Airway smooth muscle in the pathophysiology and treatment of asthma

Diana C. Doeing and Julian Solway

Department of Medicine, University of Chicago, Chicago, Illinois

Submitted 2 August 2012; accepted in final form 9 January 2013

Doeing DC, Solway J. Airway smooth muscle in the pathophysiology and treatment of asthma. J Appl Physiol 114: 834–843, 2013. First published January 10, 2013; doi:10.1152/japplphysiol.00950.2012.—Airway smooth muscle (ASM) plays an integral part in the pathophysiology of asthma. It is responsible for acute bronchoconstriction, which is potentiated by constrictor hyperresponsiveness, impaired relaxation and length adaptation. ASM also contributes to airway remodeling and inflammation in asthma. In light of this, ASM is an important target in the treatment of asthma.

airflow obstruction; inflammation; airway remodeling

Asthma is a chronic disease of the airways affecting over 24 million people in the United States (94). It is characterized by intermittent airflow obstruction and airway inflammation, producing symptoms of chest tightness, wheezing, and cough. Structural and inflammatory changes throughout the airway wall lead to bronchial thickening and edema as well as increased mucus production and bronchoconstriction, all of which contribute to the episodic airflow obstruction typically found in asthma (Fig. 1). In recent years, there has been much attention on inflammation in asthma, for example, whether the type of inflammatory cell predominately found in the airway denotes a specific phenotype in asthma or whether targeting antibodies, inflammatory cytokines, and inflammatory cells is helpful for the treatment of asthma (56, 96, 115). Although airway smooth muscle (ASM) has been implicated in constrictor hyperresponsiveness in asthma for decades, other important roles of ASM have recently been identified. Through impaired airway relaxation and mediation of structural changes and inflammatory signaling, the ASM cell plays multiple diverse roles in the pathophysiology of asthma. This review is meant to update practicing physicians with current knowledge about these less discussed direct effects of ASM on airway narrowing and indirect influences on airway remodeling and inflammation in asthma (Fig. 2).

FUNCTIONAL CHANGES IN ASTHMATIC ASM

ASM is most well known for its role in acute bronchoconstriction. Smooth muscle surrounds the airway in a circumferential pattern, reducing the airway luminal diameter as it contracts. It is this function of ASM that causes the acute airflow obstruction, shortness of breath, and wheezing most commonly associated with the clinical syndrome of asthma. In asthma, ASM is primed to contract, often excessively, in response to various stimuli, but in addition, it resists relaxation. These two phenomena are now discussed in turn.

Airway Hyperresponsiveness

The excessive contractile response of ASM in asthma results in inordinate bronchoconstriction and airflow obstruction in response to relatively little provocation; this phenomenon is denoted as airway hyperresponsiveness. A variety of chemical and physical stimuli can trigger bronchoconstriction (Table 1). Contractile agonists, like methacholine, can directly activate receptors on ASM cells that initiate myocyte contraction and consequent bronchoconstriction, and this is the basis of the methacholine challenge test sometimes used to diagnose asthma. Substantial respiratory heat and water loss, as occur during exercise in temperate or cold climates, can also provoke bronchoconstriction, likely mediated by contractile agonists released from mast cells or nerves exposed to a hyperosmolar milieu (4, 44). Why individuals with asthma are hyperresponsive compared with healthy individuals is complex. Contributing mechanisms include both an increased availability in asthmatic airways of contractile mediators such as histamine from mast cells (12) and increased ASM mass. Mathematical models initially proposed that excessive ASM generates abnormally increased force (77), but increased dynamic muscle stiffness (due to impaired breathing-induced muscle softening) may actually be the more important mechanism (102). Other explanations for airway hyperresponsiveness in asthma include increased vagal tone (13, 26), cytokine-potentiated increases in intracellular free calcium that enhance ASM cell contractility (51) and activation of the procontractile Rho kinase pathway (19, 124). Increased RhoA protein levels have also been identified in animal models of allergic asthma (20, 21, 123), and inhibition of the RhoA-Rho kinase pathway can prevent or reverse airway hyperresponsiveness (Table 2) (121, 122).

Impaired Relaxation

Aberrant shortening of ASM in asthma can also partly be explained by inadequate relaxation. There is no direct sympathetic innervation in human ASM (17). Additionally, β2-adrenergic receptors may become downregulated when bom-
barded frequently with β₂-agonist medications, in a fashion that depends in part on genetic polymorphisms (69). This phenomenon has been observed in a number of cell types, including ASM (50, 93), and may further potentiate the imbalance of autonomic neurotransmitter influences on the airway in asthma. In fact, patients with asthma can develop tolerance to β-agonist therapy (57). Inflammatory cytokines further potentiate this effect. Interleukin-1β (IL-1β), a cytokine produced by a variety of lung cells, reduces β-adrenergic responsiveness in cultured human ASM cells (79). Another important inflammatory cytokine, IL-13, has a similar effect on adrenergic receptors, albeit through a different mechanism (78). Prevention or reduction of β₂-adrenergic receptor desensitization with agents that preserve receptor expression and function, such as ascorbate (31) or alendronate (67), might conceivably be helpful in the treatment of asthma.

Breathing-Induced Reversal of Bronchoconstriction and Length Adaptation

Other properties of ASM function may also contribute to airway narrowing in asthma. It has long been observed that in normal people, deep breathing can reverse bronchoconstriction (3, 98). Within the lung, the airways are connected to the lung parenchyma, which is firmly attached to their adventitial surfaces. With each inspiration, the lung parenchyma surrounding each airway expands and pulls radially outward on the airway, stretching it partially during the breath. Isolated ASM that is forcibly lengthened while still contracting reduces its force of contraction (49), likely due to perturbation of actin-myosin interactions (41). Furthermore, fluctuations in the force applied to isolated contracting smooth muscle, simulating the tidal stretches that occur with breathing, cause it to relengthen, even when the mean force is held constant (33, 76, 80). As a result of these behaviors of ASM, stretching of bronchoconstricted airways by breathing in part reverses the luminal narrowing that had been present (102). However, in individuals with asthma, the ability of deep breaths to reverse bronchoconstriction seems blunted; this might stem from increased muscle mass and increased muscle stiffness as noted above or might reflect other mechanisms that are not yet fully understood. Nonetheless, the role of airway distension during a deep breath seems certain, for pronounced bronchoconstrictor responses to methacholine, similar to those of patients with asthma, can be elicited in normal subjects when deep breathing is restricted (127). Recently, we and others have found pharmacological interventions that potentiate ASM relengthening in response to force fluctuations in vitro (32, 33, 75, 76). Pharmacologically potentiating the ability of deep inspirations to reverse bronchoconstriction might represent a novel therapeutic approach to relieve or prevent airflow obstruction in the future. Indeed, corticosteroids, a mainstay of asthma treatment, might exert some of their therapeutic effect through this mechanism (72).

Another inherent property of smooth muscle may in part explain why asthmatic airways are not as susceptible to deep breathing-induced stretch during an asthma attack. When a smooth muscle cell shortens, it adapts by reorganizing its contractile filaments in a way that will allow it to generate the same force at its new length (125). This can create a vicious...
cycle in asthma, because once ASM has shortened, it quickly becomes primed to shorten further (89). Now more severely shortened, the muscle may be stiffer and less influenced by the antibronchoconstrictor effects of deep breathing (102). In sheep trachealis, passive stiffness of ASM is also increased at shorter lengths (10). Indeed, chronic application of continuous positive airway pressure (CPAP; which presumably chronically holds airway muscle at greater length) reduced ASM contractility in ferrets (149), reduced airway hyperresponsiveness in rabbits with experimental asthma induced by ovalbumin sensitization and challenge (148), and most importantly reduced airway constrictor responsiveness in volunteers with stable asthma and normal spirometry (15). But if CPAP reduces airway hyperresponsiveness, why doesn’t the pulmonary hyperinflation that accompanies acute asthma attacks simply reverse the bronchoconstriction? We speculate that the pulmonary hyperinflation that attends acute asthma attacks may be less effective in reversing bronchoconstriction because the patients’ tidal volumes are likely reduced by the dynamic hyperinflation. If dynamic stretch is more important than mean stretch in determining overall airway smooth muscle shortening [as appears to be the case (40, 41)], then the adverse effect of pulmonary hyperinflation (reducing dynamic stretch) during acute bronchoconstriction might outweigh its potential beneficial effect (enhancing mean stretch). No studies have specifically addressed this balance in acute asthma to date, and the potential for CPAP treatment to reduce asthma symptoms or medication use is currently under study.

### Table 1. List of stimuli provoking bronchoconstriction in asthma

<table>
<thead>
<tr>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct stimuli</td>
<td></td>
</tr>
<tr>
<td>Cholinergic agonists (e.g., methacholine)</td>
<td>11</td>
</tr>
<tr>
<td>Histamine</td>
<td>12</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td></td>
</tr>
<tr>
<td>Leukotrienes</td>
<td></td>
</tr>
<tr>
<td>Indirect chemical stimuli</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>138</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Tachykinins, bradykinin</td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td></td>
</tr>
<tr>
<td>Indirect physical stimuli</td>
<td></td>
</tr>
<tr>
<td>Exercise with heat and/or water loss</td>
<td>4, 44</td>
</tr>
<tr>
<td>Hypertonicity (hypertonic saline or mannitol)</td>
<td>102</td>
</tr>
<tr>
<td>Increased ASM mass</td>
<td></td>
</tr>
<tr>
<td>Increased vagal tone</td>
<td>13</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; ASM, airway smooth muscle.

### Table 2. Potential new therapeutic targets of ASM function in asthma

<table>
<thead>
<tr>
<th>ASM Function</th>
<th>Potential Therapy</th>
<th>Status of Therapeutic Development</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractility</td>
<td>Inhibition of Rho kinase pathway</td>
<td>Animal models</td>
<td>124</td>
</tr>
<tr>
<td>β2-adrenergic receptor modulation</td>
<td>Adrenergic enhancement</td>
<td>Animal models</td>
<td>31</td>
</tr>
<tr>
<td>Relaxation</td>
<td>Potentiation of breathing-induced relengthening</td>
<td>In vitro animal studies</td>
<td>32, 33, 75, 76</td>
</tr>
<tr>
<td>Stiffness</td>
<td>CPAP</td>
<td>Reduction of AHR demonstrated in asthma</td>
<td>Clinical trials re asthma control ongoing</td>
</tr>
<tr>
<td></td>
<td>Reduce ASM mass</td>
<td>Bronchial thermoplasty FDA-approved 2010</td>
<td>140</td>
</tr>
</tbody>
</table>

AHR, airway hyperresponsiveness; CPAP, continuous positive airway pressure; FDA, Food and Drug Administration.
obtained from endobronchial biopsies of individuals with asthma demonstrate more rapid proliferation than do those from normal individuals (70). This might be explained by the absence of an antiproliferative transcription factor, C/EBP\(_\alpha\) (116). As C/EBP\(_\alpha\) also mediates the antiproliferative effect of corticosteroids in normal ASM, its reduction in asthmatic ASM may represent the underlying mechanism (116).

Another possible mechanism of increased ASM mass is the migration and differentiation of fibrocytes from bone marrow (120). Fibrocytes exposed in culture to TGF-\(\beta\) acquire characteristics of smooth muscle cells (120), and the number of circulating fibrocytes in the peripheral blood of individuals with asthma with chronic airflow obstruction correlates with their rate of decline in lung function over time (142). Therefore, interest has developed in TGF-\(\beta\) as a therapeutic target in asthma (Table 3). Animal models of allergen-induced asthma have shown significant reductions in ASM proliferation following TGF-\(\beta\) neutralization (88) or inhibition (83).

**ASM Role in Airflow Obstruction**

It remains unknown whether the mechanism driving ASM hyperaccumulation has a deleterious impact on airway contractile function directly. However, it is clear that excessive ASM mass (145) and airway wall thickening (which can be gauged by CT scan) (84, 100) are associated with airway hyperresponsiveness. Furthermore, asthma patients with fixed and severe airflow obstruction (postbronchodilator FEV\(_1\) < 50%) have significantly thicker airway walls than those with reversible airflow limitation (14). Those with fixed airflow obstruction also have longer disease duration (14), suggesting that airway remodeling contributes to the decline in lung function seen in individuals with asthma. These studies indicate that ASM remodeling contributes to both transient and chronic airflow obstruction in asthma.

In light of its importance in airflow obstruction in asthma, ASM has been an important target for asthma therapies, including bronchodilators (5) and bronchial thermoplasty (140), a novel therapy for severe asthma. Bronchial thermoplasty is a bronchoscopic procedure in which the proximal airways are treated with radiofrequency current that heats the airway wall to 65°C with consequent reduction in ASM mass and some alleviation of bronchial constriction. In early trials with dogs, bronchial thermoplasty reduced airway responsiveness and ASM mass for up to 3 years; the reductions in airway responsiveness and in ASM mass were correlated, suggesting that the structural change in ASM mass could explain the functional change in constrictor responsiveness (29). A reduction in ASM was also seen in eight patients with lung cancer undergoing thermoplasty prior to lobectomy for their malignancies (90). The only randomized, double-blind, sham-controlled study in humans went on to show reduced exacerbations and health care visits and improved quality of life of individuals with asthma that received active treatment (18). The mechanism by which thermoplasty reduces ASM in the airways is not understood, although bovine ASM treated with thermal energy shows immediate loss of contractility and disruption of actin-myosin connections (36). Further study is needed to elucidate the mechanism driving the apparent beneficial effects of bronchial thermoplasty. It might also be possible to develop alternative less invasive means to ablate ASM in asthma (129).

**ASM AS A CONTRIBUTOR TO AIRWAY INFLAMMATION IN ASTHMA**

There is evidence that ASM plays a pivotal role in the airway inflammation characteristic of asthma as well. Not just a bystander in this process, ASM releases and expresses several molecular signals that contribute to bronchial inflam-

![Fig. 3. Photomicrograph of a normal airway (top) compared with the airway of an asthmatic (bottom) showing marked thickening of sub-basement membrane (SBM), submucosal eosinophils (E), smooth muscle (SM) hyperplasia, and mucus filling the airway lumen (AL). Note that contraction of the asthmatic airway may contribute in part to the increase in apparent thickness of airway wall compartments. [Images courtesy of Aliya N. Husain, MD.]

---

**Table 3. Potential new therapeutic targets of ASM structural changes in asthma**

<table>
<thead>
<tr>
<th>ASM Structural Change</th>
<th>Potential Therapy</th>
<th>Status of Therapeutic Development</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased ASM mass</td>
<td>Bronchial thermoplasty</td>
<td>FDA-approved 2010</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>Anti-TGF(\beta) therapy</td>
<td>Animal models</td>
<td>83, 88</td>
</tr>
</tbody>
</table>

ASM, airway smooth muscle; FDA, Food and Drug Administration.
mation (28) and have become targets of novel therapeutic strategies (Table 4).

**Cytokines**

**Interleukin-5.** Interleukin (IL-5) is a T-helper type 2 (Th2) cytokine. It is crucial in the survival, migration, and activation of mast cells and eosinophils, key inflammatory cells in allergic asthma (91). Although T lymphocytes are thought to be the main producers of IL-5 in the lung, human ASM cells in culture release IL-5 when exposed to serum from individuals with atopic asthma (52). Increased levels of IL-5 also appear in the bronchoalveolar fluid of individuals with atopic asthma (134), and animal studies have highlighted the role of IL-5 in allergic airway inflammation and bronchoconstriction (39, 55, 82). In addition, IL-5 deficiency inhibited airway remodeling in an ovalbumin sensitization mouse model of asthma (22). These findings led to initial interest in IL-5 modulation therapy for asthma, although the clinical effectiveness of this approach remains controversial (91) as studies have shown promise in reducing exacerbations in patients with severe eosinophilic asthma but not in consistently improving symptoms or lung function (54, 99, 106).

**IL-13.** Another important cytokine in asthma is IL-13. It, like IL-5, also induces eosinophilia in addition to goblet cell hyperplasia and immunoglobulin class switching to IgE (101). In mice, genetic deletion (141) or neutralization (48, 144) of IL-13 ablates allergen-induced experimental asthma. IL-13 receptors have been identified on ASM, and IL-13 induces proliferation and hypercontractility in human ASM (95, 114). IL-13 ablates allergen-induced experimental asthma. IL-13 induces differentiation of the myofibroblast, an intermediate cell phenotype between fibroblasts and ASM cells thought responsible for fibrosis in the lung (117). Blocking TGF-β can reduce airway remodeling, including ASM proliferation, in mice (88). However, clinical trials of TGF-β blockade in asthma have not yet been reported.

**Other Immunomodulatory Factors**

**Eotaxins and eosinophils.** ASM can produce chemokines, such as eotaxin, that recruit eosinophils from the systemic circulation to the lungs (43). Eotaxin is upregulated in asthma, and eosinophils collected from individuals with allergies and asthma have an enhanced response to eotaxin compared with those from normal subjects (119). Various inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF-α) induce eotaxin production and release by cultured human ASM (23, 92). ASM expresses cell adhesion molecule receptors that bind eosinophils and other inflammatory cells (62). A sizable number of individuals with asthma with an eosinophilic phenotype may especially respond to specific treatments such as anti-IgE, anti-IL-5 monoclonal antibodies (e.g., mepolizumab) or anti-eotaxin monoclonal antibodies (e.g., pranlumab).

### Table 4. Potential new therapeutic targets of inflammation in asthma

<table>
<thead>
<tr>
<th>Inflammatory target</th>
<th>Potential Therapy</th>
<th>Status of Therapeutic Development</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td>Anti-IL-5 monoclonal antibodies (e.g., mepolizumab)</td>
<td>Clinical trials</td>
<td>54, 99, 106</td>
</tr>
<tr>
<td>IL-13</td>
<td>Anti-IL-13 monoclonal antibodies</td>
<td>Clinical trials</td>
<td>108</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Anti-TGFβ antibody</td>
<td>Animal model</td>
<td>88</td>
</tr>
<tr>
<td>Eosinophils mast cells</td>
<td>Anti-IgE monoclonal antibody</td>
<td>Omalizumab FDA-approved 2003</td>
<td>130</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>Anti-IL-2 receptor monoclonal antibody (e.g., daclizumab)</td>
<td>Clinical trials</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Anti-CD4 monoclonal antibody (e.g., keliximab)</td>
<td>Clinical trials</td>
<td>72, 73</td>
</tr>
</tbody>
</table>
anti-IL-5, and anti-IL-13 therapies (126, 146). In our opinion, the interactions between eosinophils and ASM merit further investigation.

Mast cells. Mast cells are also important in the pathophysiology of asthma. Activated mast cells release histamine and other inflammatory mediators that cause bronchoconstriction and the recruitment of immune cells to the airway (109). Mast cells accumulate in the ASM layer of the airways in individuals with asthma (2, 8), including those with both eosinophilic and noneosinophilic bronchial inflammation (9). In culture, human ASM cells attract mast cells by producing cytokines such as TGF-β1 (7). An adhesion molecule expressed by the mast cells then allows them to adhere to ASM cells directly (150). This adhesion interaction is further enhanced in ASM cells from individuals with asthma (45). Airway myocyte cells can promote survival of mast cells, thereby augmenting the opportunity for persistent airway mast cell activation (60).

T lymphocytes. CD4+ T lymphocytes have also been identified within ASM bundles along asthmatic airways. In fact, T lymphocyte burden within the ASM layer of individuals with asthma was correlated with severity of disease (110). Parallel to its interactions with other inflammatory cell types described above, ASM secretes CCL5 or RANTES, a chemokine that signals T lymphocyte migration to the lung (68). Likewise, adhesion between these two cell types has also been described, although this has not yet been confirmed in asthma specifically (81). And although ASM is not usually thought of as an antigen-presenting cell, there is evidence that ASM cells not only express major histocompatibility complex class II molecules but also are capable of presenting antigens. For example, ASM can present superantigens from staphylococcus to T helper lymphocytes, resulting in their nonspecific activation (139). Whether this is a significant mechanism of antigen presentation in vivo or in individuals with asthma, however, has yet to be determined.

GENETIC CONTRIBUTORS TO ASM CHANGES:
GENE POLYMORPHISMS

Although many genes can affect airway hyperresponsiveness and ASM function, variations in only a few genes are thought to influence asthma through their effects on ASM (Table 5). For example, polymorphisms in the β2-adrenergic receptor gene have been identified (113, 128, 143), and patients with asthma with the Arg16/Glu16 genotype exhibit reduced bronchodilator responses to inhaled β-agonists (143). On the other hand, the Glu27 form of the receptor seems to provide protection against downregulation of the β2-adrenergic receptor (47). Another gene product, ADAM33, is expressed on the surface of human airway cells including ASM. Polymorphisms in the ADAM33 gene have been linked to asthma and bronchial hyperresponsiveness in various populations (45, 77). However, because certain ADAM33 polymorphisms are associated with greater decline in lung function over time, it has been suggested that the mechanism by which ADAM33 (which can exhibit metalloproteinase activity leading to airway remodeling) contributes to asthma pathogenesis centers more on structural changes within the airway than contraction or hyperresponsiveness (55).

CONCLUSION

ASM is a crucial player in the pathogenesis of asthma. Its plays a hyperresponsive contractile role in the acute airflow limitation that is characteristic of asthma and exhibits impaired relaxation. It also modulates the chronic airway remodeling and inflammation that are essential features of the asthma syndrome. For these reasons, ASM should be considered as an important therapeutic target. Questions ripe for study include: How can the persistent shortening of ASM in asthma be prevented? How can ASM mass be controlled or reduced beyond bronchial thermoplasty? How important quantitatively is the ASM contribution to asthmatic airway inflammation, and can this contribution be targeted specifically by reducing ASM mass or by novel pharmacological interventions?

GRANTS

This work was supported by National Institutes of Health Grants T32-HL07605, R01-HL097805, U10-HL098096, P50-HL107171, and U19-AI095230.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: D.C.D. and J.S. prepared figures; D.C.D. drafted manuscript; D.C.D. and J.S. edited and revised manuscript; D.C.D. and J.S. approved final version of manuscript.

REFERENCES


