



Remodeling, inflammation and airway responsiveness in early childhood asthma

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Purpose of review

Remodeling and inflammation together with airway hyperresponsiveness are essential components of asthma but their role in development of the disease is still obscure.

Recent findings

Recent data imply that remodeling can occur early in childhood, not necessarily subsequent to but rather, in parallel with inflammation. The assumption of thickening of the reticular basement membrane being a prerequisite for chronic asthma is questioned but development of airway responsiveness is a significant factor. Airway responsiveness is at least partially linked to bronchial inflammation but there are several other genes and pathways regulating airway responsiveness. Increased airway smooth muscle in early childhood is associated with later development of asthma and may be one link between inflammation and airway responsiveness. Novel findings on genetic variation in genes regulating lung growth and remodeling in early childhood shed light on the pathophysiological mechanisms leading to chronic asthma.

Summary

Even young children with chronic asthma have detectable elements of airway remodeling, inflammation and increased airway responsiveness, which all contribute to impaired lung function.

Keywords

airway responsiveness, inflammation, outcome, remodeling

INTRODUCTION

Asthma has been thought to be a consequence of a long-standing airway inflammation followed by healing, resulting in an altered structure referred to as remodeling. However, the studies during the last 10 years have questioned this belief and instead, remodeling might be due to worsening of airway inflammation associated with asthma exacerbations supporting the paradigm that inflammation and remodeling occur in concert instead of remodeling being a consequence of long-standing airway inflammation [1]. Both inflammation and remodeling may be important contributors to increased airway responsiveness (airway responsiveness), one of the main pathophysiological manifestations of asthma, but several questions remain open about the origin of airway responsiveness. The childhood studies on remodeling, inflammation and airway responsiveness are summarized and the most recent findings are presented.

REMODELING

Airway remodeling in asthma is characterized as structural changes such as epithelial injury,

thickening of reticular basement membrane (RBM), airway smooth muscle (ASM) and goblet cell hypertrophy and hyperplasia, and angiogenesis [2].

Thickening of RBM is the most commonly studied component of remodeling. Tsartsali *et al.* [3^{*}] studied the RBM development of cartilaginous bronchi obtained postmortem from 47 preterm babies and infants [median age 40 weeks gestation (22 weeks gestation – 8 months)], 40 children [2 years (1 month–17 years)] and 23 adults [44 years (17–90)]. RBM was microscopically identifiable by 30 weeks' gestation. RBM was reported to increase with age until term, subsequently increase rapidly until 6 years of age (being around 3.5 μm at 3 years of age), and thereafter increase at a slower rate until the age of 17 years. Thickened RBM has mainly been

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KEY POINTS

- Early remodeling markers such as ASM hypertrophy and increased RBM thickness are associated with later respiratory morbidity and need for treatment.
- Increased ASM fraction may be a link between airway inflammation and airway responsiveness.
- Infant airway responsiveness is a stronger predictor of asthma than neonatal lung function.
- Elevated FeNO in symptomatic infants correlates with increased airway responsiveness.
- Variation occurs in alleles of genes regulating lung growth and remodeling in early childhood.

found in school children with severe and moderate asthma but even in preschoolers with a severe recurrent wheeze and in moderate and mild asthma. Table 1 summarizes the bronchial biopsy studies [4–10,11[■],12–14,15[■],16,17[■],18[■],19[■]] in children.

The relationship of early RBM thickness and development of lung function has been studied recently. A group of 53 Finnish corticosteroid naive infants [median age 12 months (3–26)] with recurrent lower respiratory symptoms, but without differences in RBM thickness [median 4.1 μm (2.7–9.2)] regardless of infant lung function, were re-evaluated for lung function and use of asthma medication at 3 years of age [11[■]]. In 50 children at the follow-up, RBM thickness in infancy correlated significantly with the use of inhaled corticosteroids (ICS) but not with lung function measured by oscillometry (decreased in 28%), whereas reduced lung function at infancy was associated with ongoing airway symptoms and with the use of ICS. In another study [15[■]], 30 previous severe preschool wheezers with increased RBM thickness [median 4.6 μm (2.9–8.0)] at median age 29 months (range 7–57) were recruited for re-evaluation for lung function at 5 years of age. The lung function was measured from 28 previous wheezers and 72 healthy control children by multiple-breath washout and pletysmographic-specific airway resistance. Past RBM thickness did not correlate with current lung function nor did the RBM thickness at 2 years of age predict wheeze at age 5 years.

Bronchial airway smooth muscle hypertrophy and hyperplasia

Signs of remodeling have been thought to discriminate severe asthma from milder forms of the disease and are associated with bronchodilator responsiveness and increased airway responsiveness [20,21].

ASM hypertrophy was first described in a case series of six children with severe, persistent, corticosteroid dependent asthma at 6–17 years of age [5]. In a recent study [19[■]] with 53 school children [median age 12 years (10–14)] with severe therapy-resistant asthma, increased ASM and RBM thickness with tissue eosinophilia were detected. More recently, the association between ASM fraction or RBM thickness in preschool wheeze and asthma at school age was determined [18[■]]. At school age [7.8 years (6–11)], 37/47 of the earlier wheezers were examined. Increased ASM, but not RBM thickness, eosinophilic inflammation or mast cell numbers, was found to discriminate those children with severe preschool wheeze from those who go on to have asthma at school age. Probably ASMs in asthmatic children are functionally distinct releasing mediators, for example, IL-33 [22], thymic stromal lymphopoietin [23] or other emerging mediators [24] related to increased bronchial responsiveness that may be important in the switch from preschool wheeze to asthma.

Angiogenesis, that is, new vessel formation, and dilation of blood vessels are features of remodeling in adult asthma. Increased numbers of subepithelial vessels have been described in the airways of children with mild/moderate asthma, together with RBM thickening and increased loss of epithelial cells [13,16]. Evidence of angiogenesis was present even in atopic children without asthma, leading to speculation that pathologic changes, although not existing at birth, appear in the preschool period [16]. Equally, angiogenesis, epithelial loss and RBM thickening were found in children with mild, moderate and severe asthma irrespective of tissue eosinophilia [17[■]]. A highly interesting recent finding is the possible effect of vascular endothelial growth factor (VEGF)-A polymorphism in lung function. Simpson *et al.* [25[■]] studied two birth cohorts and found that C-allele homozygotes of rs3025028 had better lung function compared with other genotype groups in both preschool and school-aged children. VEGF may have an effect on the lung function either by regulating early growth of the lung or modulating angiogenesis and remodeling through inflammatory pathways.

INFLAMMATION

The chronic airway wall inflammation in asthma is characteristically thought to compose of eosinophils, mast cells, and T-lymphocytes.

Bronchial epithelial and tissue eosinophilia has been contradictory in childhood asthma. Several studies in the early phases of asthma do not show eosinophilic inflammation. Bronchial eosinophils

Table 1. Summary of the bronchial biopsy studies in children

Severity of symptoms	Medication	N	Age	Bronchial biopsy findings	Study
Moderate asthma	No ICS in 1 month	10	9.3 years (5–14)	RBM thickened 9/10; lymphocytes and mast cells 6/10; eosinophils 1/10	Cokugras <i>et al.</i> [4]
Severe asthma	Oral corticoid dependency	6	6–17 years	RBM thickened: 6–10 μm 3/6; >10 μm 3/6; ASM hyperplasia 4/5; mild eosinophilia and lymphocytes 2/6	Jenkins <i>et al.</i> [5]
Difficult asthma	ICS >1600 μg	10	6–16 years	RBM 8.2 μm (5.4–11.1)*	Payne <i>et al.</i> [6]
		10 controls	7–16 years	4.4 μm (3.2–6.3)	
Mild-moderate asthma/atopy	ICS 2/9	9 asthma (mild 7)	4–12 years	RBM 6.0 μm (4.5–9.5)*	Barbato <i>et al.</i> [7]
		6 atopy, no asthma	3–13 years	4.9 μm (4.2–6.6)*	
		8 no atopy or asthma	4–12 years	4.2 μm (3.3–4.9)	
				Increased bronchial eosinophils in asthmatics and atopics	
Difficult asthma	ICS $\geq$ 800 μg	13 persistent symptoms	10 years (10–13)	RBM 7.2 μm (4.9–8.2)	De Blick <i>et al.</i> [8]
		15 few or no symptoms	13 years (10–15)	6.7 μm (5.5–9.7)	
				Increased eosinophils and neutrophils with persistent symptoms	
Recurrent respiratory symptoms	ICS 3/27	27	1.2–11.7 years	Increased RBM thickness and bronchial eosinophils associated with asthma 22–80 months later	Pohunek <i>et al.</i> [9]
Recurrent lower respiratory symptoms	No ICS	16 abnorm LF+BDR	12 months (3–26)	RBM 4.3 μm (2.8–9.2)	
		22 abnorm LF	12 months (5–26)	4.2 μm (2.7–5.8)	
		15 normal LF	12 months (3–24)	3.8 μm (2.7–5.5)	
				Paucity of bronchial eosinophils	
		50 re-evaluated	3 years	Past decreased LF, RBM & mast cells correlated with purchased ICS at 3 years	Malmström <i>et al.</i> [11]
Moderate-severe asthma	ICS 10/16	7 moderate	5–15 years	RBM 4.4 μm (4.0–5.0)*	Fedorov <i>et al.</i> [12]
		9 severe		4.1 μm (3.0–5.0)	
		7 controls		2.6 μm (2.5–2.7)	
				Bronchial eosinophils did not differ between groups	
Mild-moderate asthma/atopy	ICS 5/17	17 asthma (mild 12)	5 years (2–15)	RBM 4.4 μm^{*+}	Barbato <i>et al.</i> [13]
		12 atopy, no asthma	4 years (1–11)	3.3 μm^{*}	
		15 no atopy or asthma	4 years (1–14)	2.7 μm	

Table 1 (Continued)					
Severity of symptoms	Medication	N	Age	Bronchial biopsy findings	Study
Severe confirmed or reported wheeze	ICS 17/30	16 confirmed wheeze	29 months (7–57)	Increased eosinophils and angiogenesis in asthma and atopy RBM 4.6 μm (2.9–8.0)*	Saglani et al. [14]
		14 reported wheeze	17 months (8–58)	3.5 μm (2.1–5.4)	
		10 controls	19 months (5–42)	3.8 μm (2.5–4.7)	
		Increased eosinophils in confirmed wheeze vs. controls			
		28 wheezers re-evaluated	5 years	Past RBM correlated with current FeNO but not with LF at 5	Sonnappa et al. [15 [¶]]
		72 healthy controls			
Multitrigger wheeze	ICS 13/30	20 nonatopic multitrigger w	5 years (2–10)	RBM 5.0 μm*	Turato et al. [16]
		18 atopic multitrigger w	5 years (2–15)	5.5 μm*	
		17 controls	4 years (2–14)	2.8 μm	
		Increased eosinophila and angiogenesis independent of atopy			
Mild-severe asthma	ICS 19/55	36 mild	4.5–7.7 years	RBM + tissue eosinophila 5.4 [2.5–11.5]*	Baraldo et al. [17 [¶]]
		15 moderate/4 severe		- tissue eosinophila 5.3 [3.8–8.6]*	
		25 controls		3.1 μm (1.8–4.9)	
		Increased preschool ASM associated with asthma at school age; a correlation between FeNO & ASM			
Severe wheeze	ICS 13/16	47	28 months (3–57)		O'Reilly et al. [18 [¶]]
	ICS 4/35	21 controls	17 months (3–55)		
Severe therapy-resistant wheeze	ICS ≥800 μg	53	12 years (10–14)	RBM 7 μm (5.0–8.1)*	
	Oral corticoid 24/53	16 controls	11 years (8–13)	4.8 μm (3.6–6.5)	Bossley et al. [19 [¶]]
				Increased eosinophils and ASM	

LF, lung function; ICS, inhaled corticosteroids; RBM, reticular basement membrane; ASM, airway smooth muscle; BDR, bronchodilator response; FeNO, fraction of exhaled nitric oxide.

*statistically significant difference between that patient group and control group.

†statistically significant difference between the asthma group and the atopic nonasthma group.

were not seen in children with moderate asthma when not treated with ICS during the preceding month, whereas lymphocytes and even degranulated mast cells were detected [4]. Corticosteroid naive infants suffering from recurrent lower respiratory symptoms and reversible obstruction did not have either bronchial eosinophilia, other inflammatory cells or thickened RBM [10]. In the follow-up of these infants, mast cells but not eosinophils correlated significantly with the use of ICS at 3 years of age [11[¶]].

Some studies did find an association with eosinophils and asthmatic symptoms in children. Preschool children [median 24 months (range 3–58)] with severe recurrent doctor confirmed wheeze ($n=16$), or reported wheeze ($n=14$) were examined for airway inflammation [15[¶]]. Children with confirmed wheeze had significantly greater eosinophilic inflammation and thicker RBM than 10 control children [median age 20 months (range 5–42)]. A positive relationship between eosinophilic inflammation and RBM thickness was found. Recently, Baraldo *et al.* [17[¶]] studied whether airway remodeling would develop in childhood asthma regardless of eosinophilic inflammation. Children 4.5–7.7 years of age with mild ($n=36$), moderate ($n=15$) and severe ($n=4$) asthma had components of remodeling (thickened RBM, increased epithelial loss and angiogenesis) and these were present in children with noneosinophilic asthma similarly to those with eosinophilic disease. The results imply that mechanisms other than eosinophilic inflammation may promote airway remodeling. More recently, 53 school children [median age 12 years (10–14)] with severe treatment-resistant asthma had varying degrees of airway eosinophilia without increased neutrophils or mast cells, even in the absence of T_H2 cytokines [19[¶]]. No relationship between the dose of inhaled or oral corticosteroids and inflammatory cells or bronchoalveolar lavage fluid, T_H2 cytokines, interleukin (IL)-4, IL-5, and IL-13 was found suggesting different mechanisms driving childhood asthma as compared with adult severe therapy-resistant asthma. Possibly, remodeling may develop independently of inflammation and in a glucocorticoid-insensitive manner.

Fraction of exhaled nitric oxide (FeNO) has been proposed as a noninvasive marker of eosinophilic inflammation in bronchial mucosa and elevated value may predict a favorable response to ICS [26].

Bronchial inflammatory cell profile was analyzed in infants with recurrent lower respiratory symptoms. Bronchial eosinophils were found only infrequently without any association with FeNO [27]. However, in a subgroup of atopic infants, FeNO was slightly higher in those with bronchial

eosinophils than in those without, whereas infants with high counts of neutrophils or plasma cells had significantly lower levels of FeNO. No correlation between FeNO and thickness of RBM was seen. In contrast, thickening of RBM and bronchial eosinophils, in a group of previously severe preschool wheezers, were associated with FeNO at 5 years [15[¶]] but no longer at 8 years. Instead, preschool ASM area fraction correlated with FeNO measured at 8 years [18[¶]].

A population based birth cohort study [28[¶]] assessed whether FeNO at 6 months was associated with the risk of wheezing in the second year of life. FeNO predicted wheezing only to a limited extent and added little to the predictive value on top of clinical characteristics in individual children. Instead, elevated FeNO in healthy 1-month-old neonates, born to mothers with asthma, preceded the development of transient early wheezing in the first year of life but not thereafter during the first 6 years of life, and was unrelated to atopy [29]. In infants with recurrent wheezing elevated FeNO predicted decline in lung function over 6 months and a risk of future wheezing episodes treated with systemic corticosteroids [30]. Future studies in symptomatic infants evaluating FeNO as a predictor of later childhood asthma should clarify whether FeNO will be suitable as a biomarker for monitoring early childhood wheezing illnesses. In an older group of children, the measurement of FeNO and specific IgE in 4-year-old children with suggestive symptoms for asthma was found to improve the prediction of asthma symptoms until the age of 8 years independent of clinical history [31].

AIRWAY RESPONSIVENESS

The studies on the relationship of FeNO and increased airway responsiveness in symptomatic infants are scarce. In a study [32] in infants with eczema, there was a correlation between FeNO and increased airway responsiveness. In our recent study [33^{¶¶}], elevated FeNO in 136 infants [median age 16 months (range 4–27)] with recurrent lower airway symptoms was related to: increased airway responsiveness, to methacholine and to maternal history of asthma, independent from the most important confounding factors including atopy, height and lung function. We could not find a correlation between elevated FeNO and blood eosinophilia. This together with our earlier results [27] in infants with recurrent lower respiratory symptoms implies that elevated FeNO reflects noneosinophilic airway inflammation.

Bisgaard *et al.* [34] studied airway responsiveness to methacholine in 402 neonates in the COPSAC

birth cohort study. Variation at the chromosome 17q12-q21 locus was associated with increased airway responsiveness in infancy and at 4 years of age, but not 6 years of age. Atopy did not pose an increased risk for airway responsiveness. This suggests an independent genetic determinant of neonatal airway responsiveness. It has been postulated that there might be a causal relationship between recurrent lower respiratory tract symptoms in infancy, development of increased airway responsiveness, and airway inflammation later in childhood [14].

Several birth-cohort studies and follow-up studies in symptomatic infants and toddlers have examined the significance of early airway responsiveness to later outcome of lung function and symptoms. The recent report from the COPSAC cohort study [35²²] tested airway responsiveness to methacholine with a raised volume rapid thoracic compression technique at 1 month of age in 362 neonates and assessed asthma by age 7 (77% follow-up). Neonatal airway responsiveness was significantly associated with the development of asthma by age 7. Neonatal airway reactivity was a stronger predictor of asthma than neonatal lung function.

Earlier in the Perth cohort airway responsiveness was measured to histamine with a forced spirometric technique at 1 month, 6 months and 12 months of age and asthma was determined by age 6 and 11 years. Airway responsiveness measured at 1 month of age associated with asthma at age 6 years (38% follow-up) [36] but not by age 11 years (73% follow-up) [37].

In the British cohort of 73 children neonatal increased airway responsiveness measured by using a forced spirometric technique at 1 month of age was associated with increased risk for early-onset asthma-like symptoms [38], but this relationship was transient and did not persist at 10 years of age (89% follow-up) [39]. Neither of these last two cohorts found an association between airway responsiveness in infancy and at school age [36,39].

Associations of increased airway responsiveness measured after neonatal period

In the Perth cohort, the persistence of increased airway responsiveness did not become apparent until the age of 12 months from which it was associated with asthma by age 11 years (46% follow-up) [40]. Factors associated with the persistence of increased airway responsiveness were early respiratory illness, parental asthma and childhood atopy but not atopy in infancy. Accordingly in the study [41] in which airway responsiveness was measured

in wheezy infants older than 6 months of age, increased airway responsiveness was associated with persistent asthma symptoms by age 10 years. Delacourt *et al.* [42] studied 129 infants who had at least three wheezing episodes and measured airway responsiveness to methacholine at the ages of 16 months and 5, 7 and 9 years. Eighty-three children completed follow-up. Persistent wheezing was not significantly associated with the degree of airway responsiveness at 16 months or 5 years. This study demonstrated that airway responsiveness itself was predictive of impaired lung function at 9 years of age. Illi *et al.* [43] found that increased airway responsiveness at age 7 years was a significant predictor of baseline lung function at ages 7, 10 and 13 years. In the Tucson study [44], airway responsiveness at 6 years of age was a risk factor for asthma at 22 years of age and in the 3D Childhood Asthma Management Program study [45] increased airway responsiveness at 5 to 12 years was a risk factor for persistent symptoms in children with asthma.

In the Perth cohort [37], atopy in infancy was not associated with the persistence of increased airway responsiveness, which differs from the common association of airway responsiveness and atopy at school age [43]. This may suggest that different exposures like viral infections may drive airway responsiveness during the first year of life. Findings from follow-up studies show that increased airway responsiveness in early childhood in symptomatic infants and toddlers associates with asthma up to school age. This suggests, to identify the children who exhibit increased airway responsiveness, that the routine measurement of airway responsiveness during infancy is not feasible; therefore, the infants likely to present with increased airway responsiveness have to be identified from their clinical characteristics. In our own study [46] with 107 infants at the age of 7 months, in addition to poor baseline lung function, several clinical characteristics including atopy and a history of physician-confirmed wheeze were associated with increased airway responsiveness.

An interesting question is whether early abnormal airway responsiveness is a determining factor for children to develop asthma or whether airway responsiveness development is connected with other pathophysiological pathways important for asthma. Results from studies are controversial, which may be related to statistical power or different outcomes. Possibly, airway responsiveness is driven by different mechanisms in the neonatal period than in later life. It is also plausible that airway responsiveness is more strongly associated with asthma in early childhood than in school-aged children and adults [35²²]. Findings from a prospective

cohort study [43] suggest that airway responsiveness may be an intermediate step in the causal pathway from early sensitization to perennial allergens and to impaired baseline lung function.

CONCLUSION

Even young children with chronic asthma have detectable elements of airway remodeling, inflammation and increased airway responsiveness which all contribute to impaired lung function. To better understand the interrelationships of these processes, studies combining lung function with bronchial biopsy findings on remodeling and inflammation in well characterized patient groups are needed. Also birth cohort studies on development of lung function and airway responsiveness combined with bronchial biopsy are warranted.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 220–221).

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