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Asthma endotypes: the right direction towards personalized medicine for asthma

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Audrey H Poon

Meakins-Christie Laboratories,
McGill University, 3626 Rue
St-Urbain, Montreal, Quebec,
H2X 2P2, Canada



Qutayba Hamid

Meakins-Christie Laboratories,
McGill University, 3626 Rue
St-Urbain, Montreal, Quebec,
H2X 2P2, Canada

Author for correspondence:

Tel.: +1 514 398 3864

ext. 00143

Fax: +1 514 398 7843

qutayba.hamid@mcgill.ca

“We are still far from practicing personalized medicine for asthma; however, the methodology to tailor treatment according to asthma endotypes is moving in the right direction.”

Asthma has generally been defined as a chronic disorder of the lung with variable airway obstruction, wheeze/cough and an underlying inflammatory process. The WHO has estimated that the economic costs associated with asthma have exceeded those of TB and HIV/AIDS combined, and the Global Initiative for Asthma Program forecasted the number of asthma patients to grow globally to greater than 400 million by the year 2025 [1,2]. Since its first description by Hippocrates, asthma remains a treatable yet incurable disease. It is now clear that asthma is a complex condition with variable severity, natural history and response to treatment [3,4]. Clinically, asthma is categorized into eosinophilic, neutrophilic, atopic, non-atopic, early onset and late onset, and into aspirin- or exercise-induced in the cases with known triggers [5]. The current international guidelines for asthma pharmacotherapy adopt a ‘step-up’ strategy. A low dose of inhaled corticosteroid alone is prescribed to treat the mildest asthmatic symptoms, and according to the resulting asthma control, varying doses of inhaled corticosteroids and combinations of long-acting β -agonists, leukotriene receptor antagonists, systemic corticosteroids, anti-IgE and theophylline compounds would be used in a step-up manner with the ultimate goal of controlling asthma [2,6–8]. For acute symptoms, reliever medications including rapid-acting β -agonists and anticholinergics are often prescribed [2,6–8]. The variability and, in the case of refractory asthma, the lack of treatment response clearly suggests that treating asthma based on observable characteristics

(e.g., symptoms) with no direct relationship to disease mechanisms is suboptimal.

The concept of classifying asthma into endophenotypes, or endotypes for short, has received a lot of attention in the last 5 years [5,9,10]. Endotyping refers to classifying subpopulations of a disease based on molecular mechanisms or treatment response, and the method has shown some successes in eliciting better treatment response in asthmatic patients [5,9,10]. Lötvall *et al.* proposed endotyping asthma into six classes: aspirin-sensitive, allergic bronchopulmonary mycosis, adult allergic, asthma-predictive indices-positive preschool wheezer, severe late-onset hypereosinophilic and cross-country skiers asthma [5]. More recently, Wenzel described the evolving five endotypes of severe asthma: early onset allergic, persistent eosinophilia, allergic bronchopulmonary mycosis, obese-female and neutrophilic severe asthma [10].

In a recent review, the authors summarized the contribution of different cytokine signaling pathways to the pathogenesis of severe asthma and further speculated the dominant signaling pathway underlying each endotype [11]. The consideration of disease endotypes in treatment design should be able to bridge the present era of treating asthma based on family history, patient characteristics and laboratory test, to the future era of personalized medicine where treatment scheme will be based on individual biological data such as genomic, proteomic and metabolic profiles [12,13]. In the case of asthma, some success has been achieved in clinical trials with targeted

treatment or when outcomes were analyzed according to asthma endotypes [14].

- Anti-IgE (omalizumab) has been effective in improving clinical outcomes, particularly in treating difficult-to-treat childhood-onset allergic asthma in which IL-4 and IL-13 signal pathways are likely the predominant underlying mechanism [15].
- Anti-IL-13 monoclonal antibody (lebrikizumab) was used in a clinical trial to treat severe asthma. A statistically significant improvement in lung function as measured by forced expiratory volume in 1 s was observed in the lebrikizumab treated group as compared to the placebo group. When the treatment group was further divided into high IL-13 activity and low IL-13 activity groups, as measured by periostin expression, a significant improvement was seen only in the high IL-13 activity group [16].
- Anti-IL-5 monoclonal antibody (mepolizumab) for the treatment of persistent eosinophilic severe asthma reported reduced numbers of symptomatic exacerbations and eosinophil counts in both the blood and sputum [17,18].
- Bronchial thermoplasty has been shown to be useful in removing airway smooth muscle mass in treating individuals

with extensive airway remodeling (i.e., severe-refractory and severe-persistent asthma) [17,19–21].

Data from these clinical trials therefore support the practice of treating asthma according to endotypes since it improved treatment response in targeted patients.

As the number of asthma patients continues to grow, failure to take into consideration the heterogeneity of this disease in its management would only increase the already heavy economic and social burden of this chronic inflammatory disease [1,2]. We are still far from practicing personalized medicine for asthma; however, the methodology to tailor treatment according to asthma endotypes is moving in the right direction.

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