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Genes and Pathways Regulating Decline in Lung Function and Airway Remodeling in Asthma.

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Asthma is a common disorder of the airways characterized by airway inflammation and by decline in lung function and airway remodeling in a subset of asthmatics. Airway remodeling is characterized by structural changes which include airway smooth muscle hypertrophy/hyperplasia, subepithelial fibrosis due to thickening of the reticular basement membrane, mucus metaplasia of the epithelium, and angiogenesis. Epidemiologic studies suggest that both genetic and environmental factors may contribute to decline in lung function and airway remodeling in a subset of asthmatics. Environmental factors include respiratory viral infection-triggered asthma exacerbations, and tobacco smoke. There is also evidence that several asthma candidate genes may contribute to decline in lung function, including ADAM33, PLAUR, VEGF, IL13, CHI3L1, TSLP, GSDMB, TGFB1, POSTN, ESR1 and ARG2. In addition, mediators or cytokines, including cysteinyl leukotrienes, matrix metalloproteinase-9, interleukin-33 and eosinophil expression of transforming growth factor-β, may contribute to airway remodeling in asthma. Although increased airway smooth muscle is associated with reduced lung function (i.e. forced expiratory volume in 1 second) in asthma, there have been few long-term studies to determine how individual pathologic features of airway remodeling contribute to decline in lung function in asthma. Clinical studies with inhibitors of individual gene products, cytokines or mediators are needed in asthmatic patients to identify their individual role in decline in lung function and/or airway remodeling.

Keywords: Airway remodeling; gene polymorphisms; lung function tests

INTRODUCTION

Asthma is a common disorder of the airways characterized by airway inflammation and by decline in lung function and airway remodeling. The estimated prevalence of asthma in the United States is approximately 8.6% for adults and 8.3% for children in 2016.1 In Korea, the prevalence of asthma is estimated as 3.1% of adults in 2017,2 and 5.3%–9.1% of children (age 6–15 years) in 2010. A subset of asthmatics develops decline in lung function and airway remodeling which this review focuses on. Airway remodeling is characterized by structural changes including airway smooth muscle hypertrophy/hyperplasia, subepithelial fibrosis due to thickening of the reticular basement membrane,
mucus metaplasia of the epithelium, and angiogenesis. Epidemiologic studies suggest that both genetic and environmental factors may contribute to decline in lung function and airway remodeling in a subset of asthmatics.

Epidemiologic studies of longitudinal lung function over a 15-year period in adult asthmatics compared to non-asthmatics demonstrated that asthmatics had a greater decline in forced expiratory volume in 1 second (FEV1) over time than non-asthmatic controls. In that large study of 17,506 subjects, asthmatics had a greater decline in FEV1 (38 mL/year) than non-asthmatics (22 mL/year). In addition, asthmatics who smoked tobacco had a greater decline in lung function than those who did not. Studies have also examined lung function changes in childhood asthmatics. As children have lungs that continue to grow until the age of 18 to 25 years, childhood asthmatics with airway remodeling may or may not attain normal lung function by adulthood before they exhibit decline in lung function. For example, longitudinal measurements of lung function in 684 childhood asthmatics followed up for 13 years demonstrated that those with persistent childhood asthma may have either normal lung function growth (25% of childhood asthmatics) or impaired lung function growth outcomes (75% of childhood asthmatics). A normal pattern of lung function growth in childhood is characterized by a normal steep increase during adolescence, a plateau in early adulthood and a gradual decline at old ages. Abnormal trajectories include 1) reduced lung function growth (i.e. do not attain normal adult lung function) (23% of childhood asthmatics), 2) normal lung function growth and an early decline in lung function (26% of childhood asthmatics), and 3) reduced lung function growth and an early decline in lung function (26% of childhood asthmatics). At the last lung function test in that 13-year longitudinal study of lung function in childhood asthma, 11% of childhood asthmatics met the global initiative of chronic obstructive lung disease criteria for lung function impairment that was consistent with chronic obstructive pulmonary disease (COPD).

Such longitudinal epidemiologic studies of lung function in adults and children with asthma demonstrate that the potential for a subset of adult asthmatics to progress with an accelerated lung function decline over time, or for a subset of childhood asthmatics either to not attain normal lung function and/or to have an accelerated decline in lung function. As not all asthmatics exhibit these lung function changes, it is likely that genetic and environmental factors contribute to the different patterns of lung function growth and/or decline in each asthmatic subject. In terms of genetic factors for decline in lung function in childhood-onset asthmatics, a recent genome-wide association study (GWAS) study investigated genes associated with decline in lung function in adults with self-reported childhood asthma who were adult tobacco smokers. Among 10,199 adult smokers, 730 (7%) reported childhood asthma. The subjects were smokers and reported a history of childhood asthma, had reduced lung function as adults, and an increased risk for COPD (odds ratio, 3.42; 95% confidence interval [CI], 2.81–4.18). Genetic associations were also found in these subjects who had childhood asthma with known asthma loci, including IL1RL1, IL13, LINC01149 and GSDMB. These findings in childhood asthmatics who smoke underscore the interaction of genetic factors in childhood asthma and environmental factors such as tobacco smoke in contributing to decline in lung function and the development of features of early COPD.

In this review, we provide update of advances in the understanding of the genetic and environmental factors contributing to pathways of decline in lung function and airway remodeling in asthma as well as highlight current gaps in our understanding.
GENES REGULATING DECLINE IN LUNG FUNCTION AND/OR AIRWAY REMODELING

A combination of genetic and environmental factors leads to the development of asthma. Although over 100 genes have been linked to the development of asthma, the most reproduced asthma-associated genes include IL33, IL1RL1, IL13, TSLP, HLA, GATA3, SMAD3 and genes localized to chromosome 17q12-21 (ORMDL3 and GSDMB). In addition, several genes (ADAM33, PLAUR, VEGF, IL13, CHI3L1, TSLP, GSDMB, TGFBI, POSTN, ESR1 and ARG2) have been associated with decline in lung function in asthma (Table 1) and/or the features of airway remodeling (Table 2) in the limited number of studies, and thus some of these observations require further replication and validation.

Table 1. Gene variants associated with decline in lung function in asthma

| Gene | Lung function associations | Study subjects | Study/year |
|------|---------------------------|----------------|------------|
| ADAM33 | rs528557 G/C | CC homozygotes had excess annual decline of FEV1 (−23.7 mL/yr) (P = 0.006) | 200 Dutch Caucasians with asthma | Jongepier/2004 |
| PLAUR | rs2356338 G/T | TT homozygotes had more rapid annual FEV1 decline (−34.8 mL/yr vs. −22.2 mL/yr, P = 0.040) | 587 UK and Dutch asthma families (n = 2,819) and 184 healthy controls | Barton/2009 |
| VEGF | rs3025028 C/G | G allele carriers (GC or GG) had significantly lower airway conductance measured from birth throughout childhood with the effect persisting into adulthood | Two general birth cohorts (1,246 from TCRS and 995 from MAAS) | Simpson/2012 |
| IL13 | rs20541 R110Q (G/A) | AA homozygotes (Q110/Q110) had lower FEV1 (P = 0.020), and rapid decline in FEV1 (32.1 mL/yr vs. 25.4 mL/yr, P = 0.040) | 336 asthmatics in Japan | Nagashima/2011 |
| CHI3L1 | rs4950928 C/G | C allele was associated with lower FEV1% (P = 0.046), FEV1/FVC (P = 0.002), and presence of AHR (P = 0.002) | 632 Hutterites | Ober/2008 |
| | rs4950930 G/A | AA homozygotes had a decreased FEV1/FVC (β = −4.2; 95% CI, −8.0, −0.4) | 6,514 Danish adults | Rathcke/2009 |
| | rs12141494 G/A | A allele was significantly associated with both post-bronchodilator FEV1% (P = 0.005; 95% CI, −5.6, −1.6) and serum YKL-40 levels (P = 0.001) | 684 SARP cohort | Gomez/2015 |

(continued to the next page)
Table 1. (Continued) Gene variants associated with decline in lung function in asthma

| Gene   | Lung function associations                                                                 | Study subjects                                      | Study/year       |
|--------|-------------------------------------------------------------------------------------------|----------------------------------------------------|------------------|
| TSLP   | C allele was correlated with decreased FEV1/FVC in adult asthma (P < 0.001)                 | 641 adult asthmatics and 376 controls in Japan      | Harada/2013      |
|        | T allele was inversely associated with FEV1, FVC and FEV1/FVC after meta-analysis (P = 0.002, 0.015, and 0.009, respectively) | 903 school-age asthmatics and 1,205 non-allergic controls (5–18 years) in China | Tang/2016       |
| GSDMB  | T allele was inversely associated with FEV1, FVC and FEV1/FVC after meta-analysis (P = 0.060) | 380 adult asthmatics in Netherlands                 | Ierodiakonou/2013 |
|        | C allele was associated with a protective role of lung function                            | 380 adult asthmatics in Netherlands                 | Ierodiakonou/2013 |
| TGFB1  | A allele was associated with accelerated FEV1 decline (P = 0.003)                          | 380 adult asthmatics in Netherlands                 | Ierodiakonou/2013 |
|        | T allele was associated with a protective role of lung function                            | 380 adult asthmatics in Netherlands                 | Ierodiakonou/2013 |
| POSTN  | Minor A allele was associated with rapid decline in FEV1 (≥ 30 mL/yr)                      | 224 adult asthmatics in Japan                       | Kanemitsu/2013   |
| ESRI   | Females but not males with T allele had more rapid decline of FEV1 compared to GG homozygotes (P = 0.010) | 200 asthma probands and their families in Netherlands (n = 1,249) | Dijkstra/2006 |
|        | Female but not male AA homozygotes had excess decline of FEV1 compared to GG homozygotes (P = 0.020) | 200 asthma probands and their families in Netherlands (n = 1,249) | Dijkstra/2006 |
| ARG2   | CC homozygotes had lower FEV1% compared to T allele carriers (P = 0.020)                   | 200 asthma probands and their families in Netherlands | Ierodiakonou/2016 |
|        | AA homozygotes had lower FEV1% compared to G allele carriers (P = 0.013)                   | 200 asthma probands and their families in Netherlands | Ierodiakonou/2016 |

CHI3L1, chitinase 3-like 1; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; SARP, Severe Asthma Research Program; TCRS, Tucson Children’s Respiratory Study; MAAS, Manchester Asthma and Allergy Study.

Table 2. Gene variants associated with airway remodeling in asthma

| Gene   | Association                                                                 | Subjects                                      | Study/Year       |
|--------|-----------------------------------------------------------------------------|------------------------------------------------|------------------|
| IL13   | AA genotype was associated with subepithelial layer thickness (P < 0.05) in endobronchial biopsies | 411 asthmatics in Japan (age ≥ 18 years) | Nakamura/2016    |
| PLAUR  | An allele was associated with basal epithelial proliferation Ki67 (P = 0.005) | Bronchial biopsy samples from 137 asthmatics | Ierodiakonou/2016 |
|        | An allele was associated with basal epithelial proliferation Ki67 (P = 0.001), and collagen III deposition (P = 0.037) | Bronchial biopsy samples from 137 asthmatics | Ierodiakonou/2016 |
| CHI3L1 (YKL-40) | AA homozygotes had higher serum YKL-40 levels in SARP cohort (P < 0.01), and higher sputum YKL-40 levels in YCAAD cohort (P = 0.043) | 259 individuals from YCAAD and 919 individuals from SARP | Gomez/2015       |
|        | Serum YKL-40 levels were well correlated with the thickness of the subepithelial basement membrane (r = 0.51, P = 0.003), and subepithelial YKL-40 positive-stained cell numbers (r = 0.55, P < 0.001) | Bronchial biopsy samples from 40 asthmatics and 12 controls | Chupp/2007       |

CHI3L1, chitinase 3-like 1; FEV1, forced expiratory volume in 1 second; YKL-40, YKL-40; SARP, Severe Asthma Research Program; YCAAD, Yale Center for Asthma and Airways Disease.

*As there are no published studies of CHI3L1 single nucleotide polymorphisms and airway remodeling in asthma, a study of serum YKL-40 (a product of CHI3L1) is included.

A disintegrin and metalloprotease domain (ADAM) 33

ADAM33 is a transmembrane protein which contains ADAM. Based on the ADAM protein structure, it is presumed that ADAM protein family members play a critical role in cell adhesion, proliferation, differentiation, signaling, apoptosis and inflammatory responses. Among ADAM gene family members, ADAM33 was the first asthma-related gene identified by positional cloning using a genome-wide screening approach. It is expressed predominantly in airway structural cells, especially in lung fibroblasts and bronchial smooth muscle cells, but not in bronchial epithelial cells, as assessed by quantitative real-time polymerase chain reaction of primary cells derived from different lung tissues. ADAM33 expression
is associated with both asthma and airway hyperresponsiveness (AHR).

Previous studies have investigated the contribution of single nucleotide polymorphisms (SNPs) in the ADAM33 gene to asthma outcomes including decline in lung function in asthma. In adult asthmatics, ADAM33 CC homozygotes of the rs528557 SNP had an excess annual decline in FEV1 compared to GG homozygotes. In addition, in studies of the general population followed up for 25 years, ADAM33 genetic variants were reported to be associated with a rapid lung function decline. For example, subjects with ADAM33 homozygous minor alleles of either rs612709 or rs528557 had a significant decline in FEV1 of 9.6 mL/year ($P = 0.021$) or 4.9 mL/year ($P = 0.033$), respectively. Another ADAM33 SNP rs3918395 AA allele was also associated with a rapid lung function decline ($P = 4.34 \times 10^{-5}$). Overall, these studies suggest that ADAM33 genetic variants are associated with a more rapid decline in lung function in adult asthmatics and in the normal general population. So far, no published studies have investigated whether ADAM33 genetic variants are associated with features of airway remodeling.

**Plasminogen activator receptor, urokinase type (PLAUR; urokinase plasminogen activator receptor [uPAR])**

PLAUR, also known as uPAR or CD87, was originally identified as a proteinase receptor for urokinase plasminogen activator(uPA) concentrating plasmin proteolysis to the surface of migrating cells. The uPA and uPAR have been associated with several inflammatory diseases including eosinophil recruitment in asthma. In asthmatics, airway eosinophils express significantly more uPA and uPAR protein compared to peripheral blood eosinophils. Since PLAUR may also contribute to tissue remodeling via uPA-mediated plasmin proteolysis, PLAUR has been proposed as a potential gene contributing to asthma development and airway remodeling. PLAUR genetic polymorphisms, including SNPs rs2356338, rs4802189 and rs4803648 SNPs, are associated with a rapid decline in FEV1 in asthmatics. In addition, these PLAUR genetic polymorphisms are associated with the features of airway remodeling, including basement membrane thickness, collagen III deposition and basal epithelial proliferation (% of Ki67+ cells) as quantitated using bronchial biopsy samples from asthmatic patients. These results suggested that PLAUR SNPs may augment airway eosinophilic inflammation and airway structural changes, resulting in a more rapid lung function decline and airway remodeling in a subset of asthmatics.

**Vascular endothelial growth factor (VEGF)**

VEGF is a potent inducer of endothelial cell growth, angiogenesis and increased vascular permeability. Therefore, it may play a role in angiogenesis, a feature of airway remodeling in asthma. VEGF messenger RNA (mRNA) expression on the airway mucosa is higher in asthmatic patients than in normal controls; VEGF levels are associated with the degree of vascularity and are inversely associated with airway caliber and level of AHR. VEGF transgenic mice have an asthma-like phenotype with inflammation, vascular remodeling, edema, mucus metaplasia, myocyte hyperplasia and AHR.

Studies have investigated the contribution of SNPs in the VEGF gene to asthma outcomes including decline in lung function in asthma. There was a significant association between VEGF-A SNP rs3025028 and lower lung function measured over a 20-year period from birth throughout childhood with the effect persisting into adulthood in the general population.
from 2 large birth cohorts\textsuperscript{22} (1,246 from Tucson Children’s Respiratory Study and 995 from Manchester Asthma and Allergy Study). In addition, in the Childhood Asthma Management Program study, longitudinal analysis confirmed an association of the \textit{VEGF} genetic polymorphism rs4711750 with FEV1/forced vital capacity (FVC) declines over approximately 4.5 years of observation.\textsuperscript{23} The \textit{VEGF} rs4711750 minor T allele was associated with decreased FEV1/FVC ($P = 0.01$) in an analysis of 968 children and 1,518 of their parents. So far, no published studies have investigated whether \textit{VEGF} genetic variants are associated with features of airway remodeling.

**Interleukin (IL) 13**

IL13 is a major effector of T-helper cell type 2 (Th2) inflammation and has the potential to induce airway remodeling in asthma.\textsuperscript{24} Previous studies have investigated the contribution of SNPs in IL13 to asthma outcomes including decline in lung function in asthma and the features of airway remodeling in asthma. In studies of Asian populations, the \textit{IL13} rs20541 AA allele was associated with lower FEV1\textsuperscript{25} and a rapid decline of FEV1%.\textsuperscript{26} It was also associated with increased subepithelial basement membrane thickness quantitated in endobronchial biopsy specimens obtained from 411 asthmatics.\textsuperscript{27} Therefore, the \textit{IL13} rs20541 AA allele maybe associated with decline in lung function and selective features of airway remodeling such as subepithelial fibrosis due to basement membrane thickening.

**Chitinase 3-like 1 (CHI3L1)**

Chitinases are family enzymes generated from innate cellular sources, such as macrophages, neutrophils, and eosinophils which can modulate and amplify airway inflammation/remodeling in asthma.\textsuperscript{28,29} Of the chitinases studied in asthma, \textit{CHI3L1}, also known as YKL-40 and AMCase, have SNPs linked to asthma, whereas \textit{CHIT1} has not been linked to asthma.\textsuperscript{29} SNPs in the \textit{CHI3L1} promoter influence YKL-40 serum levels and these SNPs are associated with asthma, AHR and decreased lung function.\textsuperscript{29} \textit{CHI3L1} genetic polymorphisms are associated with decreased lung function. For example, the \textit{CHI3L1} SNP rs4950928 C allele was significantly associated with lower FEV1% ($P = 0.046$), FEV1/FVC ($P = 0.002$) and presence of AHR ($P = 0.002$) in a study of 632 Hutterites.\textsuperscript{30} In a study of Danish adults, \textit{CHI3L1} SNPs rs10399931 and rs4950930 were associated with FEV1/FVC.\textsuperscript{31} The \textit{CHI3L1} SNP rs12141494 A allele was significantly associated with higher serum YKL-40 levels and decreased post-bronchodilator FEV1% in the Severe Asthma Research Program cohort.\textsuperscript{32} The same associations were replicated in Japanese asthmatics, in whom the \textit{CHI3L1} SNP rs12141494 AA genotype was associated with decreased FEV1%.\textsuperscript{33} Furthermore, the \textit{CHI3L1} SNP rs12141494 A allele was associated with higher levels of YKL-40 in the asthmatic airway as measured in both sputum ($P \leq 0.05$)\textsuperscript{32} and bronchoalveolar lavage (BAL) ($P < 0.05$, 770.8 pg/mL for AA vs. 179.3 pg/mL for GG).\textsuperscript{33} These findings suggested that \textit{CHI3L1} genetic polymorphism modulated expression of YKL-40 in the airway and contributed to lung function in asthma. However, longitudinal studies are needed to determine whether SNPs in \textit{CHI3L1} are linked to decline in lung function in asthma over time.

In limited studies of airway remodeling, serum YKL-40 levels have correlated with the thickness of subepithelial basement membrane in bronchial biopsy specimens.\textsuperscript{34} Further studies are needed to determine whether YKL-40 levels correlate with other features of airway remodeling.
Thymic stromal lymphopoietin (TSLP)
TSLP is an epithelial cell-derived cytokine that triggers Th2- inflammatory responses and is highly expressed in airway epithelial cells during allergic inflammation. In asthmatics, both TSLP and Th2-cytokine mRNA are increased, and TSLP mRNA expression is inversely correlated with FEV1%. Limited studies have investigated the contribution of SNPs in TSLP to asthma outcomes including lung function in asthma. For example, the TSLP genetic variant rs2289278 CC allele was significantly correlated with decreased FEV1/FVC in adult asthmatics in Japan (641 adult asthmatics and 376 controls). A study in non-asthmatics did not find an association with TSLP SNPs and decline in lung function. At present no published study has investigated whether TSLP genetic variants are associated with features of airway remodeling.

Chromosome 17q21 genes (GSDMB and ORMEL3)
The importance of the 17q21 gene locus to asthma was initially suggested from a GWAS study which identified the 17q21 region as an important asthma susceptibility locus for childhood onset asthma. This 17q21 locus harbors a cluster of genes including ORMEL3, and GSDMB. The association between 17q21 gene polymorphisms and childhood-onset asthma has been demonstrated in many studies.

GSDMB
The human GSDMB gene belongs to the Gadermin gene family, and it is highly expressed in bronchial epithelial cells and T cells. Transgenic mice expressing human GSDMB develop an asthma phenotype characterized by the spontaneous development of increased AHR and airway remodeling (increased airway smooth muscle mass and peribronchial fibrosis) without development of airway inflammation. In vitro overexpression of human GSDMB in human bronchial epithelial cells upregulates several genes associated with airway remodeling (i.e. TGF-β1, 5-LO and MMP-9). At present no published human studies have investigated whether GSDMB genetic variants are associated with features of airway remodeling in asthma. In limited human studies of GSDMB genetic variants and decreased lung function, the GSDMB SNP rs2305480 was associated with early-onset asthma and its minor allele was associated with decreased lung function (P < 0.01).

ORMEL3
ORM1-like-3 (ORMEL3) is localized to the endoplasmic reticulum and regulates downstream pathways including sphingolipids, the activating transcription factor 6α pathway of the unfolded protein response, metalloproteases, remodeling genes and chemokines. In mouse models, ORML3 plays an important role in airway remodeling, including increased airway smooth muscle, sub-epithelial fibrosis and mucus. To date, few human studies have reported whether ORMEL3 genetic variants are associated with features of airway remodeling or decline in lung function in asthma.

Transforming growth factor (TGF)-β1
TGF-β1 is a pleiotropic mediator which can affect the function of airway structural cells (including fibroblasts, smooth muscle cells and epithelium) implicated in the remodeling process of patients with asthma. TGF-β1 is expressed in asthmatic airway, promotes the differentiation of fibroblasts to myofibroblast, and may contribute to sub-epithelial fibrosis and proliferation of airway smooth muscle in asthma. The importance of TGF-β1 and its signaling through the Smad-3 pathway in airway remodeling has been demonstrated in Smad-3 deficient mice. Smad-3 deficient mice challenged with allergen develop significantly less peribronchial fibrosis, smooth muscle proliferation, and mucus production compared to
Epithelial overexpression of Smad2 can also increase subepithelial collagen deposition and smooth muscle hyperplasia without an increase in airway inflammation. Moreover, TGF-β1 modulates proliferation of airway smooth muscle. TGF-β1 in the asthmatic airway can be derived from multiple cellular sources including eosinophils, macrophages and epithelium. The importance of eosinophil expression of TGF-β1 is suggested in studies of asthmatics treated with anti-IL-5 to deplete eosinophils. These studies demonstrated that asthmatics treated with anti-IL-5 (mepolizumab) for 3 months had significantly lower levels of BAL eosinophils as anticipated, although they had significantly lower levels of BAL TGF-β1 due to depletion by anti-IL5 of eosinophils in BAL expressing TGF-β1. This depletion of eosinophils expressing TGF-β1 by anti-IL-5 was associated with reduction in the levels of extracellular matrix proteins deposited in the airway, suggesting that anti-IL-5 by depleting eosinophils expressing TGF-β1 exerted an inhibitory effect on airway remodeling. In addition to eosinophils expressing TGF-β1, TGF-β2 is expressed mainly by eosinophils and is prominent in severe asthma.

To date, there has been only 1 study of 419 asthmatics investigating whether TGFB1 genetic polymorphisms are associated with decline in lung function. In this study, among 6 candidate TGFB1 SNPs, 1 TGFB1 SNP rs4803455-A was associated with an accelerated FEV1 decline in asthma (P = 0.003), while 2 other TGFB1 SNPs rs1800469-T and rs1800470-C were associated with protecting against lung function decline (P = 0.06 and P = 0.002, respectively). Thus, at present there is evidence that some TGFB1 SNPs are associated with an accelerated FEV1 decline, while other TGFB1 SNPs protect against lung function decline. No studies have reported whether TGFB1 SNPs are linked to airway remodeling.

**Periostin**

Periostin is a member of the matricellular family of proteins that are highly expressed at the site of injury or inflammation. Periostin can potentially interact with other extracellular matrix proteins in asthma to mediate airway remodeling in particular fibrosis. Th2 cytokines, such as IL-13, are potent inducers of periostin, and periostin has thus been utilized as a Th2 biomarker. Periostin has the potential to mediate peribronchial fibrosis as it activates TGF-β1, up-regulates type I collagen, induces differentiation of fibroblasts to myofibroblasts, and promotes epithelial-mesenchymal transition. Overexpressed periostin in epithelial cells upregulates collagen fibrils.

To date, there has been only one published genetic polymorphism study of periostin and decline in lung function in asthma. Periostin is encoded by the POSTN gene, which is located on chromosome 13q13.3. The POSTN SNP rs9603226 minor A allele, located at the 66 bp upstream of exon 21 in the C-terminal region, has been associated with a rapid decline in FEV1 of 30 mL or greater per year in a study of 224 asthmatics in Japan (P = 0.01). No studies have reported whether POSTN SNPs are linked to airway remodeling.

**Estrogen receptor α (ESR1)**

Sex hormones may contribute to the higher prevalence and severity of adult asthma in women compared to men. As female asthmatics in their reproductive years may have perimenstrual worsening of asthma symptoms, changes in levels of hormones, such as estrogen, may contribute. Estrogen acts via the ESR1 and β. In a longitudinal study of ESR1 SNPs and lung function in 200 asthma probands and their families (males and females) with a median 20.1 years of follow-up, 2 ESR1 SNPs (rs2077647 and rs9340799) were significantly associated with the rapid decline of FEV1 (15.7 mL/year for TT of rs2077647 and 16.1 mL/year for TT of rs2077647 and 16.1 mL/year...
year for AA of rs9340799, \( P = 0.01 \) for both SNPs in the cohort combining females and males in the analysis) and was also significant in the female but not male subgroup analysis.\(^4\) No studies have reported whether \( ESRI \) SNPs are linked to airway remodeling.

**Arginase (ARG)**

ARG converts L-arginine into L-ornithine and urea, and may thus be involved in the pathogenesis of asthma through dysregulation of L-arginine metabolism and modulation of nitric oxide homeostasis.\(^5\) ARG has 2 isoenzymes, ARG1 and ARG2, and SNPs in these genes have been studied in relation to asthma, but not in relation to decline in lung function or airway remodeling. The ARG2 SNPs rs17249437 and rs3742879 were significantly associated with decreased FEV1\% in an asthmatic family study (\( P = 0.020 \) and \( P = 0.013 \)).\(^5\) However, none of the investigated SNPs in \( ARG1 \) and \( ARG2 \) showed a significant association with FEV1 decline in longitudinal observation for 10.3 years. There have been no reports of \( ARG1 \) or \( ARG2 \) genetic polymorphisms and airway remodeling in asthma.

**CANDIDATE MEDIATORS OF AIRWAY REMODELING IN ASTHMA**

The following are additional candidate mediators of airway remodeling in asthma (Table 3) based on studies demonstrating that they are expressed at increased levels in the lungs of asthmatics as well as based on in vivo studies in animal models of asthma supporting their role in airway remodeling. Among these candidate mediators of airway remodeling in asthma, matrix metalloproteinases (MMP)-9, cysteinyl leukotrienes (CysLTs) as well as IL33 and its receptor IL1RL1 are discussed in greater detail below.

**MMP-9**

MMPs are involved in extracellular matrix turnover and tissue repair. Studies in asthma have particularly focused on the role of MMP-9 (gelatinase B) in airway remodeling,\(^6\) as it plays a key role in extracellular matrix turnover. Additional support for MMP-9 playing a role in asthma are derived from studies demonstrating that in asthma, the levels of MMP-9 are elevated\(^7\) in blood, sputum, BAL and exhaled breath condensates from patients with asthma exacerbations. MMP-9-deficient mice have slightly less peribronchial fibrosis and total lung collagen compared to wild type mice.\(^8\) However, MMP-9 deficient mice still have mucus hypersecretion, smooth muscle thickness and AHR, suggesting that in mice many of the features of airway remodeling are not controlled by MMP-9.\(^8\)

At present, there are no studies of SNPs in MMP-9 and their effect on decline in lung function or airway remodeling in asthma.

**CysLTs**

CysLTs are important proinflammatory lipid mediators derived from the lipoxygenase pathway of arachidonic acid metabolism.\(^9\) The CysLTs may play an important role in airway remodeling as they increase airway smooth muscle, myofibroblasts, airway fibrosis and mucus.\(^10\) In mouse models of asthma, a CysLTs antagonist (Montelukast) reduced the features of airway remodeling including smooth muscle hyperplasia and mucus plugging.\(^11\)

Studies have also investigated whether SNPs in genes regulating enzymes in the CysLT pathway are associated with lung function. For example, previous studies have investigated...
the effect on lung function of SNPs in 5-lipoxygenase (encoded by ALOX5) as well as SNPs in 5-lipoxygenase activating protein also known as FLAP (encoded by ALOX5AP).

The ALOX5 genetic variant rs5943948 has been associated with lower FEV1% levels (84% vs. 91%, \( P = 0.017 \)) and higher urinary LTE4 levels (\( P = 0.0134 \)) in 270 children with poorly controlled asthma.

The ALOX5AP SNP rs9506352 has been associated with FEV1% (\( P = 0.032 \)) in a healthy population.

At present, there have been no published studies investigating whether ALOX5 or ALOX5AP SNPs are associated with decline in lung function or the development of airway remodeling in asthma.

IL33 and its receptor IL1RL1

IL33 is a member of the IL-1 family that potently drives production of Th2 cytokines by Th2 cells, mast cells, basophils and ILC2. IL33 is a ligand for IL1RL1 (also called ST2), an IL-1 family receptor. In mouse models, both IL33 and its ligand IL1RL1 induce airway inflammation, mucus production and airway remodeling. At present no human studies have investigated whether IL33 or IL1RL1 genetic variants are associated with features of airway remodeling in asthma. While both SNPs, for IL33 (rs1342326; \( P = 9 \times 10^{-6} \)) and IL1RL1 (rs3771166; \( P = 3 \times 10^{-7} \)), have significant associations with asthma, there have been no studies demonstrating genetic associations between SNPs in IL33/IL1RL1 and lung function decline in asthma.
ASTHMA EXACERBATIONS, DECLINE IN LUNG FUNCTION AND AIRWAY REMODELING

Acute asthma exacerbations and decline in lung function

Large scale epidemiologic studies of lung function in asthma over time generally measure lung function annually, suggesting that there is an annual linear rate of decline in lung function. However, studies comparing asthmatics who have frequent acute asthma exacerbations versus those who do not have suggests that asthma exacerbations may trigger a step-wise decrease in lung function in asthma over time in a subset of genetically predisposed individuals. For example, a cohort study of 93 non-smoking asthmatics followed for over 5 years, showed that asthmatics with frequent asthma exacerbations had a significantly larger annual decline in FEV1 compared to those with infrequent asthma exacerbations (median difference, 16.9 mL/year; 95% CI, 1.5–32.2). In addition, severe asthma exacerbations predicted an excess decline in FEV1, such that 1 severe asthma exacerbation per year was associated with a 30.2 mL greater annual decline in FEV1. In another study of 128 non-smoking well-controlled asthmatics followed up for 3-years, FEV1 also declined according to the number of asthma exacerbations (no exacerbation, 13.6 mL/year; 1 exacerbation, 41.3 mL/year; 2 or more exacerbations, 58.3 mL/year). The changes in bronchodilator reversibility were also significantly correlated with the annual rates of change in FEV1. Using linear modeling analysis, a recent study of severe eosinophilic asthmatics estimated lung function decline per asthma exacerbation was 50mL in FEV1. There is also some evidence that preventing acute exacerbations in asthma can reduce decline in lung function in asthma. For example, using inhaled corticosteroid treatment as a regular therapy in early asthma demonstrated that low doses of inhaled corticosteroid were associated with attenuation of decline in lung function. In the placebo-treated group of asthmatics, decline in lung function was significantly greater in those who had a severe asthma exacerbation (~6.44% of FEV1%) than in those who did not (~2.43% of FEV1%). In contrast, in the inhaled corticosteroid-treated group of asthmatics, decline in lung function was much less in those who had severe asthma exacerbation (~2.48% of FEV1%) or who did not (~1.72% of FEV1%) than in the placebo-treated group of asthmatics (~6.44% of FEV1%). Therefore, adequate asthma treatment with inhaled corticosteroids may reduce not only the frequency of asthma exacerbations, but also decline in lung function associated with asthma exacerbations.

Respiratory viruses and airway remodeling

Viral respiratory infections are the most common cause of an acute asthma exacerbation in both children and adults. Respiratory viruses that have been linked with asthma exacerbations include rhinoviruses, respiratory syncytial virus (RSV), enteroviruses, influenza A/B, parainfluenza viruses, coronavirus and adenovirus. Of these viruses, rhinoviruses are the most commonly detected virus in acute asthma exacerbations. The potential mechanisms by which rhinoviruses could trigger airway remodeling have been investigated in vitro in airway epithelial cells. These studies demonstrated that rhinovirus infection of human epithelial cells induced marked up-regulation of amphiregulin, activin A and VEGF levels. Since these mediators have been implicated in the remodeling processes, it is possible that rhinovirus infection induction of these or other mediators can induce airway remodeling during an asthma exacerbation triggered by rhinovirus. Interestingly, there is a genetic predisposition to the development of rhinovirus wheezing illness in early life. Chromosome 17q21 variants (linked to genes ORMDL3 and GSDMB) were associated with rhinovirus wheezing illnesses in early life, but not with RSV wheezing illnesses. The associations of 17q21 variants with asthma were restricted to children who had had rhinovirus wheezing illnesses, resulting in
a significant gene virus interaction effect with respect to the risk of asthma. Moreover, the expression levels of ORMDL3 and GSDMB were significantly increased in rhinovirus-stimulated peripheral blood mononuclear cells (PBMCs), as compared to unstimulated PBMCs. Further studies are needed to determine whether children harboring 17q21 variants and exposed to rhinovirus have an accelerated decline in lung function or increased airway remodeling.

**Tobacco smoke, environmental tobacco smoke (ETS), decline in lung function and airway remodeling**

Epidemiologic studies of decline in lung function over a 15-year period in asthmatics who smoked tobacco demonstrate that asthmatics who smoke tobacco have a greater decline in FEV1 compared to asthmatics who did not. In addition, tobacco smoking affects asthma severity, airway inflammation, accelerated decrease in lung function and impaired responses to corticosteroid therapy. Studies have also investigated airway wall thickness as a surrogate measure of airway remodeling in asthmatics who do not smoke compared to those who smoke tobacco and have an asthma-COPD overlap (ACO). Multidetector chest computed tomography performed to measure airway wall thickness and airway inner luminal area revealed that patients with ACO had a thicker airway wall than those with asthma who did not smoke tobacco, suggesting that airway remodeling is more prominent in ACO than in asthma. Therefore, tobacco smoking likely contributes to decline in lung function and to the development of airway remodeling in asthma. In addition to tobacco smoking affecting lung function and airway remodeling, it is possible that second-hand smoke, also called ETS, can influence remodeling and lung function in children with asthma whose parents smoke tobacco. Studies using a mouse model of allergen-induced airway remodeling showed that ETS alone did not induce airway remodeling, but chronic co-exposure to ETS and allergen significantly increased the level of airway remodeling compared to allergen alone. If these studies were confirmed in human subjects, it would suggest that children with asthma who were co-exposed to mothers who smoked and to indoor allergens may have enhanced airway remodeling.

**Corticosteroids, decline in lung function and airway remodeling**

Corticosteroids are currently the most effective anti-inflammatory therapy in asthma as they reduce asthma symptoms and the frequency of rescue β2-adrenergic agonist inhaler use as well as prevent asthma exacerbations and deaths from asthma. Corticosteroids are also effective in improving pulmonary function and in reducing AHR. Several studies using bronchial biopsies have also demonstrated that corticosteroids reduce airway inflammation in asthma. However, the ability of corticosteroids to reduce airway remodeling is not well established. There are numerous studies that support as well as refute the role for corticosteroids in reducing airway remodeling. Although the majority of studies demonstrate that corticosteroids reduce the features of airway remodeling in asthma, several studies do not support a role of corticosteroids in reducing airway remodeling. The differences in the results may be due to differences in the dose, duration, and compliance with corticosteroid therapy, as well as the site of biopsy (most studies have proximal and not small airways in biopsy), severity of asthma and remodeling end points studied (most studies do not have smooth muscle in biopsy).

**CONCLUSIONS**

Epidemiologic studies suggest that both genetic and environmental factors may contribute to decline in lung function and airway remodeling in a subset of patients with asthma.
Environmental factors that can contribute to decline in lung function in asthma include virus-triggered asthma exacerbations and tobacco smoke. In terms of genetic factors contributing to decline in lung function in asthma, several genes have been linked to decline in lung function, but these studies require replication to determine if any of these genes is important for lung function decline in asthma as well as the magnitude of the effect. As rhinoviral infections are an important trigger of asthma exacerbations which are associated with decline in lung function in asthma, it is of interest that children harboring chromosome 17q21 variants (linked to the genes \textit{ORMDL3} and \textit{GSDMB}) were predisposed to develop rhinovirus wheezing illnesses in early life, but not RSV wheezing illnesses. In addition to studying genes and environmental factors, studies of asthmatic airway biopsies have also identified mediators, cytokines, and pathways associated with airway remodeling. Ultimately, intervention studies in asthmatics inhibiting a specific mediator, cytokine, or pathway associated with airway remodeling will need to be performed to determine the importance of each intervention. Although at present there is insufficient evidence for targeting a specific molecular pathway to reduce airway remodeling or decline in lung function in asthma, continued research will help identify the most promising targets to be considered in the subset asthmatics with the greatest decline in lung function.

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