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Airway molecular endotypes of asthma: dissecting the heterogeneity

Agata Wesolowska-Andersen^a and Max A. Seibold^{a,b}

^aIntegrated Center for Genes, Environment, Health, National Jewish Health, Denver, Colorado, USA

^bDepartment of Pediatrics, National Jewish Health, Denver, Colorado, USA

Abstract

Purpose of review—This review will cover advances over the past year in defining airway endotypes in asthma by gene expression and the relationship between these endotypes and clinical traits.

Recent findings—Expression profiling studies of asthmatic airway samples continue to reveal significant heterogeneity in airway inflammation and dysfunction. Recent studies have indicated multiple distinct, but related Th2 inflammatory asthma endotypes. Moreover, novel biomarkers of Th2 inflammation are being identified in more accessible nasal brushing and induced sputum cell samples. New data suggest the presence of multiple non-Th2-driven asthma molecular endotypes, including ones related to neutrophilic inflammation, airway remodeling, and chemosensory dysfunction. Many of these endotypes are associated with clinical disease features and treatment response.

Summary—Molecular endotyping of asthmatic patients using gene expression profiling of airway samples is helping to uncover disease mechanisms and potential novel treatment targets. The advancement of endotyping methods holds the promise of future personalized treatment for asthma.

Keywords

airway brushing; asthma; endotypes; epithelium; sputum

Introduction

Evidence is mounting that asthma rather than being a single disease is a collection of disease groups with distinct causes and partially overlapping clinical and physiological characteristics. The phenotypic heterogeneity among asthmatic patients is evident at multiple levels including the degree of airway obstruction, type of airway inflammation, presence of airway remodeling, and response to medication. Based on this knowledge,

Correspondence to Max A. Seibold, PhD, National Jewish Health, 1400 Jackson St, Denver, CO 80206, USA. Tel: +1 303-270-2544; SeiboldM@NJHealth.org.

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efforts are underway to ‘endotype’ asthma or identify subgroups sharing an underlying disease pathobiology. Endotyping can be applied at the molecular level by gene expression profiling of patient airway samples. The establishment of molecular asthma endotypes would allow therapies to be developed that address root disease biology rather than clinical symptoms. Moreover, the application of molecular asthma endotyping to the clinical setting holds the promise of asthma management personalized to a patients' specific disease pathophysiology.

Airway epithelial and immune cells have been prominently implicated in asthma disease pathogenesis. Therefore, most efforts to define molecular asthma endotypes have focused on characterization of bronchial airway brushings (epithelial cells) and induced sputum (airway immune cells). The power of these approaches was first displayed by a study [1] that used expression profiling of bronchial brushings to identify a ‘Th2-high’ subset of asthmatic patients characterized by significant airway inflammation driven by Th2 cytokines. The first genome-wide expression profiling study [2] of asthmatic sputum resulted in identification of molecular profiles associated with eosinophilic and neutrophilic asthma. The success of these studies resulted in a multitude of molecular endotyping studies in different asthma populations. In this review, we discuss the progress made during the past year, with focus on identification of novel endotypes, their application to distinct asthmatic populations, and development of simplified and less-invasive molecular endotyping techniques.

Bronchial Airway Epithelial Endotypes

The seminal study by Woodruff *et al.* [1] applied whole-genome microarray expression profiling to bronchial airway brushings of adult mild asthmatic patients. Analysis of this data established an airway inflammatory endotype identified by clustering subjects based on expression of three epithelial genes: *CLCA1*, *periostin*, and *serpinB2*. The group exhibiting high expression of these genes was termed ‘Th2-high’, as these genes were shown to be greatly induced by the Th2 cytokine IL-13, and bronchial biopsies from these subjects demonstrated high levels of IL-13 and IL-4. Importantly, only 50% of the asthmatic patients were Th2-high and the remaining Th2-low asthmatic patients clustered with healthy controls, revealing that Th2 inflammation is not a universal asthma characteristic. The Th2-high group exhibited higher airway eosinophil levels and greater bronchial hyperresponsiveness than Th2-low subjects. Moreover, the Th2-high group was responsive to inhaled corticosteroids (ICS) whereas the Th2-low group was not. This study revealed how exquisitely sensitive airway epithelial cells are to inflammatory cytokines and that profiling of brushed airway epithelial cells can be used to type asthmatic airway inflammation.

Recently, the same group established a ‘three-gene-mean’ metric of Th2 inflammation, based on quantitative real-time polymerase chain reaction (qPCR) expression of *CLCA1*, *periostin*, and *serpinB2* in airway epithelial brushings, which differentiated Th2-high from Th2-low populations[3■]. The authors also demonstrated correlation of the new metric with other Th2 biomarkers, including the fraction of exhaled nitric oxide (FeNO) and blood eosinophils. The new metric successfully predicted response to ICS treatment determined by an increase in FEV₁ % predicted. This simplified method, not requiring microarray-based

expression or clustering analysis, should allow more investigators to apply Th2-typing to their asthmatic populations.

A recent study [4■■■] used whole-genome microarray expression analysis to investigate airway endotypes among 155 asthmatic and healthy control patients in the Severe Asthma Research Program. This study applied a novel approach to endotyping, using the Th2 biomarker, FeNO, as an intermediate phenotype. The authors identified 549 genes whose bronchial airway epithelial expression was correlated with the subject FeNO levels. They clustered subjects into five groups based on expression of these FeNO-correlated genes and used differentially expressed genes between these groups to determine coexpressed gene clusters, reflecting the biological nature of each group. Interestingly, three subject clusters exhibited high levels of FeNO, IgE, and bronchoalveolar lavage (BAL) eosinophils, including two severe (2 and 3) and one mild asthmatic cluster (5). Both severe clusters exhibited higher expression of Th2-high signature genes, inducible nitric oxide synthase (iNOS), type II and III interferon, and TNF- α signaling genes and lower expression of cilia-related genes. Subject clusters 2 and 3 were differentiated by high neutrophil levels among cluster 3 subjects and high mast cell gene expression among cluster 2 subjects. Subjects in cluster 2 also had lower levels of host defense genes (*BF1FA1* and *MUC5B*). The mild Th2-type cluster included the youngest asthmatic patients with the highest IgE levels and these subjects exhibited high expression of both Th2-high epithelial and mast cell genes. By extending molecular airway endotyping to severe asthmatic patients, this study has identified clinically distinct subgroups of asthmatic patients all with evidence of Th2 inflammation. The molecular characteristics of these subject groups are also distinct and indicate differential involvement of host defense, TNF- α signaling, and mast cell mechanisms between the groups.

The epithelial cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) have all been reported to be necessary and sufficient for production of Th2 cytokines and to drive asthmatic airway phenotypes in mouse models [5–7]. Therefore, Cheng *et al.* [8] measured expression of these genes in bronchial biopsies from 43 asthmatic patients and 21 healthy controls and evaluated whether their expression was reflective of Th2 inflammation and ICS response. Neither *IL33* nor *TSLP* was increased in asthmatic subjects. However, they identified a subset of asthmatic patients with higher *IL25* levels compared with healthy controls. The *IL25*-high subjects exhibited greater airway hyperresponsiveness, higher serum IgE, more subepithelial thickening, and higher expression of Th2-high asthma genes. Significant response to ICS was also restricted to the *IL25*-high subgroup. These results indicate that IL-25 may be a significant driver of Th2 inflammation in asthma and a potential drug target. Finally, the authors report that plasma levels of IL-25 correlated with its bronchial expression, suggesting that a noninvasive plasma test could be used to identify asthmatic patients that will likely respond to ICS therapy.

IL-33 pathway involvement in Th2 inflammation was also investigated by Traister *et al.* [9] through investigation of *ST2L* gene expression, which is the *IL1RL1* gene transcript encoding the IL-33 receptor. Bronchial expression of *ST2L* was increased specifically in severe asthma and was associated with several Th2 markers, including blood eosinophils, FeNO, and Th2-high gene expression markers such as *CLCA1* and *eotaxin-3*. Finally, the

expression levels of both the *ST2L* and *sST2* splice variants were shown to be under cis-genetic regulation. These results suggest that IL-33 signaling may underlie Th2 inflammation among severe asthmatic patients and that *IL1RL1* locus variants may predispose to the Th2 asthma endotype.

Another recent study attempted to identify an asthmatic airway endotype driven by dysfunction in the airway sensory response to physical and chemical irritants. Namely, McGarvey *et al.* [10] investigated expression of the transient receptor potential vanilloid 1 (*TRPV1*) channels in the bronchial epithelium of healthy controls and asthmatic patients. The TRPV1 channel has been genetically implicated in asthma and is responsive to physical (low pH) and chemical stimuli (lipoxygenase products), common to the asthmatic airway [11]. The authors found that bronchial *TRPV1* expression was higher among refractory asthmatic patients and that capsaicin stimulation of the channel led to production of the proinflammatory cytokine, IL-8, in bronchial epithelial cells. These findings suggest a refractory asthma endotype may exist, characterized by high TRPV1 channel expression, and that this channel may be a therapeutic target for this asthmatic group.

Nasal Airway Epithelial Endotypes

Despite the power of bronchial airway brush endotyping, the expansion of this method to children, larger research studies, and clinical practice is limited by the need to perform an invasive bronchoscopy to collect the brushing specimen. Nasal airway brushings represent an alternative that can be collected in a few seconds without anesthesia and yields high-quality biomolecules for molecular analysis. Our group recently investigated the suitability of nasal airway brushings as a surrogate for bronchial brushings in the endotyping of childhood asthmatic patients. In this study [12], we first performed whole transcriptome RNA sequencing on nasal airway brushing RNA from 10 asthmatic children and 10 healthy controls. Comparing the nasal transcriptome with published bronchial transcriptome data, we found high overlap (>90%) and strong correlation ($r=0.87$) in gene expression between the two airway sites. Moreover, investigation of asthmatic fold changes for 40 bronchial airway asthma biomarker genes from the study by Woodruff *et al.* [1] revealed a strong correlation ($r=0.77$) with our nasal transcriptome data. These results show much of the transcriptional diversity of lung airways is represented in the nasal airways, and that most of the bronchial airway asthma disease expression changes are reflected in the nasal airway.

In addition, we applied targeted RNA-seq methods to measure the expression of 103 biomarker and genetic/biological asthma candidate genes in a larger group of 50 asthmatic children and 50 controls. We found that 48 of these genes were associated with asthma. Importantly, these methods were sensitive enough to detect Th2 cytokine levels (*IL13*, *IL4*, and *IL5*), allowing us to determine the Th2-driven nature of nasal airway differential expression in asthma. We found 68% of differentially expressed genes were correlated with *IL13* gene expression levels. Supporting that many airway changes in asthma are reflective of a Th2 skew in the systemic immune system, we found that nasal expression for 70 of these genes was associated with atopic status. Hierarchical clustering of expression levels for these 70 genes differentiated Th2-high and Th2-low subjects. This Th2-high signature was characterized by high expression of *IL13*, bronchial Th2-high signature genes, and was

associated with high blood eosinophils, atopic status, rhinitis, and atopic asthma. In addition, we found nasal *IL13* levels were 3.9-fold higher in asthmatic patients who experienced an asthma exacerbation in the past year. Together, our results indicate that the Th2-high asthma endotype can be identified in children with minimally invasive nasal brushings and present an opportunity to extend this endotyping to large clinical and research populations of adults and children alike. Moreover, this targeted RNA-seq method allows direct measurement of Th2-cytokines in the airway, information that could be used to identify asthmatic patients at risk for exacerbations or to accurately stratify patients in the multiple Th2-inhibitor trials currently underway.

Finally, nasal expression of several other genes was associated with asthma status independently of atopy or *IL13* levels. Two of these genes, *MUC5B* and *KRT5*, are markers of secretory and basal airway epithelial cells, respectively. Changes in these genes may reflect cellular remodeling in the airway reflective of asthma status. Supporting this expression of *oncostatin M*, previously associated with airway remodeling, was upregulated in the nose of asthmatic patients. Further work will be needed to determine if clinically informative nasal airway remodeling endotypes exist.

Another recent study [13] compared nasal mucosa candidate microRNAs (miRNA) expression between 150 subjects with asthma alone, asthma and allergic rhinitis, or healthy controls. The authors found that several of these miRNAs (e.g. miR-18a, miR-126, and let-7e), previously associated with allergic rhinitis or allergic inflammation, were dysregulated in the asthmatic subjects. The asthmatic changes in miRNA expression were similar among subjects with and without rhinitis. This study extends asthmatic expression changes of the nasal airway to miRNAs and is in line with the previous studies [14,15] that found miRNA expression changes in the bronchial airway of asthmatic patients.

Additional studies employing nasal brushings are investigating airway transcriptome responses to stimulus. Notably, recent studies have successfully used nasal airway tissue to study asthmatic airway responses to viral infections *in vivo* [16] and *in vitro* [17]. These studies may lead to the development of accessible biomarkers for significant adverse responses to viral infections in asthma.

Sputum Inflammatory Endotypes

The molecular analysis of cells isolated from induced sputum presents a noninvasive alternative to airway brushings for query of inflammation present in the airway of asthmatic patients. Cellular analysis of sputum from asthmatic subjects has revealed significant heterogeneity with eosinophilic, neutrophilic, and paucigranulocytic subtypes of disease. Initial sputum transcriptional profiling studies segregated asthmatic patients largely as a function of these three groups and suggested dysregulated IL-1 β and TNF- α /NF κ B signaling in the neutrophilic group [2]. Significant advances in sputum endotyping have been made in the past year as expertise to perform this technique becomes more widespread.

Prominent among these studies was the work by Baines *et al.* [18], which used a multistep approach to define biomarkers of sputum inflammatory endotypes. Specifically,

whole-genome differential expression analysis of induced sputum was conducted in 47 asthmatic patients with eosinophilic, neutrophilic, or paucigranulocytic disease, to identify biomarkers for each inflammatory endotype. This analysis resulted in 28 genes, 23 of which were confirmed by qPCR in a validation cohort of 59 asthmatic patients. A variety of analytical techniques were used to narrow this gene group to the six most informative genes. Higher expression of *CLC*, *CPA3*, and *DNASE1L3* genes defined eosinophilic asthma, whereas higher expression of the *IL1 β* , *ALPL*, and *CXCR2* genes characterized neutrophilic asthma. This gene signature likely has clinical relevance, as it was also demonstrated to predict ICS treatment response better than sputum eosinophil percentage alone.

The IL-1 β endotype in neutrophilic asthma was studied further by the same research group [19]. The authors suggested that the NLRP3 (nucleotide-binding domain and leucine-rich repeats containing pyrin domain 3) inflammasome is a key regulator of neutrophilic airway inflammation in asthma, as it is required for induction of proteolytic cleavage of pro-IL-1 β to its active form. The authors demonstrated that the components of the NLRP3 inflammasome – NLRP3, caspase-1, caspase-4, and caspase-5, as well as the mature IL-1 β and the pro-inflammatory cytokine IL-8 – were all significantly elevated in sputum of participants with neutrophilic asthma. These findings suggest a novel mechanism for neutrophilic asthma and potential targets for intervention.

Another recent study [20] sought to determine if the bronchial brushing defined Th2-high asthma endotype could also be identified in more accessible sputum samples. The authors demonstrated the classic Th2 cytokines (*IL13*, *IL4*, and *IL5*) could be measured directly in sputum RNA. A ‘Th2 gene mean’ defined by expression of these three genes identified Th2-high asthma status and was associated with increased sputum and blood eosinophils, higher FeNO, and greater airway obstruction. Two of the three previously defined bronchial Th2-high biomarkers (*CLCA1* and *periostin*) were elevated in the sputum of Th2-high subjects. Interestingly, the authors demonstrated that sputum Th2 gene mean remained elevated in many patients after ICS therapy. This is in contrast to Th2-status defined by bronchial brush, which is highly sensitive to ICS therapy, and suggests that sputum can be used for endotyping even if the patient is being treated. Moreover, this group may represent an ICS-resistant Th2-high population that would benefit from one of the novel anti-Th2 therapies under development.

The use of sputum cytokines to endotype patients was also investigated by Seys *et al.* [21], who measured a panel of 12 cytokines in 40 controls and 66 adult asthmatic patients. Defining high cytokine status as exceeding the 90th percentile level among controls, the authors found distinct groups of *IL4* and *IL5* high asthmatic patients, as overlap in the two groups was surprisingly limited. The authors reported large overlap in subject *IL5*, *IL17A*, and *IL25*-high status, defining a novel endotype associated with worse lung function and lack of asthma control. The authors hypothesized that this endotype may be the result of epithelial IL-25 and IL-17A cytokines driving increased IL-5 production. Further studies are needed to confirm this endotype and investigate its relationship to treatment response.

Conclusion

Progress in the endotyping of asthmatic patients has accelerated over the past year as novel endotypes have been identified and known endotypes refined. Asthmatic patients with excessive Th2 inflammation can now be identified using expression of a few genes in bronchial brushing specimens, as well as in more accessible nasal brushing and induced sputum samples. Applying these methods, subpopulations with excessive Th2 airway inflammation, originally identified in mild adult asthmatic patients, have now been shown to be present among childhood and severe adult asthmatic patients. Other data suggest that further stratification of the Th2-inflamed group may be possible based on mast cell involvement or specific Th2 cytokines. Enhanced methods and the use of induced sputum samples are allowing endotypes to be developed that center around cytokines such as IL-13, IL-4, IL-5, IL-25, and IL-33. Direct measurement of these mediators of airway inflammation should guide future drug development and will allow the actual target of anti-Th2 therapies to serve as the biomarker in clinical trials.

Advancement has been slower in defining endotypes for the significant percentage of asthmatic patients that do not exhibit airway Th2 inflammation. However, the recently identified markers of neutrophilic inflammation such as IL-1 β /TNF- α may be fruitful targets for new antibody therapies. In addition, the potential chemosensory and cellular remodeling signatures recently observed in both bronchial and nasal epithelial brushings may point to new endotypes relevant in asthmatic patients without significant airway Th2 inflammation.

The minimally invasive endotyping methods validated in the past year will need to be applied to significantly more and larger cohorts of asthmatic patients to fully define the range of asthma endotypes. The continued identification of asthma airway endotypes along with evaluation of clinical implications for these endotypes is necessary to achieve personalized management of asthma disease.

Acknowledgments

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Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

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Key Points

- More accessible airway samples, combined with simpler and more powerful analysis methods are allowing the broader application, including to novel populations, of asthmatic airway endotyping.
- Multiple asthmatic airway endotypes exist and these endotypes are associated with clinical characteristics and treatment responses.
- Recent studies indicate several related variants of the Th2-high asthma endotype exist in both childhood and severe asthmatic patients.
- Prominent among non-Th2 asthmatic airway endotypes is a neutrophilic pattern that is characterized by increased expression of IL-1 β and TNF- α pathway genes.