Chapter

Role of Airway Smooth Muscle Cells in Asthma Pathology

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Abstract

Airway smooth muscle (ASM) cells have been shown to play an important role in bronchial asthma. As the research progresses, the mechanism becomes more and more complex. This chapter reviews the role of ASM in asthma pathological mechanisms including inflammatory reaction, extracellular matrix proteins, cell contraction, cell structure, neuromodulation, airway remodeling, apoptosis, autophagy, miRNA, mitochondria, etc. In brief, ASM is similar to a "processing station." It is not only affected by various signals in the body to produce biological effects and secrete various signals to act on downstream target cells but also feeds back to the upstream pathways or receives feedback from downstream pathways to form a complex network. The results summarized in this chapter are expected to provide new targets for the clinical treatment of asthma.

Keywords: airway smooth muscle cells, asthma, inflammation, airway hyperreactivity, airway remodeling

1. Introduction

Bronchial asthma is a chronic airway inflammatory disease involving a variety of airway inflammatory cells, airway structural cells, and cellular components of which airway smooth muscle (ASM) cells have received the most intensive investigation. ASM has been shown to play an important role in the structure, function, and contraction of the airways. Evidence suggests that some ASM signaling mechanisms can help regulate the release of pro-inflammatory and anti-inflammatory mediators, which are factors that regulate immunity; different types of airway cells (such as epithelial cells, fibroblasts, and nerve cells); intracellular Ca^{2+} concentration-mediated airway contraction and relaxation; cell proliferation and apoptosis, autophagy, production, and regulation of the extracellular matrix (ECM); and neuromodulation. These mechanisms cause structural changes in the narrowing and dilatation of the airway, resulting in airway hyperreactivity (AHR) and airway stenosis, hence affecting airway compliance.

2. ASM participates in asthma by releasing pro-inflammatory or anti-inflammatory factors and immune regulators

ASM can produce a variety of pro-inflammatory and anti-inflammatory factors triggered by inflammation, injuries, and microbial products [1], including interleukin-1β (IL-1β), IL-5, IL-6, IL-8, IL-17, platelet-derived growth factor

(PDGF), transforming growth factor-β (TGF-β), etc., which constitute a complex network that participates in airway inflammation. For example, IL-6 induces ASM cell proliferation and further modulates immune cell function [2], and TNF-α exerts its mediating effects by enhancing interferon (IFNβ) secretion [3]. Recent studies have confirmed that ASM can produce and release thymic stromal lymphopoietin (TSLP) and can also act as a target of TSLP to participate in the recruitment of dendritic cells to regulate airway immune responses [4, 5]. ASM cells also produce chemokines such as RANTES and eotaxin [6]. The specific mechanism may be mediated by mitogen-activated protein kinase (MAPK), janus kinase/signal transducer and activator of transcription protein signaling pathway (JAK/Stat), and c-jun N-terminal kinase (JNK) [7, 8]. There is also evidence that ASM can also secrete growth factors such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BNDF), and these growth factors may be involved in ASM proliferation and contraction through autocrine effects [9].

3. ASM acts on asthma by secreting extracellular matrix (ECM)

The action of ASM ECM proteins on airway remodeling by autocrine or paracrine effects is a current research focus in asthma. ASM can produce a series of ECM proteins [10]. In the airway, ECM proteins surround cells in the form of reticular collagen or noncollagen, and their density and structure affect cellular characteristics such as proliferation, migration, differentiation, and survival. The related components include collagen, fibronectin, the matrix metalloprotein (MMP) family (MMP-2, MMP-3, MMP-9, MMP-13, etc.), and metalloprotein antagonists (TIMP-1 and TIMP-2) (**Figure 1**) [1, 11, 12]. Meanwhile, ECM protein signaling groups can in turn regulate other cells such as epithelial cells and ASMs. The ECM can control its own conformation, release growth factors, and MMPs and regulate the activity of local growth factors (such as neurotrophin and VEGF) and cytokines by cleavage

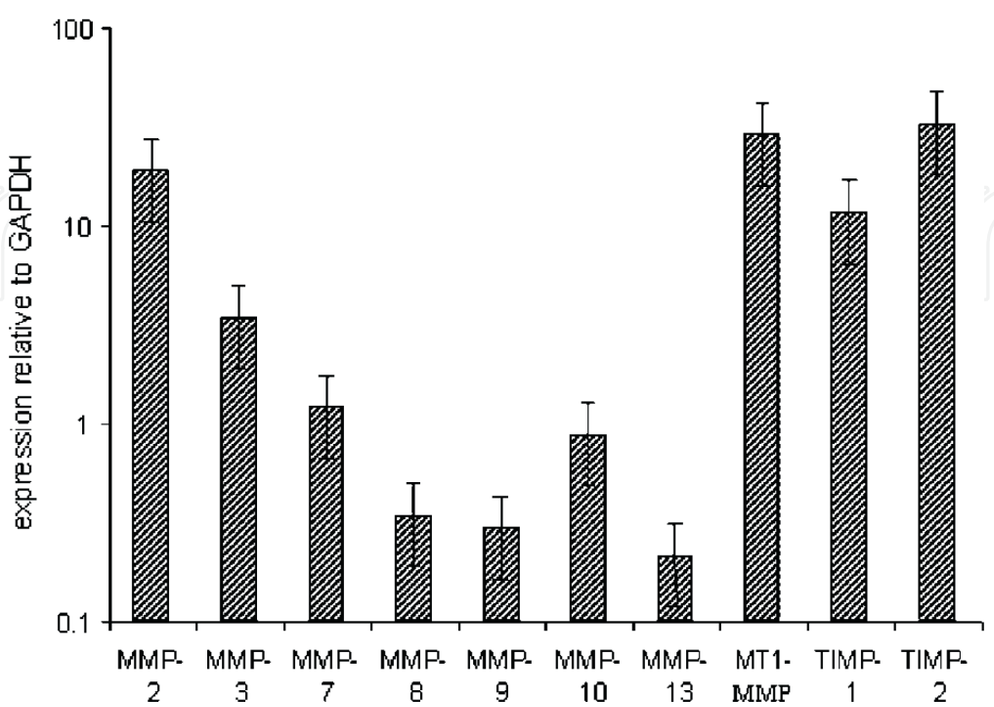

Figure 1.
MMP and TIMP mRNA expression by qRT-PCR five primary ASM cell cultures and expressed relative to GAPDH. It was originally published on "Matrix metalloproteinase expression and activity in human airway smooth muscle cells" of the British Journal of Pharmacology by Shona R. Elshaw et al.

and inactivation [13], thereby forming a complex signaling network to regulate airway remodeling. For example, IL-1β can interact with tumor necrosis factor-α (TNF-α), thus increasing MMP-12 [14] and MMP-9 [15], promoting cell migration and remodeling, and further regulating growth factor activity.

In terms of the regulatory mechanisms of the ECM, Rho kinase inhibitors can prevent ECM-induced airway remodeling [16]. The Wnt/β-catenin pathway can regulate TGF-β regulation of ASM-derived ECM [1, 17]. In contrast, decorin (an ECM proteoglycan) binds to TGF-β and reduces ECM production [18]. Even infections can regulate ECM products via ASM, and rhinovirus-induced infections increase fibronectin and basement membrane glycans, especially in the ASM of asthma patients [19]. Thus, altering the production of ECM, thereby modulating the inflammatory mediators or growth factors produced by the ASM or other cells, may result in cross reaction of airway structures and functions.

4. ASM is involved in asthma through other mechanisms

In addition to inflammatory mediators and growth factors, many emerging mechanisms have been reported to be involved in ASM and airway remodeling. For example, vitamin D has been shown to inhibit remodeling in vitro and in vivo [20]. However, its mechanism involving airway ASM cells is still under investigation [21]. Another emerging mechanism is thyroxine, which has been reported to enhance ASM proliferation [22], while low thyroxine levels cause airway developmental malformations [23]. Some reports also suggest that insulin appears to enhance ASM proliferation and ECM formation [24]. In addition, sphingolipids participate in airway inflammation, AHR, and remodeling. In particular, sphingosine-1-phosphate can promote ASM contractility and regulate inflammation and airway remodeling [25, 26].

5. Roles of ASM, $[Ca^{2+}]_i$, and contraction mechanisms in asthma

The cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) is a well-established pathway for the regulation of ASM contraction. The $[Ca^{2+}]_i$ can affect voltage-gated channels, receptor-regulated channels, and calcium pool-regulated channels. These channels are subjected to regulation by pathways such as phospholipase C (PLC), inositol triphosphate (IP3), ryanodine receptor (RyR), etc. (**Figure 2**). Meanwhile, sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA), bidirectional Na^+-Ca^{2+} exchangers (NCX), and mitochondrial buffers can limit $[Ca^{2+}]_i$ and regulate calcium storage by inhibiting the activation of $[Ca^{2+}]_i$. In addition to $[Ca^{2+}]_i$, Ca^{2+}-calmodulin-dependent myosin light chain (MLC) kinase and MLC act in tandem to regulate ASM contractility by excitatory myosin interaction. Studies have shown that the Rho-associated coiled-coil containing kinases (ROCK) pathway inhibits the contraction of Ca^{2+}-sensitive cells by inhibiting the sensitivity of MLC kinase [27]. IP3 can activate Ca^{2+} influx [28] in ASM and regulate local Ca^{2+} release [29].

5.1 GPCR mechanism and asthma

G-protein-coupled receptors (GPCRs) are a superfamily of cell membrane proteins that transduce extracellular signals, causing intracellular cascades and leading to different cellular functions. This mechanism is used to treat diseases such as asthma and chronic obstructive pulmonary disease (COPD). In ASM, most of the existing research focuses on the expression and function of different GPCRs (G_q, G_i, and G_s) in ASM contraction/relaxation. For instance, traditional

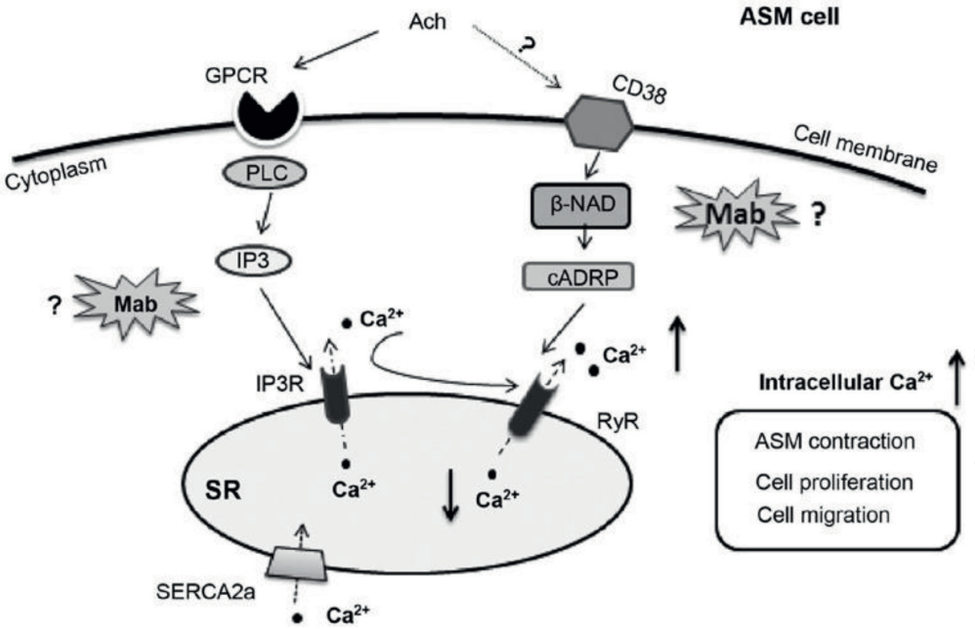

Figure 2.
Signaling pathways of Ca^{2+} concentration in ASM involving IP3R and RyR and the potential targets of mabuterol hydrochloride (Mab) that intervene in the increased level of intracellular Ca^{2+} induced with Ach. Binding with a G-protein-coupled receptor, Ach activates PLC to generate IP3, which encourages the clusters of IP3R on SR to release Ca^{2+}. RyR may also be activated or potentiated by cADP ribose (cADPR). It may be sequestered by the superficial sarcoplasmic reticulum (SR) through sarcoendoplasmic Ca^{2+} ATPase 2a (SERCA2a), although much of the calcium is released from stores and enters the cytoplasm. The increased level of intracellular Ca^{2+} leads to the contraction, proliferation, and migration of the ASM. It was originally published on "Matrix metalloproteinase expression and activity in human airway smooth muscle cells" of the British Journal of Pharmacology by Shona R. Elshaw et al. It was originally published on "Suppression of the increasing level of acetylcholine-stimulated intracellular Ca2+ in guinea pig airway smooth muscle cells by mabuterol" of Biomedical Reports by Xirui Song et al.

bronchoconstrictor agonists such as acetylcholine (ACh), histamine, and endothelin act through the G_q-coupled pathway, activating the PLC-IP3 pathway and thereby increasing Ca^{2+}. However, bronchiectasis caused by the G_s-coupled pathway (increasing cAMP) is the major mechanism of action of the β2-adrenergic receptor [30]. Moreover, GPCRs alone or in combination with other pathways, such as receptor tyrosine kinases acting through cell proliferation/growth, secretion of growth factors, and inflammatory mediators, promote the "synthesis function" of ASM, and its remodeling of airways is gaining increasing attention [31].

The current common GPCRs include gamma-aminobutyric acid (GABA), calcium-sensing receptor (CaSR), thromboxane (TXA2), bitter taste receptor (BTR), and prostaglandin E2 (PGE2). The present research status is summarized as follows.

GABA is a major inhibitory neurotransmitter in the mammalian central nervous system and activates both the ligand-gated ionotropic GABAA receptor and the G-protein-coupled metabotropic GABAB receptor. Functional GABAB receptors are present in ASM [32, 33] and airway epithelium [34]. GABAB produces airway contraction through G_i, and the GABAA receptor on ASM appears to be a potent bronchodilator [35]. Since the human ASM GABAA receptor only expresses the α4 and α5 subunits, recent studies have shown that selective targeting of the ASM GABAA receptor can improve the efficacy of anti-asthmatic drugs and minimize side effects [36]. The reported data suggest that the heterogeneity of selective targeting of ASM GABAA receptor features is a novel approach to bronchiectasis.

CaSR, a GPCR, is often expressed in non-Ca^{2+}-regulated tissues such as blood vessels and breasts and can regulate the extracellular Ca^{2+} concentration ($[Ca^{2+}]_e$), gene expression, ion channels, and ECM through the parathyroid glands, kidneys, and bones. Abnormal expression of CaSR is usually associated with inflammation, vascular

calcification, and tumors. Although CaSR is important in the development of the lungs, studies on the expression or function of CaSR in the airways are still rare. CaSR has been reported to be expressed in the developing airway epithelium [37] and regulates the morphology of the lung bronchus through $[Ca^{2+}]_e$ levels, thereby affecting tracheal remodeling [38]. In adults, CaSR is present in the human respiratory tract, especially in ASM, and CaSR expression is increased in ASM of asthmatic subjects [39], which may become a new target for future asthma treatment. Depending on the cell type, the expression and function of CaSR are regulated by signaling pathways such as ROCK, extracellular signal-regulated kinase (ERKs), and protein kinase C (PKC) [40]. Therefore, this receptor can be considered a multimode sensor and effector for the integration of composite signals and has an important impact on airway structure and function.

TXA2 is a potent endogenous bronchoconstrictor that is observed to have increased levels in asthmatic airways [41]. TXA2 induces and enhances the contraction of allergic bronchi primarily through interaction with the thromboxane prostaglandin (TP) receptor coupled to G_q and the PLC/IP3/Ca^{2+} pathway. Studies have shown that the TXA2 effector mechanism is complex and involves indirect effects of neuronal stimulation leading to ACh release and mechanical stimulation [42].

The BTR is a recently discovered bronchodilator. It was originally thought to act through the taste 2 receptors (TAS2R) family of GPCRs to increase $[Ca^{2+}]_i$ and induce bronchiectasis [43]. TAS2Rs exhibit low specificity and affinity for a wide range of bitter compounds, and the corresponding result is a diversity of signal combinations. Factors affecting TAS2Rs include agonist concentration and receptor desensitization [44]. BTR can induce membrane hyperpolarization [45] via the blocker-sensitive Ca^{2+}-activated K-channels [43, 46] and nonselective cation channels and interact with specific bronchoconstrictors [46]. Moreover, studies have suggested that BTRs can activate different Ca^{2+} signaling pathways under specific conditions. For example, TAS2R stimulation activates Gβγ under baseline conditions to increase $[Ca^{2+}]_i$ [47]. Other studies have also shown that the bronchodilating effect of BTR may also depend on interactions with β2-adrenergic receptor expression and signaling [48]. When TAS2R is activated, relaxation can be induced even under adrenergic receptor desensitization [48], which may be an alternative treatment method for asthma patients with bronchiectasis who are desensitized to β-agonists. Through extensive research, BTR has also been shown to affect genetic variations that result in sinusitis and asthma [49]; the mechanism by which BTR relaxes the airway has not yet been elucidated.

PGE2 and its epoprostenol (EP) receptor subtype are produced by airway epithelium and ASM and have complex effects on bronchoconstriction and expansion. Previous studies have shown that endogenous PGE2 has a bronchial protective effect in asthma. The PGE2 signal acts through four different GPCRs (EP1–EP4). Since different pathways have different G-protein coupling and downstream signals, and some downstream pathways can counteract each other [50], the mechanism of action is complicated. Studies have shown that EP1 increases Ca^{2+} and EP3 reduces cAMP synthesis, leading to ASM contraction, while EP2 and EP4 induce bronchodilation by increasing cAMP. In addition, EP3 can also cause an opposite reaction by promoting ASM migration [51].

In addition to the above GPCR-related mechanisms, many studies have been performed on Wnt signaling in the airways in recent years. Wnt proteins act through coreceptors such as lipoprotein receptor-associated protein (LRP)-5/LRP-6, receptor-like tyrosine kinase (Ryk), and receptor tyrosine kinase-like orphan receptor 2 (Ror2) to promote binding to the extracellular domain of the frizzled (Frz) family of GPCRs. The Wnt signaling pathways include the classical β-catenin-dependent and β-catenin-independent pathways and the noncanonical Wnt/Ca^{2+} pathway. In ASM, Wnt signaling is thought to be closely related to airway remodeling [52].

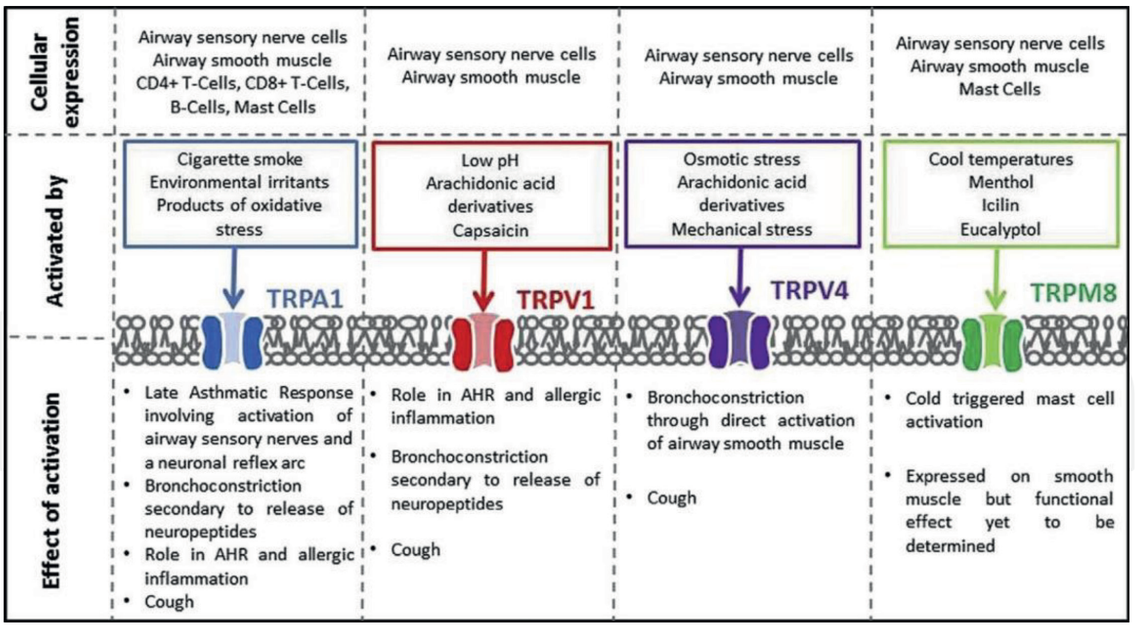

Figure 3.
The role of TRP channels in ASM. It was originally published on "Novel drug targets for asthma and COPD: Lessons learned from in vitro and in vivo models" of Pulmonary Pharmacology & Therapeutics by Katie E. Baker et al.

In fibroblasts, Wnt5B can increase the secretion of IL-6 and chemokine ligand 8 (CXCL-8) and indirectly affect airway remodeling (69). In epithelial cells, Wnt signaling in inflammation produces ECM and indirectly induces remodeling [53].

5.2 Non-GPCR mechanisms and asthma

Regarding airway contraction controlled by non-GPCR mechanisms, the mechanism of Ca^{2+} signaling regulation has been intensely investigated. For example, calcineurin can regulate local Ca^{2+} signaling and contractility in ASM. Meanwhile, the Ca^{2+} influx channel TRPC3 can activate the calcineurin/nuclear factor of activated T cells (NFAT) pathway to regulate airway contraction [54].

In addition, ASM can also express some specific receptors such as the transient receptor potential ankyrin 1 (TRPA1) or polysaccharides for non-GPCR-mediated airway regulation. In particular, TRPA1 and capsaicin receptor 1 (TRPV1) channels can be activated by PKC resulting in neuromodulation of airway contraction [55]. Studies have shown that ASM expresses TRPA1 [56] and TRPV1 [57] as well as TRPV4 [58, 59]. TRPA1 has been shown to promote IL-8 secretion in ASM, enhance airway inflammation and AHR [60], and mobilize $[Ca^{2+}]_i$ [56] while inhibiting the proliferation of ASM [61]. In contrast, TRPV1 appears to promote proliferation [62]. TRPV4 is associated with an increase in $[Ca^{2+}]_i$ [59] and ASM contraction and proliferation (**Figure 3**) [58, 63]. In addition to TRPA, ASM can also express epidermal growth factor receptor (EGFR) and hyaluronic acid to participate in airway inflammation [64]. The expression of hyaluronic acid is increased during inflammation [65] and is involved in the homeostasis of aqueous fluids, cell matrix signaling, cell proliferation and migration, and regulation of inflammation [66].

6. ASM cell structure and asthma

Some intracellular and extracellular structures of ASM are closely related to the pathological changes of asthma. Caveolae and their regulatory caveolin and cavin

proteins are a focus of research. Caveolae have been shown to contain excitatory contractile receptors and activate Ca^{2+} influx channels (including transient receptor potential channel (TRPC) subtypes and calcium release-activated calcium channel protein 1 (Orai1)) [67, 68]. The decreased expression of its important component, caveolin-1, induces an increase in ASM $[Ca^{2+}]_i$ and a contractile response and promotes ASM proliferation [69]. The relevant mechanisms include a reduction in $[Ca^{2+}]_i$ influx, increase in sarcoplasmic reticulum Ca^{2+} release, and reduction in Ca^{2+} sensitivity through the RhoA pathway. Conversely, pro-inflammatory factors such as TNF-α can enhance the expression and function of caveolin-1 [70].

7. Proliferation and apoptosis of ASM cells and airway remodeling during asthma

Airway remodeling is an important pathological change in asthma. The increased mass of ASM may be a key feature of airway remodeling, and its hyperplasia and hypertrophy are unevenly distributed in bronchi of different sizes. This process can enhance airway contraction and airway stenosis, further leading to decreased lung function or severe asthma [71]. The underlying causes of ASM hypertrophy have been extensively explored. For example, excessive mechanical stretching can lead to the release of EGF, which participates in remodeling [72]. In addition, Wnt, glycogen synthase kinase 3 beta (GSK3β) [73], or rapamycin target protein (mTOR) [74] may also be involved in the regulation of reconfiguration caused by mechanical forces. Studies have also shown that hypertrophy is associated with increased MLC kinase in ASM [75]. In addition, many signaling pathways have been found to be related to ASM proliferation, including p38, p42/p44 MAP kinase and PI3/Akt.

During the pathogenesis of asthma, some pro-inflammatory mediators are involved in the regulation of ASM proliferation, such as TNF-α, IL-4, IL-5, IL-13, TGF-β, thymic stromal lymphopoietin (TSLP), and Th17 family members. In addition, some conventional stimuli such as agonists of airway bronchial contraction [76] and other locally produced factors [9, 77] may also trigger an increase in proliferation under certain circumstances. Recent studies have shown that a nonreceptor tyrosine kinase, Abl, promotes ASM mitosis and enhances ASM proliferation [78]. It has also been suggested that sex hormones can affect the structure and function of the airway because, in some cases, estrogen can reduce mitosis and exert antiproliferative effects in the airway [79]. In addition, within ASM cells, microRNAs are thought to play an important role in the regulation of ASM cell proliferation and migration [80].

Overall, current information indicates that the interaction of multiple signaling mechanisms leads to airway remodeling represented by ASM cell proliferation. Although many inflammatory pathways can cause cell proliferation, limited data exist regarding how to inhibit or block proliferation. Studies have shown that regulating the ECM (such as the collagen density) or inducing increased expression of caveolin-1 can limit ASM cell proliferation [81] and some therapeutic drugs such as corticosteroids and β2 receptor agonists can also reduce proliferation [82]. In addition, peroxisome proliferator-activated receptor (PPAR)-γ ligands can attenuate ASM proliferation [83].

In the context of airway remodeling, an increase in ASM mass indicates an increase in cell proliferation and reflects a decrease in apoptosis. However, based on the current data, the mechanisms of the two are quite different. Th17-associated cytokines, IL-18, eotaxin, monocyte inflammatory protein-1a [84], and TRPV1 agonists [85] can alleviate ASM apoptosis. Other studies have found that peroxisome

proliferator-activated receptor gamma (PPAR-γ) [86], collagen [87], and vitamin D can regulate ASM proliferation without affecting apoptosis.

8. ASM autophagy and asthma

At present, autophagy is considered an adaptive response of cells to survival that can promote cell death in the context of disease. This process is essential in maintaining homeostasis, managing external stress, and regulating cellular capacity. Autophagy plays a major role in the immune response to various pathogens, particularly viruses. In the case of asthma, autophagy in the airway epithelium or ASM may occur in the context of infection [88]. The current research on the role of autophagy in asthma and the types of cells involved is relatively limited. For example, pharmacological inhibition of gamma-glutamyltransferase 1 (GGT1) has been found to induce p53-dependent autophagy in human ASM cells [85]. In addition, excessive reactive oxygen species (ROS) that may be present during airway inflammation can induce autophagy, thus contributing to the pathophysiology of asthma [89].

9. ASM, miRNA, and asthma

Many studies have examined miRNA-mediated regulation of ASM. During the asthma process, many specific miRNAs are thought to play multiple roles in ASM [90]. For example, pro-inflammatory cytokines such as IL-1β, TNF-α, and IFNγ can downregulate 11 miRNAs, particularly miR-25, miR-140, miR-188, and miR-25. In contrast to the above results, another study [80] showed that expression levels of miR-146a and miR-146b were elevated in ASM in an IL-1β, TNF-α, and IFNγ-treated asthma group. Other studies have shown that only miR-146a is an endogenous negative regulator of human ASM cells [91].

In terms of airway remodeling, miR-140-3p regulates the important enzyme CD38 [92], which may have multiple downstream effects, such as affecting $[Ca^{2+}]_i$ and proliferation [93–95]. Under the induction of mechanical elongation, miR-26a causes ASM hypertrophy by attenuating GSK3β [96]. However, ASM proliferation appears to be driven by multiple miRNAs, including miR-10a [97], miR-23b [98], miR-138 [99], miR-145 [100], and miR-203 [101]. In general, we have found many miRNA pathways in ASM, but many problems remain unresolved, and miRNAs will be a focus for targeted asthma therapy in the future.

10. Mitochondria and ASM

Mitochondria in the airway not only produce ATP but are also involved in functions such as Ca^{2+} buffering [102–104], endoplasmic reticulum pathways, Ca^{2+} influx (such as store-operated Ca^{2+} entry (SOCE)), and cell proliferation and survival. These functions mostly involve fission and fusion of mitochondrial structures, mitochondrial biogenesis, mitochondrial autophagy, and ROS destruction [102, 105]. For example, consumption of mitochondrial DNA attenuates the concentration of $[Ca^{2+}]_i$ in ASM [106]. In terms of regulation, TGF-β enhances ASM mitochondrial ROS and promotes cytokine secretion [107]. Conversely, airway inflammation impairs mitochondrial Ca^{2+} buffering, resulting in an increase in $[Ca^{2+}]_i$. This damage leads to not only an increase in ROS but also an increase in endoplasmic reticulum stress and the unfolded protein response (UPR) [108]. These pathways are relevant because they can further influence protein expression and function as well as airway remodeling [109, 110].

11. Conclusions

With the rapid progress in molecular biology, cell biology, and various experimental techniques, research on ASM has developed rapidly, and an increasing number of functions have been discovered. When investigating ASM, we should consider the presence of surrounding cells and the ECM. Investigation of the role of ASM is no longer limited to its contractility, remodeling, and secretion. ASM is similar to a "processing station." It not only is affected by various signals in the body to produce biological effects and secrete various signals to act on downstream target cells but also feeds back to the upstream pathways or receives feedback from downstream pathways to form a complex network. Therefore, a univariant study of the mechanism of ASM action is unrealistic. More comprehensive studies integrating bioimaging, informatics, and other technologies are needed to conduct more accurate target interventions, obtain more precise pathway information, and provide new therapeutic targets for asthma.

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Conflict of interest

The authors declare that they have no conflict of interest.

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