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Airway Smooth Muscle:
Is There a Phenotype Associated with Asthma?

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1. Introduction

Increases in airway smooth muscle (ASM) mass characterize the pathology of patients who died of asthma. Recent studies also show that bronchial biopsies from individuals diagnosed with mild-to-moderate asthma also have increased ASM mass. As a consequence of such increases and the role of ASM in regulating bronchomotor tone, ASM plays a pivotal role in asthma pathophysiology. In the following review, we summarize the clinical and basic science evidence that suggests that ASM is a phenotypically distinct tissue whose therapeutic manipulation is critical for overall asthma management.

1.1 ASM and airway mechanics

In developed lungs, ASM modulates ventilation and perfusion dynamics and expedite clearing of foreign particulates from distal airways. As with other myocytes, ASM shortening is largely dependent upon Ca^{2+} homeostasis. Unlike cardiac and vascular myocytes, however, where membrane depolarization induces Ca^{2+} influx via voltage-dependent Ca^{2+} channels, the pharmacological inability of Ca^{2+} channel blockers to affect bronchoconstriction implies a limited capacity of extracellular Ca^{2+} sources in regulating excitation-contraction coupling. This unique contractile property of ASM could be due to outward rectification that counteracts membrane depolarization. Such rectifying currents are mediated by the opening of large conductance Ca^{2+}-activated and delayed rectifier K^+ channels, responsible for repolarizing or hyperpolarizing ion fluxes imparting electrical stability to ASM (Parameswaran et al., 2002).

Also integral to ASM are functional receptors for acetylcholine, cysteinyl leukotrienes, prostaglandins, thromboxanes, neurokinins, bradykinin, endothelin, thrombin and serotonin, whose pharmacological manipulation regulates airway contractile mechanics. Extracellular engagement of these receptors elicits intracellular inositol trisphosphate (IP_3) and diacylglycerol (DAG)-mediated biphasic Ca^{2+} responses. Post-stimulus, the primary phase tension development is modulated by IP_3R agonism at the sarcolemma, stimulating peak release of sarcoplasmic Ca^{2+} stores (Amrani, 2006; Deshpande & Penn, 2006). The secondary phase of tension is characterized by prolonged Ca^{2+} levels albeit lower than peak thresholds, regulated by PLC-β1-mediated production of IP_3 and DAG. The IP_3-induced release of Ca^{2+} complexes with calmodulin (CaM) activates the enzymatic domain of myosin light chain kinase (MLCK), in turn phosphorylating the regulatory 20 kDa light chain

(MLC_{20}) subunit of myosin. Sympathomimetics via cAMP/PKA-dependent mechanisms in part mitigate IP_3R-mediated Ca^{2+} mobilization altering airway hyperresponsiveness (AHR). In addition, recent studies show that enhanced expression of MLCK in disease or upstream manipulation of its activity by therapeutic engagement of β-adrenoceptor could also alter mediator-induced ASM contractility. Contractile agents such as acetylcholine (ACh) induce regenerative and propagative Ca^{2+} oscillations and airway narrowing. Once initiated in ASM cells, Ca^{2+} oscillations remain resistant to IP_3R antagonists, as shown by the limited ability of heparin to suppress methacholine (MCh)-induced bronchoconstriction in individuals with asthma. Interestingly, agonist-induced Ca^{2+} oscillations can be inhibited by antagonists of the SR-resident ryanodine receptor (RyR), such as ryanodine and ruthenium red. These observations imply that Ca^{2+} release through RyR channels cooperates with IP_3-mediated Ca^{2+} mobilization to integrate the Ca^{2+} responses of ASM triggered by contractile agonists. Mechanistic studies show that RyR channel-dependent Ca^{2+} oscillations are regulated by CD38, a cyclic ADP ribose hydrolase that catalyzes the conversion of β-NAD to cADPR (Jude et al., 2008). Formation of cADPR and its interactions with several accessory proteins including tacrolimus (FK506)-binding protein modulate RyR-mediated Ca^{2+} kinetics. Similarly, cADPR could stimulate CaM-mediated mechanisms leading to Ca^{2+}-induced Ca^{2+} release, enhancing the overall propagation of Ca^{2+} oscillations throughout the cytosol. Several extracellular stimuli enhance CD38 expression and cADPR generation in human ASM; however, the precise mechanism by which extracellular cADPR is shunted to Ca^{2+} intracellular stores remains unknown (Bara et al., 2010).

1.2 ASM as a structural cell immunomodulator

Cytokine secretions of $CD4^+$ Th2 subtypes play a pivotal role in integrating inflammation and hypercontractile responses in airways of individuals with asthma. Studies in sensitized knock-out or transgenic murine models illustrate Th2 cytokine prominence in regulating abnormal airway physiology. As structural and spatially organized tissue throughout the airways, ASM cells serve as effector cells for most cytokines. After cytokine stimulation, ASM alters pro-inflammatory gene expression in an autocrine-paracrine manner promoting inflammatory processes within airways (Damera et al., 2009b). In isolated ASM tissue, IL-4 or IL-13 stimulates eotaxin that is inhibited by anti-IL-4Rα antibodies and antisense oligonucleotides to STAT-6 (Hirst et al., 2002; Peng et al., 2004). Based on the demonstrated ability of several disease-specific mediators including tumor necrosis factor alpha (TNFα), IL-1β, transforming growth factor beta (TGFβ), thymic stromal lymphopoietin (TSLP), IL-17A, endothelin-1 and sphingosine-1-phosphate (S-1-P) to induce IL-6 secretion in ASM, airway myocytes may directly contribute to IL-6 production in asthma (Ammit et al., 2001; Iwata et al., 2009; McKay & Sharma, 2002; Shan et al., 2010; Tliba & Panettieri, 2009). Pharmacological inhibition of cellular ligand for herpes virus entry mediator and lymphotoxin receptor (LIGHT), a leukocyte expressed member of TNF family, reduces allergen-induced lung fibrosis, smooth muscle hyperplasia, cytokine levels (IL-13) and AHR in murine models of chronic asthma, despite having little effect on airway eosinophilia (Doherty et al., 2011). In a more complex role, TNFα induces interferon beta (IFNβ) secretion from ASM which, by its autocrine actions, alters TNFα-mediated IL-6 and regulated upon activation, normal T cell expressed and secreted (RANTES) secretion (Tliba et al., 2003). ASM in spatial proximity to epithelium also selectively enhances basal or TNFα-induced IL-6 and IP-10 secretion, with little effect on fractalkine levels (Damera et al., 2009c). Despite the lack of a membrane-adherent IL-6R in ASM, IL-6 induces eotaxin secretion via a soluble IL-6R (sIL-6Rα) receptor (Ammit et al., 2007). Evolving evidence also shows that conditioned serum from ASM cells treated with a combination of TNFα, IL-1β and IFNγ advances an eosinophilopoietic potential on CD34$^+$ bone marrow-derived cells, a phenomenon ablated by neutralizing antibodies to IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Fanat et al., 2009). Modulating eosinophil activation and survival, ASM cells secrete GM-CSF in response to TNFα/IL-1β alone or in combination with serum, or mast cell-derived tryptase. Endothelin (ET-1) and TNFα also elicit GM-CSF and ET-1 secretion via an intricate mechanism sensitive to bosentan and specific inhibition of ET-R (Knobloch et al., 2009). Another constituent member of the IL-6 superfamily, oncostatin M (OSM), enhances IL-1R1 abundance and augments IL-1β-mediated VEGF, monocyte chemotactic protein-1 (MCP-1) and IL-6 secretion, or synergizes with IL-13 to augment eotaxin-1 expression in airway myocytes (Faffe et al., 2005a; Faffe et al., 2005b) as summarized in Table 1.

Mediator in Asthma	***In Vitro***	**Biopsies**	**Function**
Cytokines			
IL-6	Yes	Yes	Inflammation
IL-33	Yes	Yes	Inflammation
CX3CL-1		Yes	Mast cell chemotaxis
CCL-11	Yes		Eosinophil chemoattractant
CXCL-8	Yes		Neutrophil chemotaxis
CXCL-10	Yes	Yes	Mast cell chemotaxis
Peptide growth factors			
TGF-β1, LAP		Yes	ASM hyperplasia
Adhesion molecules			
CD51, CD44	Yes		Cell-ECM interactions
CD40, OX40, CD54	Yes		Cell-cell interaction
Integrin alpha(5)	Yes		ECM deposition
CD106		Yes	Leukocyte ligand
ECM components			
Collagen type I α1	Yes		Airway remodeling
Perlecan	Yes		Airway remodeling
Collagen III	Yes	Yes	Airway remodeling
Fibronectin	Yes		Airway remodeling
Transcription factors			
mtTFA, NRF-1, PGC-1 α	Yes		Mitochondrial biogenesis
Receptors			
E-prostanoid receptor 2/ 3	Yes		ASM hyperplasia
Proteases			
ADAM-33		Yes	Cell-matrix interaction

Table 1. Mediators expressed by airway myocytes from asthmatics *in vitro* and in biopsies. References are included within the text.

In individuals with severe asthma, airway neutrophil abundance correlates with enhanced CXCL-8 levels. Enhanced CXCL-8 in supernatants from ASM cultures activates CXCR-1 receptors and promotes mast cell trafficking. An increase in CXCL-8 secretion can also increase binding of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), CCAAT/enhancer-binding protein beta (C/EBPβ), and RNA polymerase 2 (RNA Pol II) transcriptional elements to CXCL-8 promoter (John et al., 2009) in ASM cells. Human ASM cells secrete IL-8 when treated exogenously with IL-1β, TNFα, or TGFβ (Chung, 2000). Likewise, phenotypic changes in ASM have been suggested to augment IL-8-dependent AHR and to enhance IgE-mediated IL-4 and IL-6 levels from ASM cells (Govindaraju et al., 2006; Govindaraju et al., 2008). Evoking a COPD-relevant phenotype, pro-inflammatory stimuli, such as TNFα and cigarette smoke, also synergize to induce IL-8 secretion from ASM (Oltmanns et al., 2005). Despite minimal effect in directly mediating ASM-derived cytokine secretion, IL-9 augments TNFα-induced IL-8- or IL-13-induced eotaxin secretion in cultured ASM cells (Baraldo et al., 2003). Further, IL-9 selectively and directly enhances eotaxin-1/CCL11 secretion that can promote airway eosinophilia (Yamasaki et al., 2010).

Leukocyte migration and retention, primarily regulated by selectins on endothelial cells, are subsequently mediated by timely expression of cell adhesion molecules (CAMs) on “primed” airway structural cells as shown in Figure 1.

Studies *in vitro* and *in vivo* show that expression of CAMs mediates cell-cell interactions during inflammation and tissue remodeling (Kelly et al., 2007). Expectedly, disease-relevant components such as cytokines, bacterial endotoxins and viral proteins enhance ASM resident intercellular adhesion molecule-1 (ICAM-1) expression (Tliba et al., 2008a). Cytokines including TNFα and IL-1β induce ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) in ASM via diverse signaling pathways enhancing localized inflammation. Others show that using blocking antibodies against ICAM-1 and VCAM-1 on ASM cells or activated T cell resident lymphocyte function-associated antigen 1 (LFA-1) and very late antigen-4 (VLA-4) greatly attenuated T cell adherence to ASM as compared to either anti-ICAM or anti-VCAM alone (Duplaa et al., 1997). Further, anti-CD44 antibodies (Abs) in combination with monoclonal Abs (mAbs) against LFA-1 and VLA-4 synergistically reduce the binding of activated T cells to the level observed for resting T cells (Lazaar et al., 1994). CAM expression could mediate T cell adherence to airways and alter airway bronchoconstriction and bronchodilation responses (Hakonarson et al., 2001; Hughes et al., 2000). In cultured ASM cells, the engagement of adhesion and immune receptors such as CD40, CD44 and VCAM-1 leads to signaling events that may be involved in proliferative responses (Lazaar et al., 1998). After successive antigen challenges, adoptive transfer of CD4+ T cells from sensitized rats induces proliferation and attenuates apoptosis of ASM in naive recipients. Concomitantly, modified CD4+ T cells expressing enhanced green fluorescent protein (GFP) were localized in juxtaposition to ASM cells conferring that cell-cell interaction participates in airway remodeling. In children or adults with asthma, respiratory viruses frequently trigger exacerbations of asthma symptoms. Empirical studies now show that replication-independent rhinovirus-15 (RV-15) induces ASM-derived IL-5 and IL-1β secretion via ASM-resident ICAM-1 molecules (Grunstein et al., 2001; Oliver et al., 2006). Expanding the role of CAMs in T lymphocyte trafficking, anti-ICAM-1 or anti-VCAM-1 depletes eosinophil and neutrophil adherence to ASM. Besides immune cells, mast cell infiltration of ASM tissue occurs via expression of a heterophilic adhesion molecule, tumor suppressor in lung cancer-1 (TSLC-1) (Yang et al., 2006). In an expanding role for

CAMs in airway inflammation, studies also determined a critical role for a β-galactoside-binding lectin, Galectin-3 (Gal-3), in eosinophil trafficking and recruitment (Ramos-Barbon et al., 2005). As compared to allergen-induced responses in Gal-$3^{+/+}$ mice, Gal-$3^{-/-}$ mice have altered CAM expression, lower AHR and Th2 responses (Zuberi et al., 2004).

Figure 1

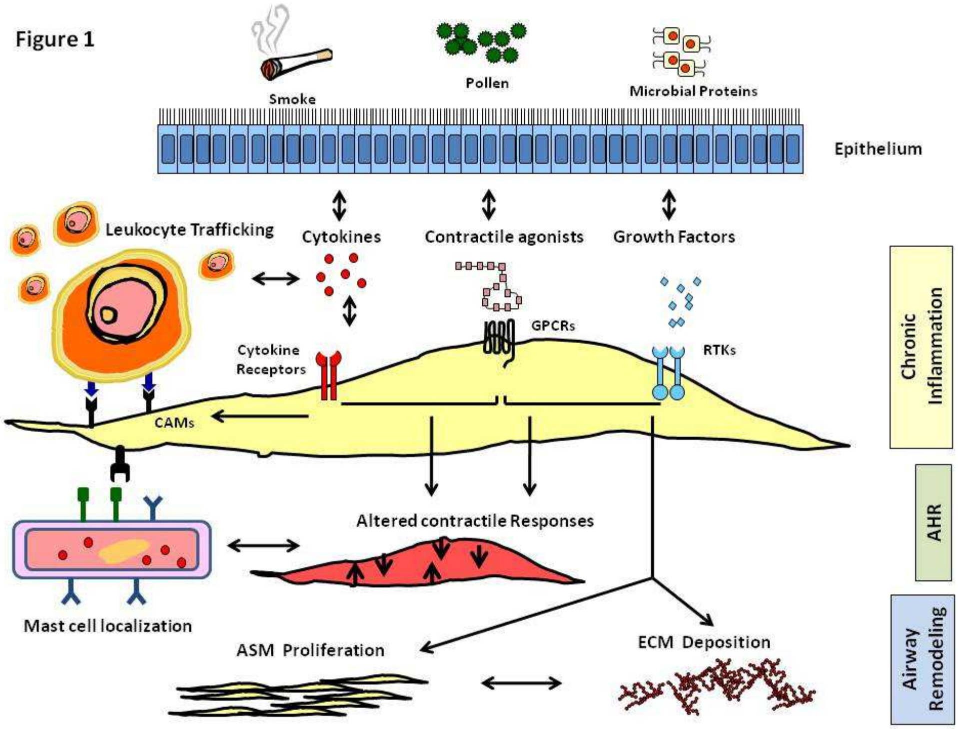

Fig. 1. Phenotypic modulation of airway smooth muscle (ASM) in asthma. Environmental stimuli induce chronic alterations in ASM characterized by hypertrophy and hyperplasia. Additionally, cytokines and growth factors modulate agonist-induced shortening of ASM that promotes airway hyperresponsiveness (AHR). Over time, ASM mass increases often in concert with extracellular matrix (ECM) deposition. The physiologic relevance of the increased ASM mass may relate to irreversible airflow obstruction. ASM also interacts directly with trafficking leukocytes and with mast cells and indirectly through the secretion of chemokines and cytokines. CAMs: cell adhesion molecules; GPCRs: G protein coupled receptors; RTKs: receptor tyrosine kinases

1.3 ASM phenotype switching

While increased ASM mass is a constitutive characteristic of remodeling in asthma, convincing studies by Ebina et al show that ASM mass increases are both physiologically discontinuous and subtype specific (Ebina et al., 1993). For instance, in some subjects with asthma, ASM mass was increased only in the central bronchi compared with others who manifested enhanced muscle thickness throughout the bronchi. In addition the number of smooth muscle nuclei in the central airways was increased, indicating the presence of ASM hyperplasia. In patients with increased mass throughout the bronchi, ASM cell volume was significantly increased, signifying ASM hypertrophy (Wenzel et al., 1999). Accordingly, examination of biopsies from patients with mild asthma shows significant increases in ASM numbers, with minimal alterations in cellular morphometry. Indeed, studies addressing the molecular mechanism inducing ASM mass in animals have convincingly shown that allergic sensitization enhances ASM mass. In murine models, ovalbumin (OVA)-induced sensitization and challenge promotes thickening of the peribronchial smooth muscle layer. Similarly, in guinea pigs, allergen challenge induces bromodeoxyuridine uptake into ASM layers, implying enhanced mitogenesis. Likewise, bronchoalveolar lavage (BAL) fluid derived from individuals with asthma enhances DNA synthesis and ASM cell numbers (Naureckas et al., 1999), implying that BAL soluble constituents likely promote ASM hyperplasia. Post-allergen challenge, quantitative increases in cytokines, enzymes including tryptases and matrix metalloproteinase (MMPs) and growth factors define airway pathology in animal studies; however, contradictory empirical outcomes limit the mitogenic potential of BAL cytokines. More prominent are the effects of airway-localized growth factors in stimulating ASM growth via the RTK-PI3K axis. Among asthma-relevant outcomes such as tissue maturation and epithelial mucin (MUC) gene expression, peptides that stimulate receptors for epidermal growth factor (EGF), insulin-like growth factors (IGFs), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF)-2 also induce ASM proliferation (Marwick et al., 2010).

Selected contractile agents such as histamine, ET-1, substance P, 5-HT, α-thrombin, thromboxane A_2 and LTD_4 also enhance ASM mitogenesis (Dekkers et al., 2009; Lazaar & Panettieri, 2005). Studies suggest that mediator-induced ASM proliferation is regulated by cell cycle proteins as surrogate markers of mitogenesis. While BAL fluid derived from subjects with asthma mediates ERK-mediated DNA synthesis in ASM, such responses are associated with increased cyclin D1 protein (Naureckas et al., 1999). Besides ERK, pharmacological inhibitors of PI3K also diminish cyclin D1 protein expression and DNA synthesis in ASM. Other studies identified two nuclear antigens, Ki67 and proliferating cell associated nuclear antigen (PCNA), as potential markers of proliferation. Investigators suggest that despite comparable mitogen-induced induction of PI3K-AKT axis, ASM proliferation results from diminished cell cycle inhibitory proteins such as C/EBPa elements. Others have shown that ASM proliferation is induced by overexpression of Src or PI3K alone, and inhibition of PI3K abrogated mitogen-induced ASM proliferation. Downstream PI3K stimulates S6K1-mediated translation of cell cycle proteins via rapamycin-sensitive events (Scott et al., 1996). Importantly, sustained activation of PI3K and S6K1 at 12h discriminated ASM mitogens from non-mitogenic agonists that otherwise equally potentiate ERK1/2 at 1h (Krymskaya et al., 2000). Similar upstream pathways also induce ASM hypertrophy via mammalian target of rapamycin (mTOR), 4E-binding protein (4E-BP), the transcription factor eIF4E and S6 kinase or the inhibition of glycogen synthase kinase (GSK)-3β (Bara et al., 2010; Berger et al., 2005)

Myofibroblasts are α-smooth actin-positive mesenchymal precursors that transiently undergo reversible phenotypic differentiation to/from a variety of resident structural populations including ASM cells (Begueret et al., 2007; Brewster et al., 1990; Gizycki et al., 1997). These cells may migrate and differentiate into resident populations within ASM bundles, thus mediating hyperplasia. In support of this phenomenon, studies show that bone marrow-derived, $CD34^+$-Collagen-1^+-α-SMA^+ circulating fibrocytes migrate towards ASM bundles during inflammatory challenge. Post allergen challenge, increased presence of myofibroblasts in the submucosa has led some to postulate that ASM cells could migrate from airway bundles towards epithelium, explaining diminished space between smooth muscle and epithelium in asthmatic airways. Varied mediators including PDGF, TGF-β and chemokines such as CCL-11 and CXCL-8 induce chemotaxis of ASM cells *in vitro* (Govindaraju et al., 2006; Hirst et al., 2004; Ito et al., 2009; Joubert & Hamid, 2005; Mukhina et al., 2000). Similarly, migration of ASM *in vitro* could be enhanced by coating with collagens III and V and fibronectin as compared with collagen I, elastin and laminin (Bullimore et al., 2011), implying that disease-specific matrix alteration could also mitigate this process. In line with *in vitro* studies, Thomson and Schellenberg hypothesized that the presence of collagen deposition in and around ASM bundles may contribute to the overall increase in the ASM content (Thomson & Schellenberg, 1998).

The overall functional impact of enhanced ASM mass on asthma symptoms including AHR seems heterogeneous and remains unclear. During proliferation, ASM cells likely manifest a phenotypic switch characterized by compromised contractile characteristics as shown after mitogen treatment or cultured on diverse ECM (Dekkers et al., 2007; Halayko et al., 2008; Halayko et al., 2006). Predictably, such alterations correlate with quantitative increases in synthetic pathways for protein and lipids and mitochondrial function with a diminished abundance of contractile proteins. Compared to specific proteins that mark pro-contractile characteristics, such as smooth muscle myosin heavy chain, SM22, calponin and smooth muscle α-actin, proliferating ASM shows increased non-muscle myosin heavy chain (MHC), caldesmon, vimentin, α/β-protein kinase C (PKC) and CD44 homing cellular adhesion molecule (Halayko et al., 2008; Hirota et al., 2009). Others appreciate the expression and accumulation of dystrophin glycoprotein complex (DGC), a multimeric sarcolemma complex that regulates caveoli organization, with altered ASM contractility (Sharma et al., 2008).

2. Is ASM different in asthma?

2.1 ASM mass and airway remodeling

Using anatomically matched bronchial samples derived from inflated lungs, Hossain and Heard show that thickness of ASM is enhanced in patients with fatal asthma (Hossain & Heard, 1970). Pursuing alternate procedures to inflate lungs via pulmonary vasculature, Dunnill et al. show that increased ASM mass accounts for 11.4 ± 3.4% of wall thickness in asthmatic airways, as compared to 4.6 ± 2.2% in normal airways (Dunnill et al., 1969). Others explain that expression of α-smooth muscle actin and myosin light-chain kinase negatively correlates with prebronchodilator and postbronchodilator FEV_1 values in patients with severe asthma (Benayoun et al., 2003). Similarly, quantitative structural analysis of peripheral airways showed that, in addition to increased luminal occlusion and immune cell infiltrates, bronchioles of subjects with fatal asthma showed enhanced smooth muscle presence (Saetta et al., 1991). In addition to acknowledged effects in fatal asthma, discontinuous increases in ASM numbers distinguish airway physiology within asthma subtypes (Ebina et al., 1993). Owing to challenges in obtaining biopsies that encompass the full thickness of ASM, few studies could define growth of ASM in patients with non-fatal asthma. In studies by Carroll et al, analysis of similarly identified central airways samples from inflated lungs of all asthma severities showed that the area of smooth muscle in large bronchioles was greater in fatal and non-fatal cases than in control cases, but there were no differences between fatal and non-fatal cases of asthma (Carroll et al., 1993). Accordingly, comprehensive evaluation of endobronchial biopsies by quantitative morphometry, laser capture microdissection, and RT-PCR also shows a two-fold increase in ASM numbers in individuals with mild asthma. These studies concluded that ASM hyperplasia and not hypertrophy is a pathologic characteristic in airways of individuals with mild-to-moderate asthma, and that gene expression of contractile proteins considered markers of a hypercontractile phenotype are not increased across asthma populations (Woodruff et al., 2004). Studying ASM growth in steroid-resistant asthmatics, Pegorier et al report that epithelium resident endothelin (EDN1) and IL-8/CXCL8 levels negatively correlate with pre and postbronchodilator FEV_1 values, and positively relate to ASM area and thickness of subepithelial basement membrane (Pegorier et al., 2007).

2.2 ASM function and AHR

Since airway smooth muscle (ASM) is the pivotal effector tissue controlling bronchomotor tone, it is suggested that ASM dysfunction contributes directly towards AHR in asthma. Mutually distinct lines of evidence show that increases in the shortening velocity of ASM could mediate AHR (Antonissen et al., 1979; Mitchell et al., 1993; Seow et al., 1998; Solway & Fredberg, 1997). Following induced bronchoconstriction, deep inspiration causes airways of both normal and asthmatic individuals to dilate transiently; yet, the subsequent reconstriction is more prompt in asthmatics (Jackson et al., 2004; Jensen et al., 2001; Pellegrino et al., 1996). Empirical evidence *in vitro* shows that bronchial ASM cells from asthmatic patients have increased shortening velocity relative to controls (Ma et al., 2002). Likewise animal models of innate and allergic AHR manifest enhanced ASM shortening (Bullimore et al., 2011). Such increase in muscle-shortening velocity may be due to augmented MLCK activity in asthmatic ASM (Ammit et al., 2000). Concurrently, others propose that altered cytosolic calcium handling within ASM could induce AHR in ASM from subjects with asthma (Janssen, 1998). Indeed, ASM $[Ca^{2+}]_i$ levels are greater in hyperresponsive Fisher rats as compared to less responsive Lewis rats (Tao et al., 1999). Since diverse excitatory stimuli, such as leukotrienes, acetylcholine, ozone, acroleins and cytokines, provoke AHR by mobilizing cytoplasmic calcium concentration, it is conceivable that the calcium handling in the smooth muscle *per se* is altered (Parameswaran et al., 2002). ASM contractility is hormone-responsive, leading some to focus on gender disparities in asthma epidemiology. Preliminary studies now suggest that oxytocin levels are enhanced in BAL fluid from asthmatic individuals and that selected cytokines (IL-13) amplify oxytocin's effects by increasing the expression of functional oxytocin receptor within ASM (Amrani et al., 2010).

As with TNFα and IL-13, pro-inflammatory cytokines modulate intracellular Ca^{2+} responses and AHR via expression of CD38. Compared to $CD38^{-/-}$ mice, airway myocytes isolated from wild-type mice exhibit higher agonist-induced intracellular Ca^{2+} responses *in vitro* while $CD38^{+/+}$ mice develop a higher magnitude of AHR after allergen challenge (Gally et al., 2009; Guedes et al., 2008; Guedes et al., 2006). Later studies in human ASM imply that differential expression of CD38 by heightened induction of common signaling cascades likely mediates AHR in asthma (Jude et al., 2010). Clinical evidence shows that ASM derived from subjects who died of asthma has enhanced immunoreactivity to receptors for receptor tyrosine kinases (RTKs) and that such increases correlate with disease severity (Chanez et al., 1995; Perkett, 1995; Polosa et al., 2002; Puddicombe et al., 2000; Yamanaka et al., 2001). Increased expression of EGFR and PDGFR ligands can be triggered by factors that modulate asthma etiology including allergens, pro-inflammatory cytokines, environmental tobacco smoke, and virus infection (Ingram & Bonner, 2006; Le Cras et al., 2011). Expectedly, EGFR ligands are elevated in samples from asthmatic airways, and mechanistic studies show that EGFR activation elicits augmented mitogenic responses in asthmatic ASM (Amishima et al., 1998). Such proliferative responses are accompanied by inhibition of cyclic AMP (cAMP) effectors such as protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac), entailing a phenotypic switch characterized by diminished expression of contractile proteins including smooth muscle actin, myosin and calponin (Roscioni et al., 2011). As seen in biopsies of severe asthmatics, empirical studies show that ASM mitogens enhanced expression of defined GTPase-accelerating proteins (GAPs) called RGS (Damera et al., 2010). Given the ability to interact with Gα subunits of GPCR and p85α-PI3K, expression of RGS molecules could induce a hypocontractile and hyperproliferative ASM phenotype reminiscent of severe asthma (Bansal et al., 2008; Liang et al., 2009).

2.3 ASM markers of chronic inflammation

As repeatedly illustrated by mechanistic studies *in vitro*, ASM-expressed cytokines, peptide growth factors, ECM proteins and adhesion molecules extensively regulate airway pathology (Damera et al., 2009b; Tliba & Panettieri, 2008). Predictably, bronchial biopsies from asthmatic individuals show a greater role of ASM in inflammation and remodeling; however, the ability of isolated ASM cells to retain this phenotype in culture has led some to propose a genetic etiology. Although functionally ambiguous, a disintegrin and metalloproteinase-33 (ADAM-33), a member of zinc-dependent metalloproteases, is associated with AHR and diminished lung function in asthma (Foley et al., 2007). Expression of active chemotactic factors by ASM promotes adherence and retention of circulating T cells and mast cells to airways. Recruitment and retention of T cells and mast cells to ASM are dependent on expression of functionally active chemotactic factors. For-instance, in airways of individuals with asthma, enhanced mast cell presence within ASM layers correlates with augmented expression of TGFβ$_1$. Among other triggers, stimulation of ASM resident protease activated receptor 2 (PAR-2) by mast cell-derived tryptase enhances TGFβ$_1$ expression, thus potentiating a “feed forward system” leading to increased mast cell recruitment (Berger et al., 2003). In addition, as demonstrated *in vitro*, TGFβ1 facilitates transformation of epithelial cells to myofibroblasts, with likely consequences to ASM hyperplasia (Zuyderduyn et al., 2008). With inflammation, expression of mast cell resident CD44 (hyaluronate receptor) and CD51 (vitronectin receptor) to ECM defines mast cell adhesion to ASM. As compared to normal cells, such interactions are enhanced in cultures derived from asthmatic airways (Girodet et al., 2010). Likewise, cytokines differentially alter expression of co-stimulatory ligands such as CD40 and OX40 among ASM from airways of normal and asthmatic individuals, implying that disease pertinent mechanisms intrinsic to ASM mitigate enhanced leukocyte adherence in asthma (Burgess et al., 2005). Besides cell adherent factors, marked increases in soluble chemotactic mediators such as IL-33, CX3CL-1 and CXCL-10 are seen in ASM tissue within bronchial biopsies in asthma (Brightling et al., 2005; El-Shazly et al., 2006; Prefontaine et al., 2009). While CXCL-10-mediated activation of mast cell resident CXCR-3 predicts ASM microlocalization, CXCL-10 is preferentially expressed in bronchial biopsies and *ex vivo* cells from individuals compared with those from healthy control subjects. As a promoter of Th2 immunity, TNFα-mediated IL-33 secretions are refractory to corticosteroid effects (Prefontaine et al., 2009). Further, immune histochemical (IHC) analysis of bronchial biopsies shows increased IL-33 localization within ASM bundles of subjects with mild-to-moderate asthma, implying a likely role in pathogenesis of asthma. During RV-induced asthma exacerbation, cytokine secretion such as IL-6 is transcriptionally triggered by specific innate immune responses. Interestingly, such responses are differentially regulated in ASM derived from asthmatic and normal individuals (Oliver et al., 2006). As with COPD, an increase in neutrophilic inflammation correlates with CXCL-8 secretion in airways of severe asthmatics. Mechanistic studies by John et al imply that augmented binding of NF-κB, C/EBPβ and RNA Pol II elements to CXCL-8 promoter likely mediates CXCL-8 increases within asthmatic ASM (John et al., 2009) as shown in Table 1.

2.4 ASM and disease matrix

As compared to healthy individuals, ASM cells from patients with asthma secrete increased amounts of collagen I and perlecan but reduced amounts of collagen IV, chondroitin sulfate, laminin α1 and hyaluronan (Johnson et al., 2004; Klagas et al., 2009). While TGFβ1 and connective tissue growth factor (CTGF) enhance collagen I and fibronectin production in normal and asthmatic ASM, differences in intrinsic signaling mechanisms likely alter ECM deposition in asthma (Burgess et al., 2003; Johnson et al., 2006). In asthma, mast cell localization to ASM bundles promotes mutual phenotypic changes that promote development of AHR (Kaur et al., 2010). For instance, in co-cultures IgE-independent mast cell release of β-tryptase augments α-SMA within ASM via autocrine actions of TGFβ. Despite minimal effects on mast cells, TGFβ enhances ASM-derived ECM proteins such as fibronectin which modulate mast cell activation and transition to a myofibroblast phenotype (Chan et al., 2006; Johnson et al., 2006; Lam et al., 2003; Moir et al., 2008; Peng et al., 2005; Swieter et al., 1993). This altered mast cell phenotype has the potential to evoke an ASM contractile phenotype, further propagating AHR. Rhinovirus infection differentially alters ECM components such as fibronectin and collagen 4 in asthmatic ASM, thus facilitating increased cell migration and remodeling at sites of infection (Kuo et al., 2011). Others speculate that asthma pertinent ECM dysregulation likely involves imbalances in ECM modifying MMP or their endogenous enzyme inhibitors called tissue inhibitors of matrix metalloproteinases (TIMP). Supported by studies using histopathological assessment, investigators showed increased MMP-9 and -12 within ASM layers in fatal asthma (Araujo et al., 2008). Comparative assessment of BAL fluid of patients undergoing mechanical ventilation in severe asthma and those with mild etiology shows enhanced MMP-3 and -9 levels in severe disease subtypes (Lemjabbar et al., 1999). Others propose that minor allelic single-nucleotide polymorphisms in the MMP-12 gene could affect FEV_1 among children with asthma (Hunninghake et al., 2009). Besides associating rs652438, a common gene variant of MMP-12, with disease severity in young asthmatic individuals, Mukhopadhyay et al show that pharmacologic inhibition of MMP-12 downregulates allergen-induced airway responses (Mukhopadhyay et al., 2010). In comparison to corticosteroid-treated asthmatics or healthy individuals, BAL resident TIMP-1 is increased in untreated asthma, implying that a potential MMP/TIMP imbalance could also orchestrate a pro-asthmatic phenotype (Mautino et al., 1999a; Mautino et al., 1999b).

ASM function is also modulated by (i) epithelial cell-derived mediator secretion post-viral infections or (ii) air pollutants due to loss of epithelial barrier function. (Chanez, 2005). Viral infections induce epithelial cell secretion such as IFNβ which inhibits ASM proliferation, shortening or pharmacological efficacy of anti-inflammatory agents (Banerjee et al., 2008; Tliba et al., 2008b). Similarly, destruction of the epithelium elicits altered ASM responses to environmental pollutants such as ozone, as demonstrated using co-culture (Damera et al., 2009c). Epithelium also expresses mediators such as prostanoids, leukotrienes, cytokines and nitric oxide which mitigate airway bronchomotor tone (Chitano, 2011). Furthermore, epithelium-derived enzymes such as acetylcholinesterase, N-methyltransferase, angiotensin-converting enzyme and neutral endopeptidase regulate neural transmission within airways (Knight & Holgate, 2003; Spina, 1998). Studies show that post RV infections, epithelium mediates desensitization of the β2-adrenergic receptor on ASM (Trian et al., 2010). Upon injury, bronchial epithelium modulates myocyte proliferation through MMP-9 secretions or via growth factors (Malavia et al., 2009).

2.5 Asthma and ASM: Altered cell signaling

As mainstay therapy in asthma, glucocorticoids suppress inflammation by complex interactions involving their cognate nuclear receptors, glucocorticoid receptors (GR). Although studies correlate impairment in GR expression or mutations in genes encoding these receptors to asthma, no evidence exists on the direct contributory function of these receptors to asthma (Adcock et al., 1996; Corrigan et al., 1991; Lane et al., 1994). While most pharmacological effects elicited by glucocorticoids involve GR-activation, downstream signaling divergence is illustrated by studies where glucocorticoids diminish serum-stimulated IL-6, yet fail to alter proliferative responses in cells from individuals with asthma. Despite comparable levels of GR in ASM derived from asthma patients, decreased levels of co-transcription factor C/EBPα may diminish transcription of glucocorticoid-induced anti-proliferative protein $p21^{(Waf1/Cip1)}$. Compensatory induction of C/EBPα by transfection of ASM from subjects with asthma restores antiproliferative effects of glucocorticoids (Roth et al., 2004). Similarly, Damera et al suggest that inhibiting mitogen-induced phosphorylation of retinoblastoma protein (Rb) and Chk1 proteins by calcitriol inhibits ASM growth in a corticosteroid-independent manner (Damera et al., 2009a). In ASM, TGFβ induces PI3K-mediated release of VEGF and IL-6 which in turn modulates cell proliferation and angiogenesis (Johnson et al., 2006; Shin et al., 2009). As compared to asthmatic ASM, specific inhibition of p110 β isoform of PI3K alone differentially attenuates TGFβ-mediated secretion in normal tissue, implying an altered role of PI3K isoforms in asthma (Moir et al., 2011). While mitogens induce proliferation via ERK and PI3K in normal ASM, intrinsic abnormalities in expression of the endogenous ERK inhibitor, MKP-1, promote predominance of the PI3K proliferative pathway within ASM from individuals with asthma (Burgess et al., 2008). Studies by John et al suggest that increased binding of transcription factors such as NF-κB, C/EBPβ and RNA Pol II to the CXCL-8 promoter modulates pro-inflammatory outcomes in asthmatic ASM (John et al., 2009). Multiple stimuli that modulate inflammation, proliferation and asthma also activate NF-κB transcription factors, and disruption of NF-κB activation through expression of a superrepressor form of IKBα substantially impairs proliferation (Brar et al., 2002; Clarke et al., 2009; Damera et al., 2009b). Explaining increased mitochondrial mass and oxygen consumption in asthmatic ASM, Trian et al show differences in mitochondrial biogenesis and expression of transcription factors such as peroxisome proliferator-activated receptor γ co-activator (PGC)-1α, nuclear respiratory factor-1 (NRF-1) and mitochondrial transcription factor A (mtTFA) in ASM derived from asthma, COPD and normal populations (Trian et al., 2007).

3. Summary and future directions

Although asthma pathophysiology represents the complex interactions among structural and trafficking cell populations, this summary identifies factors and signaling events within ASM that promote an asthma phenotype. Evidence supports that altered cell function in cultured ASM derived from individuals with asthma exists and supports the hypothesis that an intrinsic ASM phenotype likely occurs in asthma. With this insight, focusing on the development of new pharmacological approaches that target ASM may offer unique approaches in asthma therapy.

4. References

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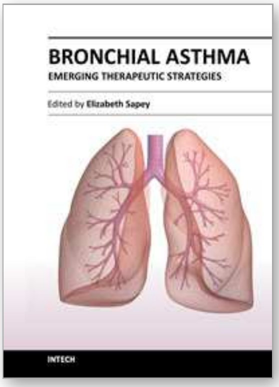

Bronchial Asthma - Emerging Therapeutic Strategies
Edited by Dr. Elizabeth Sapey

ISBN 978-953-51-0140-6
Hard cover, 260 pages
Publisher InTech

Published in print edition February, 2012

Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

How to reference

Gautam Damera and Reynold A. Panettieri, Jr. (2012). Airway Smooth Muscle: Is There a Phenotype Associated with Asthma?, Bronchial Asthma - Emerging Therapeutic Strategies, Dr. Elizabeth Sapey (Ed.), ISBN: 978-953-51-0140-6, InTech, Available from: http://www.intechopen.com/books/bronchial-asthma-emerging-therapeutic-strategies/airway-smooth-muscle-is-there-a-phenotype-associated-with-asthma-

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