MUCing up the airway in asthma

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Airflow obstruction is the major mechanism of dyspnea that occurs in asthma and largely results from a combination of smooth muscle constriction and defective mucociliary clearance. 1 Secretory cells that line the conducting airways of the lung include goblet and club cells, and these cell types are important contributors to the apical mucus gel. Mucous cells contained in gland acini are also a major producer of mucin. The airway mucus gel, along with the ciliated epithelium and periciliary layer, are the components of the mucociliary escalator that push airway mucus upwards where it can be eliminated from the lung. The major function of airway mucus is to protect the epithelium from detrimental environmental factors such as pathogenic microorganisms, particulate matter, and aerosols that contain toxic or irritating substances. Efficient mucociliary clearance is critical in clearing these potentially harmful environmental substances trapped within the airway mucus. However, ineffective mucociliary clearance can lead to airflow obstruction from mucus that cannot be expelled, thus reducing airflow. Airway obstruction by retained mucus in the airway is a major contributor to asthma pathophysiology in even mild and moderate asthma. In fatal asthma, airflow obstruction from mucus plugs can cause asphyxiation. In human lungs, MUC5AC and MUC5B are the major components of airway mucus. MUC5AC expression is specific to the surface epithelium, whereas MUC5B is present in both secretory cells in the surface epithelium and submucosal glands. 2 IL-13, a central mediator in asthma pathogenesis, drives MUC5AC production, while decreasing MUC5B expression. This possibly explains why MUC5AC is increased, and MUC5B is decreased, in persons with type 2 asthma. 3 Although MUC5AC protects the airway from harmful environmental antigens, epithelial cell tethering of MUC5AC-rich mucus impairs mucociliary transport in asthma, causing mucostasis and mucus plugs, thus contributing to airway obstruction. 4

Very recently, Altman et al 5 queried data from the Urban Environment and Childhood Asthma (URECA) birth cohort study to determine genetic and environmental factors that were associated with asthma severity. The URECA birth cohort is composed of children in urban areas in the United States (Baltimore, Boston, New York, and St Louis) with high rates of poverty. In this cohort, pregnant women who had a history of asthma, allergic rhinitis, or eczema were enrolled antenatally as a result of their offspring having a high risk for developing asthma as a result of the mothers’ medical conditions. The offspring were followed on a very strict protocol after birth with periodic questionnaires, anthropometric measurements, pulmonary function testing, blood draws, and skin testing. In addition, house dust samples were obtained annually for the first 3 years of life to assess for antigen exposure and bacterial microbiota. Thus, the URECA cohort provided a rich database from which to examine gene-environment interactions that could contribute to the development and maintenance of asthma. In this study in which the children’s data were assessed at age 10 years, the authors reported that a phenotype of children defined as high wheeze, high atopy, low lung function (HW-HA-LF) had the highest rate of health care utilization. This phenotype specifically had greater expression of genes in the MUC5AC hypersecretion module compared with the other 5 phenotypes of subjects, in addition to increased type 2–high pathways that included perioxidin, leukotriene metabolism, mucus hypersecretion, and mast cell genes. The authors conjectured that “our findings in the URECA birth cohort suggest that allergic sensitization and frequent viral wheezing episodes in early life, which are characteristic of HW-HA-LF, could promote long-term overexpression of MUC5AC and, in turn, lead to progressive airway obstruction.” 6

In this issue of the Journal of Allergy and Clinical Immunology, Altman et al performed quantitative locus analysis of the MUC5AC gene expression in nasal epithelial cells and hypothesized that MUC5AC genotypes differentially regulate the expression of this gene in the airway, specifically in the course of an acute asthma exacerbation. 7 Using the URECA cohort, they obtained RNA-sequencing data from the nasal airway epithelial cells and then performed expressive quantitative tract loci (eQTL) and allelic-specific expression and found that there were 2 distinct groups of genetic polymorphisms of MUC5AC that independently related to the expression of this gene. Interestingly, the effects of these single nucleotide polymorphisms (SNPs) in MUC5AC were increased in respiratory illnesses, which could lead to asthma exacerbations. The authors propose that overexpression of these MUC5AC genes induced during asthma exacerbations might further promote MUC5AC expression and lead to greater airway mucus, thus providing a positive feedback mechanism for worsening airway obstruction. The investigators validated their results from the URECA cohort by performing eQTL and allelic-specific expression analysis in the Mechanisms Underlying Asthma Exacerbations Prevented and Persistent with Immune-based Therapy (MUPPITs) cohort. The MUPPITs cohort enrolled children aged 6 to 17 years with preexisting asthma that was prone to exacerbation. These subjects came from 9 US cities, and the subjects were demographically similar to the URECA cohort subjects in being predominantly African

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American and Hispanic. In this cohort, nasal lavage samples were collected during respiratory illnesses. The benefit of including the MUPPITS study was that the samples were obtained during respiratory illness, thus providing the opportunity to determine the effects of asthma exacerbations on the eQTLs. They found that 2 SNPs, rs1132436 and rs1292198170, had an additive inducible eQTL effect. They then analyzed these SNPs in relationship to pulmonary function testing and reported that the minor allele at rs1132436 was significantly associated with a lower FEV1/FVC ratio in the URECA cohort and lower FEV1/FVC and FEV1% predicted in the MUPPITS cohort. FVC, Forced vital capacity.

![FIG 1. Single nucleotide at MUC5AC minor allele rs1132436 had an additive inducible eQTL effect. rs1132436 was significantly associated with a lower FEV1/FVC ratio in the URECA cohort and lower FEV1/FVC and FEV1% predicted in the MUPPITS cohort.](image)

- **MUC5AC** and airway mucus
- **rs1132436**
- **Asthma exacerbation**
- **FEV1/FVC**
- **FEV1% predicted**

In this issue of the *Journal of Allergy and Clinical Immunology*, Altman et al outlined future studies that will be important in further defining the pathogenic mechanisms of their SNP findings. These include determining the relationship between the SNPs and lower airway MUC5AC protein expression and performing lung imaging to determine whether the SNPs of interest are associated with mucus plugging as determined by multidetector computed tomography lung scans. Because MUC5AC is an IL-13-responsive gene, it is tantalizing to consider that patients with asthma with MUC5AC SNPs that are functionally similar to rs1132436 might preferentially benefit from precision medicine to target this cytokine. Future clinical trials will be necessary to determine the utility of such a strategy. In addition, quantities of MUC5AC and MUC5B in sputum have been successfully measured by ELISA, and these changes in mucin glycoprotein are present in both stable asthma and during exacerbation, further suggesting that such precision targeting of the IL-13 pathway may not be far away. For now, these results are an important piece in the puzzle of how host genes regulate asthma phenotypes.

**REFERENCES**