



# Cellular sources of airway smooth muscle cells in asthmatic airway remodeling and their clinical relevance: a narrative review

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**Background and Objective:** Airway remodeling in asthma refers to numerous structural changes in the airway in asthmatic patients, with thickening of the airway smooth muscle layer as its core feature. However, the nature and sources of the abnormally increased airway smooth muscle cells (ASMCs) in airway remodeling remain unclear. ASMCs play a key role in the pathogenesis of fatal asthma; therefore, it is important to clarify the properties and sources of these ASMCs responsible for asthmatic airway remodeling, which may provide a new direction for the precise treatment for asthma.

**Methods:** We performed a narrative review of the literature on PubMed, Web of Science, and Google Scholar databases searching for the cellular sources of ASMCs in asthmatic airway remodeling and their clinical relevance.

**Key Content and Findings:** It has long been thought that ASMCs are the result of abnormal proliferation of the native ASMCs in asthma; however, increasing evidence suggests that increased “ASMCs” may be due to the differentiation/transdifferentiation of other cells including mesenchymal stem cells (MSCs), myofibroblasts (MYFs), pericytes, and epithelial-mesenchymal transition (EMT). Recently, several pharmacological and biological therapies aimed at “reducing asthmatic ASMCs” have been developed, among which gallopamil, JQ1 [an inhibitor of the bromodomain and extra-terminal domain (BET) protein family], and histone deacetylase (HDAC) inhibitors can alleviate asthma airway remodeling and hyperresponsiveness and improve asthma symptoms in both mouse models and preclinical experiments.

**Conclusions:** As one of the core features of asthma, ASMCs are an important effector of airway remodeling. It has become extremely important to develop therapies for the reduction and prevention of the “ASMCs” on the basis of the properties and sources of “ASMCs”. Many studies have shown that epigenetic regulation is closely related to the abnormal increase of ASMCs in asthma, and interfering with epigenetic regulation factors can reduce the increased smooth muscle cells. Although the epigenetic regulation of asthma is still in its nascent stage, epigenetic therapy targeting “ASMCs” may become another new strategy for asthma prevention and treatment.

**Keywords:** Asthma; airway remodeling; airway smooth muscle cells (ASMCs); epigenetic regulation; therapy

Submitted May 16, 2022. Accepted for publication Jul 15, 2022.

doi: 10.21037/atm-22-3219

View this article at: <https://dx.doi.org/10.21037/atm-22-3219>

## Introduction

Airway remodeling is a collective term for changes in the cellular and molecular constituents of the airway wall (1-6), among which the thickening of airway smooth muscle layer caused by abnormal increase of airway smooth muscle cells (ASMCs) is the core feature of airway remodeling. These abnormally increased ASMCs have long been considered the result of an imbalance between proliferation and apoptosis of the native smooth muscle cells in the airway (7,8). In recent decades, however, many studies have found that these airway smooth muscle-like cells (“ASMCs”) in the thickened asthmatic airway myometrium may be transdifferentiated from other cells and can migrate around the airway wall (9). However, the exact cellular resources and biological properties of these “ASMCs” remain unclear.

ASMCs, featured by contractile phenotype marker genes [e.g., alpha smooth muscle actin ( $\alpha$ -SMA), calponin, SM22 and smooth muscle myosin heavy chain], are the primary effector cells of bronchial contraction and recruit immune cells, which predominantly contribute to asthmatic airway hyperresponsiveness, narrowing, remodeling and inflammation through enhanced responsiveness to stimuli, contracting to a greater extent, increased volume and increased secretion of inflammatory mediators (e.g., Cxcl8, Cxcl10), respectively (10). Therefore, it is particularly important to clarify the properties and sources of these “ASMCs” responsible for asthmatic airway remodeling and thickening of the airway smooth muscle layer. In addition, the inhibitors to reduce the accumulated and contractile ability of ASMCs and attenuate inflammation of ASMCs are necessary to be developed. In this article we summarize the recent studies on the sources of “ASMCs” and the corresponding targeted therapies for the abnormal increased “ASMCs” of airway remodeling in asthma. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3219/rc>).

## Methods

Databases including PubMed, Google Scholar, and Web of Science were searched for articles on the sources of ASMCs in airway remodeling in asthma as of 1<sup>st</sup> January of 2022 by using subject terms including “airway smooth muscle cells and asthma”, “airway smooth muscle cells and airway remodeling”, “epigenetic regulation and asthma” and “airway smooth muscle cells and epigenetic regulation”. Database

resources were summarized in *Table 1* and *Table S1*.

## Discussion

### *Sources of ASMCs in asthmatic airway remodeling*

#### **Abnormal proliferation of ASMCs**

For decades, the proliferation of ASMC itself has long been considered the main reason for the increase of ASMCs in asthmatic airway remodeling and is closely related to the development of severe asthma (9,11). In 2001, Johnson *et al.* for the first time cultured ASMCs from asthmatic patients *in vitro* and found that the proliferative capacity of ASMCs in asthmatic patients was significantly stronger than that in healthy individuals (12). In 2010, Hassan *et al.* obtained bronchoscopic biopsies from participants with moderate or severe asthma and concluded that the proliferation rate of ASMCs calculated in the immunoreactive area of  $\alpha$ -SMA was significantly increased (13), suggesting that the thickening of the asthmatic airway smooth muscle layer may be due to the abnormal proliferation of ASMCs themselves. In contrast, in 2018 James *et al.* assessed the continuous cross-sectional area of the intact airway wall in fatal and non-fatal asthma patients and controls and found that smooth muscle layer thickening in asthmatic patients was not accompanied by active ASMC proliferation (14). In 2020, Saunders *et al.* identified ASMC proliferation based on the proliferating cell nuclear antigen (PCNA), a proliferation marker, in biopsies of asthmatic and non-asthmatic samples and found no significant differences between asthmatic and non-asthmatic patients (15). Unfortunately, it might be due to the technical limitations, these studies on “abnormal proliferation of ASMCs originating from the airway itself” only observed whether ASMC proliferated or not, but ignoring including the properties and sources of increased “ASMCs” in the experimental design, the design was flawed.

#### **Mesenchymal stem cells (MSCs)**

MSCs are a subset of stem/progenitor cells with the abilities of multi-directional differentiation and self-renewal (16). Due to their specific differentiation potentials and immunomodulatory capabilities, tissue-resident MSCs can promote tissue healing, repair, and regeneration and suppress inflammatory and immune responses. Although MSCs, as a novel therapeutic approach, have facilitated progress in treating chronic inflammatory lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma in preclinical studies and clinical trials (17-19),

**Table 1** The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	01/01/2022
Databases and other sources searched	PubMed, Web of Science, and Google Scholar
Search terms used	See <a href="#">Table S1</a> for details
Timeframe	Mar 1, 1962 to Sep 15, 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	English literature including clinical trial, meta-analysis and review were collected for reviewing
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Lifei Li and Wei Zhang searched the database independently, all authors jointly discussed and selected the literature for this review
Any additional considerations, if applicable	None

the role of MSCs in asthma remains controversial. Despite the lack of robust evidence (9), lung-resident MSCs have shown their potential to undergo transformation to form smooth muscle-like cells in studies over the past few decades, suggesting that MSCs may be the cellular source of “ASMCs” during asthmatic airway remodeling. Transcriptional profiling of human fetal lung cells has shown that the presence of a group of smooth muscle-like cells in airway smooth muscle is characterized by the co-expression of fibroblast growth factor 18 (Fgf18) and actin alpha 2 (Acta2) (20). Between them, Acta2 is a commonly used molecular marker of smooth muscle cells, whereas Fgf18 is a key gene driving MSC cell differentiation (21). In 2010, Bentley *et al.* found that ASMCs expressed Stro-1, a molecular marker of MSCs in mouse models of ovalbumin (OVA)-induced asthmatic airway remodeling (22). In addition, GLI family zinc finger 1 (Gli1) and axin-like protein (Axin2), 2 key markers of stem cells, were found to be co-expressed in the SMC lineage (23). These studies supported that MSCs may differentiate into ASMCs through muscle differentiation and thus participate in airway wall thickening in asthmatic patients.

### Myofibroblasts (MYFs)

MYFs are characterized with both fibroblast and smooth muscle cell phenotypes, with the co-expression of CD34 and  $\alpha$ -SMA as their typical marker. It is considered that MYFs are the immediate precursors of ASMCs and are derived from a wide variety of cells. Normally, MYFs reside temporarily during lung development and then undergo apoptosis (24). The number of MYFs in the airways of severely asthmatic patients was shown to increase by approximately 47-fold compared with non-

asthmatic patients (25-27). Electron microscopy and immunohistochemistry have revealed the close proximity between MYFs and smooth muscle layers in the airways of asthmatic patients (4), suggesting that MYFs with high cellular plasticity may be involved in asthmatic airway remodeling by migrating and/or differentiating ASMC-like cells, leading to the thickening of the smooth muscle layer. Primary fibroblasts cultured with transforming growth factor beta (TGF- $\beta$ ) *in vitro* can acquire a smooth muscle-like cell phenotype after myofibroblast activation (28). In 2018, by using a combination of transcription factors including myocardin (Myocd), GATA-binding protein 6 (Gata6), and myocyte enhancer factor 2 (Mef2C), Hirai *et al.* successfully reprogrammed mouse embryonic fibroblasts (MEFs) and human dermal fibroblasts (hFB) to transdifferentiate them into smooth muscle-like cells (29). In 2020, by comparing the characteristics of the airway smooth muscle layer in asthma and COPD patients, Saunders *et al.* confirmed that fibroblasts, as the myofibroblast precursors, were significantly increased and localized only in the airway smooth muscle layer of asthmatic patients, where they may form a smooth muscle-like phenotype and obtain a higher  $\alpha$ -SMA expression level and stronger cell contractility (15). It has been shown that MYFs are significantly increased in number and enriched in the airway smooth muscle layer in patients with severe asthma, suggesting that, due to their recruitment and differentiation potentials, MYFs may serve as a cellular source of ASMCs for the increased asthmatic airway remodeling (30,31).

### Pericytes

Pericytes, known as supporting mesenchymal cells, usually wrap around the extraluminal surface of the vascular system

and play a key role in vascular homeostasis and angiogenesis. Platelet-derived growth factor subunit  $\beta$  (PDGF $\beta$ ) is essential for the recruitment of pericytes to blood vessels (32). Recent evidence has suggested that tissue-resident pericytes have stem cell characteristics that allow them to differentiate into a variety of cell types (33). In mouse models of chronic allergic asthma induced by exposure to house dust mite (HDM), upregulation of  $\alpha$ -SMA expression in NG2+ pericytes was observed; in addition, lineage tracing techniques showed that pericytes tended to accumulate in and integrate into the airway smooth muscle layer. Therefore, pericytes may be one of the cellular sources of increased ASMCs in asthmatic airway remodeling (34,35).

### Epithelial-mesenchymal transition (EMT)

EMT is a reversible cellular transformation process during which epithelial cells lose intercellular adhesion and acquire quasi-mesenchymal characteristics (36). Transforming growth factor  $\beta$  (TGF- $\beta$ ) is the core inducer of this cellular transformation process. In asthmatic airway remodeling, EMT is a key biological process (37). Dominated by epigenetic regulation, the upregulation of SNAIL1 and SNAIL2 can lead to an increase expression level of vimentin and  $\alpha$ -SMA in epithelial cells (38). The airway epithelium of asthmatic patients is fragile and vulnerable, with reduced E-cadherin expression and loss of intercellular junctions; meanwhile, it acquires fluidity and has higher ability to secrete extracellular matrix (ECM). Therefore, epithelial cells may transdifferentiate to a smooth muscle-like phenotype directly or via MYFs (39,40). Currently, there are insufficient *in vivo* data to support whether the damaged epithelial cells can be directly converted into ASMCs in asthmatic patients.

Due to the difficulty in obtaining an intact airway smooth muscle layer from bronchial biopsies, the cellular composition and properties of the intact airway smooth muscle layer in non-lethal asthmatic patients are still unclear. It is also unclear whether “ASMCs” differentiated from other cells and abnormally proliferating ASMCs of the airway itself differ in cellular phenotype and function. Therefore, there are still many challenges to clarifying these issues and the underlying regulatory mechanisms.

### Targeted therapies for reducing ASMCs

Glucocorticoids and bronchodilators are currently routine treatments for asthma and can significantly improve some airway inflammation and smooth muscle spasms; however,

whether they can reverse and/or prevent airway remodeling remains unclear (41). Gallopamil, a calcium receptor antagonist, has been shown to inhibit ASMC proliferation *in vitro* (42,43). A 12-month, double-blind, randomized, placebo-controlled clinical trial evaluating the therapeutic effect of gallopamil on bronchial asthma showed that gallopamil reduced the increased thickness of bronchial smooth muscle layer and prevented acute exacerbations in asthma patients without obvious side effects (41,42). Fevipiprant, a prostaglandin D2 type 2 receptor antagonist, was found to significantly decrease myofibroblast/fibroblast migration and reduce ASMCs in bronchial biopsies from asthmatic patients (44).

Notably, epigenetic alterations, including DNA/histone modifications, long non-coding RNAs, and microRNAs (miRNA), have presented another new frontier for asthma therapy (45-48). Epigenetic modifications are caused by genetic and/or environmental drivers (49,50). Notably, epigenetic regulation, with a particular focus on histone modification and chromatin remodeling, is the key mechanism mediating gene-environment interaction, which prominently contribute to the genetic heterogeneity and various phenotypes in asthma (51). Abnormal epigenetic regulation can lead to multiple pathological processes in asthma, including airway inflammation, remodeling, constriction, and hyperresponsiveness. Recent study revealed epigenetic changes in ASMCs have been found to worsen airway remodeling and perpetuate inflammation (51). These findings suggest the investigation of altered epigenetic marks and corresponding mechanisms in the pathogenesis of asthma may provide more insight into novel biomarkers for assessing phenotype and treatment response as well as new therapeutic targets. The miRNA miR-142-3p can regulate the balance between ASMC proliferation and differentiation by controlling Wnt signaling in asthma, which makes it a potential target for preventing ASMC hyperproliferation (46). As readers, the extra-terminal [bromodomain and extra-terminal domain (BET)] domain family of proteins including bromodomain-containing protein 2 (BRD2), bromodomain-containing protein 3 (BRD3), bromodomain-containing protein 4 (BRD4), and bromodomain testis associated (BRDT) can recognize acetyllysine residues in histones and non-histones to regulate the transcription of target genes such as contractile proteins, ECM, and collagen (52). Among them, BRD4 has been confirmed as a potential therapeutic target of airway remodeling (53). The BET bromodomain inhibitor JQ1 can inhibit the increase in

ASMCs, prevent ASMCs from secreting proinflammatory cytokines, and attenuate airway inflammation in asthmatic patients and OVA-induced asthmatic mice (50,54,55). In addition, a variety of changes in cell status including EMT, pericyte-myofibroblast transition, myofibroblast activation, and even myofibroblast-to-smooth muscle cell transdifferentiation can be interfered with or even reversed via the pharmacological inhibition of BET, thus effectively alleviating airway remodeling (56-58).

In addition, decreased histone deacetylase (HDAC) activity, increased histone acetyltransferase (HAT), and histone H3 (H3) panacetylation have been found in the bronchial biopsies of asthmatic patients, and acetylation was shown to affect the expressions of multiple genes associated with airway inflammation and airway remodeling (59). Treatment of asthmatic mice with trichostatin A, a potent HDAC6 inhibitor, reduced the expression level of  $\alpha$ -SMA in ASMCs, decreased the number of inflammatory cells, and alleviated airway hyperresponsiveness (60). Ren *et al.* found that an HDAC8 inhibitor (PCI-34051) could reduce the proliferation, differentiation, and contractility of ASMCs in mouse models of asthma and simultaneously relieve airway remodeling and airway hyperresponsiveness (61). Although these experiments did not distinguish whether ASMCs in these mouse asthma models were the abnormally proliferated native airway ASMCs or “ASMCs” that had been differentiated/transdifferentiated from other cells, these epigenetic targeting therapies did offer attractive prospects.

## Conclusions

The relationship between airway inflammation and airway remodeling remains controversial. On one hand, airway remodeling was considered as a secondary event to airway remodeling supported by numerous findings that asthmatic patients benefited from steroid treatment with amelioration of both airway inflammation and remodeling (62); on the other hand, measurements on patient airways cut in cross-section demonstrated some patients with increased airway smooth muscle mass in the absence of inflammation (63). Considering asthma is a heterogeneous disease with various phenotypes, inflammation-dependent and independent airway remodeling might coexist in the pathological process of asthma, which requires more research to identify. Nevertheless, ASMCs are a core feature of asthma and an important effector of airway remodeling and regulator of airway inflammation. Research on the properties, sources, and targeted therapies of “ASMCs” during

asthmatic airway remodeling and airway inflammation has become particularly important. New research techniques including single-cell multi-omics, genetic lineage tracing, and flow cytometric sorting are expected to explore the biological properties, morphological structure, and other characteristics (e.g., to what extent these “ASMCs” drive the pathological process of asthmatic airway remodeling) of abnormally increased “ASMCs” in a multifaceted manner. Recent multi-omic studies have shown that epigenetic regulation is closely related to the abnormal increase of ASMCs in asthmatic airway remodeling, and interfering with epigenetic regulation factors can reduce the thickened smooth muscle layer in asthmatic patients and thus reverse airway remodeling in asthma. Although the epigenetic regulation of asthma is still in its nascent stage, epigenetic therapy targeting “ASMCs” may become another new strategy for asthma prevention and treatment.

## Acknowledgments

*Funding:* This work was supported by the National Natural Science Foundation of China (No. NSFC:81770028).

## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3219/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3219/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- (English Language Editor: J. Jones)

**Cite this article as:** Li L, Zhang W, Qiu C. Cellular sources of airway smooth muscle cells in asthmatic airway remodeling and their clinical relevance: a narrative review. *Ann Transl Med* 2022;10(15):838. doi: 10.21037/atm-22-3219



## Supplementary

**Table S1** Detailed search strategy of PubMed database

Terms	Database	Number of results
Airway smooth muscle cells and asthma	PubMed	2,923
Airway smooth muscle cells and airway remodeling	PubMed	1,281
Epigenetic regulation and asthma	PubMed	370
Airway smooth muscle cells and epigenetic regulation	PubMed	20