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Modulation of Bronchomotor Tone Pathways in Airway Smooth Muscle Function and Bronchomotor Tone in Asthma

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Introduction

ASM is the primary cell modulating airway resistance and hyperreactivity, hallmark features of the asthma and exacerbations of the disease. The inflammatory milieu generated in allergic asthma modulates contractility of ASM however, anti-inflammatory therapies often inadequately controls asthma morbidity or mortality. A study of asthma and non-asthma subjects examining inspiratory volume noted that non-asthma subjects dilate their airways to baseline measurements following methacholine provocation, whereas those with asthma were unable to reverse methacholine-induced bronchospasm after deep inspiration¹. Additionally, the airways of the non-asthma subjects recovered faster than those of asthma subjects. The differences between asthma and non-asthma individuals may be attributable to characteristic differences in the ASM phenotypes. A study of isolated human ASM also noted increased velocity of force generation in asthma-derived ASM as compared to non-asthma-derived ASM (see review²). In some asthma subjects, airway hyperresponsiveness exists even in the absence of airway inflammation^{3,4}. Taken together, such findings suggest there is an underlying intrinsic abnormality in ASM that evokes hyperresponsiveness and airway narrowing associated with asthma. Mechanisms underlying a hypercontractile phenotype have only been more recently investigated^{2,5–9}. Current evidence is derived from animal models of allergic airways disease, airway biopsies from asthma and non-asthma subjects, ASM cells derived from subjects with and without asthma and from ex vivo

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tissue model of precision cut lung slices (PCLS) derived from donors with and without asthma. To date, there exists no method to study ASM *in vivo*, thus evidence suggesting that there are intrinsic differences in ASM have only been observed in *in vitro* models.

Pathways modulating contractility in ASM

Shortening of ASM is primarily induced by GPCR agonists, and modulated by downstream pathways that are calcium (Ca^{2+})-dependent and -independent (see Figure 1). In the canonical Ca^{2+} mobilization pathway, phospholipase β ($\text{PLC}\beta$) activation generates inositol triphosphate (IP_3) that then binds to the IP_3 receptor on the sarcoplasmic reticulum (SR) to elicit $[\text{Ca}^{2+}]_i$ release. The increased $[\text{Ca}^{2+}]_i$ activates calmodulin (CaM) and myosin light chain kinase (MLCK) to phosphorylate myosin light chain (MLC) and induce actin-myosin crossbridge cycling and HASM shortening. In parallel, increased expression of CD38 evokes generation of cyclic ADP-ribose (cADPR), that binds to the ryanodine receptor (RyR) to promote SR $[\text{Ca}^{2+}]_i$ release. The sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) refills the SR with the cytosolic $[\text{Ca}^{2+}]_i$ inhibiting HASM shortening (as reviewed in¹⁰).

Contractile agonists such as methacholine, thrombin, histamine, and leukotriene D_4 elicit $[\text{Ca}^{2+}]_i$ release in ASM. Following release of intracellular stores of Ca^{2+} from the SR, there is an activation of cell surface channels to facilitate extracellular Ca^{2+} refilling of cytosolic stores. This occurs through activation of the Orai/STIM pathway, modulating store-operated Ca^{2+} entry (SOCE) through plasma membrane channels when intracellular stores of Ca^{2+} are depleted following IP_3 receptor-mediated $[\text{Ca}^{2+}]_i$ release from the SR. Calcium sensitization pathways that are relatively Ca^{2+} -independent are mediated by activation of RhoA, stimulating Rho kinase (ROCK), which phosphorylates myosin light chain phosphatase target subunit (MYPT1) to inactivate it. Under resting conditions, MYPT1 is active and limits HASM shortening; upon its phosphorylation and hence its inhibition, HASM shortening is enhanced. Components of each of these pathways can be modulated by the inflammatory environment present in asthma. Table 1 illustrates signaling molecules that differ between asthma and non-asthma-derived ASM that may contribute to the enhanced contractile phenotype observed in asthma.

Modulation of ASM pro-contractile pathways in asthma

At first glance, changes in expression of components of signaling pathways modulating constriction of the airways could explain the contractile differences between asthma-derived and non-asthma-derived ASM. Studies have showed that components of contractile signaling pathways are increased in ASM derived from asthma subjects compared to those from non-asthma subjects^{11–13}. Ma *et al* noted that in asthma-derived ASM, there was increased expression of Myosin Light Chain Kinase (MLCK)¹² that is the kinase that phosphorylates MLC to promote actin-myosin cross-bridging. Others showed that the fast myosin isoform was found to be more highly expressed in bronchial biopsies from asthma subjects compared to non-asthma subjects¹³. Similar results were observed in human ASM derived from severe asthma subjects and age/gender matched non-asthma subjects¹¹. However, in addition to studies examining gene expression in ASM from biopsies, the intrinsic differences in contractile pathways in asthma subjects may not be at the level of gene expression but rather at the level of translation, post-translational modification of proteins, or alterations in enzymatic activity of proteins.

Underlying changes in sensitivity to Ca^{2+} may modulate contractile responses in ASM in asthma. Consistent with this concept, Mahn and colleagues showed that ASM derived from asthma subjects manifest a sustained $[\text{Ca}^{2+}]_i$ release in response to contractile agonists and an attenuated expression of SERCA2, a protein that negatively regulates changes in $[\text{Ca}^{2+}]_i$ levels⁸. These data suggest that the inflammatory milieu of asthma alters the contractile phenotype of ASM. Inflammatory cytokines release in asthma and exacerbations of asthma increase the sensitivity of ASM to contractile agonists. $\text{TNF}\alpha$, a prominent cytokine present in the airways during allergic airway inflammation¹⁴, evokes AHR¹⁵. Recently, evidence suggests that HASM derived from subjects with asthma expresses higher levels of $\text{TNF}\alpha$ -induced CD38 expression in comparison to HASM derived from non-asthma subjects¹⁶. $\text{TNF}\alpha$ increases CD38 expression/cADPR activity and augment contractile agonist-induced $[\text{Ca}^{2+}]_i$ release in ASM^{16,17}. IL-13 produced by Th_2 cells, mast cells, basophils and eosinophils induces hyperresponsiveness of rabbit tracheal smooth muscle, increases in contractility of human ASM, and augments narrowing of human small airways to methacholine^{18,19}. Additionally, $\text{TNF}\alpha$ augments methacholine-induced airway narrowing in a model of human small airways¹⁸. Antagonism of other cytokine receptors that modulate contractile and non-contractile properties of ASM have also been investigated as potential therapies in asthma. Etanercept, a $\text{TNF}\alpha$ receptor/IgG fusion protein that is a TNF receptor antagonist, significantly improved methacholine-induced AHR, increased FEV_1 , and improved quality of life scores²⁰. IL-13 augmented $[\text{Ca}^{2+}]_i$ release in ASM induced by bradykinin, histamine, and methacholine²¹. IL-13 and $\text{TNF}\alpha$ stimulation also enhance aggregation of STIM1 and increase SOCE following SR $[\text{Ca}^{2+}]_i$ depletion²⁵. Unfortunately, neither anti $\text{TNF}\alpha$ nor IL-13 monoclonal antibodies were effective in preventing asthma exacerbations and as such have been abandoned as potential asthma drugs.

Although $\text{TGF}\beta 1$ is generally thought to be important in remodeling of the airways observed in asthma, recent evidence suggests that it also directly induces airway hyperresponsiveness in asthma. $\text{TGF}\beta 1$ stimulation of human ASM induces activation of contractile pathways and augments activation of agonist-induced contractile pathways^{23,24}. Gao *et al* showed that $\text{TGF}\beta 1$ treatment induces expression of both STIM1 and Orai1 in human ASM, as well as enhancement of basal $[\text{Ca}^{2+}]_i$ levels and SOCE in response to thapsigargin, a compound that stimulates $[\text{Ca}^{2+}]_i$ release from the SR²². The amplitude of arachidonic acid (AA)- activated $[\text{Ca}^{2+}]_i$ oscillations is enhanced in ASM derived from asthma subjects compared to ASM from non-asthma subjects. AA-induced $[\text{Ca}^{2+}]_i$ oscillations in ASM are also inhibited by the knockdown of STIM1 and Orai3²⁶. These data suggest a role for alterations in Orai/STIM-dependent modulation of SOCE may contribute to enhanced airway hyperresponsiveness associated with asthma.

In ASM, RhoA and ROCK-associated airway hyperresponsiveness is associated with exposure to inflammatory cytokines^{23,27–30}, sphingolipids^{31,32}, and mechanical stress³³. Additionally, Koziol-White *et al* demonstrated elevated activity of Rho kinase, a component of the calcium sensitization pathway, in ASM derived from severe asthma subjects as compared to those from age- and gender-matched non-asthma controls⁶. These findings suggest that there an intrinsic hypercontractile phenotype occurs in ASM derived from subjects with asthma. IL-13 has been shown to augment canonical calcium mobilization pathways²¹, and enhance calcium sensitization pathways³⁴. Additionally, inhibition of RhoA

induced relaxation of methacholine- constricted human small airways³⁵. TGF β 1-induced phosphorylation of MLC was found to be ROCK-dependent in human ASM²³.

Cytokines and chemokines released in the airway may directly modulate ASM function, but other inflammatory mediators including lipid mediators alter the contractile status of the ASM. Prostaglandins (PG), products of metabolism of AA by cyclo-oxygenase (COX) enzymes, are mediators that modulate airway hyperresponsiveness associated with allergic airways disease, and in many cases can act directly on ASM. Prostaglandins like PGD₂ and thromboxane (TXB) can act as bronchoconstrictors³⁶. In fact, TXB has been found to be a more potent and effective bronchoconstrictor than methacholine, and amplifies methacholine responsiveness in asthma subjects³⁷. Receptors for leukotrienes LTC₄ and LTD₄, including CysLT 1, are expressed on ASM³⁸. IFN γ , a mediator increased in viral exacerbations of asthma, increased cell surface expression of CysLT 1 receptors and markedly increased contraction of ASM in culture to lipid mediators³⁹.

Modulation of relaxation of ASM in asthma

Agonists of the β_2 adrenergic receptor (β_2 AR) induce generation of cAMP and attenuate myosin light chain kinase activity to abrogate actin-myosin crossbridging and induce relaxation of ASM. β_2 AR agonists provide the mainstays for rescue therapy to reverse bronchoconstriction associated with airways disease. Jiang and Stephens demonstrated that in canine ASM, isolated muscle from allergen sensitized dogs showed a failure to relax following increased maximum shortening velocity⁴⁰, suggesting that there may also be intrinsic differences in asthma-derived ASM that drive hyperreactivity of the muscle/hyposensitivity to a relaxant. As with contractility, the inflammatory environment of the lung in asthma modulates reversal of ASM shortening. TNF α synergizes with IL-1 β to promote β_2 AR hypo-responsiveness that is ablated by selective COX-2 inhibition, thereby suggesting that arachidonic acid derivatives serve to desensitize the airway smooth muscle to bronchodilation. IL-13, TNF α and IL-1 β stimulation of human ASM modulated contractile agonist signaling pathways by enhancing agonist-induced calcium responses and/or inhibiting cAMP production^{21,41}. Additionally, exposure to IL-13 attenuated β_2 agonist-induced dilation of human small airways in an *in vitro* model¹⁸ that was reversed by inhibition of PI3K δ and administration of budesonide^{6,42}. Interestingly, an AA metabolite, PGE₂, abrogates early- and late-phase responses to antigen challenge and serves as a bronchodilator; in murine models of allergen-induced AHR, the lack of EP₃ receptors for PGE₂ increases AHR to OVA⁴³.

While effective at bronchodilation, β_2 AR agonists induce desensitization of the β_2 receptor, which that attenuates the efficacy of such treatment. Modulation of the pathways downstream of the β_2 AR has been an attractive approach for developing novel therapeutics. In addition to pathways activated by the β_2 AR, modulation of smooth muscle relaxation can also be achieved through generation of cGMP via soluble guanylate cyclase (sGC) using nitric oxide (NO) or pharmacologic sGC agonists that activate sGC independently of NO. Ghosh and colleagues demonstrated that an NO donor induces dilation of human small airways, and that pharmacologic agonists of sGC reversed airway hyperresponsiveness in a murine model of allergic airway disease⁴⁴. These investigators also noted in the murine

asthma model that there was oxidative damage to sGC that rendered it unresponsive to NO. Such oxidative damage was also observed in human ASM, suggesting that the elevated NO levels measured in severe asthma subjects may render their airways insensitive to NO donors for bronchodilation, but may offer a target for pharmacologic intervention to activate sGC independently of NO. New evidence shows that inhibition of PI3K, primarily to inhibit airway inflammation to allergen, induces bronchodilation in a human PCLS model. Interestingly, inhibition of PI3K p110, more specifically the δ isoform, induces bronchodilation despite β_2 AR desensitization or IL-13 treatment⁶. Inhibition of PI3K and agonism of sGC may serve as novel targets to induce bronchodilation in a Th2 inflammatory milieu characteristic of asthma, as well as during an exacerbation where a β_2 AR agonist may be ineffective due to overuse.

Summary and Future Directions

While antagonists of contractile receptors and agonists of the β_2 AR have been used extensively as asthma therapies, these therapeutics are restricted to specific classes of receptors and may be ineffective in severe disease. Emerging evidence suggests that manipulation of components of contractile signaling pathways that may be altered in ASM of asthma subjects, may serve as novel targets to inhibit constriction of the airways or to promote bronchodilation. Given the intrinsic differences in excitation-contraction pathways between ASM derived from asthma and non-asthma subjects, specific signaling molecules whose activity is altered by the disease state may offer unique therapeutic opportunities. Such opportunities leverage intrinsic functional differences in ASM to enhance therapeutic responses while potentially minimizing systemic off-target or adverse effects.

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Key points:

- Airway smooth muscle (ASM) serves as the pivotal tissue regulating bronchomotor tone.
- Evidence suggests a hypercontractile phenotype in the airway smooth muscle of subjects with asthma that in part is driven by intrinsic abnormalities in excitation-contraction signaling pathways in ASM.
- ASM shortening occurs through activation of mechanisms that are calcium-dependent and that are partially calcium-independent.
- Modulation of ASM contractility is achieved through independent mechanisms of inhibiting receptor-mediated bronchoconstriction or stimulating bronchodilation.

Synopsis: Airway smooth muscle (ASM) is the primary cell mediating bronchomotor tone. The milieu created in the asthmatic lung modulates ASM contractility and relaxation. Experimental findings suggest intrinsic abnormalities in ASM derived from asthma subjects in comparison to ASM from those without asthma. These changes to excitation-contraction pathways may underlie airway hyperresponsiveness and increased airway resistance associated with asthma.

Figure 1 -

Calcium-dependent (blue box) and calcium sensitization (red box) pathways that modulate ASM contraction. Abbreviations: phospholipase C (PLC) β , phosphatidylinositol 4,5-bisphosphate (PIP₂), diacylglycerol (DAG), inositol triphosphate (IP₃), IP₃ receptor (IP₃R), sarcoplasmic reticulum (SR), sarco/endoplasmic reticulum calcium-ATPase (SERCA), calmodulin (CaM), myosin light chain kinase (MLCK), myosin light chain (MLC), cluster of differentiation 38 (CD38), cyclic adenosine phosphate ribose (cADPR), ryanodine receptor (RyR), phosphoinositide 3-kinase δ (PI3K δ), guanine nucleotide exchange factor (GEF), myosin phosphatase target subunit (MYPT1), calcium release-activated calcium modulator 1 (Orai1), stromal interaction molecule 1 (STIM1).

Table 1

Signaling proteins involved in contraction and relaxation of ASM that are altered between asthma and non-asthma-derived ASM

	Signaling Protein	Expression/Activity	AHR/Responsiveness to Bronchodilator	Reference(s)
Procontractile signaling	MLC	↑ Expression/phosphorylation	↑	11–13,23
	Rho kinase	↑ Activity	↑	6,23,27–30
	CysLTI receptor	↑ Expression	↑	38
	PGD ₂ , TXB	↑ Expression/release	↑	36–38
	IL-13	↑ Expression/release	↑	18,19,21
	TGFβ1	↑ Expression/release	↑	23–25
	SERCA	↑ Expression/activity	↓	8
	MLCK	↑ Expression/activity	↑	12
	TNFα	↑ Expression/release	↑	14,15,18
	CD38/cADPR	↑ Expression/activity	↑	16,17
	Orai/STIM	↑ Expression/activity	↑	26
Relaxation signaling	TNFα/IL1β	↑ Expression/release	↓	21,41
	pge ₂	↑ Expression/release	↑	43
	IL-13	↑ Expression/release	↓	18,21,41
	IL-1β	↑ Expression/release	↓	21,41
	Corticosteroid	Stimulation with	↑	6,42
	PI3K	Inhibition	↑	6
	sGC	↑ Expression/activity	↑	44
	NO	↑ Expression/stimulation	↑	44
	RhoA	↓ Expression/activity	↑	35

Abbreviations: ↑, increased; ↓, decreased; ASM, airway smooth muscle; MLC, myosin light chain; MLCK, myosin light chain kinase; PG, prostaglandin; SERCA, sarco/endoplasmic reticulum Ca²⁺ ATPase; TGF, transforming growth factor; TNF, tumor necrosis factor; TXB, thromboxane.