



Asthma phenotypes and endotypes

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Purpose of review

It is increasingly clear that asthma is not a single disease, but a disorder with vast heterogeneity in pathogenesis, severity, and treatment response. In this review, we discuss the present understanding of different asthma phenotypes and endotypes, and the prospects of personalized medicine for asthma.

Recent findings

The recognition of diverse biological backgrounds in which asthma, and particularly severe asthma, can manifest has prompted the search for refined phenotypes and endotypes in asthma. Such appreciation of the heterogeneity in asthma is also prompting clinical trials to focus on specific subgroups of asthma, as demonstrated by the clinical trial of lebrikizumab.

Summary

Patients with severe asthma have asthma symptoms that are difficult to control, require high dosages of medication, and continue to experience persistent symptoms, asthma exacerbations or airflow obstruction even with aggressive therapy. Although asthma is traditionally viewed as an eosinophilic inflammatory disorder associated with a T-helper cell type 2 (Th2) immune response, recent studies have identified involvement of other effector cells, nonclassical Th2 cytokines and non-Th2 cytokines in severe asthma pathogenesis. Results of several clinical trials of anticytokine antibodies demonstrated the effectiveness of tailoring asthma treatment on the basis of an individual's biology.

Keywords

asthma, endotypes, personalized medicine, phenotypes

INTRODUCTION

Asthma has generally been defined as a chronic disorder of the lung with variable airway obstruction, wheeze/cough, and an underlying inflammatory process. However, considerable heterogeneity exists within the population of patients with asthma-like symptoms. The disease is currently recognized as a complex condition with variable severity, natural history, and response to treatment. Such heterogeneity in the disease demands nonuniform treatment schemes. Treating asthma based on phenotypes, which are observable characteristics with no direct relationship to disease mechanisms, demonstrated some successes yet remains suboptimal, given the variability in treatment response; however, when combined with endotypes, which refers to subpopulations of a disease with similar molecular mechanisms or treatment response, it elicited more effective treatment responses [1–3]. In this review we will highlight the nature of heterogeneity in asthma in terms of pathogenesis, pathophysiology, and treatment response and give a perspective on the future of personalized medicine in the treatment of asthma.

TRADITIONAL CLASSIFICATION OF ASTHMA AND SEVERITY

Asthma is usually defined by observational characteristics. It is commonly defined by atopy status, serum total immunoglobulin E (IgE) and blood eosinophils levels [2]. Traditionally, asthma has been categorized as either atopic/extrinsic or nonatopic/intrinsic. The classic paradigm of atopic/extrinsic asthma begins with allergen exposures, followed by progressive allergic inflammation, hyperresponsiveness and symptoms in the airways [3]. Individuals with atopic asthma often developed their asthma in their childhood, have a family history of asthma, and responded to treatment against anti-

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KEY POINTS

- Severe asthma is a different disease entity from mild and moderate asthma.
- Vast heterogeneity exists within severe asthma in terms of pathogenesis and treatment response.
- An asthma treatment scheme must take into consideration both an individual's asthma phenotype and endotype.

T-helper cell type 2 (anti-Th2) inflammation. On the contrary, nonatopic/intrinsic asthma is often associated with an adult onset form of the disease and an absence of family history [1,2]. Within the category of intrinsic asthma, individuals with adult onset are associated with more severe symptoms and nasal polyps, and persistent airflow limitation in men [4[¶]]. Both intrinsic and extrinsic asthma share the common feature of Th2 airway inflammation [5–7].

To define asthma severity, the National Asthma Education and Prevention Program outlined four levels on the basis of the underlying physiological changes in the airways and treatment responses: intermittent, mild persistent, moderate persistent, and severe persistent [8]. The Global Initiative for Asthma (GINA) guidelines has reclassified asthma severity into five levels on the basis of the treatment schemes needed to attain good asthma control [9].

Conventionally, the terms 'severe asthma', 'difficult-to-treat asthma', or 'refractory asthma' have been used interchangeably to describe asthmatic individuals who could not attain good symptom control in spite of high dosages of medication. However, one needs to distinguish individuals with truly severe asthma from those who have failed to achieve good symptom control due to poor treatment compliance. To distinguish the 'true' severe asthmatic individuals from those who would have a milder form of the disease if treatment was complied with, various health organizations further defined severe asthma into subclasses. GINA defined 'difficult-to-treat asthma' as an asthmatic patient who could not achieve good asthma control in spite of high dosage of inhaled corticosteroids (ICS) [9]. The American Thoracic Society and European Respiratory Society defined refractory asthma and 'difficult/therapy-resistant asthma', respectively, on the basis of the treatment scheme needed to attain good asthma control [10,11]. The WHO further categorized severe asthma into untreated severe asthma, difficult-to-treat-asthma, and treatment-resistant severe asthma on the basis of the defined criteria [12]. Finally, the Innovative Medicine

Initiative proposed to subdivide 'problematic asthma' into 'difficult asthma' and 'severe refractory asthma', on the basis of treatment adherence and asthma control [13[¶]]. In this review, the terms 'severe asthma' refers to asthmatic individuals who have adhered to treatment yet need an aggressive treatment scheme to attain adequate asthma control.

PATHOGENESIS OF ASTHMA

In the past two decades, Th2-mediated inflammation has been the focus of understanding asthma pathogenesis [14]. Briefly, upon binding of antigens to their receptors on dendritic cells in the epithelium, dendritic cells are activated and present antigen to naive T cells, which differentiate into Th2, one of several T-helper cell types (e.g. Th1, Th2, and Th17). Different T-helper cells have different cytokine production profiles, and for Th2 cells interleukin (IL)-4 and IL-13 are the canonical cytokines [15]. IL-4 promotes the differentiation and stimulation of Th2 cells and IgE production from B cells. IL-13 mediates smooth muscle contraction, mucus secretion, and airway hyperresponsiveness [16,17[¶]], and induces eosinophil chemoattractants in the airways [18]. IL-5, another Th2 cytokine, is a critical cytokine for eosinophilic asthma and is essential for the recruitment, differentiation, and activation of eosinophils [19[¶]].

It has become apparent that severe asthma is a different disease than mild and moderate asthma, in which the dysregulation of the Th1/Th2 cytokines production in severe asthma differs from the milder forms of asthma. It has been postulated that specific sets of cytokines might be associated with different phenotypes and inflammatory markers production, which suggests that there are different phenotypes for asthma, at least at the cellular level [19[¶]].

AIRWAY REMODELING

Remodeling is believed to be the adaptive changes in the quantity and/or quality of structural cells and extracellular matrix (ECM) in response to various stress stimuli [20]. In asthma, the thickening of the bronchial reticular basement membrane, an increase of ECM, and angiogenesis have been observed in some asthmatic children, implying that remodeling could be a feature in subgroups of asthmatic individuals even at the early stage of the disease development [21,22].

Airway remodeling is also a hallmark characteristic of severe asthma and contributes to the problem of airflow obstruction, irreversibility, and severity [23[¶],24,25]. Numerous studies have

reported thickened airway wall and increased airway wall area and submucosal area in severe asthmatic individuals with persistent airway obstructions as compared to asthmatic individuals of lesser severity [26–30]. Furthermore, in severe asthmatic individuals, forced expiratory volume in 1 s (FEV₁)% predicted was found to be inversely correlated with airway wall/area thickness and smooth muscle area [26,30]. Hence, structural changes in the airway walls contribute to airway remodeling and affect lung function and asthma severity. However, controversies exist on the correlation between subepithelial fibrosis and asthma severity, suggestive of heterogeneity in not only asthma *per se* but also in ‘severe asthma’. Such heterogeneity in severe asthma has great clinical implications.

CORTICOSTEROID RESPONSIVENESS

ICS are the mainstream asthmatic medications because of their relatively nonspecific anti-inflammatory property. Under steroid responsive conditions, inflammatory stimulants signal the acetylation of DNA, which is wrapped around core histones, leading to the opening up of DNA chromatin for the initiation of inflammatory gene transcription [31]. Glucocorticoid acts by binding to glucocorticoid receptors in the cytoplasm, and histone acetyltransferase acetylates glucocorticoid–glucocorticoid receptor α complex and facilitates the translocation into the nucleus. The resulting complex binds to DNA and suppresses inflammation by regulating the expression of several immune genes [32]. However, for individuals with steroid hyporesponsiveness, extensive airway remodeling is common and nonreversible even when treatment is aggressive and has been adhered to.

Steroid hyporesponsiveness in severe asthma

Steroid resistance in asthma largely relates to glucocorticoid receptor dysfunction and dysregulation of histone acetylation and deacetylation. Glucocorticoid receptor dysfunction includes either altered glucocorticoid receptor binding affinity or glucocorticoid receptor β overexpression [33–40]. Two forms of glucocorticoid receptor exist, glucocorticoid receptor α and glucocorticoid receptor β [41]. Glucocorticoid receptor β binds to DNA but not glucocorticoid; hence, glucocorticoid receptor β inhibits glucocorticoid receptor α -mediated gene expression by forming transcriptionally inactive glucocorticoid receptor α/β heterodimers in the nucleus [42–44]. Upregulation of glucocorticoid receptor β has been reported in the airway and

inflammatory cells of severe asthmatic patients [33]. Inflammatory cytokines such as IL-2, IL-4, IL-17A, and IL-17F have been shown to induce glucocorticoid receptor β expression in airway structural and immune cells [38,45,46]. Dysregulation of histone acetylation and deacetylation contribute to steroid resistance when transcription sites of immune genes could not be deacetylated by histone deacetylase (HDAC) [32]. In severe asthmatic individuals, reduced HDAC activity in peripheral blood mononuclear cells was detected when compared to nonsevere asthmatic patients [47,48,49].

HETEROGENEITY OF INFLAMMATORY RESPONSES IN SEVERE ASTHMA

Asthma has been traditionally viewed as an eosinophilic airway inflammatory disorder associated with bronchial hyperresponsiveness (BHR) [50,51]. Asthma severity has been found to be associated with the number of eosinophils in the lung and has been used as an index to assign clinical phenotypes and respective therapy in severe asthma [50,52–54]. The focus on eosinophilia in the past reflected a view of asthma as a manifestation of the Th2 response, which is characterized by the production and secretion of Th2 cytokines such as IL-4, IL-5, IL-9, IL-13, and IL-33. These cytokines, in turn, drive eosinophilic inflammation and tissue damage, leading to BHR and release of additional mediators. However, in severe asthma, increased expression of other cytokines including interferon- γ , IL-8, IL-18, and IL-17 has been found in bronchial biopsies of severe asthmatic patients [20,55,56,57], and genetic studies have found non-Th2 genes to be associated with severe asthma [21,22,58]. Furthermore, neutrophils and mast cells are appearing to be important effector cells in some severe asthmatic individuals [59–66]. Once again, these observations are indicative of the vast heterogeneity in severe asthma.

ASTHMA PHENOTYPES VERSUS ENDOTYPES

Variability in clinical characteristics, inflammatory profiles and responses to treatment has made it increasingly clear that severe asthma is not a single disease. Treating asthma based on phenotypes has been shown to be suboptimal. Although phenotyping refers to grouping individuals with similar observable characteristics, endophenotyping, or ‘endotyping’ for short, groups individuals on the basis of underlying molecular mechanisms or treatment responses [67,68]. At present, some successes

have been achieved in clinical trials when treatments are tailored to endotypes.

Therapeutic evidence for severe asthma endotypes

By definition, to endotype is to group patients according to treatment response, hence, observations that better treatment outcomes are seen in subgroups of severe asthma patients implied the existence and usefulness of treating severe asthmatic patients according to both phenotypes and endotypes.

Mepolizumab, an anti-IL-5 monoclonal antibody, did not show clinical benefit for mild-to-moderate asthmatic patients [69,70]; however, in trials on severe asthma with persistent eosinophil expression, mepolizumab could reduce acute exacerbations accompanied by reduction in eosinophils in both the airways and blood [53,69]. These findings demonstrated the effectiveness of treating asthma based on the underlying disease mechanism.

Blocking of the IL-4/IL-13 signaling pathway with anti-IL-4 and anti-IL-13 antibodies has been ineffective in treating mild atopic asthma and moderate persistent asthma; however, lebrikizumab (anti-IL-13 antibody) has shown promising effects in those severe asthma patients with a high Th2 response [71,72,73].

A clinical trial of golimumab, an anti-tumor necrosis factor- α antibody, for the treatment of severe persistent asthma has ended with the conclusion of ineffectiveness; however, subgroup analysis indicated that golimumab reduced risk of exacerbation in those asthmatic patients with a history of sinusitis or with a bronchodilator response reversibility of 12% or more [74].

Bronchial thermoplasty involves using radiofrequency to remove airway smooth muscle cells via a bronchoscopic procedure [75–78]. Bronchial thermoplasty has been shown to be effective in reducing exacerbations and improving asthma control in well controlled asthma and improving FEV₁ and asthma control in severe refractory asthma [76,78].

PROSPECTS OF PERSONALIZED MEDICINE IN ASTHMA TREATMENT

Current clinical practice and clinical trials in disease treatment tend to aim at achieving the average of the best approaches to patient care. Such a 'one size fits all' treatment approach is facing major challenges when it is becoming clearer that complex and common diseases such as asthma are heterogeneous in pathogenesis. Thus, personalized medicine has become the realm of future medicine. The ultimate goal of personalized medicine is to

bring the right drug to the right patient at the right dose in order to maximize therapeutic efficacy and diminishes side effects [79,80].

In order to practice personalized medicine, physicians must consider the molecular/biological profile of an individual patient and recognize the interactions with the environment. With the advance of the 'omic' era, physicians are getting closer to being able to 'tailor' a treatment scheme on the basis of the unique individual's biological data such as genomic, transcriptomic, and proteomic profiles, in addition to the traditionally defined asthma phenotypes. As aforementioned, some successes have been achieved in clinical trials when treatments are tailored to endotypes. Although the exact molecular mechanisms underlying asthma pathogenesis and treatment response are far from understood, targeting therapy on the basis of asthma phenotypes and endotypes would at least allow physicians to target treatment on the basis of individual biology.

CONCLUSION

It has become clear that severe asthma represents a disease entity that differs from mild and moderate asthma in pathology and disease mechanisms. The classical Th1/Th2 paradigm has been the focus of asthma pathogenesis for decades, and in severe asthma regulation of Th1/Th2 cytokines production has been shown to be different from mild and moderate asthma.

Furthermore, within the conventional definitions of severe/refractory asthma, vast heterogeneity exists in the types of effector cells present, responses to treatment, and other clinical characteristics. Hence, in order to move toward personalized medicine for asthma, one must combine an individual's phenotype and endotype in designing an individualized treatment scheme.

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Conflicts of interest

There are no conflicts of interest.

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- The article is a discussion on the challenges and promises of personalized medicine for asthma from the perspective of genetics.