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Letter to the Editor

Serum Folliculin Is Related to Lower Pulmonary Function in Patients With Asthma

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To the Editor,

Folliculin, a protein expressed in various types of cells including airway epithelial cells and encoded by the *FLCN* gene, is associated with the 5′AMP-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1) signaling pathways and is thought to alter cell-to-cell adhesion.[1-4] The gene *FLCN* regulates the E-cadherin-LKB1-AMPK axis, which controls lung epithelial cell survival and alveolar size.[2] A previous *in vitro* study showed that human airway epithelial cells (HAECs) exposed to leukotriene E4 and peripheral blood eosinophils released folliculin and interleukin (IL)-8, resulting in destruction of the integrity of these epithelial cells. The knockdown of folliculin expression resulted in decreased IL-8 release and suppression of epithelial cell activation, restoring the epithelial integrity of HAECs. In the same study, serum folliculin levels were found to be higher in asthmatics than in healthy control groups and high folliculin levels were associated with increased airway hyperresponsiveness in asthmatics.[5]

To investigate the relationship between clinical characteristics and folliculin levels in asthmatics, the data of a total of 404 patients with asthma and 94 of controls were retrospectively reviewed. To correct for the heavily skewed distributions of serum folliculin levels, the values were log-transformed. The study methods, design, and definitions used are found in the online supplement (**Supplementary Data 1**). This study was conducted under IRB-approved protocols from Asan Medical Center.

The proportions of males and smokers were higher among the asthmatics than in the controls, and the mean serum folliculin level was higher in asthmatics than in controls (4.80 pg/mL versus 4.13 ng/mL) (**Supplementary Table S1**). We compared the serum folliculin levels between asthmatics and controls subdivided by sex and smoking status. In these subgroups, the folliculin levels were still higher in asthmatics than in the control group (**Supplementary Tables S2**, **S3**, and **S4**). Receiver operating characteristic (ROC) curve analysis revealed a difference in serum folliculin levels between asthmatics and controls; the

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optimal cutoff value of folliculin level that distinguished asthma patients from controls was 4.31 pg/mL (**Supplementary Fig. S1**). When we performed ROC curve analysis only including males, the optimal cutoff folliculin level was 4.33 pg/mL (**Supplementary Fig. S2**). We compared folliculin levels among 4 groups divided by lung function and found a difference in folliculin levels (**Supplementary Fig. S3**). In a simple linear regression analysis, serum folliculin levels were correlated with pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV1%) predicted (β-coefficient = −4.848, $P = 0.013$).

Asthmatics were divided into 2 groups using the mean serum folliculin level (4.80 pg/mL). Patients were older at the onset of symptoms, heavier smokers and had significantly lower lung function in the high folliculin group (HFG) than in the low folliculin group (LFG) (**Table 1**). When asthmatics were divided by the upper quartile of folliculin levels and the lower 3 quartiles combined, those in the HFG in the upper 25th percentile were older and had less atopy and poorer lung function than those in the LFG including patients in the lower 75th percentile combined (**Supplementary Table S5**). Likewise, we divided the patients into 4 quantile

Table 1. Clinical characteristics of patients with asthma with low and high log-transformed folliculin levels

Characteristics	Low folliculin group (n = 210)	High folliculin group (n = 194)	*P* value
Log (folliculin level) (pg/mL)	4.4 ± 0.3	5.2 ± 0.4	< **0.001**
Age (yr)	206 (48.8 ± 14.2)	188 (53.1 ± 14.7)	**0.003**
Sex (male)	88 (42.72)	88 (46.81)	0.475
BMI (kg/m^2)	202 (23.7 ± 3.3)	187 (23.8 ± 3.0)	0.688
Age at diagnosis (yr)	196 (43.8 ± 15.7)	177 (46.1 ± 17.5)	0.091
Age at symptom onset (yr)	202 (38.6 ± 16.3)	185 (42.7 ± 17.6)	**0.018**
Smoking (pack-yr)	197 (7.2 ± 13.3)	182 (10.6 ± 18.0)	**0.043**
Smoker*	90 (45.7)	90 (49.5)	0.528
Smoking status			0.615
Never smoker	107 (54.3)	92 (50.6)	
Ex-smoker	62 (31.5)	66 (36.3)	
Current smoker	28 (14.2)	24 (13.2)	
Skin prick test (% positive, n/total)	64 (42.4)	39 (34.5)	0.242
Acute exacerbation, past 1 yr (yes)	36 (17.5)	26 (13.8)	0.393
Acute exacerbation (/1 yr)	53 (3.3 ± 5.0)	70 (4.4 ± 8.3)	0.349
Pre-BD FEV1 (%)	201 (73.5 ± 19.8)	183 (69.1 ± 22.8)	**0.045**
Pre-BD FVC (%)	201 (88.5 ± 18.6)	183 (84.3 ± 18.4)	**0.026**
Pre-BD FEV1/FVC	202 (0.69 ± 0.13)	184 (0.67 ± 0.16)	0.098
Post-BD FEV1 predicted (%)	98 (76.3 ± 21.4)	117 (70.0 ± 22.0)	**0.034**
Post-BD FVC predicted (%)	98 (89.4 ± 18.2)	117 (83.6 ± 17.4)	**0.018**
Post-BD FEV1/FVC predicted	98 (0.69 ± 0.13)	117 (0.67 ± 0.19)	0.507
PC20	89 (4.5 ± 5.0)	59 (5.6 ± 6.3)	0.260
Blood eosinophils (%)	177 (5.6 ± 5.6)	148 (4.7 ± 4.8)	0.131
Blood eosinophil count (cells)	177 (396.6 ± 445.0)	148 (336.2 ± 334.9)	0.164
Neutrophils (%), sputum	24 (44.7 ± 37.7)	29 (39.0 ± 34.5)	0.557
Eosinophils (%), sputum	24 (18.9 ± 27.0)	29 (14.4 ± 24.3)	0.495
CRP (mg/dL)	111 (0.6 ± 1.4)	104 (0.6 ± 1.6)	0.902
Serum total IgE (IU/mL)	60 (362.5 ± 490.6)	53 (589.5 ± 1,034.1)	0.161

Data are presented as mean ± SD or number (mean ± SD), or number (%). Low folliculin group: patients with a log-transformed folliculin level < 4.80, High folliculin group: patients with a log-transformed folliculin level ≥ 4.80. Acute exacerbation: previous 1 year: patients who had an acute exacerbation at least once during the previous 1 year at the time of enrollment. Acute exacerbation (/1 year): the average number of acute exacerbations that occurred during the first 3 years after enrollment. *P* values are based on the *t*-test and Wilcoxon test for continuous variables and the χ^2 test for categorical variables. *P* values less than 0.05 are reported in bold font. Statistical significance defined as $P < 0.05$.
BMI, body mass index; BD, bronchodilator; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PC20, methacholine provocative concentration causing a 20% drop in FEV1; CRP, C-reactive protein; IgE, immunoglobulin E; SD, standard deviation.
*The combination of current smokers and ex-smokers. Each percentage is calculated after excluding patients with unknown smoking status.

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groups by serum folliculin levels and identified differences between individual groups in the function and age (**Supplementary Tables S6** and **S7**).

A previous *in vitro* study showed that knockdown of folliculin expression resulted in a decrease in IL-8 release and suppression of epithelial cell activation. In this study, folliculin was suggested to be associated with increased serum transforming growth factor-β1 levels.[5] As folliculin is released from bronchial epithelial cells in response to compressive stress that mimics bronchospasm,[6,7] we postulate that chronic airway inflammation produces mechanical stress affecting the airway epithelium, thereby inducing oxidative damage and folliculin release with changes in the epithelial cell structure. Therefore, we assume that folliculin is associated with airway inflammation and remodeling pathways in asthmatics.

In our study, serum folliculin levels showed no association with serum laboratory variables, suggesting that increased folliculin levels following mechanical stress are independent of changes in other inflammatory markers. Thus, folliculin may have possibility to represent a biomarker related to decreased pulmonary function in asthmatics and further studies are warranted to evaluate its mechanism of action and to test our hypothesis.

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SUPPLEMENTARY MATERIALS

Supplementary Data S1
Study method

Click here to view

Supplementary Table S1
Clinical characteristics of the study population and serum folliculin levels

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Supplementary Table S2
Clinical characteristics of male study participants by smoking status: male patients only

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Supplementary Table S3
Clinical characteristics of male study participants by smoking status: male and smoker

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Supplementary Table S4

Clinical characteristics of male study participants by smoking status: male and never-smoker

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Supplementary Table S5

Clinical characteristics of patients with asthma with low and high log-transformed folliculin levels

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Supplementary Table S6

Clinical characteristics of each group by serum folliculin levels

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Supplementary Table S7

Post-hoc inter-group analysis of clinical variables

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Supplementary Fig. S1

Receiver operating characteristic curve of serum folliculin levels; area under the curve = 0.846, confidence interval 0.80–0.89, $P < 0.001$. The cutoff serum folliculin level that discriminated patients with asthma from healthy control subjects was 74.45 pg/mL (4.31 pg/mL after log-transformation) with 83.91% sensitivity and 77.66% specificity.

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Supplementary Fig. S2

Receiver operating characteristic curve of serum folliculin levels in males. The cutoff serum folliculin level that discriminated patients with asthma from healthy control subjects was 4.33 pg/mL after log-transformation with 82.95% sensitivity and 77.66% specificity.

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Supplementary Fig. S3

Log-transformed serum folliculin levels and lung function. Serial increases in folliculin levels with decreased lung function. Mean ± standard deviation: healthy control subjects, 4.12 ± 0.48; Pre-BD FEV1 (%) > 80, 4.74 ± 0.42; Pre-BD FEV1 (%) 60–80, 4.76 ± 0.56; Pre-BD FEV1 (%) < 60, 4.12 ± 0.48; Data are presented as the mean ± standard error ($P < 0.0001$). Data were analyzed using one-way analysis of variance.

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