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TARGETING THE AIRWAY SMOOTH MUSCLE FOR ASTHMA TREATMENT

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Abstract

Asthma is a complex respiratory disease whose incidence has increased worldwide in the last decade. There is currently no cure for asthma. While bronchodilator and anti-inflammatory medications are effective medicines in some asthmatic patients, it is clear that an unmet therapeutic need persists for a subpopulation of individuals with severe asthma. This chronic lung disease is characterized by airflow limitation and lung inflammation and remodeling that includes increased airway smooth muscle (ASM) mass. In addition to its contractile properties, the ASM also contributes to the inflammatory process by producing active mediators, modifying the extracellular matrix composition, and interacting with inflammatory cells. These undesirable functions make interventions aimed at reducing ASM abundance an attractive strategy for novel asthma therapies. There are at least three mechanisms that could limit the accumulation of smooth muscle – decreased cell proliferation, augmented cell apoptosis, and reduced cell migration into the smooth muscle layer. Inhibitors of the mevalonate pathway or statins hold promise for asthma because they exhibit anti-inflammatory, anti-migratory, and anti-proliferative effects in pre-clinical and clinical studies, and they can target the SM. This review will discuss current knowledge of ASM biology and identify gaps in the field in order to stimulate future investigations of the cellular mechanisms controlling ASM overabundance in asthma. Targeting ASM has the potential to be an innovative venue of treatment for patients with asthma.

Keywords

airway smooth muscle; asthma; contractile; cytokine; hyperplasia; hypertrophy; inflammation; mevalonate; progenitor cells; statins; TGF beta; translational

The Smooth Muscle in Lung Diseases: An Overlooked Target for Therapy

The majority of the smooth muscle present in the human lung localizes within two major compartments, the vasculature and the airways. The function of the pulmonary vascular smooth muscle (VSM) in maintaining appropriate gas exchange is well established. The peristaltic activity of the ASM is known to contribute to the normal branching of the respiratory tree during lung embryogenesis (1) (2). While ASM plays a central role in regulating the airway caliber, the real function of the ASM in the adult lung remains unclear and controversial. It has

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been suggested that ASM can assist with mucus clearance (3) or that ASM is vestigial and unfortunately, prone to disease (4). Interestingly, these hypotheses do not take into consideration the secretory properties of the ASM cells that have been described recently.

Abnormal presence of smooth muscle in the lung occurs in some common as well as less frequent respiratory pathologies. For example, increased ASM mass due to hypertrophy and hyperplasia (5) (6) (7) is a key feature of asthma, a chronic syndrome characterized by airway inflammation, excessive mucus production, airway hyperresponsiveness (AHR) and lung remodeling (8). Although not firmly established yet, it is likely that each of these characteristics contributes in different degrees to the genesis of airflow obstruction seen in asthmatics.

Abnormal appearance of nodules of smooth muscle-like cells (9) (10) (11) is a hallmark of lymphangioleiomyomatosis (LAM) (12), a rare disease that affects mostly women of young age (13). Augmented smooth muscle abundance is also present in the small airways of patients with chronic obstructive pulmonary disease COPD (14) (15), a respiratory condition of millions of smoker and non-smoker adults.

Overabundant smooth muscle mass within the remodeled airways of asthmatic patients would have important consequences in lung function (16) that stem from at least two potential mechanisms. First, an increase in ASM abundance may exacerbate airway contraction resulting in more pronounced airway narrowing. Second, the discovery that the ASM myocyte produces a plethora of biologically active agents like pro- and anti-inflammatory mediators, cell adhesion molecules, lipid mediators, chemokines and cytokines (17) suggests that the ASM cells are active participants in the pathophysiology of this disorder. It seems thus reasonable to expect that diminution of the overabundant airway smooth musculature would alleviate some symptoms exhibited in asthmatics by improving air flow. Current interventions for asthma include the use of steroids to control lung inflammation, and short and long acting β -2-adrenoceptor agonists that modulate the contractile function of the ASM. Lately, drugs such as leukotriene-receptor antagonists (18) and anti-immunoglobulin E (19) have been added to the arsenal for asthma treatment with some success. However, with the exception of bronchial thermoplasty that results in removal of airway muscle tissue (discussed below), there are no therapeutic approaches that restrict the increase in ASM mass and/or affect ASM synthetic properties. The paucity of approaches to target ASM is due largely to our limited knowledge about the origin of the cells that constitute and maintain the adult airway smooth muscle tissue, the turnover rates of the airway smooth muscle myocyte in normal and pathological conditions and the mechanism that regulate these processes (20). Understanding these key issues will be essential for the development of new treatment strategies that target airway smooth muscle remodeling.

Origins of Excess Smooth Muscle in the Airway

There are various potential, not mutually exclusive processes that could contribute to the remodeling of the smooth muscle within the airway wall. They include ASM myocyte proliferation and migration, fibroblast activation and differentiation into myofibroblasts, and recruitment of circulating fibrocytes and circulatory mesenchymal progenitor cells into the airway wall (Figure 1). These processes, which are described below, represent potential targets of new therapeutics as shown by the rich literature describing the effect of pharmacological and molecular interventions on the proliferation, migration and survival characteristics of normal and diseased myocytes of the vasculature. However, with a few exceptions, this is in marked contrast with the lack of studies that focus on airway smooth muscle, especially from asthmatics. The contribution of lung stem cells and the role of epithelial–mesenchymal transition (EMT) to the genesis of ASM remodeling remain mostly unexplored and speculative.

Contribution from airway smooth muscle proliferation, migration

Several groups have demonstrated that ASM from asthmatics exhibit increased proliferation capacity *in vitro* compared to myocytes from non-asthmatic individuals (21). Unfortunately, no comparable studies are available that evaluate the migratory properties of smooth muscle myocytes from asthmatic vs. non-asthmatics. The impact of pharmacological agents, of drugs used in pulmonary medicine, and of some cell components on the migratory properties of normal ASM has been reviewed (22,23). It is clear that stimulation of ASM with growth factors and cytokines such as interleukin (IL)-8, transforming growth factor (TGF) β 1 and IL-1 β as well as with some extracellular matrix components like collagens, fibronectin and laminin promotes cell migration. Interestingly, many of these molecules are present at abnormal levels in asthmatic lungs. On the other hand, retinoic acid (24), the immunomodulatory agents rapamycin and corticosteroids as well as β -adrenergic agonists and theophylline, inhibit ASM migration in response to various attractants. Several studies showed that the signaling pathways involved in these cell responses include the p38 and ERK mitogen-activated protein kinases (MAPK), ROCK (Rho-activated kinase), phosphatidylinositol 3-kinase (PI3K) and protein kinase A (PKA), for which some specific inhibitors exist. The negative effect of the inhibitors of the mevalonate pathway (statins) on the proliferation and migration capabilities of the VSM myocytes has been widely demonstrated (25) (26), and a suppressive effect of simvastatin administration on proliferation of airway smooth muscle cells was recently reported (27). This suggests that, if similar inhibitory action on proliferation could be elicited in ASM cells of asthmatics, statins may alter airway remodeling.

Contribution of cell turnover

To fully understand how and why abnormal accumulation of smooth muscle occurs, we need to gain more knowledge on two related and poorly investigated areas. First, the turnover rates of human airway myocytes in health and disease are unknown. It was estimated using metabolic labeling that smooth muscle cells of mouse aorta divide with a half-life in the range of 300 (28) to 800 (29) days. On the basis of this observation, it would not be surprising to discover that the human airway smooth muscle, including that of asthmatic individuals, would turnover rather slowly. This prediction makes attempts at controlling abnormal smooth muscle expansion a challenge that is both intriguing and attractive: how to limit amassing more musculature which is in addition markedly stable? Second, little attention has been paid to the nature of the apoptotic and survival characteristics of the ASM myocyte, including the signals that it receives under diverse (patho)physiological conditions. In this regard, it is certain that the composition of the environment that surrounds the airway myocyte as well as its exposure to both altered mechanical stress during disease and new incoming cells and their products, will influence the ability of the smooth muscle cell to preserve its integrity. Consistent with this, proteases released from neutrophils results in matrix degradation and loss of myocyte cell attachment and consequently leads to human ASM cell apoptosis (30). Moreover, *ex vivo* studies revealed that decorin, an extracellular matrix proteoglycan, induces human ASM apoptosis (31) and interestingly, a decreased expression of decorin was documented in the airway wall of individuals with fatal asthma (32). However, a mechanistic link associating decorin expression and myocyte survival has yet to be established. We reported that Fas is expressed both in normal human ASM and on the surface of proliferating ASM cells in culture (33) suggesting that apoptosis may participate in normal smooth muscle turnover. In proliferating cultured cells, Fas-mediated apoptosis occurs by Fas crosslinking and is enhanced by TNF- α stimulation. However, non-proliferating differentiated airway myocytes exhibit decreased expression of Fas, and Fas-mediated apoptosis could be elicited only in the presence of TNF- α . Similarly, VSM cells are normally resistant to Fas or cytokine-induced apoptosis but can be sensitized with pharmacological concentrations of some statins (34). Interventions that enhance airway myocyte death seem worthy to explore and may prove to be critical to limit the exuberant ASM growth seen in asthma.

Contribution from other cell sources

The existence of intra-pulmonary and extra-pulmonary airway smooth muscle precursor cells is an exciting discovery that should open new lines of research to determine for instance, whether current asthma medicines have any effect on the number and activity of these cells. Studies using vessel allograft transplants in β -galactosidase transgenic mice recipients showed that some VSM cells in the intima layer were derived from circulating mesenchymal stem cells from the bone marrow (35). These cells express stem cell antigen 1 (Sca1), are negative for hematopoietic markers, and are distinct from fibrocytes.

Fibrocytes are CD34 positive circulatory cells that produce collagen I and are considered significant participants in lung remodeling. Indeed, studies with asthmatics showed that allergen exposure results in fibrocyte-like smooth muscle- α -actin positive cells accumulation in the subepithelium within areas rich in collagen deposition (36). Fibrocytes are increased in the bronchoalveolar lavage fluid (BALF) of steroid-naïve patients with mild asthma, and the number of the recruited fibrocytes in the airways correlate with the thickness of the basement membrane (37). Moreover, fibrocytes may contribute to airway obstruction in asthma because the number of these cells were increased in asthmatics with chronic airflow obstruction compared to asthmatics with no obstruction, and the decline in the forced expiratory volume in 1 second (FEV1) correlated with the percentage of circulating fibrocytes (38). This is consistent with pre-clinical studies in a mouse model of allergic asthma in which fibrocytes were found to be recruited into the lung and to differentiate into myofibroblasts following allergen exposure (36).

In addition to these circulatory bone marrow derived cells, a heterogeneous cell “side population” (SP) that excludes Hoechst dye in flow cytometry was isolated from the mouse lungs. SP cells can give rise to a variety of cell types *in vitro* including smooth muscle myocytes (39). These mesenchymal precursor cells are CD45 and CD31 negative and reside within the embryonic and adult lung parenchyma after removal of circulating cells and large airways (40). Elegant studies of cells derived from human lung allografts even after several years of transplantation demonstrate the existence of a multipotent mesenchymal cell population that resides within the adult donor lung (41). It is not clear yet whether any of these cell precursor sources contribute to airway remodeling during disease.

EMT has been mainly studied as a mechanism for generation of fibroblasts or myofibroblasts in fibrotic disorders, rather than for generation of smooth muscle cells. Thus, the role of EMT in the genesis of airway smooth muscle cells is hypothetical at the present time. The concept of the epithelial–mesenchymal unit communication in chronic asthma was introduced in the recent past (42). Alveolar as well as bronchial EMT has been observed to occur *in vitro* (43) as well as in elegant studies *in vivo* that demonstrated smooth muscle- α -actin positive cells in the subepithelium of bronchi and terminal bronchioles of bleomycin-treated mice (44) and also in epithelial cells isolated from antigen sensitized and challenged mice (45). TGF β , a cytokine abundant in asthma and other lung disorders (46) is a typical inducer of EMT in normal development and during carcinogenesis and fibrotic processes (47) (46). New studies have described the participation of novel pathways in addition to TGF β signaling in EMT. They include the activation of proteinase-activated receptor (PAR) 4 with thrombin that results, at least in culture, in morphological changes of cobblestone human primary alveolar epithelial cells into elongated cells (48). These alterations were accompanied by concomitant downregulation of epithelial markers and induction of smooth muscle- α -actin expression, a mesenchymal cell protein (48). It is important to note that there is still a controversy about the occurrence and role of EMT in humans as other groups have failed to detect expression of dual markers of mesenchymal and epithelial phenotype in specimens from normal lung parenchyma or from patients with idiopathic pulmonary fibrosis (49).

Targeting the Airway Smooth Muscle: Statins as Potential Medicines for Lung Diseases

At present, there is no cure for asthma. Good compliance to bronchodilators and anti-inflammatory medications together with educational and environmental measures are effective interventions for a large number of asthmatic patients. However, a subpopulation of individuals with severe asthma respond poorly to these medicines and thus, more successful therapies are desired (50). On the basis of investigations from several groups, a few promising molecular targets within the ASM has been identified, and a recent review summarized the status of drugs that aim or could aim the contraction, the remodeling, and the inflammation aspects of the ASM (51). We suggest the addition of two promising interventions to that list, bronchial thermoplasty and the use of inhibitors of the mevalonate pathway or statins.

Bronchial thermoplasty (52) is a novel bronchoscopic procedure that delivers heat through radiofrequency waves that results in reduction of the muscle mass in the airways of animal models of lung remodeling and in asthmatic patients (52). Subjects who underwent bronchial thermoplasty experienced diminishing smooth muscle-mediated bronchoconstriction (53), and prospective clinical trials demonstrate that bronchial thermoplasty can help control asthma symptoms and stabilize the disease by diminishing the number of episodes of bronchospasm and exacerbations (54). The procedure appears to be safe (55) and significant decreased bronchial hyperresponsiveness was observed in various studies after 12 months of treatment (53). Five-year follow-up evaluations are currently underway and they will determine the long term effects of bronchial thermoplasty.

Statins are inhibitors of the synthesis of mevalonate, the building block of cholesterol and isoprenoids. These medicines became the first-line therapy for the primary and secondary prevention of coronary artery disease. Statins reduce the levels of blood cholesterol, which is a chief component of cell membranes and of caveolae, the specialized cellular structures wherein many receptors reside and whose activation initiates a variety of cellular responses (56). Isoprenoids are bioactive derivatives of the mevalonate pathway required for a myriad of cell functions some of which involve protein modification of the small G-protein RhoA. Notably, statins show additional beneficial effects in the cardiovascular, renal, musculoskeletal and nervous systems that are cholesterol-independent. These pleiotropic properties of statins comprise mechanisms that modify an array of molecular and cellular events that result in improved endothelial barrier function, reduced inflammatory cell migration, inhibition of platelet activation and thrombosis, and inhibition of smooth muscle contraction and migration as well. These statin actions are mediated through the inactivation of ROCK, reduction of oxidative stress, decreased cell proliferation, and enhanced apoptosis (reviewed in (57)). Several statins, including atorvastatin, lovastatin, fluvastatin, simvastatin, pravastatin, and cerivastatin share these properties although they also exhibit some distinct efficacies (58). Despite their wide range of actions, HMG-Co A reductase inhibitors have relatively few adverse effects and surveillance for muscle or liver damage allows broad indication of their use (59).

In pre-clinical settings, a large body of studies *ex vivo* and in models of several lung insults has examined various aspects of statin actions. For instance, it was reported favorable effects of simvastatin like attenuation in the increase in pulmonary artery pressure and inhibition of vascular remodeling in a rat model of chronic pulmonary hypertension (60), reversal of pulmonary arterial neointimal formation after a toxic injury in rats (61), and regression of established chronic hypoxic pulmonary hypertension in rats (62). Statins also slowed the development of smoking-induced emphysema in rats with reduction in matrix metalloproteinase (MMP)-9 activity. In a mouse model of allergic airway inflammation, statin administration decreased the magnitude of inflammatory cell infiltrate and eosinophilia and reduced the levels of IL-4 and IL-5 in BALF as well (63). Furthermore, evidence for the anti-inflammatory

properties of statins in other conditions of the lung has been recently reviewed (64). Mast cells (MC) are critical components of the allergic process including asthma (65) because they release a diverse range of autacoid mediators, chemokines, cytokines and growth factors. Activated MCs infiltrate ASM bundles (66) and a physical contact between human ASM myocytes and human lung MC elicit changes that are relevant to the pathogenesis of asthma. For example, direct ASM-MC interaction promotes MC survival and proliferation, induces MC degranulation that is allergen-independent (67), and stimulates ASM differentiation to the contractile phenotype by an autocrine mechanism involving TGF β (66). Moreover, simvastatin inhibited the production of TNF- α and IL-6 from mouse activated MC (68). Interestingly, cerivastatin, atorvastatin, lovastatin to a lesser extent but not simvastatin or pravastatin inhibit growth and function of human MC (69). Studies on the immunomodulatory properties of statins is an extensive area of current research.

Among clinical studies, published and unpublished work report promising results of statin use in some lung disorders. An open-label study of patients with pulmonary hypertension demonstrated that simvastatin treatment was safe, improved 6-minute walk performance and cardiac output, and decreased right ventricular systolic pressures (70). Statin use among smokers and former smokers was associated with a slower decline in pulmonary function independent of the underlying lung disease (71). Fewer episodes of exacerbations and need of intubations were found in a retrospective cohort design of COPD patients who received statins compared to those with no such treatment (72). No clinical trial has directly evaluated however, the clinical effects of statins in patients with COPD in terms of induced sputum MMP profile, alveolar nitric oxide (NO) or pulmonary physiology. Notably, a prospective observational cohort study showed an association of prior therapy with statins with a reduced rate of severe sepsis and ICU admission (73). Finally, it was shown that the risk of both COPD (74) and influenza deaths was markedly reduced among moderate-dose statin users (75). Several clinical trials examining the effect of statins in septic and COPD patients are underway.

Statins and Asthma

There are two published reports about the use of statins in asthma. The first one by Menzies et al. is a randomized, placebo controlled, doubled-blind crossover trial of mild or moderate asthmatics (76). The protocol included withdrawal of all anti-inflammatory medications and a placebo run-in period prior to randomization to 4 weeks of simvastatin (20 mg/day for 2 weeks, then 40 mg/day for the next 2 weeks) or placebo. With the exception of a modest (14%) reduction in exhaled NO, a marker of lung inflammation, the study based on 16 participants (out of 26 who were recruited and 20 who were randomized) found no significant differences in doubling dilution shift in methacholine provocation, various inflammatory outcomes, lung volumes, or airway resistance between simvastatin and placebo. It is important to recognize that several study limitations might have precluded demonstrating a beneficial effect of simvastatin in this trial. They include the substantial number of drop-outs, the small sample size, a relatively short duration of the intervention, and the lack of clear definition of patients' asthma status. Furthermore, a study design that includes a withdrawal of all anti-inflammatory medications might have inadvertently led to a population with relatively mild asthma and therefore relatively little room for further improvement. The second study recently published by Thomson's group (77) reports no short-term improvement in asthma control in 54 adults with atopic mild to moderate asthma who received atorvastatin added to inhaled corticosteroids. This was an 8-week randomized, placebo controlled, doubled-blind crossover trial of 40 mg/day atorvastatin with 6-weeks washout period. The clinical outcomes that included morning peak expiratory flow, FEV1, asthma control questionnaire score, and responsiveness to methacholine were not different between the placebo and atorvastatin groups. However, there was a significant reduction in both leukotriene B4 and absolute macrophages counts in the sputum after atorvastatin compared with placebo. This is consistent

with a report that showed that cerivastatin diminished the accumulation of macrophages in aortic atheroma in rabbits, and reduced macrophage growth (78).

In contrast to these two negative reports, there is a third study (79) presented at the recent meeting of the American Academy of Allergy, Asthma and Immunology that demonstrated that statin exposure is associated with significant risk reduction for recurrent asthma-related hospitalizations and emergency room visits over one year in adult asthmatics with inhaled corticosteroid therapy. The main difference between this study and those mentioned above is the more severe nature of asthma suffered by the 6500 subjects who participated. This encouraging result is certainly consistent with the idea that beneficial effects of statins might be apparent in more severe asthma.

New Clinical Trails of Statins in Asthma

There are currently five clinical trials listed in ClinicalTrials.gov evaluating statins in asthmatic populations. One is the recently completed “Trial to Evaluate the Effect of Statins on Asthma Control of Patients With Chronic Asthma” carried out at the University of Glasgow by Dr. Thomson’s team that determined the effectiveness of oral atorvastatin in a 22-week randomized, double-blind, placebo controlled, crossover study. A second study, “Effect of Statins on Asthma Control in Smokers with Asthma + Pilot Study of Effect of Statins on Lung Function in COPD” by the same group is still ongoing. This is a randomized, placebo controlled, double-blind parallel group trial of atorvastatin in 80 asthmatics who are active smokers. Primary outcome is the change in peak flow after 8 weeks, and secondary outcomes are measures of sputum cell counts, exhaled and alveolar NO, lung function, immunological tests in blood, symptom scores, and exacerbation rates. The third trial, “Statin Treatment in Patients With Asthma” at Queen’s University is a randomized, double-blind, placebo controlled study on the effect of high dose atorvastatin (80 mg/day) for a short period (4 weeks) in 45 moderate to severe but stable asthmatics. The primary outcome is change in PC20 methacholine dose; and secondary outcomes include post bronchodilator FEV1, sputum eosinophil count, daily dose of inhaled corticosteroids, and number of exacerbations or infections during the study period. The forth study, “The Additive Anti-Inflammatory Effect of Simvastatin in Combination With Inhaled Corticosteroids in Asthma” is a phase III trial at the Mahidol University in Thailand. It is a randomized, double-blind, parallel, placebo control study to compare the additive effect of simvastatin plus inhaled corticosteroid (10 mg oral once daily; 1000 mcg/day of beclomethasone or equivalent) with vitamin B1-6-12 as placebo for 8 weeks on airway inflammation. The expected recruitment is 60 subjects with persistent asthma; and the primary and secondary outcome measures are eosinophil counts in induced sputum, and FEV1 and PC20, respectively. These four studies focus almost exclusively on the anti-inflammatory properties of statins, and together are likely to provide new insights into the efficacy of statins on asthma control. However, none of them is mechanistic or proposes to analyze potential effects of statins on structural cells in the asthmatic airway or to examine their impact on the smooth muscle that contributes to airway remodeling in bronchial asthma (27).

The fifth study listed is our clinical trial “Evaluation of Lovastatin in Severe Asthma (ELiSPA)”, which will test the novel hypothesis that inhibition of the mevalonate pathway with lovastatin has favorable effects on asthma by blocking the pathological increase of smooth muscle and lung inflammation. It is a double-blind, placebo control study in which we expect to obtain critical information about the underlying airway inflammation and to evaluate smooth muscle structure and biology as a primary outcome in biopsy specimens obtained by bronchoscopy before and after statin administration. Secondary outcomes are changes in asthma control, lung function, and quality of life. A pilot trial will enroll 12 non-smokers adults with severe asthma to receive oral lovastatin (20 mg/day for 4 weeks followed by 8 weeks of

60 mg/day) or placebo. We are using lovastatin because our pre-clinical data were obtained with this drug and because the pleiotrophic effects of individual statins differ. This raises the possibility that treatment with a different statin might produce a beneficial result not revealed by the other inhibitors used in the above mentioned trials. Evaluation of the primary outcome is supported by the described actions of statins in reducing accumulation of smooth muscle (80) through modulation of cell proliferation and apoptosis, and interference of expression of contractile-associated proteins (81) via disruption of RhoA activation. Perturbation of caveolae-dependent signaling could be considered an attractive biological outcome in future investigations.

It is plausible that statins might be effective co-therapies in asthma and may benefit patients who are resistant to treatment with glucocorticoids. For these reasons, further evaluation of statin effects on ASM biology in severe asthma remains warranted.

Future Directions

Successful asthma treatment should result in an efficient, lasting, and complete control of asthma symptoms, permanent restoration of healthier lung function parameters and ultimately, improvement of the molecular and histological abnormalities found in affected cells and tissues. Whether these goals can be accomplished with statin monotherapy or in combination with other medicines remain to be determined by the clinical trials. Although statins are remarkable in their safety profile, an infrequent side effect of statins is myopathy (82). Consistent with this, it was not surprising that we and others (27) showed a negative impact of lovastatin on cell viability of airway myocytes in culture. These observations indicate that the skeletal and smooth muscle may share a common mechanism of injury, i.e., mitochondrial myopathy, which has been suggested to occur during skeletal muscle loss and damage in some patients who received statins. Ironically, muscle damage that is detrimental for skeletal muscle structure and function in susceptible individuals could otherwise be a desirable feature to occur in the airways of severe asthmatics if it results in ablation of overabundant smooth muscle. This adverse effect might seem to challenge the usefulness of statins for asthma treatment. However, there are scenarios that could lessen this concern. First, whether the potential beneficial effect of statins in the airway musculature could manifest much sooner than their deleterious consequences on the body musculature is an open question. Second, it is conceivable that the negative effects of statins on the skeletal muscle could be confined to a subpopulation of susceptible individuals. In this regard, a recent genome-wide study of patients taking statins identified a strong association between myopathy and two variants in the *SLCO1B1* gene, present in 15 % of European descendents (83). This finding was confirmed in patients in a second randomized trial of simvastatin. Third, it is possible that different statins might exert differential actions on the skeletal musculature vs. the smooth muscle. For example, pitavastatin and simvastatin but not pravastatin enhanced the oxidant-induced apoptosis of VSM through a mechanism that requires protein prenylation (84). Moreover, Kiyan et al. reported interesting effects of rosuvastatin in VSM depending on whether the myocytes exhibit the proliferative or the differentiate phenotype (85). Thus, in porcine coronary artery organ culture, rosuvastatin was able to decrease injury-induced neointima formation and proliferation of medial VSMC, inhibit migration and proliferation of dedifferentiated human coronary VSMC, prevent serum-dependent dedifferentiation of vascular myocytes, and induce expression of markers of the contractile phenotype in long term serum-deprived cells. Parallel pre-clinical studies comparing the intensity of cell damage of skeletal and smooth muscle myocytes both *in vivo* and *in vitro* models elicited by diverse statins will surely enlighten this important issue.

The favorable prospect of statin administration in asthmatics needs to consider any potential adverse effect of premature termination of statin use. From the cardiovascular literature,

retrospective studies of clinical trials in patients with myocardial infarction and with ischemic and acute coronary syndromes revealed that the beneficial effects of statins on acute outcomes are lost, and that hospital morbidity and mortality rates are increased if statins are interrupted during hospitalization. This was likely the consequence of the absence of the therapeutic effect of statins, the lack of enhanced NO production, and a defective downregulation of angiotensin receptors (86), endothelin-1, vascular adhesion molecules and inflammatory cytokines (87) upon statin withdrawal. Whether discontinuation of statins is also harmful in patients who suffer chronic cardiovascular conditions was not examined. Results from such studies as well as from planned experiments in animal and cell models could be of interest and value in light of the current clinical trials of statins in chronic respiratory disorders including asthma.

An area of interest derived from animal and human studies is the suggestion that statins could affect airway smooth muscle remodeling by a mechanism that targets muscle cell precursors. For instance, measures of mRNA expression in blood mononuclear cells of healthy volunteers demonstrated that pravastatin significantly decreased the number of smooth muscle progenitor cells derived from the bone marrow (88). Surprisingly, this effect was cell selective because pravastatin increased, instead, the amount of endothelial progenitor derived cells from the same population. In addition, Lee et al. found that by suppressing the activity of RhoA, simvastatin inhibits the self-renewal capacity of mouse embryonic stem cell lines as determined by downregulation of specific stem cell markers and cell proliferation (89). Establishment of animal models of asthma using for example transgenic mice in which cell lineages can be traced and analyzed in the smooth muscle layer and airway wall will be useful in delineating the contribution of cell precursors to the smooth muscle of asthmatic and whether they are affected by statins.

Statins have become one of the most popular drugs worldwide in the last several years. This fact makes studies on the pharmacogenomics of statins timely and imperative. For low-density lipoprotein cholesterol lowering, more than 30 candidate genes likely involved in the pharmacokinetics and pharmacodynamics of statins have been investigated (90). Not surprisingly, no studies are reported yet that analyze the association of genetic variants with responses to statins in respiratory chronic diseases.

Concluding Remarks

Asthma has increased at epidemic proportions during the last decade. Although a cure is unlikely to be developed in the immediate future, greater understanding of the mechanisms that perpetuate the disease will bring a cure nearer to reality. Novel strategies such as inhaled p38 MAPK inhibitors and antioxidants that target specific pathways or mediators may prove helpful in severe asthma as monotherapies or in combination (91). Although asthma exhibits functional and structural abnormalities in various cell types, the ASM is with no doubt a major player in this disorder. It remains to be seen whether bronchial thermoplasty or the development of new medicines that target the abnormal ASM will provide significant and persistent clinical benefit. In the meantime, better understanding of the multifaceted actions of statins coupled with a clearer elucidation of the mechanisms that contribute to airway smooth muscle remodeling hold promise for improving outcomes in severe asthmatics. Various clinical trials are underway that interrogate the anti-inflammatory effects of statins and their impact on smooth muscle biology. Additional translational studies will be needed to discover specific genetic, genomic or biochemical markers that will assist in establishing whether excess asthmatic muscle cells originate from a defined cell progenitor and/or through the expansion of differentiated cells. Moreover, it is anticipated that specific phenotypic alterations of the airway smooth musculature in asthma will be relevant to the pathophysiology of the disease and correlate with distinctive individual genetic makeup. Although a complete analysis of each

patient's genome, proteome, and kinome is beyond today's technology, this information will eventually lead to patient- centered rational therapies for asthma in the not so distant future.

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Abbreviations

AHR	airway hyperresponsiveness
ASM	airway smooth muscle
BALF	bronchoalveolar lavage fluid
COPD	chronic obstructive pulmonary disease
EMT	epithelial–mesenchymal transition
FEV1	forced expiratory volume in 1 second
IL	interleukin
MAPK	mitogen-activated protein kinases
MC	mast cell
MMP	matrix metalloprotease
NO	nitric oxide
PI3K	phosphatidylinositol 3-kinase
ROCK	Rho-activated kinase
TGF	transforming growth factor
VSM	vascular smooth muscle

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* Potential statin-sensitive events

Figure 1. Origins and Causes of Excess Smooth Muscle in the Airway

Hypothetical cell sources that could contribute to the excessive abundance of smooth muscle in asthma comprise circulatory extra-pulmonary cells (boxes) and cells commonly residing in the lung (smooth muscle myocytes and other mesenchymal cells) including progenitor cells. Some of the processes and bioactive molecules (italics) suspected to promote remodeling of smooth muscle are potential targets for statins (asterisks). Less information is available for some of these candidate paths (broken arrows) making them attractive to further investigation.