

Airway Smooth Muscle as a Target for Asthma Therapy

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The precise role of airway smooth muscle in the pathogenesis of asthma remains uncertain. The contraction of airway smooth muscle certainly causes acute narrowing of the airway and airflow obstruction in asthma, and smooth-muscle mass is increased in asthmatic airways. However, whether airway smooth muscle generates sufficient force in vivo to account for the excessive airway obstruction that characterizes asthma is unknown. Abnormalities in the dynamics of contraction,¹ in the capacity of smooth muscle to maintain shortening in the face of load fluctuations imposed by tidal breathing,² or in the capacity to relax³ represent other important mechanisms by which airway smooth muscle might contribute to airway narrowing in asthma. Beyond these mechanical effects, airway smooth muscle probably contributes to inflammation of the airway by secreting cytokines,⁴ modifying the tissue matrix, binding migratory inflammatory cells, or all three (Fig. 1). Whatever its role in asthma may be, it seems clear that airway smooth muscle could not contribute to asthma pathogenesis if it were absent.

In this issue of the *Journal*, Cox and colleagues⁵ report a clinical benefit of a novel approach to asthma therapy — bronchial thermoplasty. In this procedure, during three separate treatment visits, radiofrequency current is applied to the walls of the central airways through a bronchoscopically placed probe. Studies in animals⁶ and humans⁷ have shown that such treatment reduces the airway smooth-muscle mass but causes epithelial damage that resolves over time.⁶ In patients with moderately severe asthma, bronchial thermoplasty reduced airway responsiveness to an inhaled constrictor and modestly increased flow rates — effects that persisted for at least a year.⁸ The study by Cox and colleagues extends those findings by showing improvements in symptoms and quality of life and by reducing the use of rescue medication in subjects with moderate or severe asthma during periods when long-acting β_2 -adrenergic agonists were withdrawn. That these effects occurred without significant increases in the forced expiratory volume in 1 second or a reduction in airway hyperresponsiveness suggests either that smooth-muscle-mediated airway constriction beyond the central airways accessible on

bronchoscopy is clinically important or that mechanisms independent of airway smooth muscle, such as airway closure,^{9,10} contribute to airflow obstruction in subjects with asthma.

The mechanism underlying the effect of bronchial thermoplasty in asthma has not been fully established and might include changes other than the loss of airway muscle. For example, conceivably, bronchial thermoplasty alters properties of airway epithelium, mucus glands, nerves, or

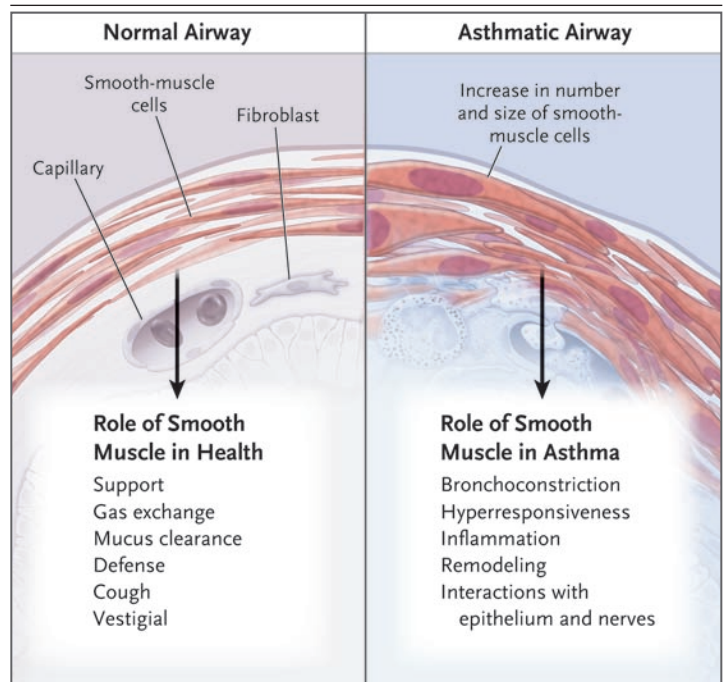


Figure 1. Features of the Normal Airway and the Asthmatic Airway.

In normal airways, smooth muscle might provide structural support, help regulate gas exchange, and contribute to mucus clearance, defense mechanisms, and cough, or it might be vestigial (resulting from lung development) and not play an important role. In asthma, airway smooth muscle mediates acute bronchoconstriction and participates in airway hyperresponsiveness. Accumulating evidence implicates smooth muscle in the pathogenesis of airway inflammation and remodeling and points to interactions with bronchial epithelium and nerves. The benefit of current asthma treatments, including bronchodilators, inhaled corticosteroids, and anti-IgE antibody, as well as bronchial thermoplasty, may be due in part to their actions on airway smooth muscle. Potential therapies (now theoretical) that target airway smooth-muscle contraction or abundance might include the induction of apoptosis of airway myocytes, alteration of transcription to shut down expression of the contractile apparatus, paralysis of airway smooth muscle, and enhancement of force-fluctuation-induced relengthening of airway smooth muscle.

blood vessels or modifies the character of airway inflammation in such a way that asthma-related symptoms are reduced as a result of either alterations in airway sensation or a genuine reduction in steady or episodic airway narrowing. What seems certain, however, is that bronchial thermoplasty reduces the smooth-muscle mass in the airway wall. This well-documented effect, together with the beneficial clinical effects suggested in the report by Cox and colleagues and in previous studies, highlights the potential usefulness of targeting airway smooth muscle in the treatment of asthma.

Indeed, a number of current treatments already exert some beneficial effects by acting on airway smooth muscle (Fig. 1). Inhaled β_2 -agonists often relax airway smooth muscle and can enhance the nuclear entry of glucocorticoids,¹¹ thereby potentiating their antiinflammatory effect. Glucocorticoids inhibit the proliferation¹² and migration of airway myocytes and suppress their expression of a number of proinflammatory cytokines. Anti-IgE antibody might also modulate the function of airway smooth muscle, since the low-affinity IgE receptor is expressed on airway smooth muscle and sensitization with IgE increases its force generation, impairs relaxation, and stimulates cytokine production.¹³ Furthermore, exposure to serum from persons with atopy increases the velocity of contraction of human bronchial rings¹⁴; this increased velocity is thought to enhance the shortening¹⁵ of airway smooth muscle and to confer resistance to the relengthening of the muscle induced by force fluctuations. Perhaps anti-IgE antibody also prevents these phenomena.

Bronchial thermoplasty represents a novel approach to targeting airway smooth muscle, but it ablates airway myocytes only in bronchi 3 mm or larger in diameter, which can be treated directly. For this reason, and because of the considerable effort involved (three separate bronchoscopic procedures, each with a small but significant risk of complications), notable adverse effects (in the short term, at least), and likely expense, bronchial thermoplasty will probably need further refinement if it is to emerge as a widely applicable, practical treatment for moderate or severe asthma. Nonetheless, the results reported by Cox and colleagues suggest that we should now contem-

plate other approaches to targeting airway smooth muscle that might prove to be less invasive, more practical, and more amenable to application throughout the airways. Among the approaches envisioned is the possibility of ridding the airways of smooth muscle by stimulating apoptosis of airway myocytes.¹⁶ Alternatively, since many of the genes encoding smooth-muscle contractile-apparatus proteins require a common, relatively muscle-specific transcription factor (serum response factor) for transcriptional activation,¹⁷ it might be possible to antagonize the activity of the serum response factor and in that way shut down expression of the contractile apparatus. Depletion of contractile proteins should prevent smooth-muscle-mediated airway constriction and thus might prevent the occurrence of acute asthma attacks.

Another approach to preventing contraction might be to attack the integrity of contractile filaments (e.g., destroying actin filaments by activating cofilin, an actin-binding protein that depolymerizes filamentous actin) or to block the linking of contractile myofilaments to focal adhesions at the cell surface, thereby preventing the transmission of the contractile force generated within each myocyte to the surrounding tissue.¹⁸ Finally, ways might be discovered to magnify the antiobstructive effect of tidal breathing, in which fluctuations in the tidal force transmitted through parenchyma-airway interactions relengthen shortened airway smooth muscle even during continued contractile stimulation.¹⁹ An airway that cannot remain constricted for long cannot cause prolonged airflow obstruction.

In medicine, pioneering approaches have often been replaced by other approaches with similar goals but better means of implementation. Vagotomy, for example, which was performed to reduce acid secretion in peptic ulcer disease, has been replaced by treatment with H_2 -receptor antagonists and proton-pump inhibitors, which also reduce acid secretion. We expect that bronchial thermoplasty may be refined to become more effective and more practically applicable, but we also hope that the lessons it has already taught will prompt the development of other novel approaches that target the contribution of airway smooth muscle to the pathogenesis of asthma.

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