Clinical and pathobiological heterogeneity of asthma—Mechanisms of severe and glucocorticoid-resistant asthma

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ABSTRACT

It is increasingly recognized that asthma represents a syndrome, and there is clinical and pathobiological heterogeneity. Many genes are reported to be associated with asthma, and may be involved in the disease heterogeneity. Diverse cells, such as T helper 1 (Th1)-cells, Th2-cells, Th17-cells, airway epithelial cells, and innate and adaptive immunity associated cells, contribute to the pathobiology of asthma independently of each other or they can also coexist and interact. Although, generally, Th2 immunity is important in most asthma endotypes, non-Th2-driven inflammation tends to be difficult to manage. Recently, increased attention has been focused on severe asthma and glucocorticoid (GC)-resistant (GC-R) asthma, in which diverse inflammatory processes may be involved. Treatment approaches should take into account pathological differences.

Keywords: Asthma Phenotype; Genome-Wide Association Study (GWAS); Glucocorticoid (GC)-Resistant (GC-R) Asthma; Severe Asthma

1. INTRODUCTION

Asthma is a chronic inflammatory disease characterized by episodic and reversible airway obstruction and bronchial hyper-responsiveness. Allergic involvement, age at onset, exacerbating factors, and response to treatment differ in each individual. In common with other complex diseases, asthma is a heterogeneous and genetically complex disease, and in some patients factors can coexist [1-3]. The recent discovery of new asthma-associated genes and new mechanisms of immunity and inflammation reinforces the concept of clinical heterogeneity of asthma. Despite conventional therapy, including bronchodilators, leukotriene modifiers, and GCs, some patients do not respond satisfactorily to therapy, and attention is now focused on severe and GC-R asthma. Accurate definition of asthmatic phenotypes may facilitate clinical investigation of the pathogenesis and be useful for treatment of asthma. This review summarizes the clinical and pathobiological phenotypes of asthma, and discusses the mechanisms of GC resistance.

2. GENETIC BACKGROUND OF ASTHMA

More than 100 genes have already been implicated. One mechanism alone cannot explain the pathogenesis of asthma. Asthma susceptibility genes fall into four main groups: genes associated with innate immunity and immunoregulation; genes associated with Th2-cell differentiation and effector functions; genes associated with epithelial biology and mucosal immunity; and genes associated with lung function, airway remodelling and disease severity [4]. Asthmatics are not always equally influenced by those genes, and the involvement of each gene may differ among individuals, suggesting heterogeneity.

Recently, two meta-analyses of asthma genome-wide association studies (GWAS) have been completed, one by the GABRIEL Consortium, which discovered that the IL18R1, IL33, SMAD3, ORMDL3, HLA-DQ and IL2RB loci were all significantly associated with asthma [5], and one by the EVE Consortium [6]. These investigations especially have highlighted the importance of variation of genes in airway epithelial cells for various immune and inflammatory processes in asthma [7].

3. CELLULAR INFLAMMATORY PHENOTYPES

Concepts of asthma pathogenesis in inflammation continue to evolve. There has been a predominant view that a Th2-predominant phenotype and Th2 cytokines such as IL-4, IL-5, and IL13 predispose to the development of asthma. Th1 cells previously had been regarded

to inhibit bronchial asthma by virtue of IFN-γ, but recently, bronchial asthma has been considered a complicated disease induced by the functions of Th1 and Th2 cells. The adoptive transfer of antigen-specific Th1 cells into ovalbumin-challenged mice led to the development of airway hyper-responsiveness and airway inflammation that was independent of IL-13 and IL-4 [8]. In addition, Th1 cells become pathological super Th1 cells when stimulated with Ag and IL-18, through the production of IFN-γ and IL-13, which in combination induces AHR, peribronchial inflammation, and lung fibrosis in a mouse model of asthma [9]. Th17 cells have come to attention and been added as a third distinct T-helper cell subset, which produces IL-17A, IL-17F, and IL-22. On allergen sensitization, Th17 cells home to the lung and enhance both Th2 cell-mediated eosinophilic airway inflammation and neutrophilic airway inflammation in mouse models of asthma [10,11]. Th17 cells, which mediate Th2-independent neutrophilic inflammation, have also been shown in IL-17F transgenic and knockout mice [12]. Although the role of Th17 cytokines in neutrophil recruitment is still unclear, IL-17 has been suggested as a mediator of neutrophil variant and severe neutrophilic asthma endotypes [13].

Recently, investigation of asthma pathogenesis has focused on innate immunity and epithelial function. Activation of innate immune responses also leads to production of Th2-type cytokines or skewing of responses toward the Th2 pattern. Epithelial cells are involved in the initiation of allergic response in the airway by releasing thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 in response to allergens. TSLP mediates migration of dendric cells (DC), resulting in presentation of antigens, differentiation of T-helper cells, and production of the Th2 cytokines IL-4, IL-5, and IL13.

4. CLINICAL PHENOTYPES OF ASTHMA

To identify the characteristic phenotypes of asthma, factor analysis from questionnaire, clinical, and laboratory data, including baseline pulmonary function and allergen skin prick test results, has been performed in physician-diagnosed asthma and symptomatic siblings in nuclear families and has demonstrated its heterogeneity [14]. Trials to discriminate asthma phenotypes by cluster analysis [15,16] have been reported. The National Heart Lung and Blood Institute-sponsored Severe Asthma Research Program (SARP) identified and characterized novel asthma phenotypes using unsupervised hierarchical cluster analysis. Five groups were identified. Subjects in Cluster 1 have early onset atopic asthma with normal lung function treated with two or fewer controller medications and minimal health care utilization. Cluster 2 consists of subjects with early-onset atopic asthma and preserved lung function but increased medication re-

quirements and health care utilization. Cluster 3 is a unique group of mostly older obese women with late-onset nonatopic asthma, moderate reductions in FEV_1, and frequent oral corticosteroid use to manage exacerbations. Subjects in Clusters 4 and 5 have severe airflow obstruction with bronchodilator responsiveness but differ in to their ability to attain normal lung function, age of asthma onset, atopic status, and use of oral corticosteroids [17]. An important contribution of the SARP study, a cluster analysis, was the creation of a decision tree from variables readily available in the clinic. Cytokine profiles in bronchoalveolar lavage (BAL) samples [18] have also been studied.

5. SEVERE ASTHMA PHENOTYPE

Asthma heterogeneity is recognized in severe asthma, where patients have diverse symptom profiles and altered responses to medication. Collaborative investigations of difficult asthma by the European Network for Understanding Mechanisms of Severe asthma [19] and the Severe Asthma Research Program in the United States [20] have been carried out.

Genetic polymorphisms are associated with asthma severity. TGFβ1 causes tissue fibrosis and extracellular tissue deposition of matrix components and is believed to be involved in airway remodeling. It has been reported that the −509T allele in the −509C > T polymorphism of the TGFβ1 gene is correlated with severe asthma [21]. It has been demonstrated that epidermal growth factor receptor (EGFR) plays an important role in tissue remodeling of the airways in asthma. Many patients with severe asthma have a small number of CA repeats in intron 1 of the EGFR gene [22]. The IL4[*]-589T allele is a risk factor for life-threatening asthma and the IL4RA[*]576R allele is a risk factor for poor lung function in asthmatic subjects [23].

Eosinophilic inflammation is a Th2-driven trait that is important in some asthma endotypes. Endobronchial biopsy [24] and induced-sputum analysis [25] in severe and persistent asthma demonstrated involvement of neutrophil influx and activation, which may be mediated by IL-8 secretion. Th1 cells play a critical role in pulmonary neutrophilia, coupled with the production of CXC chemokines [26]. High mobility group box 1 (HMGB-1), a ligand of the receptor for advanced glycation end products (RAGE), is a mediator of neutrophilic airway inflammation in asthma, and imbalance between HMGB-1 and esRAGE is related to the severity of asthma [27]. Neutrophilia has been noted during acute asthma exacerbations [28], and has been reported to be associated with infection, exposure to pollutants, smoking, and obesity [29]. In general, the condition of patients with neutrophilic asthma tends to be severe, and this comprises one endotype of asthma.

Mast cells (MCs) contribute to the pathophysiology of asthma, and airway smooth muscle (ASM) infiltration is important in determining the asthma endotype. Mast cells infiltrate the airway mucous glands and show a positive correlation with the degree of mucus obstructing the airway lumen, suggesting their role in regulation of mucous gland secretion. Comparison of subjects with asthma and normal subjects in the Severe Asthma Research Program revealed that severe asthma is associated with a predominance of MCs in the airway submucosa and epithelium [30].

Eosinophilic inflammation and airway remodelling occur in children with early respiratory symptoms before a clear clinical diagnosis of bronchial asthma can be made [31]. Remodeling has been postulated to be the result of persistent inflammation in the bronchial wall, associated with the production of inflammatory cytokines and growth factors. Reportedly, severe asthma is different from non-severe asthma by increased airway wall remodelling rather than by differences in inflamematory cell numbers [32].

6. GC-R ASTHMA

The response to GCs in asthma is very heterogeneous [33], and may have a genetic basis. Variations in the stress-induced-phosphoprotein-1 (STIP-1) gene, which encodes components of the GR complex [34], and the glucocorticoid-induced transcript 1 (GLCCI1) gene might be involved in GC response [35].

Mostly, GC sensitivity is modified by inflammatory response. Generally, non-Th2-dependent, non-eosinophilic asthma is associated with a poor response to GCs [36]. Th1-dependent inflammation [37,38], neutrophilic inflammation [39], and Th17-driven inflammation are recognized to be associated with GC-R asthma [40-42]. Factors related to innate immunity may result in GC resistance [37].

The phosphorylation status of GR plays a critical role in controlling GR properties such as nuclear translocation. The status is largely influenced by kinase signaling and phosphatases [43-45]. An increase in the inactive GRβ isoform alters GC response in GC resistance [46] by controlling HDAC2 expression [47]. However, the roles of GRβ in modulating GC sensitivity have been highly debated [48].

Most of the anti-inflammatory actions of GCs can be accounted for by inhibition of transcription factors, mainly activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB), which regulate inflammatory gene expression. The interaction is mutually antagonistic, suggesting its contribution to GC-R asthma. Protein-protein interactions between activated GR and other transcription factors may also play an important role in GC-R asthma. Whereas interferon regulatory factor-1 (IRF-1) [49] inhibits GR action, CCAAT enhancer-binding protein (C/EBP) [50], activating transcription factor 3 (ATF3) [51], and nuclear factor (erythroid-derived 2)-related 2 (Nrf2) [52] promote GR function.

p38 mitogen-activated protein kinase (MAPK) acts on a variety of substrates including transcription factors, such as NF-κB and AP-1. MAPK-mediated inhibition of GR function appears to be key to GC resistance [53-55]. Phosphoinositide 3-kinase (PI3K) plays an integral role in the immune system, in both MC and eosinophil function, and may be crucial in mediating GC insensitivity after oxidative stress via decreased activity of HDAC2 [56].

Preventable risk factors that modify GC-responsiveness, such as vitamin D deficiency [57], smoking [58,59], and obesity [60] are recognized.

7. FUTURE PROSPECTS

GWASs are revealing new asthma susceptibity genes that are expressed in the airway epithelium and innate immunity pathways. Advances in understanding of the sentinel role played by airway epithelium function and innate immunity in asthma promote the concept of non-Th-2-driven pathways underlying airway inflammation. The association of asthma-related genes and different cellular phenotypes with clinical phenotypes and response to therapy is a big issue, which should be analyzed. Despite widespread use of inhaled GCs, there are still patients with severe asthma phenotypes. Although dissociated GCs may provide greater steroid potency with fewer adverse-effects, GC therapy does not always cover all asthma phenotypes. Immunosuppressants, such as methotrexate and cyclosporine A, and biological molecules, such as omalizumab, mepolizumab and etanercept, may have useful steroid-sparing effects in severe asthma. Among severe asthma phenotypes, GC-R asthma is one particular phenotype that is expected to be treated by new therapeutic strategies, such as p38 MAPK inhibitors and PI3Kδ inhibitors.

8. CONCLUSION

Genetic background and various inflammatory pathways contribute to asthma phenotype. There is great hope that clinical clustering analysis will be useful to predict disease severity and response to therapy. Recognition of the phenotype of asthmatic patients may offer a better understanding of the pathobiology of the disease and lead to personalized therapy.

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