

THE ROLE OF SMOOTH MUSCLE AND SUBMUCOSAL GLANDS IN THE AIRWAY REMODELING IN ASTHMA

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THE ROLE OF SMOOTH MUSCLE AND SUBMUCOSAL GLANDS IN THE AIRWAY REMODELING IN ASTHMA (Abstract): **Aim:** Bronchoconstriction, chronic inflammation, and airway remodeling are the main factors associated with the airflow restriction in patients with asthma. Airway remodeling includes all morphological changes of the bronchial wall in asthma, contributing to clinical manifestations and progressive loss of lung function. The aim of this study was to evaluate the morphological changes associated with airway remodeling, being focused on submucosal glands and muscular tissue, in a group of asthmatic patients. **Materials and methods:** We performed a retrospective analysis on 38 patients with a history of bronchial asthma, with different degrees of severity. All patients were classified according to the latest Global Initiative for Asthma (GINA) criteria and underwent a fibro bronchoscopy examination associated with biopsy of tissue samples for microscopy. **Results:** The study included 38 asthmatic patients, with a female predominance (68.42%) and a mean patient age of 49 ± 16 years. The microscopic exam revealed an increase of smooth muscle and submucosal glandular areas in asthmatic patients in comparison to healthy persons and a close correlation with the asthma severity, reflected by FEV1 values. The statistical analysis showed an inverse correlation between FEV1 (%) values and muscular ($r = -0.8997$, $p < 0.001$) and glandular area hypertrophy ($r = -0.887$, $p < 0.01$). **Conclusions:** The increase of muscle and submucosal glands areas, as part of the airway remodeling process, represents a specific pathological feature mainly associated with severe forms of asthma, being correlated with lung function restriction. **Keywords:** ASTHMA, BRONCHIAL SMOOTH MUSCLE, SUBMUCOSAL GLAND, FEV1.

INTRODUCTION

Airway hyper-responsiveness, added to chronic airway inflammation and reversible airflow limitation, are the most important features of asthma (1). These changes occur as a result of bronchial wall remodeling, leading to its thickening (1, 2). Morphologically, these features are represented by epithelial cell damage, goblet cell hyperplasia, basement membrane thickening with subepithelial fibrosis, edema and neo-

angiogenesis in the lamina propria, submucosal glandular hypertrophy, and smooth muscle hyperplasia or hypertrophy (2- 4).

Variations of the airway wall thickness have been correlated with lung function and they may therefore reflect the severity of asthma (5). Airway hyper-reactivity is also determined by the contractile activity of bronchial smooth muscle, which is the principal effector in bronchoconstriction. Notably, chronic inflammation of the bron-

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chial wall plays a central role in modulating both bronchial smooth muscle activity and the other structural changes that characterize airway remodeling, including mucus hypersecretion (3).

In recent years, numerous studies have focused on the mechanisms underlying bronchial smooth muscle and submucosal glandular hypertrophy in asthmatic patients, with the aim of identifying novel therapeutic targets (1). Thus, increased bronchial wall thickness has been associated with impaired lung function and reduced spirometry parameters, such as Forced Expiratory Volume in 1 second (FEV1) and the FEV1/Forced vital capacity (FVC) ratio, particularly in uncontrolled (severe) asthma (6). Corticosteroid therapy in asthmatic patients has been also demonstrated to reduce the bronchial wall inflammation, with a limited effect on submucosal glandular hypertrophy and bronchial smooth muscle hypertrophy (6, 7). However, the molecular mechanisms underlying submucosal glandular and smooth muscle hypertrophy or hyperplasia associated with airway remodeling are extremely complex and remain only partially deciphered (6, 7).

In this context, this study aims to demonstrate the airway remodeling and its relationship with spirometry parameters in a group of asthmatic patients, being focused on bronchial glandular and smooth muscle hypertrophy or hyperplasia.

MATERIALS AND METHODS

The study group included 38 adult asthmatic patients diagnosed in the Specialty Ambulatory of the Pneumology Clinic Hospital, Iasi, Romania. All patients were non-smokers (totally non-smoker or former occasional smoker), receiving treatment with inhaled corticosteroids, without other chronic or acute lung diseases, and able to

adequately and correctly perform a spirometry test. The inability to adequately and correctly perform a spirometry test along with the presence of other chronic or acute lung diseases or the patient declaring himself a smoker were used as exclusion criteria from the study group. Patients' history, chest X-ray, and spirometry assessment using FEV1 were used to classify the asthmatic patients according to the last GINA classification (8). Subsequently, a fibro bronchoscopy exam was performed with the collection of five to seven tissue fragments for each case, to limit the risk of insufficient material or inconclusive results (2, 9). The collected tissue fragments were fixed in buffered formalin, processed for paraffin embedding, and stained with Hematoxylin & Eosin and Goldner-Szekely trichrome staining.

The thickness of the bronchial smooth muscle and submucosal glandular areas was assessed using a semi-quantitative scoring system [score 1 (+) = almost normal, score 2 (+) = moderate increase and score 3 (+++) = severe increase] as the distance between the epithelial layer/basal membrane and smooth muscle or submucosal glandular areas at 4 x magnification, by two independent pathologists (10, 11). The control group included two patients without asthma symptoms, which have been investigated for tumor suspicion.

The proliferation potential of bronchial muscle cells and submucosal glandular areas was evaluated by Ki-67 index, using immunohistochemistry (clone MIB-1; Dako), according to the manufacturer protocol.

The study was conducted in accordance with the Declaration of Helsinki for research involving human subjects and patients were included in the study group based on informed consent.

The statistical analysis was performed using *SPSS version 25* (IBM, Armonk, NY, USA). Associations between continuous variables were assessed using Pearson's and Spearman's correlation coefficients and linear regression analysis was performed to estimate the slope of the relationships. Statistical significance was set at $p < 0.05$.

RESULTS

Following clinical examination and spirometry testing, the 38 patients included in the study were classified into three severity degrees, according to the GINA 2025 criteria: 17 cases (44.73%) of well-controlled (intermittent/mild) asthma, 16 cases (42.10%) of partially controlled (moderate) asthma, and five cases (1.31%) of uncontrolled (severe) asthma. The mean value of FEV1 (% of predicted) was $78.3 \pm 22.6\%$, the lowest mean values being registered in the uncontrolled (severe) asthma cases (43.6 ± 10.8), followed by partially controlled asthma ($66.7 \pm 6.2\%$), and well-controlled asthma ($100.4 \pm 10.1\%$).

The median age of asthmatic patients

was 49 ± 16 years (range: 22-72), most of cases being included in the 6th and 7th decades of life (26.32% each), followed by the 3rd decade (21.05%), the 4th decade with 7.89% cases, and the 8th decade with 2.63% cases. The study population was predominantly female ($n = 26$; 68.42%) and the mean age was higher among women (52 ± 15.6 years) than in men (42.4 ± 15.5 years). The majority of patients were from urban areas ($n = 28$; 73.68%), with only 10 patients (26.32%) from rural areas, and most had a duration of bronchial asthma between 15 and 20 years.

A bronchial wall thickening due to smooth muscle hypertrophy or hyperplasia (score 3) was detected in four cases of uncontrolled asthma, while a moderate smooth muscle hypertrophy or hyperplasia has been registered in 16 cases (15 cases of partially uncontrolled asthma and one case of uncontrolled asthma). The remaining cases exhibited a near-normal appearance of the muscle layer (figs. 1 and 2). Ki-67 immunopositivity was negative in all cases, except in two cases of uncontrolled asthma, with weak and rare positivity (figs. 3 and 4).

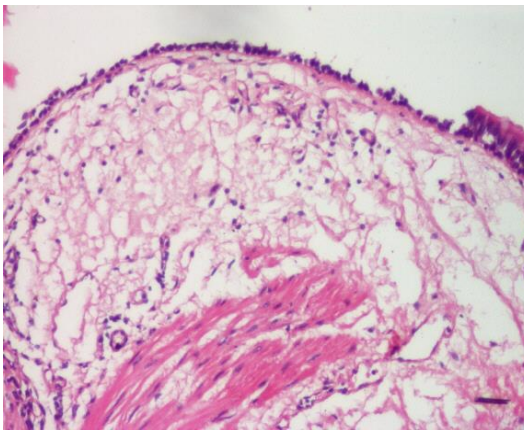


Fig. 1. Near-normal histologic features of the muscle layer in well-controlled asthma, H&E, 4x

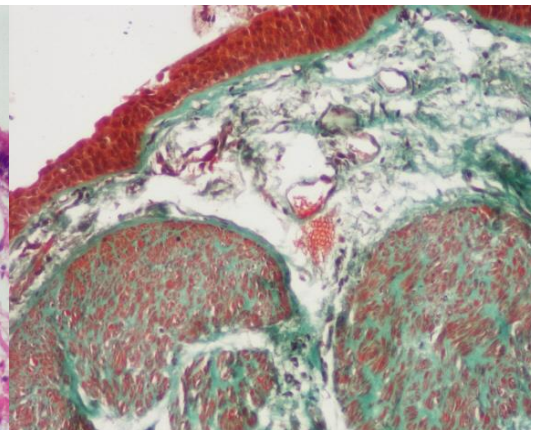


Fig. 2. Significant increase of smooth muscle surface area in uncontrolled asthma, Goldner-Szekely trichrome, 4x

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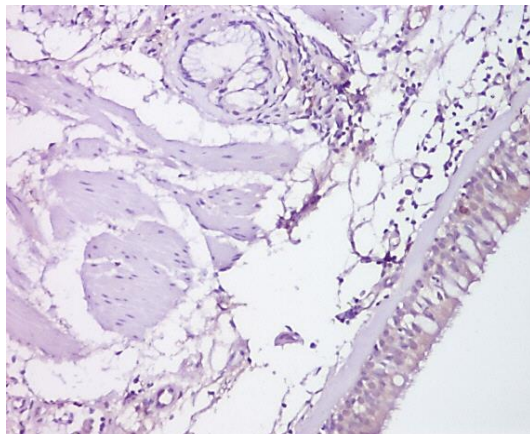


Fig. 3. Negative Ki-67 immunorexpression in bronchial muscle cells in partially controlled asthma, 10x

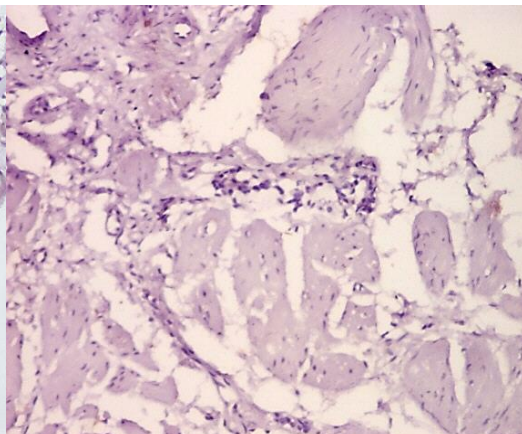


Fig. 4. Ki-67 immunorexpression: weak and rare positivity of bronchial muscle cells in uncontrolled asthma, 10x

A significant submucosal glandular hypertrophy has been also registered in all patients with uncontrolled asthma and in two cases of partially uncontrolled asthma. Near-normal glandular areas have been observed in 16 cases (42.10%) of well-controlled asthma, while a moderate increase of submucosal glandular area of the

bronchial wall has been observed in 15 cases (39.47%) (14 cases of partially controlled asthma and one case of well-controlled asthma) (figs. 5 and 6). A negative Ki-67 immunorexpression of the bronchial glandular area has been observed in all biopsies of asthmatic patients (figs. 7 and 8).

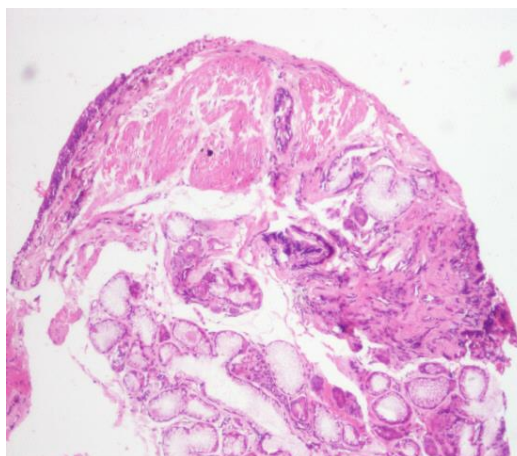


Fig. 5. A moderate submucosal glandular area hypertrophy in partially controlled asthma, H&E, 2x

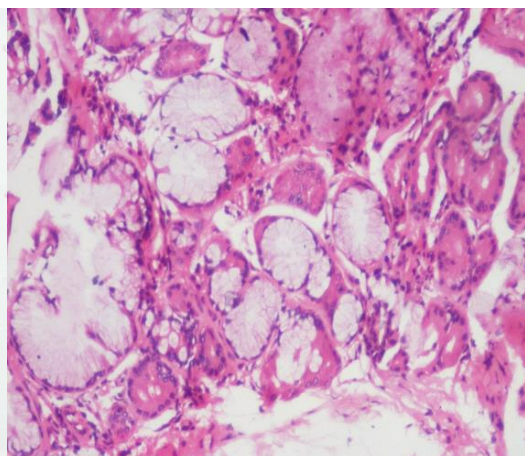


Fig. 6. A significant submucosal glandular area hypertrophy in uncontrolled asthma, H&E, 10x

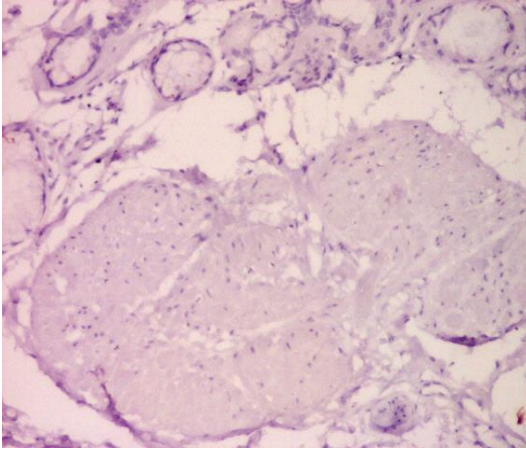


Fig.7. Negative Ki-67 immunohistochemical expression in bronchial glands and muscular area in partially controlled asthma, 10x

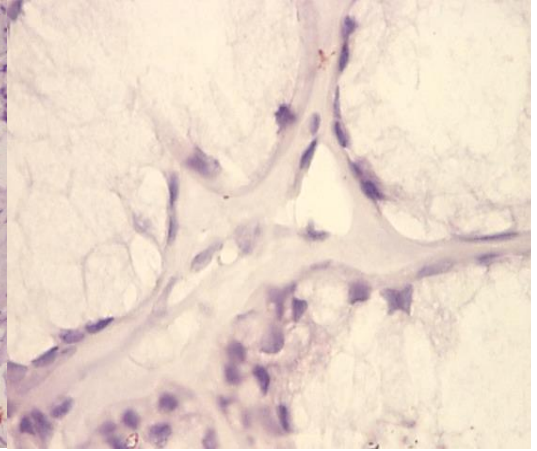


Fig. 8. Negative Ki-67 immunohistochemical expression in bronchial glands in uncontrolled asthma, 40x

The statistical analysis applied to evaluate the association between muscle mass hypertrophy and bronchial asthma severity revealed a Spearman correlation coefficient of $\rho = 0.93$, $p < 0.01$ (tab. I). Moreover, the bronchial wall muscular hypertrophy was mainly noted in patients with low FEV1 values, this inverse association between FEV1(%) values and muscle mass hypertrophy or hyperplasia of bronchial wall being supported by the high value of the correlation coefficient ($r = -0.8997$, $p < 0.001$) and confirmed by a significant negative regression slope (fig. 9).

Regarding submucosal glandular area

hypertrophy, the statistical analysis revealed a strong positive correlation between asthma severity and the glandular area hypertrophy of the bronchial wall (Spearman's $\rho = 0.92$, $p < 0.01$) (tab. II). A significant inverse correlation between FEV1 (%) values and the submucosal glandular area hypertrophy was observed ($r = -0.887$, $p < 0.01$), which was further supported by linear regression analysis (fig. 10).

Mean FEV1 (%) values were higher in asthmatic patients with a near-normal glandular area and lower in cases with marked submucosal glandular hypertrophy.

TABLE I.

Statistical parameters estimated in the testing of the association of muscular area hypertrophy or hyperplasia vs. bronchial asthma severity

	Pearson's chi-square test	df	<i>p</i> 95% CI
Pearson's chi-square - χ^2	58.66844	df=6	0.000
M-LChi-square	62.82472	df=6	0.000
Correlation coefficient (Spearman Rank R)	0.9352601		0.000

CI - confidence interval; df - degrees of freedom; M-L Chi-square - Maximum Likelihood Chi-Square

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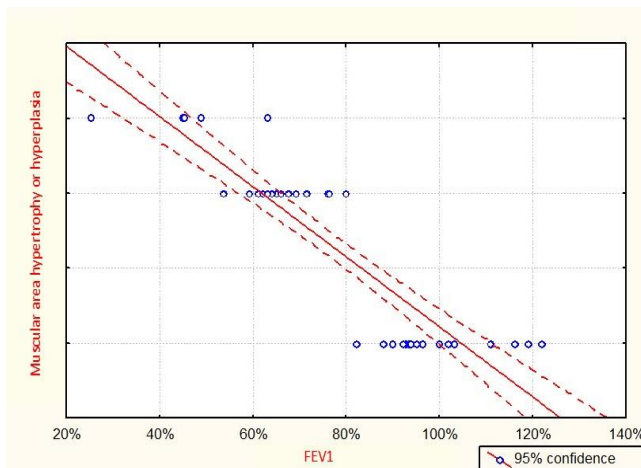


Fig. 9. The regression line showing a negative correlation FEV1 vs. bronchial wall muscular area hypertrophy or hyperplasia

TABLE II.

Statistical parameters estimated in testing the association of submucosal glandular area hypertrophy vs. bronchial asthma severity

	Pearson's chi-square test	df	P 95% CI
Pearson's chi-square - χ^2	57.64917	df=6	0.000
M-L Chi-square	60.69115	df=6	0.000
Correlation coefficient (Spearman Rank R)	0.9211776		0.000

CI - confidence interval; df - degrees of freedom; M-L Chi-square - Maximum Likelihood Chi-Square

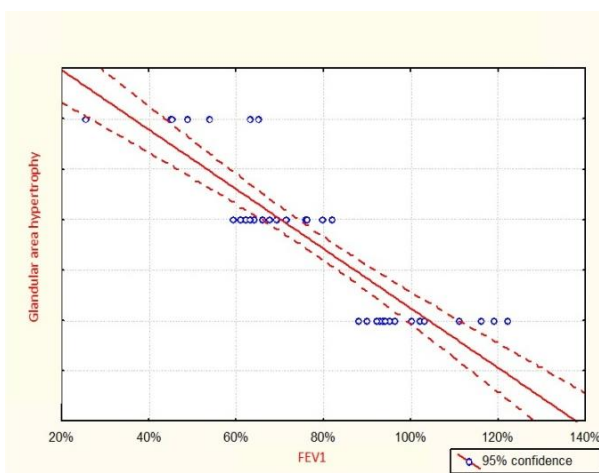


Fig. 10. The regression line showing a negative correlation FEV1 vs. bronchial wall submucosal glandular area hypertrophy

DISCUSSION

Bronchial wall remodeling is a consequence of chronic airway inflammation in asthma, a feature which was also observed in other chronic inflammatory diseases (12-15). As a part of the airway remodeling process, an abnormal increase of submucosal glandular and smooth muscle bronchial areas has been mainly detected in severe forms of asthma, features modulated by IL-5, IL-13, and other non-T2 cytokine-dependent mechanisms (1, 16, 17). In this context, a 50-100% thickening of the bronchial wall was observed in patients with fatal asthma, compared to patients with non-fatal asthma, this increase being correlated with pulmonary functional status (1).

Although bronchial submucosal gland hypertrophy has been demonstrated as a key contributor to mucus hypersecretion, together with goblet cell hyperplasia of the respiratory epithelium (1), the origin and the molecular mechanisms underlying the thickening of the airway smooth muscle layer remain partially elucidated (6, 18).

In recent decades, different studies have explored the potential proliferation of muscle cells in the airway wall in asthmatic patients, with contradictory results. In this context, an increased proliferative capacity of airway muscle cells was observed in asthmatic patients compared to control individuals, especially in the case of partially uncontrolled or uncontrolled asthma (19, 20), while other studies suggest that the thickening of the asthmatic bronchial smooth muscle layer is not associated with active muscle cells proliferation (21, 22). A very limited proliferative activity of airway muscle cells was observed in uncontrolled asthmatic cases in

our study, suggesting that the increase of muscle thickness involves other mechanisms, such as hypertrophy or cellular differentiation or trans differentiation. According to recent data, myoblasts, mesenchymal stem cells, epithelial cells, and pericytes may contribute to the thickening of the bronchial muscle mass by migration and trans differentiation into smooth muscle cells, mainly in severe asthma (23, 24). Furthermore, glucocorticoid administration may reduce the microvascularisation in the lamina propria and may decrease the basement membrane thickness in asthmatic cases (25, 26). However, their effect on the decrease of the size of the smooth muscle area associated with airway wall remodeling in asthmatic patients is limited (25, 26). Our results reinforce this data, showing that among asthmatic patients receiving chronic inhaled corticosteroid therapy, bronchial muscle area was significantly increased and correlated with asthma severity, as indicated by reduced FEV1 values. Furthermore, a significant increase of the smooth muscle area was observed in patients with uncontrolled asthma compared to partially controlled or well-controlled asthma patients, which is consistent with other studies (10, 27, 28). In this context, a mean bronchial muscle area of $0.24 \pm 0.03 \text{ mm}^2$ was registered in patients with uncontrolled asthma compared to partially controlled patients ($0.05 \pm 0.01 \text{ mm}^2$) in a group of 28 asthma cases (10). In addition, smooth muscle cells accounted for 27% of the subepithelial tissue, in a group of 24 children with asthma (28), a proportion that can increase up to 40% in patients with uncontrolled asthma (27). All these data support the direct relationship between asthma severi-

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ty, reflected by reduced spirometry parameters, and increased muscle area associated with the bronchial wall remodeling process that can occur in asthmatic patients, as also observed in our study.

Another morphologic component of the airway remodeling process in asthma is the submucosal glandular area hypertrophy (1). Goblet cell hyperplasia added to hypertrophy of bronchial glandular area may lead to a three-fold increase in mucin secretion in asthma (17, 29). Mucus hypersecretion induces “mucus plugs” occurrence that is associated with airflow obstruction (1, 29). Thus, a 30-fold increase in goblet cell count (30) and a greater increase in submucosal glandular area in the bronchial wall was observed in fatal asthma patients compared to those with non-fatal asthma ($p=0.003$) (31). In addition, mucus hypersecretion due to increased bronchial submucosal glandular areas has been demonstrated to be associated with asthma attacks (30). Thus, an increased mucous gland area and percentage of the relaxed lumen area occupied by mucus have been detected in asthma cases ($p < 0.05$) compared with healthy patients (32), with mucus hypersecretion being also partially related to goblet cell hyperplasia even in well-controlled asthma (33, 34). Moreover, mucus hypersecretion has been detected to be inversely correlated with FEV1 (Spearman’s $\rho = -0.51$, $p < 0.001$) and FEV1/FVC ratio (Spearman’s $\rho = -0.54$, $p < 0.001$) in a large cohort of asthmatic cases (35), data which are consistent with our observation.

Although an increased two- to four-fold compare to controls of the submucosal gland area in asthma has been detected, the glandular hypertrophy is not a

constant morphologic feature in all asthmatic patients (36). This feature is in accordance with our results, showing a near-normal appearance of the submucosal glandular area in most cases. Moreover, the increased airway submucosal glandular area is due to hypertrophy of the mucous glands, demonstrated by the Ki-67 negative immunoexpression in all cases examined tissue fragments. Given their impact on lung function, preventing mucus plug formation driven by mucus hypersecretion represents a new therapeutic strategy to prevent airflow obstruction, particularly in patients with uncontrolled asthma.

CONCLUSIONS

Airway remodeling is characterized by long-term changes of the airway’s architecture in asthmatic patients, associated with lung function decline. This process is characterized by the reorganization of the epithelial and subepithelial tissues, which also includes mucus hypersecretion and thickening of the bronchial smooth muscle layer. Increased areas of muscular and submucosal glands are mainly observed in patients with uncontrolled bronchial asthma, despite treatment with high doses of inhaled corticosteroids. Thus, the new therapeutic strategies should be targeted to prevent bronchial wall remodeling in asthmatic patients, by reducing the increase of the bronchial muscle area and limiting the mucus hypersecretion.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no funding regarding this research.

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