Endotypes of Asthma in Children
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Abstract
Asthma is a syndrome that includes several disease variants. Definition of asthma is a chronic disorder of the lung with variable airway obstruction, wheeze/cough, and an underlying inflammatory process with remodeling.

It appears that atopic genes are not necessarily directly related to childhood asthma. Airway epithelial cells express genes that encode proteins directly related to asthma. Maternal asthma and child’s sex are also a significant risk factors for asthma development. Hygiene hypothesis applies with regards to the atopic status but not to asthma symptoms. Early-life respiratory syncytical virus (RSV) infection or human rhinovirus infection is correlated to maternal atopic predisposition and to decreased lung function at age 8 years in the high-risk birth cohort, both conditions indirectly linked with asthma development. Airway responsiveness may be more strongly associated with asthma in infancy and early childhood than in school age and adolescence. Endotypes of asthma need to base in their cause or pathogenic mechanism. In childhood asthma three endotypes were proposed. Type 1: Mild to intermittent asthma In this group, asthma was more often controlled with low doses of ICS than in the other groups. Type 2: Asthma with severe exacerbations and multiple allergens. This type is associated with inflammation that is predominantly "allergic" (with eosinophil and basophil cells) in combination with multiple allergic sensitizations and elevated total serum IgE. Type 3: Severe obstructive asthma with neutrophilia This phenotype is characterized by a significant decrease in FEV1 even if it remains within the accepted limits of normal, as in other studies in severe asthmatic children. Different guideline need to address the management of endotype of childhood asthma. (J Pediatr Resp Dis 2014;10:51-58)

Key words: asthma, endotype, epigenetics, remodeling

INTRODUCTION
Asthma is a syndrome that includes several disease variants. Definition of asthma is a chronic disorder of the lung with variable airway obstruction, wheeze/cough, and an underlying inflammatory process with remodeling. Treating asthma based on phenotypes, which are observable characteristics with no direct relationship to disease mechanism, demonstrated some successes yet remains suboptimal, given the variability in treatment response. However, when combined with endotypes, which refers to sub-populations of a disease with similar molecular mechanisms or treatment response. In this review, we will discuss childhood asthma in association with genetics, epigenetics, endotypes and inhaled corticosteroid (ICS) response.

Genetics
It appears that atopic genes are not necessarily directly related to childhood asthma. Airway epithelial cells express genes that encode proteins directly related to asthma. Genome wide association studies (GWAS) studies have identified a locus on chromosome 17q21 (encoding ORMEL3 and GSDMB) strongly associated with childhood-onset asthma1 and specific to wheezing phenotypes (rs8076131, near ORMDL3), whereas less association was seen for intermediate-onset wheezing.
The genes controlling IgE level only little overlap with the genes mediating asthma susceptibility. FCER1A, the genes encoding a ligand-binding subunit of the high-affinity IgE receptor, is a major susceptibility locus for serum IgE level. However, FCER1A polymorphism dose not influence development of asthma. Two GWAS meta analyses of asthma point to the epithelium as a primary player in asthmatic susceptibility. Chromosome 17q21 gene variants are predominately associated with childhood-onset asthma and exacerbations but not atopy. It suggests that atopy is a secondary rather than primary epithelial damage contribute to the adaptive immune response, leading to airway inflammation and recurrent severity. Airway epithelial cells express gene that encodes protein directly related to asthma.

Maternal asthma and child’s sex are also a significant risk factors for asthma development. Maternal microchimerism (different rates of transmission or persistence of maternal cells to children of asthmatic mothers) may protect against the development of asthma.

Maternal smoking, ambient air pollution, diet and microbial exposure during pregnancy have been associated with DNA methylation at several CpG sites.

**Epigenetic-Infections-Hygiene Hypothesis**

Hygiene hypothesis applies with regards to the atopic status but not to asthma symptoms. From the study in Rural Environments (PASTURE) birth cohort to investigate the effect of farm exposure on epigenetic patterns in asthma candidate genes demonstrated that the farming environment decreases DNA methylation at specific asthma-related genes.

Exposure to endotoxin is associated with the risk of asthma. A meta-analysis of studies examining the association of endotoxin exposure with wheeze and asthma in children showed that endotoxin is a risk factor for wheeze in younger children, but a protective factor for asthma in older children. However respiratory infections early in life are not always protective over asthma.

Early-life respiratory syncytial virus (RSV) infection or human rhinovirus infection is correlated to maternal atopic predisposition and to decreased lung function at age 8 years in the high-risk birth cohort, both conditions indirectly linked with asthma development. A recent study following children who had experienced an early human rhinovirus infection with wheeze showed an increased risk of asthma development at age 5-10 years. Lower exposure to microbes does not always result in atopic/responsive phenotype. Ege et al described seven bands of bacteria to be inversely associated with childhood asthma.

**Airway remodeling**

Airway remodeling characterized as structural changes including epithelial injury, thickening of reticular basement membrane, airway smooth muscle and goblet cell hypertrophy, hyperplasia and angiogenesis. Several birth cohort and follow-up about the significance of early airway responsiveness to subsequent outcomes of lung function and symptoms demonstrated that neonatal airway responsiveness was significantly associated with the development of asthma by age 7 and it was a stronger predictor of asthma than neonatal lung function. Some studies including bronchial biopsies in asthmatic children investigated airway remodeling in children suffering from non-eosinophilic asthma. They demonstrated that in asthma children, airway remodeling early in life could be promoted by other mechanism. Airway smooth muscle is increased in preschool children with severe wheeze who will later develop asthma at school age. Therefore, airway responsiveness may be more strongly associated with asthma in infancy and early childhood than in school age and adolescence.

**Moving from phenotype to endotype**

Asthma is a syndrome. Thus "observable characteristics" is phenotype. In the context of phenotype includes clinical, physiological, morphological, biomarkers and response to different treatments. Phenotypes are clinical relevant and do not give any insight of pathophysiological mechanism. Endotypes are different from phenotypes with a defining etiology and/or a consistent pathphysiological mechanism (Fig.1). An acceptable starting point to define endotypes would be the identification of corresponding molecular
biomarkers for such a pathogenetic mechanism as shown if Fig.2. The challenge is to link pathobiology from these phenotypes to endotypes. Till now, none of the phenotype approaches identified a specific pathobiology, biomarker, genetic element, a robust response to therapy targeted to the biology. Probably, we need to a “subtype” of a condition which is defined by a distinct functional or pathophysiological mechanism’. In childhood asthma three endotypes were proposed (Fig.3). Each of these three proposed endotypes fulfills the majority of the necessary characteristics. However, the true underlying pathogenetic mechanism remains poorly identified. A better understanding of pathobiology will lead to endotypes initially defined molecularly, with the accompanying clinical characteristics, molecular process secondary to the therapeutic approach.

**Endotypes of childhood asthma**

Endotypes of asthma need to base in their cause or pathogenic mechanism,

**Type1: Mild to intermittent asthma**

This group was characterized by the highest average value of FEV1, less sensitization to inhaled or food allergens and no elevation of either white blood cells or immoglobulin(Ig). In this group, asthma was more often controlled with low doses of ICS than in the other groups. Girls more frequently had non-atopic uncontrolled wheezing associated with infections agents and responded to montelukast alone. FeNO might be a biomarker.

**Type2: Asthma with severe exacerbations and multiple allergens**

This type of severe asthma is associated with Th2 driven inflammation that is predominantly”allergic” (with eosinophil and basophil cells) in combination with multiple allergic sensitisations and elevated total serum IgE. There was a link between intra-alveolar eosinophilia and atopy. Moreover, it is know that blood eosinophilia is closely correlated to eosinophil inflammation in the deep lung tissues. This phenotype is associated with sever exacerbations requiring hospitalisations and uncontrolled asthma despite high doses of ICS. Many studies have confirmed that asthma at risk of severe exacerbations of difficult to control asthma in mainly associated with allergic asthma in children. Severe acute asthma requiring intensive care was more frequently found in cases of food allergy. Roverts et al. compared 19 asthmatic children ventilated for severe exacerbation with 38 mild asthmatic children and showed that the two independent risk factors were the severity of asthma
**Figure 2.** Linking essential pathogenic mechanisms with phenol-types of asthma.
Finally, in the phenotype with a higher duration of asthma (frequency>5 yrs), FEV1 values were slightly lower compared with the FEV1 values observed in the type1 mild asthma cluster. This was also reported in the Severe Asthma Research Program (SARP) study, in which the most allergic children had severe exacerbations despite a high level of therapy but did not have severely decreased FEV1 values. Indeed, severe exacerbations could be responsible for the more rapid decline in lung function. This type may respond to allergen specific immunotherapy, anti-IgE, anti-IL-5 or anti-IL-13 therapy.

Type3: Severe obstructive asthma with neutrophilia

This phenotype of severe asthma is characterized by a significant decrease in FEV1 even if it remains within the accepted limits of normal, as in other studies in severe asthmatic children. This endotype was also characterized by a significant elevation in neutrophils in peripheral blood in comparison with the other endotype. Many studies have shown an association between the severity of asthma and neutrophilic inflammation detected by induced sputum. Furthermore, our study supports the findings of Siroux et al. who reported that the phenotype of “active treated allergic childhood-onset asthma” is associated with blood eosinophilia, while “active treated adult-onset asthma” is associated with blood neutrophils. Systemic neutrophilic inflammation is mainly described in inflammation of infectious type. In the same way, elevation of Ig has been related to an inflammation in asthma originating from a bacterial colonization. This type is associated with activation of innate immune response. It is well known that this inflammation type induces uncontrolled asthma and corticosteroid resistance and, therefore, probably increases the risk of tissue remodeling, which would explain the lower FEV1 values in this endotype.

This endotype was also associated with a higher BMI. The association between obesity and severe asthma...
has been reported in several studies.\textsuperscript{36-38} Haldar et al.\textsuperscript{37} showed that a distinct cluster of asthmatic subjects with high BMI was associated with symptomatic asthma without eosinophilic inflammation. The study by Moore et al.\textsuperscript{38} also found a cluster of asthma associated with a moderate reduction in FEV1 in females who were overweight with delayed onset. Therefore, asthma severity is not related to a markedly low FEV1 or to the GINA severity score.\textsuperscript{27} Serum of sputum epithelial cell IL-17A level and FeNO might be serve as biomarkers.

**Biomarkers**

Epigenetic biomarkers (DNA methylation, modification of his tone tails and noncoding RNAs) from easily obtained samples (buccal, nasal or peripheral blood cells) or from bronchial biopsies might identify individuals patients at risk for asthma, phenotypes driven by environmental stress, or the likelihood of response to environment. Targeting epigenetic biomarkers might lead to corticosteroid-resistant asthma.

Flow cytometry analysis of leukocytes in induced sputum might improve the diagnostic accuracy of phenotype.\textsuperscript{39} Treatment using anti-IL-5 or anti-IL-13 humanized monoclonal antibody have been successful based on sputum eosinphllic asthma. FeNO, Th2-high and genetic biomarkers can be used to predict response to ICS.

**Treatment**

Currently, treatment guidelines assume that asthma is a useful disorder with a common inflammatory mechanism and the nature of this mechanism is responsive to corticosteroids. Using clinical characteristics, biomarkers, lung function, genetics, histopathology, epidemiology and response to treatment childhood asthma can be differentiated three endotypes. Different guideline need to address the management of endotype of childhood asthma. The response to a targeted intervention in asthma may vary between individuals or for the same individual in relation to the outcome measurement. Endotype-driven treatment of asthma has improved the response rate to targeted treatment but did not solve completely the dissociated effect of the intervention nor the variability in response due to drug efficacy at target site. Further deep endotyping of airway smooth muscle and epithelial cell components of asthma is needed to improve efficacy of treatment. Early identification of persistent wheezing endotype reinforced by family history of asthma, and early tailored treatment may allow for optimal lung function and disease control, and decreased burden.

**REFERENCES**


