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Asthma phenotypes: the evolution from clinical to molecular approaches

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Although asthma has been considered as a single disease for years, recent studies have increasingly focused on its heterogeneity. The characterization of this heterogeneity has promoted the concept that asthma consists of multiple phenotypes or consistent groupings of characteristics. Asthma phenotypes were initially focused on combinations of clinical characteristics, but they are now evolving to link biology to phenotype, often through a statistically based process. Ongoing studies of large-scale, molecularly and genetically focused and extensively clinically characterized cohorts of asthma should enhance our ability to molecularly understand these phenotypes and lead to more targeted and personalized approaches to asthma therapy.

The evolving definition of asthma

Asthma affects 5–10% of the population in many developed countries and is associated with a large socioeconomic burden. Yet 'asthma' is a vague term that describes a group of clinical symptoms with reversible expiratory airflow limitation or bronchial hyperresponsiveness. Although international asthma guidelines have added "in the presence of airway inflammation" to the list of criteria for disease, inflammation is almost never measured in practice, and a consistent inflammatory process is rarely confirmed. Thus, the term asthma, like 'arthritis', equates to a definition of grouped clinical and physiological characteristics (**Fig. 1**). These characteristics could identify syndromes, phenotypes or even multiple diseases rather than a single disease. Even leading international clinical journals such as *The Lancet* have suggested that the term asthma is out of date and that the evolution of more detailed clinically and biologically focused definitions of this condition should be encouraged[1]. Yet, most mechanistic studies of asthma focus only on a highly specific process related to allergic airway inflammation, despite the fact that the overall importance of this single process to human disease remains poorly understood.

In the 1990s and early 2000s, this vague clinical definition of asthma led to successful clinical trials of nonspecific anti-inflammatory and bronchodilator medications. At the same time, researchers working with mouse models of allergic asthma and/or inflammation identified the crucial role of T helper (T_H2) immune pathway elements (**Fig. 2**) in both inflammation and airway hyperresponsiveness[2–4]. Thus, asthma was widely believed to be an allergic, eosinophilic and T_H2-mediated (and corticosteroid-responsive) disease[5–7]. Unfortunately, negative initial results from T_H2-focused human clinical trials virtually halted biological approaches to treating asthma.

Simultaneously, a subgroup of people with severe asthma were observed to have refractory disease in the absence of eosinophils, with further studies suggesting that responses of people with asthma to nonspecific anti-inflammatory drugs, such as inhaled corticosteroids, were dependent on the presence and type of airway inflammation[8–11]. It was then shown that an antibody to the allergy-related factor IgE showed efficacy in reducing exacerbations in a targeted population with 'allergic' asthma[12,13]. Thus, 'asthma' began to evolve from a term describing a single disease to one encompassing multiple subgroups or, as they are now termed, phenotypes[14,15].

Definition of 'phenotype'

A phenotype is defined as the "observable properties of an organism that are produced by the interactions of the genotype and the environment"[16]. The concept of the phenotype have been suggested to be the prelude to that of the 'endotype', wherein a specific biological pathway is identified that explains the observable properties of a phenotype[17,18]. Although several endotypes of asthma have been proposed, none has been widely agreed upon; the acceptance even of asthma phenotypes is evolving, and the topic is controversial. Despite these difficulties in agreeing on endotypes, asthma phenotypes based on clinical characteristics, triggers or general inflammatory processes have been proposed, but there have been few attempts to link all of these characteristics together to better define phenotypes[19]. The definition of a true phenotype (or endotype) requires a unifying and consistent natural history, consistent clinical and physiological characteristics, an underlying pathobiology with identifiable biomarkers and genetics and a predictable response to general and specific therapies[18] (**Table 1**). Although both biased and unbiased approaches have begun to link the characteristics of asthma together to form phenotypes, no present system of subgrouping achieves all the requirements for a true phenotype or endotype. In addition, there are a number of co-morbidities and confounders that have been identified that can alter asthma phenotypes (**Box 1**).

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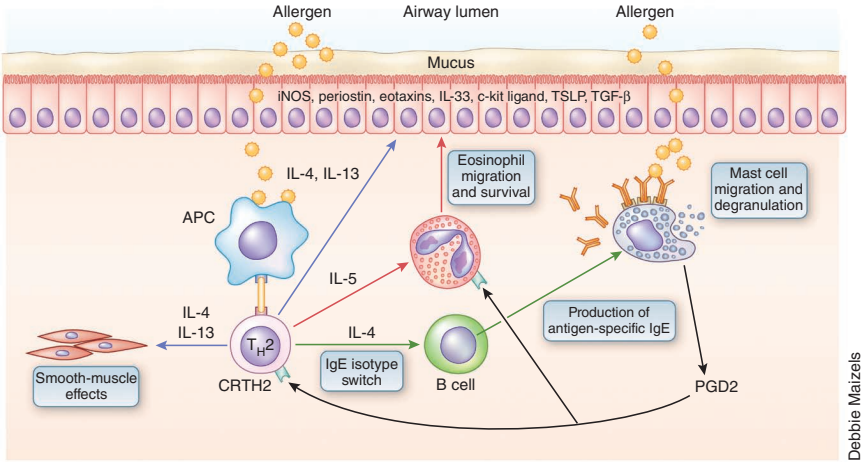

Figure 2 T_H2 immune processes in the airways of people with asthma. The pathway begins with the development of T_H2 cells and their production of the cytokines IL-4, IL-5 and IL-13. These cytokines stimulate allergic and eosinophilic inflammation as well as epithelial and smooth-muscle changes that contribute to asthma pathobiology. APC, antigen-presenting cell; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; iNOS, induced nitric oxide synthase; PGD2, prostaglandin D2; TSLP, thymic stromal lymphoprotein.

mild corticosteroid-naïve asthma had a T_H2-high signature in their airway epithelial tissue. Individuals who had asthma but did not have this signature had a similar gene-expression signature (T_H2-low) to that of healthy control subjects. Subjects classified as T_H2 high were subsequently found to have higher amounts of tissue IL-13 and IL-5 mRNA and greater numbers of eosinophils and mast cells, and they showed more atopy and SBM thickening compared to T_H2-low people[36]. Perhaps most importantly, these subjects responded to inhaled corticosteroid therapy, whereas the T_H2-low group did not, suggesting that this distinction may have profound clinical implications. Although clear patterns of clinical phenotype in relation to T_H2 gene expression have emerged from these studies, further long-term studies are needed to assess the stability of the identified phenotypes, integrate clinical clusters with biomarkers and, finally, identify responses to targeted therapies.

T_H2-associated asthma

Almost since the inception of the concept that immunity can be divided into T_H1 and T_H2 type processes, asthma has been considered a T_H2 process that is linked strongly to atopy and allergy, type I hypersensitivity reactions, eosinophilic inflammation and response to corticosteroids. Indeed, data from biased and unbiased studies suggest that the majority of—but, clearly, not all—asthma cases fit this traditional view[28,29]. Current phenotyping approaches support the existence of an early-onset (usually during preadolescence), mostly atopic and allergic asthma phenotype, and most have additionally identified a later-onset (often age 20 or later) eosinophilic phenotype. The molecular and targeted therapy data support an overall T_H2 association with both of these phenotypes, such that these two clinically different yet immunologically overlapping phenotypes may fall into a broader category of T_H2-associated asthma (**Table 1** and **Fig. 3**). Finally, the clinical phenotype of exercise-induced asthma (EIA) is also likely to have a T_H2 component, given its eosinophil- and mast cell–related profile[37–39].

Early-onset allergic T_H2 asthma

Clinical and biological features. Although a specific age cut-off for early-onset asthma has not been determined, most persistent adult asthma that originates in early childhood has an atopic and allergic component, and most people with asthma are likely to have this phenotype. However, the lack of responsiveness to corticosteroids and the lower concentrations of IgE in some children with asthma suggest that not all early-onset asthma is T_H2 associated[31,40].

Studies have suggested that age of onset is a better discriminator of adult asthma phenotypes than allergic factors, consistent with previous reports suggesting that allergic exposure and sensitization in childhood are only modestly associated with asthma development later in life[28,29,41]. Despite this, consistent relationships exist between allergic factors and onset of asthma in childhood. Early-onset asthma is typically associated with other atopic diseases, including allergic rhinitis and atopic dermatitis[14,25,28,29]; for example, 40% of people with early-onset asthma have a history of atopic dermatitis, whereas 4% of people with late-onset asthma do. The amounts of total and allergen-specific IgE are also higher in early-onset asthma than in later-onset asthma. People who have atopic asthma have higher

Table 1 Asthma phenotypes in relation to characteristics

	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Genetics	Response to therapy
Early-onset allergic	Early onset; mild to severe	Allergic symptoms and other diseases	Specific IgE; T_H2 cytokines; thick SBM	17q12; T_H2-related genes	Corticosteroid-responsive; T_H2-targeted
Late-onset eosinophilic	Adult onset; often severe	Sinusitis; less allergic	Corticosteroid-refractory eosinophilia; IL-5		Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory
Exercise-induced		Mild; intermittent with exercise	Mast-cell activation; T_H2 cytokines; cysteinyl leukotrienes		Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9
Obesity-related	Adult onset	Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear	Lack of T_H2 biomarkers; oxidative stress		Responsive to weight loss, antioxidants and possibly to hormonal therapy
Neutrophilic		Low FEV1; more air trapping	Sputum neutrophilia; T_H17 pathways; IL-8		Possibly responsive to macrolide antibiotics

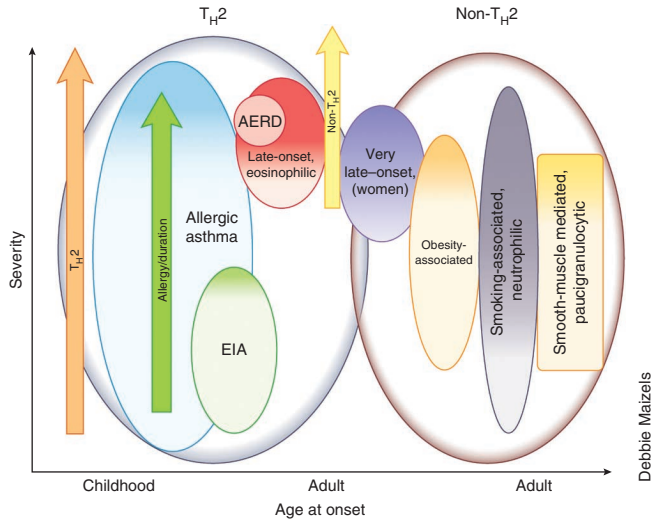

Figure 3 Theoretical grouping of emerging asthma phenotypes based on the distinction between T_H2-high asthma and non-T_H2 asthma. T_H2 asthma consists of both early- and later-onset disease over a range of severities. It is likely that the majority of early-onset allergic asthma is mild but that an increasing complexity of immune processes leads to greater severity. Later-onset eosinophilic asthma without traditional allergic elements is more likely to be severe, whereas EIA is a milder form of T_H2 asthma. Non-T_H2 asthma includes very late–onset, obesity-associated asthma as well as smoking-related and neutrophilic asthma, and asthma in which affected individuals show little inflammation. The intensity of the colors represents the range of severity; the relative sizes of the subcircles suggest relative proportions of affected individuals.

antibody (omalizumab) is the only biological agent now approved for asthma. Although IgE-specific antibody treatment has been targeted toward allergic asthma, this classification is loosely defined as minimal elevations of total IgE in the presence of any IgE specific to a particular allergen. With this definition, IgE-specific antibodies affect both early- and late-phase allergic physiological reactions and eosinophilic inflammation[56].

Even more specifically targeting T_H2 immunity than antibodies to IgE, the four-week administration of an inhaled IL-4Rα antagonist improved physiological responses to allergen inhalation and decreased FeNO in people with mild, corticosteroid-naïve asthma[32,58]. There may also be a pharmacogenetic response to anti–IL-4Rα treatment, as known risk alleles in the gene encoding IL-4Rα identified participants with better treatment responses[59]. In contrast, a monoclonal antibody to IL-5 did not show efficacy in an allergen-challenge model despite causing profound reductions of blood eosinophils[7]. In addition, two weeks of systemic anti–IL-13 treatment affected physiological responses to allergens but not eosinophilic inflammation[57]. Although the reasons for the differing effects of IL-4 and/or IL-13 from those of IL-5 in allergic responses are not known, the observed efficacy of antibodies to IL-13 in the absence of a reduction in eosinophils and the failure of antibodies to IL-5 despite a reduction in eosinophils suggest that noneosinophilic components may be of greater importance than eosinophils in these specific allergic responses.

Specific T_H2 pathway inhibition in nonphenotyped, corticosteroid-treated individuals with chronic asthma has generally been ineffective[5]. In contrast, even modest phenotyping, as shown by the case of antibody to IgE above, improves overall efficacy to some degree, reducing asthma exacerbations and improving symptoms and quality of life[12,13,60]. Yet, as many as 50–60% of individuals did not respond to IgE-specific antibody treatment, particularly those with greater severity of disease, and there are no biomarkers other than IgE to predict response[60,61]. Perhaps the most robust clinical response to IgE-specific antibody therapy was observed in a study of African-American children living primarily in inner-city environments[62], a population enriched for highly T_H2-skewed asthma[43,63]. Thus, it remains to be determined whether using a potential T_H2 biomarker to define T_H2-allergic asthma would improve the likelihood of a response to IgE-specific antibody treatment.

Interestingly, a recent study of treatment with a monoclonal antibody to IL-13, lebrikizumab, showed modest but significant improvements in FEV1 (ref. 64) in people with moderate to severe corticosteroid-treated asthma. Conventional markers of allergic inflammation (IgE, atopy and blood eosinophils) did not define lebrikizumab responders. However, recent studies have suggested that serum periostin, an epithelial protein that is induced by IL-13 and present in greater amounts in the airways of some people with mild asthma, may be a biomarker for a more general T_H2 asthmatic phenotype[65–67]. FeNO has also been proposed as a T_H2 biomarker because it is produced by inducible nitric oxide synthase, an enzyme that is induced in human airway epithelial cells by IL-13 and present in greater abundance in asthma[33,68,69]. In the lebrikizumab study described above, a subgroup of individuals who had asthma with persistent elevations in serum concentrations of periostin showed greater improvements in airway function and fewer exacerbations after treatment than those with lower concentrations of serum periostin[64]. Interestingly, in a *post hoc* analysis, FeNO levels were as helpful as periostin in identifying T_H2-high individuals who would respond to lebrikizumab, but these biomarkers were not compared with the percentages of sputum eosinophils. Although this study suggests that periostin may be an easily obtainable T_H2 biomarker, whether it will be better than FeNO or sputum eosinophils remains to be determined in prospective studies.

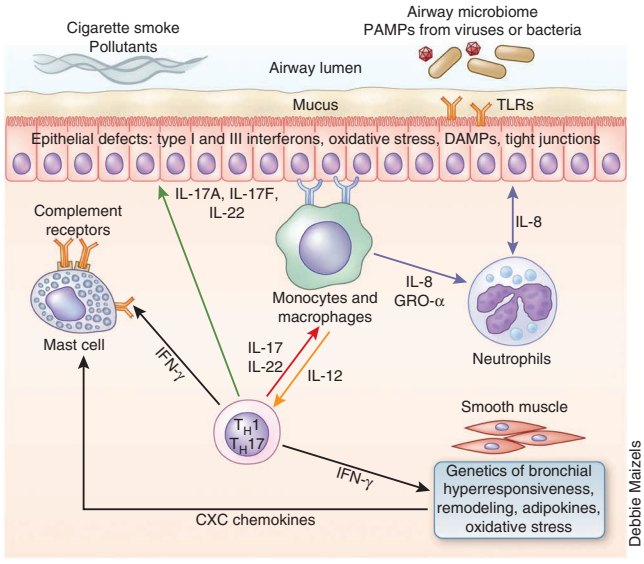

Figure 4 Theoretical range of factors that may be involved in the development of non-T_H2 asthma. These factors include infection-related elements, T_H1 and T_H17 immunity, non-T_H2–associated smooth-muscle changes including genetics and oxidative stress, and the development of neutrophilic inflammation. IFN-γ, interferon-γ; GRO-α, growth-regulated oncogene-α; PAMP, pathogen-associated molecular pathway; DAMP, danger-associated molecular pathway; TLR, Toll-like receptor.