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Why Is ORMDL3 on Chromosome 17q21 Highly Linked to Asthma?

In a landmark genome-wide association study in 2007, Moffatt and colleagues demonstrated that genetic variants on chromosome 17q21 that regulate ORMDL3 expression contribute significantly to the risk of childhood-onset asthma (1). The linkage of chromosome 17q21 to asthma was subsequently replicated in multiple genetic epidemiology studies in populations of diverse ethnic backgrounds (2, 3). Although the linkage of chromosome 17q21 to asthma is very well established, the biologic mechanism (s) underpinning this association is not as well established (3). Because the SNP linking chromosome 17q21 to asthma is associated with increased levels of ORMDL3 (1–3), studies have examined the phenotype of mice expressing increased levels of the human ORMDL3 transgene, and shown that these mice exhibit spontaneous increases in airway responsiveness that are associated with increased airway remodeling (increased airway smooth muscle and increased peribronchial fibrosis) in the absence of airway inflammation (4). Precision-cut lung slices from ORMDL3 transgenic (TG) mice exhibit increased airway smooth muscle calcium oscillation and increased contractility to methacholine (5). Because mouse lung slices do not have a blood supply, this suggests that a lung structural cell expressing ORMDL3 mediates the increased contractility to methacholine (5). In addition to studies suggesting an important role for ORMDL3 expression by mouse and human lung structural cells (i.e., airway smooth muscle and airway epithelium) (2, 3, 5, 6), studies have also suggested an important role for ORMDL3 expression by human CD4 lymphocytes (1, 7–9) and mouse eosinophils (10) in contributing to the pathogenesis of asthma. In support of a role for ORMDL3 in CD4 cells, allergen-challenged ORMDL3 TG mice were found to exhibit increased T-helper cell type 2 (Th2) responses and further increases in airway hyperresponsiveness (AHR) (4). In human studies of T-cell lines and normal human peripheral blood mononuclear cells, genetic variants of ORMDL3 increased transcriptional regulation of ORMDL3, which correlated with changes in Th2 cytokine levels (8). Studies of normal human CD4⁺ T cells showed the greatest increase in ORMDL3 expression in individuals carrying asthma-risk alleles, and that ORMDL3 negatively regulated IL-2 production (7). Thus, there is evidence that expression of ORMDL3 in both structural cells and CD4 cells is important for the pathogenesis of asthma.

In this issue of the *Journal*, Zhang and colleagues (pp. 478–488) provide novel information about ORMDL3-regulated

pathways in human lung structural cells (i.e., lung epithelial cells) *in vitro* (11) that may explain the association of ORMDL3 with rhinovirus (RV)-induced asthma in children (12), as well as the association of ORMDL3 with the obesity asthma phenotype (13). Prior studies demonstrated that 17q21 variants were associated with RV wheezing illnesses in early life, but not with respiratory syncytial virus wheezing illnesses (12), identifying a selective gene–virus interaction effect with respect to the risk of asthma. Zhang and colleagues used the A549 alveolar epithelial cell line and, in selected experiments, normal human bronchial epithelial (NHBE) cells, and made the novel observation that ORMDL3 expression in A549 epithelial cells regulated the expression of ICAM-1, the receptor for RV. In these studies, siRNA knockdown of ORMDL3 in IL-1 β -stimulated A549 epithelial cells resulted in reduced expression of ICAM-1 mRNA and protein. This suggests that individuals with low levels of expression of ORMDL3 in airway epithelium would have reduced RV binding to airway epithelium and reduced RV load. Although it was not investigated in this study, one could hypothesize that experiments to increase the levels of expression of ORMDL3 (as noted in subjects with asthma and 17q21 SNPs) (14) in epithelial cells would result in increased expression of ICAM-1, as ORMDL3 siRNA resulted in decreased expression of ICAM-1. If so, this would suggest that individuals with SNPs linked to chromosome 17q21 and increased expression of ORMDL3 would exhibit increased RV binding to airway epithelium and increased RV load. Such an airway epithelial ICAM-1 pathway regulated by ORMDL3 may help explain why ORMDL3 is important for RV wheezing illness (12), but may not explain why the 17q21 variants associate with selected respiratory viruses (i.e., RV, which binds to ICAM-1) (12), as *in vitro* studies have demonstrated that anti-ICAM-1 antibodies inhibit respiratory syncytial virus binding to ICAM-1 expressed by NHBE cells (15). In addition, for a subset of RV viruses (i.e., RV-C), the cadherin-related family member 3 may be more important than ORMDL3-regulated ICAM-1 expression in RV-C binding and replication (16). Interestingly, in relation to ORMDL3 regulating ICAM-1 adhesion molecule expression, prior studies using mouse eosinophils demonstrated that knockdown of ORMDL3 significantly reduced adhesion molecule expression of CD49d ($\alpha 4$ integrin) and CD18 ($\beta 2$ integrin), which was associated with reduced eosinophil adhesion and recruitment to sites of inflammation *in vivo* (10). Thus, ORMDL3 may regulate several adhesion molecules and requires further investigation.

A second novel observation made by Zhang and colleagues relates to ORMDL3-regulated metabolic pathways in human lung epithelial cells, which may help to explain the association of ORMDL3 with the obesity asthma phenotype (13). For these studies,

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they used a metabolomics approach, globally profiling metabolites in epithelial cells by gas chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry platforms. They demonstrated that ORMDL3 siRNA-treated A549 cells had significant increases in carbohydrates (glucose, glucose-6-phosphate, fructose, sorbitol, and lactate), lysophospholipids, and amino acids (kynurenine and creatinine). Further study is needed to determine whether any of these metabolic pathways are deranged in NHBE cells, as well as in individuals with asthma, the obesity phenotype, and the SNP linked to increased ORMDL3 expression. It would also be interesting to know whether any of these ORMDL3-regulated metabolites have effects alone or in combination on pathways associated with asthma.

Zhang and colleagues also demonstrated that siRNA knockdown of ORMDL3 in NHBE cells reduced cytokine (IL-6 and IL-8) production. These knockdown studies complement prior overexpression studies of ORMDL3 and epithelial cytokine/chemokine production, which showed that NHBE cells transfected to express increased ORMDL3 had increased levels of IL-8, expressed increased levels of metalloproteases and chemokines, and activated the endoplasmic reticulum ATF6 α pathway (6). Thus, individuals with asthma and SNPs linked to increased ORMDL3 expression are likely to have a proinflammatory airway epithelial response to environmental triggers. Finally, Zhang and colleagues demonstrated that siRNA knockdown of ORMDL3 in NHBE cells increased sphingolipid metabolism (i.e., increased ceramides C24:1, C24:0, and C26:1, and sphingosine-1-phosphate [S1P]). These human epithelial studies extend prior studies of ORMDL3 and sphingolipid metabolism in mouse airway epithelium, which similarly showed that levels of S1P were significantly increased in mice selectively deficient in ORMDL3 in airway epithelium (*Ormdl3* ^{$\Delta 2-3/\Delta 2-3$} /*CC10* mice) (17), and that S1P was elevated in mouse airway epithelial cells in which ORMDL3 was inhibited with siRNA *in vitro* (17). ORMDL3 inhibits the enzyme serine palmitoyltransferase, the rate-limiting first step in the generation of sphingolipids, and ORMDL3 TG mice were found to have reduced levels of sphingolipids, including S1P and ceramide (18). Administration of a ceramide inhibitor to wild-type mice *in vivo* was shown to induce increased AHR (19). Serine palmitoyltransferase heterozygous knockout mice have decreased sphingolipid synthesis as well as increased AHR in the absence of inflammation (20). Although these studies support a role for ORMDL3 in regulating sphingolipids, further studies in humans with asthma are needed to determine whether any of these ORMDL3-regulated sphingolipid pathways contribute to the pathogenesis of asthma.

In summary, the study by Zhang and colleagues provides important novel information related to how ORMDL3 expressed in lung epithelial cells may contribute to the pathogenesis of asthma. In particular, the demonstration that ORMDL3 regulates ICAM-1 expression has the potential to explain why there is a significant gene-environment association between ORMDL3 and RV (12). Because these studies of ORMDL3 regulation of ICAM-1 were performed in an alveolar epithelial cell line, further studies of bronchial epithelial cells derived from individuals with asthma, with and without SNPs linked to increased ORMDL3 expression, will help investigators discern the importance of these pathways in RV-induced asthma. Such future studies of the biology of ORMDL3 will help to

explain why ORMDL3 on chromosome 17q21 is highly linked to asthma. ■

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New Biologics for Severe Asthma: What Patients, What Agents, What Results, at What Cost?

“New Biologics for Severe Asthma: What Patients, What Agents, What Results, at What Cost?” was the title of a well-attended symposium initiated by the editor of the *New England Journal of Medicine* at the recent meeting of the European Respiratory Society in Paris. Physicians treating patients with asthma need guidance on how to best manage severe disease and what drugs are the most appropriate in chronic care. Although this generally applies to all therapeutic measures, the further development of biologics requires a proper, patient-centered approach that is economically responsible. This discussion is not new, and since the introduction of antibodies targeting IgE, investigators have searched for a clinically applicable rule to identify patients who would benefit from this treatment, and for indicators to estimate how long such a costly treatment should last. One approach that has been used, the Global Evaluation of Effectiveness scale (1), largely relies on subjective impressions of treatment success by the physician and the patient.

Major efforts to further unravel the mechanisms of severe asthma have been undertaken and have delivered a wide range of new drug targets, such as IL-5, the transcription factor GATA-3, IL-4, IL-13, TSLP (thymic stromal lymphopoietin), and the prostaglandin DP2 (CRTH2) receptor (2). Among these, the cytokine IL-5 and its receptor are the most advanced and have yielded a number of drugs that are now available for clinical use. They are finding their way into clinical practice and owing to their efficacy will be used globally and not only in specialized centers.

A recent expert consensus statement aims to provide guidance regarding the use of these new classes of drugs, and suggests that in patients with severe eosinophilic asthma, biologics should be tried for at least 4 months before a decision is made to continue treatment for a year (3). The remaining principal problem in assessing the efficacy of the available antibodies, however, lies in the lack of validated assessment tools and reliable biomarkers of treatment success. The level of IgE in patients is not related to disease severity, and a change under therapy is not indicative of treatment outcome.

For the new anti-IL-5 monoclonals, serum eosinophils are predictors of success above a threshold, but there are still nonresponders despite high eosinophil levels, and a change in eosinophilia does not allow for any judgment regarding the length of treatment.

In a study presented in this issue of the *Journal*, Bateman and colleagues (pp. 489–495) examined data from two clinical trials for the anti-IL-5 monoclonal antibody reslizumab (4), which was used as an add-on maintenance treatment for patients with uncontrolled asthma and eosinophilia (5). The two trials recruited patients ≥ 18 years of age who met Global Initiative for Asthma 4 or 5 criteria and received intravenous reslizumab. The authors developed an algorithm based on clinical indicators to predict response at 52 weeks.

A mathematical model was constructed based on the change from baseline to 16 weeks in the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire, lung function, and number of asthma exacerbations during the year before enrollment and the first 16 weeks of treatment. The 16-week data were used to evaluate the algorithm’s ability to predict outcomes at 52 weeks. The algorithm predicted that 276 patients would be classified as responders, and in 248 (89.9%) the prediction was correct. However, for the 26 patients predicted to be nonresponders, this was only correct in 50.0% of the cases, and 19 patients remained indeterminate. The authors describe a 95.4–95.5% sensitivity and 40.6–54.1% specificity, adding a rather sophisticated jackknife resampling and cross-study validation confirming the robustness of the algorithm; however, this approach may not be obvious to the nonaficionado of biostatistics and requires profound in-depth knowledge. The authors conclude that the algorithm allows prediction at 16 weeks of treatment of the response to reslizumab at 52 weeks, but is actually not suitable for predicting nonresponders.

This study clearly addresses a relevant issue, and the authors are to be commended for their approach to guide clinical decision-making regarding these novel and expensive compounds. The study follows earlier attempts to predict clinical outcomes in asthma and other chronic pulmonary diseases under treatments, and Bateman and colleagues previously identified clinical factors associated with an increased risk for severe asthma exacerbations based on another