were emulsified with 200 mg/mL aluminium hydroxide (Fuchen Chemistry Inc., Tianjin, China) in saline (Hualu Inc., Shandong, China) before intraperitoneal injection of 1 mL per rat at day 1 and 8. From day 15 to 21, rats were nebulized daily with a 5% (w/v) OVA solution for 30 minutes in a 30-cm $\times$ 24 cm $\times$ 50 chamber. The control group received intraperitoneal injections of saline followed by nebulization with saline. The rats were killed, and the lungs were removed for isolation of alveolar epithelial cell II (AECII) or for immunohistochemistry analysis. Animal studies were performed according to animal welfare and local ethics committee regulations of Qilu Hospital of Shandong University.

Culture of Alveolar Epithelial Type II Cells (AECII)

AECII were isolated from rat lung as described previously (15) by trypsin (Sigma, St. Louis, Montana, USA) digestion and rat immunoglobulin (IgG) panning (Xitang Inc., Shanghai, China). Briefly, bronchoalveolar lavages were performed eight times with solution I (NaCl 140 mM, KCl 5 mM, HEPES 10 mM, Glucose 6 mM, EGTA 0.2 mM, Na₂HPO₄•12H₂O 2.5mM) and twice with solution II (NaCl 140 mM, KCl 5 mM, HEPES 10 mM, CaCl₂ 2 mM, MgSO₄ 1.3 mM, Na₂HPO₄•12H₂O 2.5 mM) (Fuchen Chemistry Inc., Tianjin, China). After that, trypsin (0.25%, 20 mL) was instilled into the trachea to release AECII. Cells bearing Fc receptors were removed from the cell suspension by panning on plates coated with rat IgG. Cells were resuspended in Dulbecco's Modified Eagle's medium (DMEM) supplemented with 2mM L-glutamine, 100U penicillin per mL, 100 μ g streptomycin per mL and 10% fetal calf serum (Gibco BRL, Rockville, Maryland, USA) and plated onto 6-well cell culture dishes. Primary cultured AECII were used without passing them. After 2 days in culture, adherent cells were consistently 90% of epithelial morphology. Cells were harvested for measuring FIZZ1 mRNA by reverse transcription and polymerase chain reactions (RT-PCR).

RNA Analysis

Total cellular RNA was extracted with Trizol reagent (Invitrogen, California, USA) according to manufacture's instruction. Primers (Biosune Inc., Shanghai, China) and expected amplified fragments shown in parenthesis are as follows:

FIZZ1 (212bp) forward: CCTGTTCCCTTCTCATCT, reverse: ACCAGTAGCAGTCATCCC;
 β -Actin (518bp) forward: TCATGCCATCCTGCGTCTG-GACCT;
 reverse: CCGGACTCATCGTACTCCTGCTTG. PCR condition was: 94°C for 2 minutes, then 30 cycles of 94°C for 30 seconds, 58°C for 60 seconds, and 72°C for 2 minutes, followed by 72°C for 10 minutes. PCR products were analyzed by 1% agarose gel electrophoresis. FIZZ1 mRNA levels were normalized to β -actin mRNA level determined by densitometry.

Immunohistochemistry Analysis

Saline- and OVA-sensitized and challenged rats were sacrificed, and the lung lobes dissected, fixed in 10% formaldehyde, and processed for conventional histology. Slides (4 = μ m thick) were dewaxed, rehydrated, and blocked with 10% goat serum for 60 minutes at room temperature. Sections were incubated with anti- α -SMA monoclonal primary antibody (1:400), overnight at 4°C and subsequently with goat anti-rat IgG-tetraethyl rhodamine isothiocyanate (TRITC) (1:800) mAb for 1 hour. DAPI (500 ng/mL in 95% ethanol) was used to stain nuclei for 20 seconds. Coverslips were mounted with 80% glycerol (Zsbio, Beijing, China). Control slides were incubated with normal Ig instead of primary antibody. Samples were examined using a microscope equipped with a digital camera (Hitachi, Japan). α -SMA positive areas were quantified by densitometry using the image-pro plus software (Media Cybernetics, USA).

Transient Transfection

Lung fibroblast cell line Rat-1 (KCB84001) was purchased from cell bank (Kunming cell bank, Kunming, China) and plated in DMEM onto 6-well cell culture plates. Fresh media were replaced the day before transfection. Transient transfections were performed using Lipofectamine 2000 reagent (Invitrogen Inc., USA) according to the manufacturer's instructions and either 4.0 μ g pEGFP-FIZZ1 (a gift from Dr. Tianju Liu) or empty vector. After 24 hours of incubation, the cells were harvested for analysis of α -SMA and collagen type I.

Analysis of Collagen Type I and α -SMA

Cell lysates were added to a 96-well ELISA plate (Xitang Inc., Shanghai, China) and incubated at 4°C overnight. After blocking with 1% bovine serum albumin, rabbit anti-rat collagen type I was added and plate was incubated overnight at 4°C. Wells were rinsed and polyclonal horseradish peroxidase-conjugated goat anti-rabbit IgG added for 60 minutes at room temperature. All samples were tested in duplicate. Collagen type I concentration was calculated by comparison to standard curve. Color developed with o-phenylenediamine substrate was read at 492 nm with

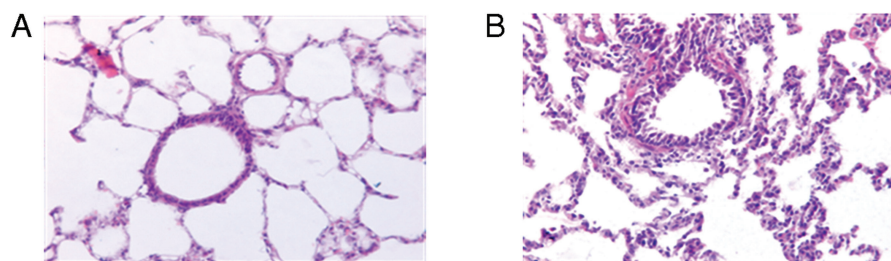


FIGURE 1.—Airway remodeling in an OVA-sensitized and challenged rat model. Hematoxylin-eosin staining of lungs from rats in the saline control group (A) shows no obvious inflammation and structural changes. In contrast, lungs from OVA-treated group (B) show wall thickening, inflammatory cells infiltration, subepithelial fibrosis, mucous metaplasia, and myocyte hyperplasia, and hypertrophy. Magnification, 200x.

universal microplate reader. The sensitivity of the enzyme-linked immunosorbent assay (ELISA) for collagen type I was 2 ng/mL. α -SMA was analyzed by western blotting; fifty μ g of cell lysate were separated by 10% SDS-PAGE, transferred to membrane, blocked, and probed with specific anti- α -SMA or anti-tubulin antibodies (Santa Cruz, California, USA), and then with horseradish peroxidase-conjugated anti-rabbit IgG. The bands were visualized immediately by exposing the membranes to ECL Hyperfilm, and intensity of α -SMA signal was normalized to that of tubulin (Santa Cruz, California, USA) using image analysis software.

Statistic Analysis

Data were presented as means $\pm$ SD. Continuous variables were tested by analysis of student *t* test. The *p* values are two-tailed and a *p* value of less than 0.05 was considered statistically significant.

RESULTS

The Rat Model of Lung Remodeling

We used the OVA-sensitized and challenged model that exhibits some characteristics of asthma, including the presence of inflammation as a major histopathological feature (6). Figure 1 demonstrates that, compared with rats in the control group, the lung from OVA-treated rats showed wall thickening, inflammatory cells infiltration, subepithelial fibrosis, mucous metaplasia, and myocyte hyperplasia and hypertrophy. We observed no obvious indication of these changes in the control group animals.

FIZZ1 mRNA Expression is Induced in AECII by Allergic Pulmonary Challenge

Previous studies demonstrated that FIZZ1 was up-regulated in AECII during lung inflammation in the mouse (8). For our studies, we used a rat model of pulmonary OVA allergic inflammation. We isolated AECII from OVA- and control-treated rats and examined the expression levels of FIZZ1 mRNA by RT-PCR. We found that AECII exhibited typical cube shape morphology. Expression of FIZZ1 mRNA normalized to β -actin was higher in AECII isolated from OVA-treated rats than in those prepared from control (Figure 2) (*p* < 0.05).

Expression of α -SMA is Increased in the Airway of OVA-treated Rats

Airway remodeling has been associated with augmented α -SMA expression and irreversible airflow limitation. As expected, in our model we found that α -SMA was highly expressed in peribronchial lung areas in the OVA-group as well as in the muscular layer of the intrapulmonary bronchus (Figure 3A). In contrast, neither the terminal bronchioles nor the bronchial epithelia showed positive α -SMA staining in the control group (Figure 3B and C) (*p* < 0.05). In pulmonary arteries and veins, α -SMA staining was consistent with the natural distribution of smooth muscle tissue.

FIZZ1 Stimulates Expression of Collagen Type I and α -SMA in Lung Fibroblast

Because AECII is a major source for FIZZ1 in OVA-sensitized and challenged rat model of allergic pulmonary inflammation, we examined the effect of FIZZ1 overexpression on certain fibroblast functions that are altered in airway remodeling. We investigated the changes in the levels of collagen type I production in lung fibroblast that were

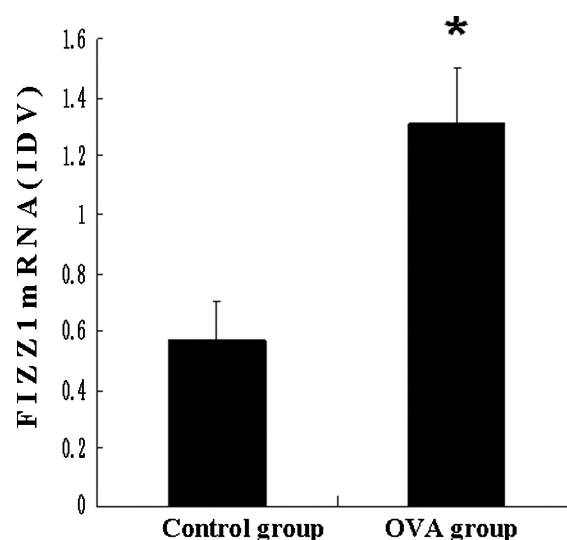


FIGURE 2.—Expression of FIZZ1 mRNA in AECII. RT-PCR analysis was performed with total RNA prepared from AECII that were isolated from OVA-treated and control rats. When normalized to β -actin, the level of FIZZ1 mRNA expressed in OVA-sensitized and challenged rats was significantly higher than those found in control rats. *p* < 0.05. IDV, Integrated density value.

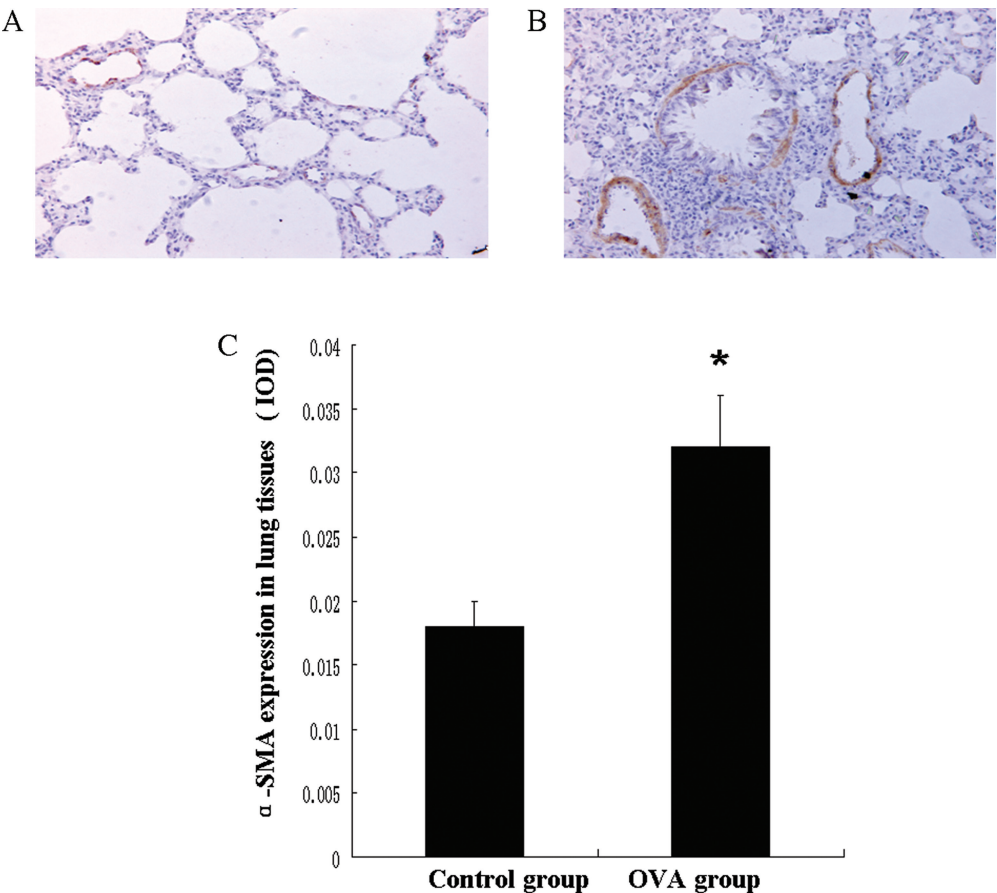


FIGURE 3.— α -SMA expression in the lung. (A) No positive α -SMA staining is evident in control group. (B) Increased positive α -SMA staining is highly restricted to peribronchial region of and the muscular layer of the airway in the intrapulmonary bronchus in OVA-induced group. Pulmonary arteries and veins exhibit similar staining in both groups. (C) Quantitation of α -SMA.

transiently transfected with the pEGFP-FIZZ1. We found significantly increased collagen type I amounts compared to cells transfected with empty vector (Table 1). Likewise, α -SMA expression in lung fibroblasts overexpressing pEGFP-FIZZ1 was enhanced (Table 1, Figure 4) ($p < 0.05$) compared to control transfected cells. These results indicate that FIZZ1 is capable of inducing expression of markers of activated lung fibroblasts.

DISCUSSION

In this study we demonstrated that FIZZ1 is upregulated in AECII during airway remodeling in a model of allergic

pulmonary inflammation in the rat and that FIZZ1 overexpression elicits an activated phenotype in rat lung fibroblasts characterized by increased synthesis of collagen I and α -SMA. These findings are consistent with previous reports on increased FIZZ1 expression in hyperplastic bronchial epithelium and in type II alveolar pneumocytes in the mouse (8,16). Our results reporting that FIZZ1 mRNA expression was increased in AECII isolated from the lungs of OVA-sensitized and challenged rats suggest that FIZZ1 may play

TABLE 1.—Comparison of expression levels of collagen type I and α -SMA in rat lung fibroblast expressing FIZZ1.

α	N	Collagen type I (ng/mL)	α -SMA(IDV)
Empty vector	20	136.23 $\pm$ 29.86	0.82 $\pm$ 0.27
PEGFP-FIZZ1	20	248.49 $\pm$ 64.21*	2.94 $\pm$ 0.21*
<i>p</i> value		1.852 $\times 10^{-6}$	2.2 $\times 10^{-10}$

*indicates a *p* value of less than 0.05, compared with the control group. Expression of collagen type I and α -SMA in cell lysates of rat lung fibroblast transfected with the pEGFP-FIZZ1 or empty vector was determined by ELISA or western blotting, respectively. Results are expressed as mean $\pm$ SD. pEGFP-FIZZ1 = plasmid encoding recombinant FIZZ1 tagged with green fluorescent protein; IDV = Integrated density value. *p* < 0.05.

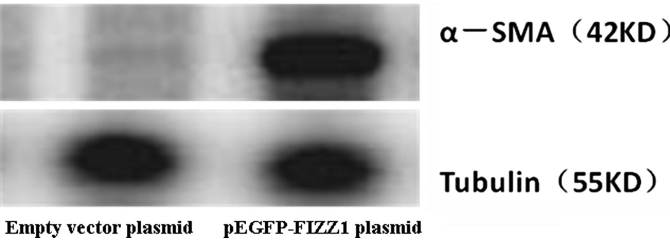


FIGURE 4.—Upregulation of α -SMA expression in rat lung fibroblasts induced by FIZZ1. α -SMA accumulation was evaluated by western blotting in rat lung fibroblasts transiently transfected with pEGFP-FIZZ1 or empty vector. FIZZ1 significantly enhanced α -SMA expression compared with control subjects. $p < 0.05$.

an important role in the process of airway remodeling in asthma and it was consistent with previously reports (17).

Airway remodeling in asthma was first reported by Huber in 1922 (18) as structural changes in the lung, including augmentation of airway smooth muscle mass, myofibroblast hyperplasia, inflammatory cell infiltration, and connective collagen deposition. Numerous studies on the pathology and morphology aspects of diseased lungs confirmed these features (19, 20). In addition, the occurrence of airway remodeling is associated with myofibroblast hyperplasia. Myofibroblasts are a well-known source of collagenous matrix molecules and α -SMA production (21). Currently, the precise mechanism of airway remodeling in asthma is not fully understood. In our animal model, we demonstrated that α -SMA expression was highly upregulated in bronchi, contributing to bronchi wall thickening (22). Liu et al. have provided some clues as to the potential role of certain genes in the pathogenesis of airway remodeling (12). FIZZ1 is highly induced in several processes that involve lung fibrosis, and high FIZZ1-expressing AECII significantly stimulated both collagen type I and α -SMA expression in fibroblasts (23). We thus hypothesized that FIZZ1 could induce myofibroblasts hyperplasia leading to airway remodeling in the course of asthma. Myofibroblasts are major producers of collagenous matrix and likely contribute to subepithelial collagen deposition and α -SMA accumulation (24). Our results demonstrated that type I collagen and α -SMA are upregulated in lung fibroblasts that overexpress recombinant FIZZ1. Therefore, it seems that FIZZ1 is capable of switch fibroblasts to acquire a myofibroblast phenotype. The appearance of α -SMA correlates with the extent of airflow obstruction and may contribute to airway wall thickening. Moreover, collagen deposition causes structural alterations in the airway, which eventually lead to airway collapse and airflow limitation (25). It has been reported that interleukin (IL)-4 and IL-13 are able to upregulate FIZZ1 expression in vitro in AECII, and this induction is mediated by STAT6 with the possible involvement of JAK1 (26–29).

The presence of vascular remodeling in asthma has recently been recognized. It was reported that FIZZ1 was able to stimulate proliferation of pulmonary vascular smooth muscle cells (30). Other studies showed that the phosphatidylinositol 3-kinase (PI3K/Akt) pathway, at least in part, mediated the proliferative effect of FIZZ1. The PI3K/Akt pathway has been shown to mediate proliferation and migration of human pulmonary vascular smooth muscle cells and to increase pulmonary arterial pressure (31).

Taken together, our results indicated a novel and perhaps critical function of FIZZ1 in the pathogenesis of lung remodeling. FIZZ1 expression is induced in airway epithelium and is able to promote differentiation of fibroblast into myofibroblast, contributing to progressive airflow obstruction in the course of airway remodeling. We propose that blockade of the expression of FIZZ1 and its downstream effects (production of collagen type I and α -SMA) could be an attractive target for treatment controlling airway remodeling.

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