CHEST Translating Basic Research Into Clinical Practice

Mechanisms of Airway Remodeling

Nobuaki Hirota, MD, PhD; and James G. Martin, MD, DSc

Airway remodeling comprises the structural changes of airway walls, induced by repeated injury and repair processes. It is characterized by the changes of tissue, cellular, and molecular composition, affecting airway smooth muscle, epithelium, blood vessels, and extracellular matrix. It occurs in patients with chronic inflammatory airway diseases such as asthma, COPD, bronchiectasis, and cystic fibrosis. Airway remodeling is arguably one of the most intractable problems in these diseases, leading to irreversible loss of lung function. Current therapeutics can ameliorate inflammation, but there is no available therapy proven to prevent or reverse airway remodeling, although reversibility of airway remodeling is suggested by studies in animal models of disease. Airway remodeling is often considered the result of longstanding airway inflammation, but it may be present to an equivalent degree in the airways of children with asthma, raising the necessity for early and specific therapeutic interventions. In this review, we consider the factors that may contribute to airway remodeling and discuss the current and potential therapeutic interventions.

CHEST 2013; 144(3):1026–1032

Abbreviations: ASM = airway smooth muscle; ASMC = airway smooth muscle cell; cysLT = cysteinyl leukotriene; EGFR = epidermal growth factor receptor; ICS = inhaled corticosteroid; PDGF = platelet-derived growth factor; RBM = reticular basement membrane; TGF-β = transforming growth factor-β; Th = T helper

Airway remodeling is the term used to describe the structural changes in the airway walls caused by repeated cycles of injury and repair. It is found in chronic inflammatory airway diseases such as asthma, COPD, bronchiectasis, and cystic fibrosis and is no doubt an important cause of irreversible airway narrowing and consequent constitutive airflow limitation. The mechanisms of airway remodeling have not been elucidated in human subjects, but useful insights have been obtained through modeling of disease.

Airway remodeling is generally considered to result from longstanding inflammation. However, studies suggest that mechanical stresses resulting from bronchoconstriction per se may also lead to remodeling.[1] Airway remodeling is found in children with severe asthma[2] and cystic fibrosis,[3] although the earliest age of onset is not known. Some studies show that airway smooth muscle (ASM) thickness is correlated with asthma severity, but not duration of asthma.[4] These observations suggest that the development of remodeling may be faster than generally envisaged.

Current therapeutics target the amelioration of inflammation and the reversal and/or prevention of bronchoconstriction. Corticosteroids, the major pillar of antiinflammatory asthma therapy, control airway narrowing and are effective against attacks of asthma, but they have not been shown to have a major effect on the aspects of remodeling that lead to decline in lung function. Given the fact that airway remodeling is observed in patients with asthma despite current therapies, novel therapeutic approaches for airway remodeling are required. In this article, we review the pathologic features and clinical relevance of airway remodeling and summarize current and potential targets for therapy.

Pathology

Asthma

Airway remodeling in asthma is characterized by an increase of ASM mass, epithelial cell hyperplasia,

Manuscript received December 24, 2012; revision accepted March 1, 2013.

Affiliations: From the Meakins-Christie Laboratories, Department of Medicine, McGill University, Montreal, QC, Canada.

Funding/Support: This work was supported in part by the Canadian Institutes of Health Research [Grant MOP-93747] and the Richard and Edith Strauss Canada Foundation.

Correspondence to: James G. Martin, MD, DSc, Meakins-Christie Laboratories, Department of Medicine, McGill University, 3626 St-Urbain, Montréal, QC, H2X 2P2, Canada; e-mail: james.martin@mcgill.ca

DOI: 10.1378/chest.12-3073

goblet cell metaplasia, reticular basement membrane (RBM) thickening (deposition of collagen, tenascin, and other matrix proteins adjacent to the basement membrane and in the subepithelial space), and angiogenesis (Figs 1A, 1B). Both hyperplasia and hypertrophy contribute to the remodeled ASM,[5] although these contributions may be patient specific, and the consequences for smooth muscle function may also differ. An increase of myofibroblasts in the subepithelial area is also observed, but loosely organized airway smooth muscle cells (ASMCs) are also found, suggesting two possible sources of new muscle that might add to existing bundles through directed migration.[6]

COPD

The main features of COPD lung are emphysema and airway wall thickening that both may lead to a reduced airway lumen size (Fig 1C). The destruction and loss of airways also contributes to reduced airflow.[7] Pathologic characteristics are airway epithelial cell hyperplasia, squamous cell and goblet cell metaplasia, RBM thickening, collagen deposition in the adventitia of the airway wall, peribronchial fibrosis, and angiogenesis. There is a loss of airway-parenchymal coupling through loss of alveolar attachments.

Cystic Fibrosis

Pathologic characteristics of cystic fibrosis lung include squamous metaplasia, submucosa mucus gland enlargement, increase of ASM mass, and RBM thickening (Fig 1D). Destruction and dilation of the airways is a prominent feature of the altered airway architecture.

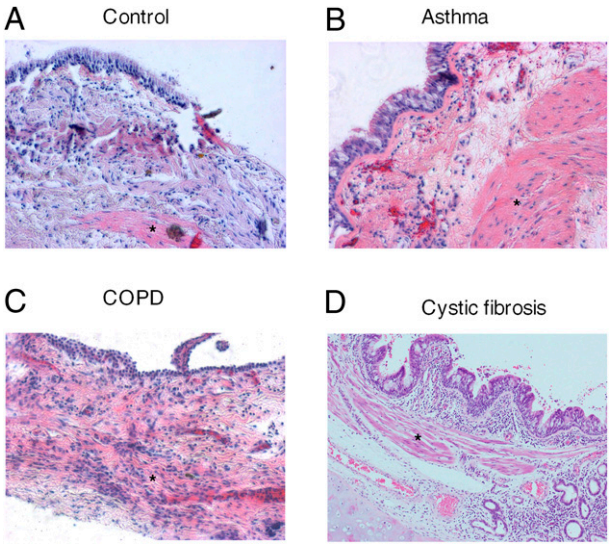

FIGURE 1. Hematoxylin and eosin staining of human airway samples (original magnifications × 100). A, Healthy control. B, Asthma. C, COPD. D, Cystic fibrosis. *Indicates airway smooth muscle.

Airway remodeling occurs in both large and small airways, but its characteristics may be different. Carroll et al[8] reported that the increase of smooth muscle occurred predominantly in small airways in nonfatal asthma, whereas it was found in both large and small airways in fatal asthma. James et al[5] observed hypertrophy of ASM in large airways in both fatal and nonfatal asthma, but they found hyperplasia of ASM in large and small airways only in fatal asthma. These studies may imply early establishment of airway remodeling in small airways.

Airway Inflammation and Remodeling Phenotypes

There are several studies showing the relationship between the phenotypes of airway inflammation and remodeling. It has been reported that eosinophilic asthma has more RBM thickening and airflow obstruction than noneosinophilic asthma.[9] Higher neutrophil counts in sputum correlate with airflow obstruction.[10] Airway eosinophilia and neutrophilia are independent of each other in asthma.

Clinical Relevance of Airway Remodeling

Although causal relationships are hard to establish, the frequency and reproducibility of association with lung function argue strongly for an influence on lung function. The increase of smooth muscle mass, a consistent feature of airway remodeling, correlates with lower lung function in patients with asthma.[11] In COPD, the more extensive the pathologic changes, including increase of ASM, squamous cell and goblet cell metaplasia, and fibrosis, the lower is lung function.[12] Patients with asthma and COPD with fixed airflow obstruction exhibited a more rapid decline in lung function and experienced more frequent exacerbations in a 5-year follow-up compared with patients with asthma with reversible airflow obstruction.[13] In cystic fibrosis, the increase of inner wall and smooth muscle area are even greater than COPD, and these dimensional changes presumably contribute to severe airflow limitation.[14]

Some investigators have argued for a favorable effect of some aspects of remodeling. For example, airway wall stiffness due to RBM thickening was reported to reduce mucosal folding during smooth muscle contraction, diminishing the magnitude of airway obstruction.[15] The advantages to the host of many aspects of airway remodeling are hard to argue.

Imaging Techniques to Detect Remodeling

The improvement of the resolution by CT scanning has enabled the measurement of airway dimensions

in relatively large airways.[16] Measuring airway wall thickness remains a challenge, and because CT scanning is incapable of analyzing the airway composition, it cannot distinguish between true increase in airway wall thickness from remodeling and the effects of bronchoconstriction that will increase airway area for a given lumen size. There are emerging techniques that have been applied during bronchoscopy to assess airway structure. Optical coherence tomography, a light-based imaging technique, has been used to quantify large airways distensibility,[17] and fibered confocal fluorescence microscopy has been used to visualize elastic fibers in central airway walls.[18]

Current Treatments of Airway Remodeling: Clinical Studies and Animal Models

No therapy is currently demonstrated to unequivocally prevent or reverse airway remodeling. Here, we summarize the effects of current therapeutics and the factors contributing to airway remodeling drawn from both clinical studies and animal models[19-27] (Table 1).

Many drugs have been shown to prevent allergen-driven airway remodeling in animal models, but there are few studies that demonstrate their ability to reverse established airway remodeling. Since airway remodeling occurs even in childhood asthma, it is possible that airway remodeling is already present in many patients with asthma at the time of onset of clinical disease. It is, therefore, pertinent to ask ourselves if remodeling is even potentially reversible. In this respect, the recent publication by Leclere et al[28] showing the partial reversal of ASM remodeling in horses with heaves, a naturally occurring asthma-like disease, following antigen avoidance as well as corticosteroid treatment provides a basis for optimism. The appropriate time to initiate therapeutic interventions deserves further consideration in addition to the search for novel therapeutic targets.

Table 1—*Effects of Current Therapies in Clinical Trials and Animal Models*

Therapy	Effects
ICS	Clinical trials
	Reduction of RBM thickness[21]
	Improvement of vascular remodeling[22]
	Decrease of α-smooth muscle actin area in peripheral airways[24]
	Animal models
	Inhibition of all the structural changes[25]
	Does not reverse the established changes
ICS + LABA	Clinical trials (additional effects of LABA)
	Improvement of vascular remodeling[26]
Montelukast	Animal models
	Inhibition of ASM mass increase, goblet cell metaplasia, epithelial cell hyperplasia[28]
	Reverse of ASM mass increase, subepithelial fibrosis[29]
Tiotropium	Animal models
	Inhibition of ASM mass increase, goblet cell metaplasia[30,31]

ASM = airway smooth muscle; ICS = inhaled corticosteroid; LABA = long-acting β-adrenoreceptor agonist; RBM = reticular basement membrane.

There are no studies reporting efficacy of therapies for cystic fibrosis airway remodeling. Indeed, this disease is not well modeled by cystic fibrosis transmembrane conductance regulator-deficient mice, but the porcine model shows more promise.[29] Although bronchiectasis is likely intractable, the aspect of airway remodeling that may lead to the asthma syndrome often accompanying cystic fibrosis may be amenable to treatment.

Inhaled Corticosteroids

Several clinical studies show that inhaled corticosteroid (ICS) reduces RBM thickness,[19] although the clinical significance of such an effect is quite uncertain, and its impact on airway function seems unlikely to be major. Vascular remodeling reportedly improves with high-dose fluticasone.[20] Whether the excessively rapid airway rewarming seen in patients with asthma after the cooling induced by hyperpnea challenge is attributable to excess vasculature or to vasodilation of existing vessels is not known. Its clinical significance is likewise uncertain but has been attributed a role in exercise-induced bronchoconstriction.[30] A decrease of α-smooth muscle actin area in peripheral airways harvested by transbronchial biopsy in subjects treated with ICS has been reported, suggesting reversibility of this lesion in peripheral airways.[21] In rat asthma models, aerosolized corticosteroid inhibits all the structural changes induced by repeated allergen challenge, including increase of ASM mass, but does not reverse established change.[22] Whether there is an additional benefit of the combination of ICS and long-acting β-adrenoreceptor agonist has not been proven in airway remodeling, with the exception of the reported improvement of vascular remodeling.[23] ICS is reported to reduce bronchial vascular remodeling in patients with COPD.[31]

Cysteinyl Leukotrienes

Cysteinyl leukotrienes (cysLTs) (LTC_4, LTD_4, LTE_4) are lipid mediators synthesized from arachidonic acid. Montelukast (a cysLT receptor 1 inhibitor) has been shown to inhibit the increase of ASM mass, goblet cell metaplasia, and epithelial cell hyperplasia in a rat model of allergic asthma.[24] Exogenous administration of LTD_4 reproduces these effects. Montelukast inhibits

but also reverses the increase of ASM mass and subepithelial fibrosis in a mouse asthma model.[25] No studies of the effect of leukotriene modifiers have been performed in human subjects with respect to airway remodeling.

Tiotropium

Somewhat surprisingly, tiotropium, a long-acting muscarinic receptor antagonist, inhibited the increase of ASM mass and goblet cell metaplasia in allergen-challenged guinea pigs[26] and mice.[27] In animal COPD models, tiotropium has been shown to inhibit goblet cell metaplasia, mucin production, and vascular remodeling but to have no effect on airspace enlargement.[32] Although bronchoconstriction per se may release growth-promoting molecules from airway epithelium, it is not clear whether the effects of tiotropium are mediated by affecting airway mechanics or through predominantly biochemical processes. The effect of tiotropium on airway remodeling has not been evaluated in human subjects.

Anti-T Helper 2 Cytokine Therapies

T helper (Th) 2 lymphocytes are present in airways of patients with asthma and synthesize and release the signature cytokines IL-4, IL-5, and IL-13. They modulate the airway inflammatory response, causing eosinophilia, enhancing IgE synthesis, and promoting airway hyperresponsiveness. Animal experiments have implicated IL-13 in goblet cell metaplasia and subepithelial collagen deposition using IL-13-deficient mice and by administration of IL-13 itself or of molecules neutralizing its effects. IL-13 causes up-regulation of contractile processes in ASMC but may not influence ASM mass. However, clinical trials have shown little or no effect of anti-IL-13 antibody therapy on lung function,[33] which may or may not be a suitable surrogate for airway remodeling.

Effects of IL-5 on airway remodeling are controversial in asthma models using IL-5 knockout mice and anti-IL-5 antibodies. IL-5 has not been proven to be involved in the increase of ASM mass. Clinical trials have shown little or no effect of mepolizumab (an anti-IL-5 antibody) on lung function,[34] but a study of matrix protein in the airway wall suggests some favorable effects mediated indirectly and attributed to the reduction of the fibrogenic cytokine transforming growth factor-β (TGF-β) that is synthesized by eosinophils.

IL-4 knockout mice were shown to be protected from airway collagen deposition in a mouse asthma model, but less impact on smooth muscle remodeling was noted. Again, effects on airway remodeling in humans have not been reported.

Omalizumab (Anti-IgE Antibody)

IgE is bound to mast cells and causes their activation when cross-linked by antigen binding. Mast cells release various mediators, such as histamine, serotonin, and cysLTs, capable of promoting airway remodeling. Mast cells are found in the smooth muscle bundles in patients with asthma. Omalizumab was reported to improve lung function slightly.[35] Its effect on airway remodeling has not been addressed. Further long-term clinical studies examining airway remodeling would be of considerable interest.

Epidermal Growth Factor Receptor Signaling

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase, and its signaling modulates cellular events such as cell adhesion, migration, and proliferation. EGFR signaling has been reported to be involved in a number of aspects of airway remodeling. Increase of ASM mass, goblet cell metaplasia, and epithelial cell hyperplasia are inhibited by AG1478, an EGFR tyrosine kinase inhibitor, in a rat "asthma" model.[24] Among the EGFR ligands, expression of heparin-binding epidermal growth factor, but not EGF, was upregulated in airway epithelium in this model. Other work using mouse "asthma" models also supports the involvement of EGFR signaling in the pathogenesis of airway remodeling.[36] Another EGFR ligand, TGF-α, was reported to cause fibrosis in transgenic mice.[37] Moreover, it was shown that the effect of cysLTs on airway remodeling was partially through the EGFR signaling.[24] Mechanical stress releases heparin-binding epidermal growth factor from the epithelial cells,[38] suggesting the possibility that bronchoconstriction per se might promote aspects of remodeling.

Imatinib

Imatinib is a tyrosine kinase inhibitor used for the treatment of chronic myeloid leukemia by inhibiting BCR-ABL kinase activity. It can also block other factors, such as c-kit ligand, stem cell factor, and platelet-derived growth factor (PDGF) receptor tyrosine kinase activity. It was reported to block the increase of ASM mass in a mouse asthma model.[39]

PDGF Signaling

PDGF receptor is a receptor tyrosine kinase. Its signaling, known as a cell migration inducer, also causes ASMC proliferation.[40] Hirota et al[41] showed its plausibility as an agent of remodeling by demonstrating an increase of ASM mass and cellular proliferation using an adenovirus-mediated PDGF overexpression mouse asthma model.

Transforming Growth Factor-β

TGF-β is a pleiotropic cytokine, which was reported to increase in the asthmatic airways.[42] Its expression can be detected in both immune cells (eosinophils, lymphocytes) and structural cells (epithelium). In a COPD mouse model, Podowski et al[43] showed the improvement of subepithelial collagen deposition and airway wall thickening by inhibition of TGF-β.

Eotaxin (CCL26)

Eotaxin (CCL26) is a chemokine that is known for its potent chemoattractant effect for eosinophils. Using a mouse model, Wegmann et al[44] reported that antagonizing CCR3, an eotaxin receptor, prevented some features of airway remodeling, goblet metaplasia, subepithelial fibrosis, and increase of number of myofibroblasts.

Potential Therapeutic Targets: In Vitro Studies

Based on the pathologic findings, the cellular events occurring in airway remodeling are smooth muscle hyperplasia and hypertrophy, epithelial cell hyperplasia and goblet cell metaplasia, subepithelial fibrosis, and neovascularization. Smooth muscle hyperplasia is inferred by the increase of their proliferation and migration. Asthmatic ASMCs in culture retain the property of more rapid proliferation rates compared with normal ASMC.[45] ASMC migration toward the airway epithelium has been suggested from the findings on proximal asthmatic airway bronchial biopsy samples.[46] It is postulated that ASMC migration may be a contributor to the expansion of smooth muscle bundles. We summarize in vitro studies relevant to airway remodeling in Table 2.[47-57]

Table 2—*A Summary of In Vitro Studies About Airway Remodeling*

Factors	Effects
EGFR signaling	ASMC proliferation and migration Airway epithelial cell proliferation and differentiation[47]
CysLTs	ASMC migration[48] Augmentation of EGFR signaling[49] Release of EGFR ligands from epithelium
Chemokines	ASMC migration and proliferation[50] Modulation of fibroblast activity[51]
Th17-associated cytokines	ASMC proliferation and migration[52]
IL-13	ASMC migration and increased contractility[53] Airway epithelial cell proliferation and differentiation[54]
PDGF signaling	ASMC migration and proliferation[40]
VEGF	Vascular remodeling[55]
Angiopoietin-1 Angiopoietin-2	Vascular remodeling[55]
TGF-β	Fibrosis[56] ASMC proliferation and hypertrophy[57] Induction of the release of VEGF

ASMC = airway smooth muscle cell; CysLT = cysteinyl leukotriene; EGFR = epidermal growth factor receptor; PDGF = platelet-derived growth factor; TGF-β = transforming growth factor-β; Th = T helper; VEGF = vascular endothelial growth factor.

Perspectives

Physiologic scales and symptoms have been used to assess the clinical states of patients with asthma. Given the fact that asthma and COPD are inflammatory syndromes and complexes of several phenotypes that cause reversible or partial airway narrowing, more detailed classification of the patients and appropriate therapies for each group are necessary. For example, treatment strategies based on monitoring sputum eosinophil counts reduce asthma exacerbations.[58] However, we are lacking specific biomarkers that reflect airway remodeling.

Studies of remodeling in asthma and other airway diseases in human subjects are lacking, in large part because of a lack of suitable surrogates. Bronchoscopy and biopsy are invasive and labor-intensive. Application of morphometric techniques is tedious, rendering the study of remodeling by these methods unsuitable for widespread clinical application. Novel imaging techniques may provide research tools in the short term and perhaps ultimately may achieve clinical application. Airway remodeling is linked to fixed airway obstruction, and perhaps this outcome should receive more attention as a target for treatment.

It is unclear that the therapies targeting inflammation are enough to prevent airway remodeling. Among current therapies, ICSs in high doses shows some effect on airway remodeling in human subjects with asthma. It also has reversed the increased peripheral ASM in patients with asthma. Omalizumab has improved lung function in patients with asthma, although slightly. Further studies to measure its effect on airway remodeling are necessary. EGFR, its ligands and signaling pathways, Th17-associated cytokines, and chemokines may provide alternative potential targets for the therapy for airway remodeling.

Unsettled Questions

- Is airway remodeling reversible?
- When in the course of disease is therapeutic inter vention appropriate?
- What are the pertinent therapeutic targets? (ASM? Epithelial cells? Immune cells?)
- Can airway remodeling be assessed by noninvasive methods?

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Grainge CL, Lau LC, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med*. 2011; 364(21):2006-2015.
2. Payne DN, Rogers AV, Adelroth E, et al. Early thickening of the reticular basement membrane in children with difficult asthma. *Am J Respir Crit Care Med*. 2003;167(1):78-82.
3. Regamey N, Ochs M, Hilliard TN, et al. Increased airway smooth muscle mass in children with asthma, cystic fibrosis, and non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2008;177(8):837-843.
4. James AL, Bai TR, Mauad T, et al. Airway smooth muscle thickness in asthma is related to severity but not duration of asthma. *Eur Respir J*. 2009;34(5):1040-1045.
5. James AL, Elliot JG, Jones RL, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. *Am J Respir Crit Care Med*. 2012;185(10):1058-1064.
6. Gizycki MJ, Adelroth E, Rogers AV, O'Byrne PM, Jeffery PK. Myofibroblast involvement in the allergen-induced late response in mild atopic asthma. *Am J Respir Cell Mol Biol*. 1997; 16(6):664-673.
7. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365(17):1567-1575.
8. Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis*. 1993;147(2):405-410.
9. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med*. 1999;160(3):1001-1008.
10. Woodruff PG, Khashayar R, Lazarus SC, et al. Relationship between airway inflammation, hyperresponsiveness, and obstruction in asthma. *J Allergy Clin Immunol*. 2001;108(5): 753-758.
11. Pepe C, Foley S, Shannon J, et al. Differences in airway remodeling between subjects with severe and moderate asthma. *J Allergy Clin Immunol*. 2005;116(3):544-549.
12. Cosio M, Ghezzo H, Hogg JC, et al. The relations between structural changes in small airways and pulmonary-function tests. *N Engl J Med*. 1978;298(23):1277-1281.
13. Contoli M, Baraldo S, Marku B, et al. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol*. 2010;125(4): 830-837.
14. Tiddens HA, Koopman LP, Lambert RK, et al. Cartilaginous airway wall dimensions and airway resistance in cystic fibrosis lungs. *Eur Respir J*. 2000;15(4):735-742.
15. Wiggs BR, Hrousis CA, Drazen JM, Kamm RD. On the mechanism of mucosal folding in normal and asthmatic airways. *J Appl Physiol*. 1997;83(6):1814-1821.
16. de Jong PA, Müller NL, Paré PD, Coxson HO. Computed tomographic imaging of the airways: relationship to structure and function. *Eur Respir J*. 2005;26(1):140-152.
17. Williamson JP, McLaughlin RA, Noffsinger WJ, et al. Elastic properties of the central airways in obstructive lung diseases measured using anatomical optical coherence tomography. *Am J Respir Crit Care Med*. 2011;183(5):612-619.
18. Yick CY, von der Thüsen JH, Bel EH, Sterk PJ, Kunst PW. In vivo imaging of the airway wall in asthma: fibered confocal fluorescence microscopy in relation to histology and lung function. *Respir Res*. 2011;12(1):85.
19. Olivieri D, Chetta A, Del Donno M, et al. Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: a placebo-controlled study. *Am J Respir Crit Care Med*. 1997; 155(6):1864-1871.
20. Chetta A, Zanini A, Foresi A, et al. Vascular component of airway remodeling in asthma is reduced by high dose of fluticasone. *Am J Respir Crit Care Med*. 2003;167(5):751-757.
21. Bergeron C, Hauber HP, Gotfried M, et al. Evidence of remodeling in peripheral airways of patients with mild to moderate asthma: effect of hydrofluoroalkane-flunisolide. *J Allergy Clin Immunol*. 2005;116(5):983-989.
22. Vanacker NJ, Palmans E, Kips JC, Pauwels RA. Fluticasone inhibits but does not reverse allergen-induced structural airway changes. *Am J Respir Crit Care Med*. 2001;163(3 pt 1): 674-679.
23. Orsida BE, Ward C, Li X, et al. Effect of a long-acting beta2-agonist over three months on airway wall vascular remodeling in asthma. *Am J Respir Crit Care Med*. 2001;164(1):117-121.
24. Tamaoka M, Hassan M, McGovern T, et al. The epidermal growth factor receptor mediates allergic airway remodelling in the rat. *Eur Respir J*. 2008;32(5):1213-1223.
25. Henderson WR Jr, Chiang GK, Tien YT, Chi EY. Reversal of allergen-induced airway remodeling by CysLT1 receptor blockade. *Am J Respir Crit Care Med*. 2006;173(7):718-728.
26. Gosens R, Bos IS, Zaagsma J, Meurs H. Protective effects of tiotropium bromide in the progression of airway smooth muscle remodeling. *Am J Respir Crit Care Med*. 2005;171(10): 1096-1102.
27. Kang JY, Rhee CK, Kim JS, et al. Effect of tiotropium bromide on airway remodeling in a chronic asthma model. *Ann Allergy Asthma Immunol*. 2012;109(1):29-35.
28. Leclere M, Lavoie-Lamoureux A, Joubert P, et al. Corticosteroids and antigen avoidance decrease airway smooth muscle mass in an equine asthma model. *Am J Respir Cell Mol Biol*. 2012;47(5):589-596.
29. Stoltz DA, Meyerholz DK, Pezzulo AA, et al. Cystic fibrosis pigs develop lung disease and exhibit defective bacterial eradication at birth. *Sci Transl Med*. 2010;2(29):29ra31.
30. Kanazawa H, Asai K, Hirata K, Yoshikawa J. Vascular involvement in exercise-induced airway narrowing in patients with bronchial asthma. *Chest*. 2002;122(1):166-170.
31. Zanini A, Chetta A, Saetta M, et al. Bronchial vascular remodelling in patients with COPD and its relationship with inhaled steroid treatment. *Thorax*. 2009;64(12):1019-1024.
32. Pera T, Zuidhof A, Valadas J, et al. Tiotropium inhibits pulmonary inflammation and remodelling in a guinea pig model of COPD. *Eur Respir J*. 2011;38(4):789-796.
33. Gauvreau GM, Boulet LP, Cockcroft DW, et al. Effects of interleukin-13 blockade on allergen-induced airway responses in mild atopic asthma. *Am J Respir Crit Care Med*. 2011; 183(8):1007-1014.
34. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360(10):973-984.
35. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139(1):28-35.
36. Le Cras TD, Acciani TH, Mushaben EM, et al. Epithelial EGF receptor signaling mediates airway hyperreactivity and

remodeling in a mouse model of chronic asthma. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(3):L414-L421.
37. Hardie WD, Le Cras TD, Jiang K, Tichelaar JW, Azhar M, Korfhagen TR. Conditional expression of transforming growth factor-alpha in adult mouse lung causes pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol*. 2004;286(4):L741-L749.
38. Shiomi T, Tschumperlin DJ, Park JA, et al. TNF-α-converting enzyme/a disintegrin and metalloprotease-17 mediates mechanotransduction in murine tracheal epithelial cells. *Am J Respir Cell Mol Biol*. 2011;45(2):376-385.
39. Rhee CK, Kim JW, Park CK, et al. Effect of imatinib on airway smooth muscle thickening in a murine model of chronic asthma. *Int Arch Allergy Immunol*. 2011;155(3):243-251.
40. Simeone-Penney MC, Severgnini M, Rozo L, Takahashi S, Cochran BH, Simon AR. PDGF-induced human airway smooth muscle cell proliferation requires STAT3 and the small GTPase Rac1. *Am J Physiol Lung Cell Mol Physiol*. 2008;294(4):L698-L704.
41. Hirota JA, Ask K, Farkas L, et al. In vivo role of platelet-derived growth factor-BB in airway smooth muscle proliferation in mouse lung. *Am J Respir Cell Mol Biol*. 2011;45(3):566-572.
42. Redington AE, Madden J, Frew AJ, et al. Transforming growth factor-beta 1 in asthma. Measurement in bronchoalveolar lavage fluid. *Am J Respir Crit Care Med*. 1997;156(2 pt 1):642-647.
43. Podowski M, Calvi C, Metzger S, et al. Angiotensin receptor blockade attenuates cigarette smoke-induced lung injury and rescues lung architecture in mice. *J Clin Invest*. 2012;122(1):229-240.
44. Wegmann M, Göggel R, Sel S, et al. Effects of a low-molecular-weight CCR-3 antagonist on chronic experimental asthma. *Am J Respir Cell Mol Biol*. 2007;36(1):61-67.
45. Johnson PR, Roth M, Tamm M, et al. Airway smooth muscle cell proliferation is increased in asthma. *Am J Respir Crit Care Med*. 2001;164(3):474-477.
46. Joubert P, Hamid Q. Role of airway smooth muscle in airway remodeling. *J Allergy Clin Immunol*. 2005;116(3):713-716.
47. Hirota N, Risse PA, Novali M, et al. Histamine may induce airway remodeling through release of epidermal growth factor receptor ligands from bronchial epithelial cells. *FASEB J*. 2012;26(4):1704-1716.
48. Parameswaran K, Cox G, Radford K, Janssen LJ, Sehmi R, O'Byrne PM. Cysteinyl leukotrienes promote human airway smooth muscle migration. *Am J Respir Crit Care Med*. 2002;166(5):738-742.
49. Panettieri RA, Tan EM, Ciocca V, Luttmann MA, Leonard TB, Hay DW. Effects of LTD4 on human airway smooth muscle cell proliferation, matrix expression, and contraction In vitro: differential sensitivity to cysteinyl leukotriene receptor antagonists. *Am J Respir Cell Mol Biol*. 1998;19(3):453-461.
50. Takeda N, Sumi Y, Préfontaine D, et al. Epithelium-derived chemokines induce airway smooth muscle cell migration. *Clin Exp Allergy*. 2009;39(7):1018-1026.
51. Monzon ME, Forteza RM, Casalino-Matsuda SM. MCP-1/CCR2B-dependent loop upregulates MUC5AC and MUC5B in human airway epithelium. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(2):L204-L215.
52. Chang Y, Al-Alwan L, Risse PA, et al. TH17 cytokines induce human airway smooth muscle cell migration. *J Allergy Clin Immunol*. 2011;127(4):1046-1053.
53. Booth BW, Adler KB, Bonner JC, Tournier F, Martin LD. Interleukin-13 induces proliferation of human airway epithelial cells in vitro via a mechanism mediated by transforming growth factor-alpha. *Am J Respir Cell Mol Biol*. 2001;25(6):739-743.
54. Risse PA, Jo T, Suarez F, et al. Interleukin-13 inhibits proliferation and enhances contractility of human airway smooth muscle cells without change in contractile phenotype. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(6):L958-L966.
55. Kanazawa H, Nomura S, Asai K. Roles of angiopoietin-1 and angiopoietin-2 on airway microvascular permeability in asthmatic patients. *Chest*. 2007;131(4):1035-1041.
56. Postlethwaite AE, Keski-Oja J, Moses HL, Kang AH. Stimulation of the chemotactic migration of human fibroblasts by transforming growth factor beta. *J Exp Med*. 1987;165(1):251-256.
57. Xie S, Sukkar MB, Issa R, Khorasani NM, Chung KF. Mechanisms of induction of airway smooth muscle hyperplasia by transforming growth factor-beta. *Am J Physiol Lung Cell Mol Physiol*. 2007;293(1):L245-L253.
58. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*. 2002;360(9347):1715-1721.