

Asthma phenotypes

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Purpose of review

Asthma is a heterogeneous disorder presenting with many phenotypes. Precise phenotypic definition has eluded the medical research community for years, despite recognition of different disease subtypes. Improved phenotypic characterization and knowledge of underlying pathobiology is necessary for linkage of specific genotypes with clinical disease manifestations.

Recent findings

Phenotyping has been difficult because asthma is likely to be comprised of overlapping syndromes with varying origins and heterogeneous pathobiology. Currently, the field is too reliant on classification by trigger or symptoms. Since genotypic and phenotypic heterogeneity are inherent in asthma, patients presenting with different asthma phenotypes may need tailored therapies. Studies have begun to link genetics with disease mechanism and therapeutic response. As disease etiology, onset, progression and severity vary greatly among patients, however, the relative contribution of genetic factors may be difficult to ascertain. Definition of the full array of complex biological consequences of molecular target modulation is a prerequisite for therapies based on this concept.

Summary

The advent of targeted therapies for asthma and clinical trials based on phenotype and genotype have raised interest in more accurate description of asthma phenotypes. Therapies based on phenotypic and genotypic characteristics may be useful in asthma management. A variety of factors, however, must be addressed before such approaches become standard.

Keywords

allergic asthma, aspirin-sensitive asthma, asthma therapy, genotypes, phenotypes, steroid resistant asthma

Abbreviations

AS	aspirin sensitive
SNP	single nucleotide polymorphism
TNF	tumor necrosis factor

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Introduction

Asthma is a chronic disorder, influenced by the interaction of a variety of asthma-related genes with numerous environmental factors. It is likely that, rather than a single disease entity, asthma consists of related, overlapping syndromes. Hallmark characteristics include airway inflammation, intermittent airway obstruction (which can have a fixed component), bronchial hyperresponsiveness, mucus hypersecretion and smooth muscle hypertrophy. Among its clinical symptoms, not all of which are necessarily present in all patients, or to the same degree, are chest tightness, wheezing, dyspnea and coughing. Asthma occurs in varying degrees of severity in both genders and in all ethnic groups. Asthma phenotypes based on age of onset, type of inflammation, pattern of severity and various other clinical characteristics have been recognized for some time. They remain poorly characterized, however, and the underlying pathobiology is ill-defined. This review will highlight just a few different asthma phenotypes, found in individuals with established disease, with an emphasis on pathogenesis, genetics (genotype/phenotype relationships) and implications for treatment.

Asthma occurrence through lifespan

Asthma can begin at anytime during life; however, recent evidence indicates that most patients with asthma experience their first symptoms before the age of 5. Children with the highest risk of developing asthma have a family history of atopy and/or asthma. Maternal history is most strongly associated with susceptibility in the child, implying both a genetic and environmental component. At this point, a number of genes have been identified that contain polymorphisms which influence immune or pulmonary development and response to environmental exposures, perhaps increasing the risk for development of asthma. These include NOS3, FCER1B, IL4RA, ADAM33, CD14 and some of the Toll-like receptors, among others [1,2,3^{*},4,5]. The genetics of asthma susceptibility is complex, with the same genotype sometimes conferring protection or risk depending on the environmental exposures encountered. Clearly environmental exposures play a critical role in determining early

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disease susceptibility. Most 'early-onset' asthma, defined as onset before the age of 12, has an allergic component. Some evidence suggests that early allergen avoidance in high-risk children or effective pharmacologic treatment of allergy in symptomatic children may attenuate disease progression [6], but this remains controversial. Studies have also suggested that viral infections associated with wheezing, in the first year of life, can confer significant risk for subsequent wheezing, bronchial reactivity, asthma and reduced pulmonary function [7–10]. The origins of childhood asthma lie in a complex interplay of genetics, environmental exposures, and immune and pulmonary system development. A full discussion of the state of the field is beyond the scope of this review.

In many children, symptoms of asthma and wheezing improve with age, but 30–40% continue to have recurrent episodes as adults. It has been suggested that certain genotypes may be associated with asthma which persists into adulthood. One study has found that Arg16–Gln27 homozygotes are more likely to have recurrent wheezing as adults; however, this genotype is of low frequency in wheezing adults [11]. 'Adult-onset' asthma involves a variety of phenotypes involving different risk factors, including specialized circumstances such as those which occur in occupational asthma. Other risk factors include smoking, chronic rhinosinusitis and an association with nasal polyps. Many of the risk factors for adult severe, difficult, refractory, near-fatal or fatal asthma may relate to behavioral traits which may have originated during childhood. Asthma in females may be correlated with endogenous and exogenous sex steroid hormones [12]. The typical patient with severe asthma is female, aged over 40, and with adult-onset asthma and atopy playing roles in this disease [13].

Allergic asthma

Allergic sensitization is the basis of allergic asthma and is one of the most common asthma phenotypes. It is particularly common in childhood asthma, but is frequently found in adults as well. Indeed, individuals presenting with this phenotype commonly experience their first symptoms in childhood with gene–environment interactions influencing the development of the innate and adaptive immune systems and allergic sensitization. The early phase of the response is triggered when an atopic individual encounters allergen, and is characterized by release of both preformed and newly synthesized mediators, such as leukotrienes, histamine, prostaglandins and cytokines, which induce bronchoconstriction and edema. The late phase is characterized by the influx and activation of lymphocytes and other inflammatory cells that, in turn, increase production of pro-inflammatory cytokines. The inflammatory response is currently thought to be largely mediated by T helper type 2 lymphocytes and cytokines. While it

is clear that individuals with allergic asthma have a maladaptive T helper type 2 response that plays a major role in the pathobiology of their disease, there is increasing evidence that other arms of the immune system may also contribute to asthma pathogenesis. Studies have indicated that the T helper type 1 response may be involved, particularly in more chronic and severe forms of the disease [14,15]. Additionally, recent studies have also indicated that invariant natural killer T cells may be involved in asthma pathogenesis. One recent study in patients with moderate to severe persistent asthma found that about 60% of pulmonary CD4⁺CD3⁺ cells were not class II major histocompatibility complex-restricted CD4⁺ T cells, but were, in fact, invariant natural killer T cells [16]. Currently, studies implicating other immune compartments are still relatively preliminary; however, they have far-reaching implications for our understanding of asthma pathobiology and the development of therapeutic modalities. Increasingly it appears that the immune response in allergic and, perhaps, in other forms of asthma is heterogeneous, which likely contributes to heterogeneity in clinical phenotypes. Similarly, over 100 genes have been implicated in allergic asthma, but the genetics of the disorder are complex and are modulated by environmental exposures. None of the genes have been shown to contribute to risk in all populations. Additional difficulties in establishing clear linkage are encountered due to disease heterogeneity, populations that have not been stratified well and potentially small effects of a particular gene being analyzed. Despite these difficulties, continued efforts to define phenotypes better based on pathobiology and confirmation of asthma genes in well-characterized populations should allow for establishment of the links between genetics and specific pathobiological and clinical disease characteristics.

Aspirin-sensitive asthma

Asthma that is induced by aspirin and other nonsteroidal anti-inflammatory drugs is commonly referred to as aspirin-sensitive asthma (AS-asthma). It is among the most easily identified phenotypes because of the specificity of the trigger. Estimates vary, but prevalence is likely to be approximately 10–20% of the adult asthma population [17]. AS-asthma patients are likely to be female and suffer from more severe disease. The frequency of atopy is low, but the phenotype is associated with eosinophilia, rhinosinusitis and nasal polyps. Non-steroidal anti-inflammatory drug sensitivity does not appear to be mediated by IgE, but instead is related to altered eicosanoid metabolism. Increased levels of cysteinyl leukotrienes and increased expression of CYSLTR1 are characteristic findings associated with this phenotype, suggesting that pathogenesis may be related to an enhanced inflammatory response due to overexpression of cysteinyl leukotrienes and CYCLTR1

[18]. Recent studies have also suggested alterations in cyclooxygenase-2, prostaglandin E₂ and lipoxin metabolism. A number of single nucleotide polymorphisms (SNPs) have been identified in the leukotriene C4 synthase, 5-lipoxygenase, CYSLT1 and -2 genes, TBX21 (which encodes the transcription factor T-bet), and prostaglandin E₂ [18,19]. The cyclooxygenase-2 and thromboxane A₂ receptor genes, while not associated with AS-asthma *per se*, may have functional effects. An additional interesting association with AS-asthma is the HLA allele. Initially identified in a Polish population, these results have also been replicated in a Korean population [20,21]. Significantly, a very recent study has identified gene–gene interaction between a SNP in the tumor necrosis factor (TNF)- α promoter and HLA-DPB1*0301 that may significantly increase susceptibility for AS-asthma [22**]. Results are intriguing, particularly in light of what is currently known about the pathogenesis of this phenotype; however, more replicate studies in diverse populations and linkage with functional studies are needed. Interestingly, HLA-DPB1*0301 was significantly associated with the requirement for long-term leukotriene receptor antagonists use in the management of AS-asthma patients [23]. Despite the relatively distinct clinical and pathologic presentation of this phenotype, AS-patients can be difficult to control, as they frequently do not respond well to corticosteroids. Leukotriene receptor antagonists can be helpful, but, as with other asthma phenotypes, not all patients respond well to the therapeutic options available. Clearly, linking genotypes with a well-defined phenotype, such as AS-asthma may provide new insights for targeted therapy.

Glucocorticoid-resistant asthma ('resistant inflammation')

In most patients, glucocorticoid therapy beneficially influences inflammatory and structural cells, targeting sources of airflow limitation, including airway smooth muscle contraction, mucosal edema, airway inflammation, increased mucus secretion and airway remodeling. Up to 10% of asthma patients, however, demonstrate poor response to glucocorticoid therapy, and experience frequent exacerbations and continual symptoms limiting activity and quality of life [24]. Glucocorticoid-resistant asthma can be induced by several mechanisms including decreased glucocorticoid receptor density, distorted affinity of ligand for the glucocorticoid receptor, diminished capacity of the glucocorticoid receptor to bind with DNA or increased expression of inflammatory transcription factors, e.g. NF- κ B and activator protein-1, that compete for DNA binding [25**]. Given numerous mechanisms associated with resistance to glucocorticoid therapy, Ito *et al.* [25**] conjecture that widely varied pathobiology may parade as a common phenotype and suggest research should focus on

subgroups of well-characterized patients with glucocorticoid-resistant asthma.

Results from several recent studies underscore the heterogeneity of asthma, and suggest the possibility that treatment resistance may not represent a distinct phenotype in children [26*] and adults [27*,28**]. Moreover, delayed treatment with sufficient dose of inhaled corticosteroid may result in poor control of asthma correlating with airflow limitation, persistent eosinophilic airway inflammation and resistance to a moderate dose of inhaled corticosteroid [27*]. These findings confirm and extend the observation that glucocorticoid-resistance is not limited to severe asthma [29].

Studies have also suggested that the types of inflammatory cells in the airways of some patients may predict responsiveness to glucocorticoid therapy [30*]. Results demonstrate that, among baseline measurements, low sputum eosinophils had highest negative predictive value for inhaled corticosteroid treatment effect on FEV₁ and on PD₂₀. Neutrophils also were greater in those patients with low baseline airway eosinophilia. Multiple regression analysis revealed that sputum eosinophilia and FEV₁ were independent significant predictors of FEV₁ increase after treatment.

Recent findings suggest that anti-IgE or anti-TNF- α strategies might benefit patients with glucocorticoid-resistant asthma [31**]. Further research is needed to identify additional and perhaps better noninvasive biomarkers related to this phenotype in order to move in the direction of targeted therapy.

Fixed airflow limitation

Fixed airflow limitation is attributed to airway remodeling – a process that includes subepithelial basement membrane fibrosis, epithelial goblet cell hyperplasia, increase in blood vessels, and a proliferative state of airway smooth muscle, with increased mass comprising hyperplasia and hypertrophy [32], and has been associated with the ADAM33 gene [33**]. Preferential expression of high levels of ADAM33 mRNA in smooth muscle, fibroblasts and myofibroblasts suggest that ADAM33 is involved in airway remodeling. Studies suggest that the way ADAM33 influences asthma disease phenotype is very complex, and it is also involved in susceptibility and origins of the disease [3*]. ADAM33 includes more than 100 SNPs. Research is needed to comprehensively SNP type ADAM33 to discover single or multiple aberrations that map to asthma phenotypes and relate to functional outcomes.

Replication of ADAM33 polymorphisms as a biomarker for asthma is inconsistent with other studies showing no association between previously identified SNPs and

asthma or asthma severity [34–36]. Conflicting findings may be because of population heterogeneity, or differences in gene–environment interactions or in haplotype structures or SNPs between ethnic groups. Thus, the role of ADAM33 in asthma remains controversial.

Observations suggest the presence of heterogeneous fibroblast phenotypes in asthmatic airways and distal lung [37**]. These differences suggest a cellular basis for regional differences in extracellular matrix and eosinophil infiltration observed in the proximal and distal airways of patients with persistent asthma. Further research is required to further elucidate the airway phenotypes, including physiology of the airways, in patients with asthma.

Investigators correlated high-resolution computed tomography of the airways with pulmonary function in patients with asthma before and after maximum bronchodilation [38**]. Authors speculate that decline in FEV₁ induced by smooth muscle tone is due to reduction in forced vital capacity secondary to increase in residual volume. They further suggest that FEV₁ and forced vital capacity fall only when the compensatory rise of total lung capacity is inadequate. Reporting lung volumes, forced vital capacity and FEV₁/forced vital capacity should be considered in asthma research [39]. Finally, new multidimensional phenotyping approaches [40] are necessary not only to allow more precise phenotyping, but to facilitate sharing of data across study populations using standard ontology. These and other approaches will lead to more precise phenotype–genotype correlations.

Conclusions

A number of asthma phenotypes have been described; however, these descriptions are not based on a clear understanding of the pathobiology of these phenotypes and it is often difficult to combine or compare studies, either due to lack of a well-characterized description of the phenotype being studied or varying characteristics of the patient population. As ongoing research efforts provide more insight into the relationship between genetics, environment, genotype–phenotype relationships and the pathophysiology of asthma, it should be possible to better define clinical phenotypes based on pathologic mechanisms and genetics. Genetic susceptibility varies with race and ethnicity which underscores the importance of population stratification and replicate studies. Future studies should consider phenotypic grouping partially based on greater rates of allele-sharing or frequencies, where appropriate, to facilitate better defined phenotype–genotype disease classifications. These efforts are urgently needed to enable better diagnosis and prognostication of treatment response of individuals or subgroups and development of new targeted therapeutic options.

References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 84–85).

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