Review Article

A narrative review of research advances in the study of molecular markers of airway smooth muscle cells

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Background and Objective: Airway smooth muscle cells (ASMCs) are an important component of the airway. Their thickening and proliferation are important in pathological situations, such as airway remodeling in asthma, but their origin remains unclear. Therefore, characterizing molecular markers of ASMCs were sought to identify the source of increased ASMCs in asthmatic airway remodeling.

Methods: Articles for this review were derived from a review of the literature related to surface markers and biological properties of ASMCs and smooth muscle cells (SMCs) using PubMed, Google Scholar, and Web of Science.

Key Content and Findings: This review discusses several SMC molecular markers, describes the different developmental stages of SMCs that express different molecular markers, and summarizes several classical SMC molecular markers. However, the establishment of a specific molecular marker detection system for ASMCs still faces great challenges.

Conclusions: Although there is no recognized molecular marker detection system for ASMCs, and the study of the properties and sources of increased ASMCs in asthma airway remodeling is still in a state of exploration, the future is promising. Among the SMC markers described in this review, Myosin heavy chain 11 (MYH11) is a molecular marker for mature SMCs and Transgelin (TAGLN) is an early marker for SMC differentiation, and different molecular markers or combinations of molecular markers can be selected for the identification of the properties and sources of increased ASMCs in asthma airway remodeling according to the differentiation period and research needs.

Keywords: Asthma; airway remodeling; airway smooth muscle cell (ASMC); molecular marker

Submitted Jan 24, 2022. Accepted for publication Mar 16, 2022.
doi: 10.21037/atm-22-800
View this article at: https://dx.doi.org/10.21037/atm-22-800

Introduction

Background

Airway smooth muscle cells (ASMCs) are an important component of the airway. Under normal conditions, Airway smooth muscle (ASM) makes up approximately 5% of the central airway. A series of pathological changes such as excessive ASM constriction and airway hyperresponsiveness leading to abnormal airway structure can be observed during acute asthma attack (1). Airway inflammation, airway hyperresponsiveness, and airway remodeling are well recognized features of asthma pathology (2), and the thickened smooth muscle layer of airway remodeling, is an important pathological basis for airway remodeling in

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	Dec. 31, 2021
Databases and other sources searched	PubMed, Web of Science, Google Scholar
Search terms used (including MeSH and free text search terms and filters). Note: please use an independent supplement table to present detailed search strategy of one database as an example	See Table S1 for details
Timeframe	By 2021-12-31
Inclusion and exclusion criteria (study type, language restrictions etc.)	English-language articles that include broad articles and reviews and cited literature
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	In this review, Li Yu and Chen Qiu collected and organized the literature, and discussed with Rongchang Chen, and jointly selected the literature related to the core content of the review
Any additional considerations, if applicable	None

asthma. It is traditionally believed that various cytokines and other pathological factors cause ASMCs to proliferate, hypertrophy, and undergo airway remodeling by continuous stimulation (3,4), but no rigorous studies on the properties and origin of these ASMCs in the thickened muscular layer of the remodeled airway have been reported. A recent study reported the presence of Ki67-positive cells in the epithelium of asthmatic patients, but not in the smooth muscle layer (5). A study of bronchial biopsies from asthmatic and non-asthmatic patients found no significant difference in proliferation between asthmatic and non-asthmatic ASMCs (5), suggesting that the thickened ASM layer cells in asthma may be derived from other cells. Therefore, the notion that asthmatic airway remodeling and thickening of the muscular layer of ASMCs is due to abnormal proliferation of its own ASM is seriously challenged.

Since molecular markers of cells are a reliable, convenient, and intuitive way to identify the properties and origin of cells, active research on characteristic molecular markers of ASMCs can help to analyze and identify the properties and origin of thickened smooth muscle layer ASMCs in pathological conditions such as airway remodeling in asthma. However, current studies on ASMCs are mainly focused on phenotypic transformation, contraction, and secretion, while studies on ASMC-specific molecular markers are rare. Therefore, the establishment of a specific molecular marker detection system for ASMCs still faces a great challenge. In this paper, we reviewed the progress of molecular marker research on ASMCs, and identifies markers that appear in the early and mature stages, providing a solid basis for exploring the source of "ASMCs" for increased 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-22-800/rc).

Methods

Articles for this review were searched using PubMed, Web of Science and Google Scholar of December 31th, 2021. The key search terms included "airway smooth muscle cells", "airway smooth muscle cells and asthma", "airway smooth muscle cells, marker and asthma. Sources listed in *Table 1* and Table S1.

Key content and findings

Structure and function of ASMCs

ASM is located in the trachea and bronchial tree up to the terminal fine bronchi; regulates bronchial diameter and bronchial motor sounds and is a major determinant of airway pathophysiology (6); ASMCs are 2 to 5 μm in diameter; their length is variable, with a length of 400 microns being the optimal length to produce tension (7). Allergens cause proliferation and/or hypertrophy of ASM cells, resulting in narrowing of the airway lumen and causing structural changes in the airway. As ASMCs have phenotypic plasticity, when airway smooth muscle

proliferates, it shows a hypocontractile phenotype accompanied by reduced expression of contractile phenotypic proteins (8). In asthma, inflammatory cells secrete cytokines that act on ASMCs, causing contraction of ASMCs and airway hyperresponsiveness; in turn, ASMCs exert immunomodulatory effects and interact with immune cells (9). In addition, epigenetic regulation also affects ASMCs proliferation and migration ability, such as MicroRNA-638 and miR217 inhibits human ASMC proliferation and migration (10,11).

Commonly used molecular markers of ASMCs

Myosin heavy chain 11 (MYH11)

Smooth muscle MYH11 (formerly known as SM-MHC) was identified by Deng *et al.* in 1993 by fluorescence *in situ* hybridization and localized to human chromosome 16p (12). MYH11 is a 230-kDa cytoplasmic protein expressed in human umbilical arteries, bladder, esophagus, and trachea (13). Major SMC-expressed mutations in the MYH11 gene can lead to thoracic aortic aneurysm and/or aortic dissection (TAAD) and patent ductus arteriosus (PDA), which manifest as medial degeneration of the aorta with very low SMC content (14). Shi *et al.* investigated the role of VEPH1 in regulating the phenotypic transition of ASMCs using MYH11 as a marker of SMCs (15). Recent studies reported that MYH11 was expressed only in mature SMCs, whereas reparative SMCs of muscle differentiation origin did not express MYH11 (16,17). Therefore, MYH11 can be used as a molecular marker of mature SMCs to differentiate SMCs from differentiated MSCs.

Transgelin (TAGLN)

TAGLN, located on chromosome 11q23.3 and earlier known as SM22α, was purified and named by Lees-Miller *et al.* in 1987 from chicken gastric smooth muscle and is also present in organs such as the uterus, intestine, callus, esophagus, and aorta (18). TAGLN consists of a 201 amino acid actin binding protein that is highly expressed in SMCs (19) and belongs to the calmodulin family of actin-binding proteins whose amino acid sequence is conserved across species. The protein encoded by TAGLN is associated with calcium independent smooth muscle contraction and is one of the earliest markers of SMC differentiation (20). TAGLN knockdown in mice resulted in a higher proportion of SMC-derived plaque cells with increased atherosclerotic lesion size and proliferation (21). In a study of the origin of SMCs in mice with increased atherosclerotic vascular remodeling using genetic genealogy tracing, Sca1+ MSCs were found to express TAGLN but not MYH11, indicating that TAGLN is an early SMC differentiation marker (16). Furthermore, Dilasser *et al.* investigated the role of Rac1 in airway remodeling associated with severe asthma using TAGLN as an ASMC marker (22). In a study of airway remodeling in a mouse model of chronic asthma, TAGLN has also been used to label ASMCs (23).

Calponin 1

Calponin 1, whose gene name is CNN1, is located on chromosome 19p13.2 (human; 8q in rats and chromosome 9 in mice) and was discovered in 2001 by Miano *et al.* (24) as a regulatory protein associated with actin filaments. Three homologous genes, CNN1, CNN2, and CNN3, exist in vertebrates, encoding calponin isoforms 1, 2, and 3, respectively. All 3 calponin isoforms are actin-binding proteins that function to inhibit actin-activated myosin ATPase and stabilize the actin cytoskeleton. Calponin 1 deletion prevents maturation of the vascular system and SMC migration (25), and plays a role in fine-tuning smooth muscle contractility. It was shown that in TGF-β-induced differentiation of myofibroblasts into ASMCs, the transcript and protein levels of calponin 1 were increased (26) and its expression was also sustained (16). Gosens *et al.* used calponin 1 as a marker of ASM in a study exploring the contractile phenotype of ASM (27).

Alpha-smooth muscle actin (α-SMA)

In humans, α-SMA is encoded by the ACTA2 gene located at 10q22-q24 and has a molecular weight of 42 kDa. Intracytoplasmic actin is expressed in a variety of cells with 4 different actin variants, including 2 which are vascular SMC (α-SM and γ-SM) specific and 2 which are cytoplasmic actin (β-NM and γ-NM actin) specific in eukaryotic cells (28). Initially, α-SMA was found to be expressed in the liver vasculature, and in pure-hybrid α-SMA knockout mice, vasoconstriction defects and reduced basal blood pressure were found, suggesting a role for α-SMA in maintaining vascular tone (29). In 1992, Marmy *et al.* used elastase to isolate and culture human primary ASMCs, and immunocytochemical staining revealed that 95% of ASMCs expressed α-SMA (30). Liu *et al.* used α-SMA as a marker of ASMCs in their study of the effect of the long-acting β2 adrenergic agonist formoterol on muscarinic M3 receptor expression in rat ASMCs, and Zhao *et al.* used α-SMA as a marker of ASMCs in their study of the effect of ginseng

injection on ASMC proliferation in asthmatic rats (31,32). In addition, TAGLN and α-SMA are skeletal proteins that are involved in cell contraction. In a study of the effect of asthma eosinophils on ASMCs contraction and migration, TAGLN, α-SMA was used as a contractile phenotypic marker (33). In a rat model of carbon tetrachloride-induced liver fibrosis, α-SMA was observed in perisinusoidal gaps and fibroblasts (34) and is now also considered to be a marker of mature myofibroblasts.

High molecular weight calmodulin-binding protein (h-caldesmon)

The h-caldesmon protein was first purified from bovine arterial smooth muscle in 1981 (35). The gene encodes calmodulin and actin binding protein and is expressed only in vascular and visceral SMCs. It is a specific marker of differentiated mature smooth muscle. In 1992, Frid *et al.* found by immunoblotting and immunofluorescence techniques that h-caldesmon was not expressed in the fetal aorta, but was significantly expressed in the adult aorta (36). With further studies, in 1996, Frid *et al.* used it as a marker of ASMCs and compared the h-caldesmon protein content between SMCs isolated from the trachea or the pulmonary artery by immunoblot analysis and found that the cells in the trachea had higher contractile protein content and faster shortening than cells in the pulmonary artery (36). In a study of TGF-β1-induced differentiation of adipose-derived mesenchymal stem cells into SMCs, h-caldesmon expression was increased, which was consistent with α-SMA, calponin, and SM-MHC (37). Furthermore, h-caldesmon, unlike α-SMA, was not expressed in perivascular cells and myofibroblasts (38), suggesting that h-caldesmon is a characteristic molecular marker of SMCs.

Smooth muscle cell differentiation-specific protein (smoothelin)

Smoothelin is a 59-kDa cytoskeletal protein discovered in 1996 by van der Loop *et al.* It is localized to chromosome 22q12.3 and defined as an SMC-specific protein. It is expressed in or as part of filopodia and is expressed in human myomas, human colon, and bovine aorta, but is not expressed in primary and long-term cultured vascular SMCs (39-41), suggesting that smoothelin is a structural protein expressed only in contractile SMCs. Smoothelin expression was increased in bronchial smooth muscle of ovalbumin (OVA)-sensitized asthmatic mice, but its expression was unstable and decreased at day 35 (42). Smoothelin expression was inconsistent in different tissue cells and under different pathological conditions, and therefore is only a marker of contractile SMCs. Smoothelin has 2 isoforms, smoothelin-A (59 kDa) and smoothelin-B (102 kDa), with smoothelin-A expressed in visceral SMCs and smoothelin-B expressed in VSMCs (37).

Desmin

Desmin was purified from the chicken stomach in 1976 by Lazarides *et al.* and was found to co-migrate with actin. Indirect immunofluorescence showed that in skeletal muscle, desmin was found to be closely associated with the Z-lines of myofilaments and extended between the Z-lines of adjacent myogenic fibers to contract myofilaments (43). In ASMCs, desmin is an intermediate filament protein that constitutes ASMCs and plays a role in maintaining myocyte integrity as well as information transfer between myonodules (44). In the developing airway and perivascular mesenchyme, junctional proteins replace wave proteins as the major intermediate filaments, specializing toward smooth muscle, and junctional proteins and smooth muscle myosin are expressed simultaneously in cells, indicating terminal differentiation of smooth muscle (45). Thus, junctional proteins become markers of smooth muscle. In a microarray analysis of myofibroblasts from asthmatic patients, desmin transcript levels increased with increasing treatment time during TGF-β2-induced differentiation of myofibroblasts into smooth muscle, as did calponin 1 and α-SMA (26), but Desmin behaved similarly to α-SMA and was also expressed in fibroblasts and myofibroblasts (46), without specificity.

Cysteine- and glycine-rich protein 1 (CSRP1)

The CSRP family is encoded by serum-induced highly conserved and widely expressed immediate early response genes (47). First proposed in 1992 and localized to chromosome lq24-1q32 (47) as a protein containing the LIM structural domain and actin backbone (27), CSRP1 is predominantly expressed in vascular and visceral smooth muscle (48), and its primary structure contains 2 LIM regions conforming to the consensus sequence CX2CX17HX2CX2CX2CX17CX2C, each followed by a glycine-rich repeat sequence, GPKG (Y/F) GQAG. CSRP1 is expressed in the vascular system, appearing at embryonic day 11.5, with an expression pattern similar to that of α-SMA and MYH11 (49). However, no smooth muscle marker is strictly conserved, such as its embryonic day 9.5 expression in the abdominal aorta and its embryonic day 16.5 expression in bladder smooth muscle (49). In

addition, CSRP1 is transiently expressed in mesenchymal cell populations during lung development and cartilaginous bone development. In recent years, it has been shown that CSRP1 deficiency impairs the ability of SMCs to redifferentiate. Mice lacking CSRP1 have an impaired response to wire-induced arterial injury (48). Because CSRP1 is mainly present in visceral and vascular SMCs, it regulates terminal differentiation in vertebrate muscle development (49,50), but the exact mechanism of its expression needs further investigation.

Classical molecular markers of ASMCs

Given the importance of identifying the properties and origin of SMCs in many pathological conditions, it is urgent to find the characteristic molecular markers of ASMCs. However, as mentioned earlier, no academically recognized characteristic molecular markers and corresponding detection systems have been established so far. Over the past 40 years of research, multiple SMC progenitors have been identified, such as neural crest, mesothelial, somatic, mesodermal, and mesenchymal stem/progenitor cells, each with a separate genetic lineage, and each producing a similar cell type that can transcribe a common set of SMC marker genes, such as α-SMA, TAGLN, calponin 1, and MYH11 (51,52). These markers were later also referred to as classical molecular markers of SMCs and have also been widely used in the study of asthmatic ASM (16). In addition, desmin, h-caldesmon, and smoothelin are also used in a small number of applications as molecular markers of ASM, particularly in the detection of asthmatic ASM, and this paper focused on an overview of the molecular markers applied to identify asthmatic ASMCs.

Conclusions

In summary, although there is no recognized molecular marker detection system for ASMCs, and the study of the properties and sources of increased ASMCs in asthma airway remodeling is still in a state of exploration, the future is promising. Among the above-mentioned SMC markers, MYH11 is a molecular marker for mature SMCs and TAGLN is an early marker for SMC differentiation, and different molecular markers or combinations of molecular markers can be selected for the identification of the properties and sources of increased ASMCs in asthma airway remodeling according to the differentiation period and research needs. With the development of single-cell transcriptome technology and genetic genealogy tracking, single-cell transcriptome sequencing and comparisons of differentially expressed genes for isolated primary ASM and vascular smooth muscle show attractive prospects for finding characteristic molecular markers of ASMCs.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (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-22-800/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-800/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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Cite this article as: Yu L, Qiu C, Chen R. A narrative review of research advances in the study of molecular markers of airway smooth muscle cells. Ann Transl Med 2022;10(6):375. doi: 10.21037/atm-22-800

