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REVIEW ARTICLE

How Early Do Airway Inflammation and Remodeling Occur?

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ABSTRACT

Eosinophilic airway inflammation and structural airway changes are present in school age asthmatics. When these changes occur, and their relationship, are controversial. Some structural airway changes, up-regulation of collagens 1 and 111, and increased distance between alveolar tethering points, may be antenatal, and independent of inflammation. We have established that there is no eosinophilic inflammation or reticular basement membrane thickening in wheezing infants median age one year; but by age three years, both are present. This accords with cohort studies, showing that children who become persistent wheezers have a drop in lung function in the pre-school years. Thereafter, lung function tracks into middle age, so the preschool years represent window during which an intervention might have long term benefit. Supportive are measurements in blood and bronchoalveolar lavage fluid, implicating the neutrophil as the key inflammatory cell in early wheeze. Models of the pathophysiology of asthma include (1) that eosinophilic inflammation is the primary event, and leads to remodelling as a secondary event, which itself results in progressive airflow obstruction (the least likely model); (2) eosinophilic inflammation is the primary event, but remodelling is protective, preventing worsening AHR. It should be noted that these first two are not mutually exclusive; rbm thickening may be protective, but other components of remodeling, for example increased ASM, may have adverse effects; (3) eosinophilic inflammation and airway remodelling are parallel processes, driven by some underlying 'asthma factor'; and (4) the primary abnormality is not airway inflammation, but some form of disordered airway repair.

KEY WORDS

Asthma, child, eosinophil, neutrophil, pre-school wheeze

INTRODUCTION

Airway inflammation and remodelling have been mainly studied in the context of asthma of all the paediatric airway diseases, and this article will only deal with this condition. Inflammation and remodelling in other airway diseases has recently been reviewed elsewhere.[1] The old asthma paradigm was that repeated cycles of acute and acute on chronic inflammation in asthma was an early event, which then leads eventually to airway remodelling, as a manifestation of incomplete or disordered repair. This would predict that remodelling would be a late feature of the asthmatic process. However, this is incompatible with much pediatric data, reviewed below. At least two other paradigms have been considered, which will be discussed in detail below:

Airway inflammation and airway remodelling are parallel processes, triggered by the same underlying problem, but the progression of each is independent

The primary abnormality in asthma is not inflammation, but a primarily a disorder of airway repair, and that inflammation is secondary to these abnormal repair processes. This idea has given rise to the concept of the Epithelial-Mesenchymal Trophic Unit (EMTU, see below).[2]

Currently, there is insufficient evidence that either of these paradigms is wholly correct, and indeed further paradigms will be discussed in this manuscript. This review will discuss the pathological evidence with regard to early remodelling, and place it in the context of what is known about the physiological changes in early asthma; the implications for the treatment of asthma will be briefly discussed.

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DEFINITIONS

Remodelling is term used to describe the structural changes seen in the airways of patients with respiratory disease. These structural alterations involve residential airway cells and, possibly, bone marrow-derived, pleotropic cells recruited from the circulation.[3] Conventionally, the changes of remodelling are said to include thickening of the reticular basement membrane (rbm, the signature feature of established asthmatic remodelling), goblet cell hyperplasia, increased numbers of submucous glands, increase in blood vessel number and area, smooth muscle hypertrophy and hyperplasia, and increased airway wall collagen. However, a paediatrician's view would be that global reduction in airway size, and interference with the tether points of alveoli to airway wall, are just as much structural changes (see below). Hence remodelling has many features, which could appear at different times, and each might bear a different relationship to airway inflammation.

Inflammation as used in the title of this article will be taken to mean chronic eosinophilic inflammation, as seen in the adult with chronic moderate asthma; it is well known that early acute viral infection, for example with respiratory syncytial virus (RSV), causes neutrophil dominated acute inflammation, with interleukin (IL)-9 production, as shown in blind BAL studies.[4,5] However, although the evidence is still debated,[6,7] most would consider that severe RSV infection is merely a marker for a previously disordered airway growth and immune maturation, events largely pre-natally determined. Hence the acute inflammation induced by RSV clears, and symptoms gradually resolve, and RSV does not cause chronic airway inflammation, at least of an eosinophilic type; there is some animal and human evidence that neurogenic inflammation may be important after RSV bronchiolitis.[8,9] The sequelae of viral infections may be structural airway wall changes, more particularly if the initial bronchiolitis was caused by particular strains of adenovirus, leading to a severe obliterative bronchiolitis, but this is a different phenomenon to asthmatic airway remodelling, although the physiological effects of the two (steroid resistant airway obstruction) may be similar.

Indeed, what is clear from early on is that the common viral infections of infancy lead to bouts of recurrent, acute, but resolving neutrophilic inflammation, quite different from the chronic persistent eosinophilic inflammation seen in later asthma. What is not at all known is, what is the trigger that leads to this switch, and how can this be modulated?

WHAT HAVE WE LEARNED FROM STUDIES IN OLDER CHILDREN?

Ethical constraints mandate that paediatric bronchoscopy should not be carried out unless it is of direct benefit to the child concerned.[10] This is different to the situation in adults, where purely research bronchoscopy is well established. However, the acquisition of samples for research, during a clinically indicated bronchoscopy, with the consent of the family and age-appropriate assent of the child, is acceptable.[11] An early study demonstrated that some school age children with severe asthma, despite steroid therapy, had eosinophilic airway inflammation.[12] One of the first blows to the hypothesis that prolonged inflammation causes remodelling came from a study of rbm thickness in children with severe asthma, and adults with severe and mild asthma.[13] Children aged 6–18 years had abnormally thick rbm compared with "normal" control children and normal adults. There was no difference between the paediatric and adult asthmatic groups, and no relationship between duration of asthma, any marker of airway inflammation, or anti-inflammatory therapy. Thus the logical conclusion was that rbm thickening at least is a non-progressive, and probably early change in the development of asthma, and was not driven by airway inflammation. Subsequent paediatric studies have shown that school age children have increased epithelial loss and rbm thickening, airway eosinophilia and increased bronchial vasculature.[14] Airway mucosal eosinophil counts correlated with symptom duration, and inversely with TGFβ-R11 expression, which was downregulated in the asthmatics, but not the atopic, non-asthmatics.[15] Neutrophil, macrophage, mast cell and CD4 positive T lymphocyte counts, and the expression of TGF-β1 and TGFβ-R1 were the same in all three groups (atopic asthmatics, atopic non-asthmatics, and normal controls. For the most part, the asthmatic children were not being treated with inhaled or oral corticosteroids. Some of these changes were seen in atopic non-asthmatics,[14,15] but the relationship of atopy without asthma to structural airway wall changes is still controversial, largely because it is difficult to justify the performance of a bronchoscopy in an atopic child with no airway disease. In a slightly different approach, de Blic *et al.*[16] compared children with severe asthma who did and did not have persistent symptoms despite high dose treatment. They found increased mucosal neutrophil and eosinophil counts in the symptomatic group, no difference in rbm thickness, and increased IFN-γ and IFN-γ: IL-4 ratio in the group with few symptoms. We have recently described airway smooth muscle (ASM) hypertrophy and hyperplasia in children with asthma, as well as other inflammatory lung diseases; in the asthmatic group, ASM changes correlated with bronchodilator reversibility.[17] Taken together, these results show that eosinophilic inflammation and many features of remodelling are both present in even early school age children, and that some features at least of remodelling are non-progressive.

Is there any evidence as to the relationship between inflammation and remodelling in older children? Payne *et al* compared airway histology in children with severe asthma who did, and did not, have persistent airflow limitation (PAL, defined as FEV_1 < 80% with FEV_1/FVC ratio < 0.8, despite high dose systemic corticosteroids), compared with non-asthmatic controls.[18] Mucosal CD4, but not CD8 positive T-lymphocytes were inversely correlated with pre- and post-bronchodilator FEV_1. Interestingly, those children who did not have PAL had a greater rbm thickness than the PAL asthmatics and controls. One could hypothesis that CD4 lymphocytes might be the key drivers both of inflammation and remodelling, as separate but parallel processes. The role of lymphocytic bronchial inflammation finds some support from an adult study[19] in which long term lung function deterioration was more rapid in those with high bronchial CD8 positive lymphocytic infiltration; CD4 cells were not reported. It seems likely that T-lymphocytes modulate remodelling in some way, but more work is needed.

These observations were taken further in a bronchoscopic study of children age 5–15 years with moderate and severe asthma who underwent bronchoscopy.[20] Control tissue was from children who had died in road traffic accidents. The authors stained for markers of epithelial stress, specifically epidermal growth factor receptor (EGFR) and the cyclin/cyclin dependant kinase inhibitor $p21^{waf}$, and the epithelial proliferation marker Ki67. There salient findings in the asthmatics as compared to normals were as expected a thickening of the rbm and increased collagen deposition; increased staining for EGFR and $p21^{waf}$; and reduced Ki67 expression. EGFR expression correlated with rbm thickness. By contrast, there was no correlation between eosinophil numbers and Ki67 or $p21^{waf}$. Indeed, there was no increase in eosinophil numbers in any of the groups. The authors concluded that the epithelium was stressed or injured without evidence of inflammation. These data are important, but not easy to interpret. Clinical details are scanty, and it is difficult to see whether there may have been confounding effects of treatment; all the severe, and one of the moderate asthmatics was receiving treatment with inhaled corticosteroids. These authors have proposed from these and other data the concept of dysfunction of the EMTU being disturbed in asthma. The EMTU concept[2] proposes that the epithelial damage in asthma is a result of disregulated EFGR-mediated repair. The damaged epithelium combined with a TH_2-mediated environment, leads to myofibroblast activation, matrix deposition, and mediator release, amplifying the airway wall remodelling. The interaction between epithelium and mesenchyme is fundamental to normal airway development, and it is proposed that this becomes dysregulated *ex utero* in the asthmatic. This would lead away from inflammation being the primary abnormality, and towards asthma being a primary disorder of airway repair and remodelling. The relationship between onset of symptoms, and airway inflammation and remodelling was studied by Pohunek *et al*.[21] They performed bronchoscopy in children with chronic respiratory symptoms, prior to a specific diagnosis having been made. The group were re-evaluated 22–80 months later, and those who were subsequently assigned a diagnosis of asthma were found to have increases in airway eosinophils and rbm thickening at the previous bronchoscopy, compared to those who were not subsequently thought to be asthmatic. As in other studies, there was no correlation between the two. They concluded that histological changes were present very early in the development of asthma, in a "pre-morbid" phase. However, some comment needs to be made. All patients had had symptoms for at least a year prior to the bronchoscopy (mean nearly 4 years). Only 3 of 27 of the children were less than five years old. Thus it is arguable that in fact the study was in patients with fairly well-developed asthma, many of whom, with retrospect, could have been given a diagnosis of asthma much earlier, at the time of, or even before, the initial bronchoscopy. These results have been challenged by subsequent studies (below).

WHAT IS THE EVIDENCE FROM EPIDEMIOLOGY?

The evidence detailed above suggests that eosinophilic airway inflammation and structural airway wall changes are present by the early school years, and the roots of the problem lie earlier in life. Different patterns of pre-school wheeze have been described, with different lung function abnormalities.[22,23] There is not complete agreement in all cohort studies, but in summary, transient wheezers (defined as wheeze in the first three years of life, symptom free at age six) have impaired lung function at birth, and show improved, but persistent airflow obstruction at age six. Persistent wheezers (wheeze throughout the first six years of life, many of whom are the future atopic asthmatics) had normal lung function at birth, but airflow obstruction age six years. Late onset wheezers (no wheeze in the first three years of life, but wheeze in the second three years) have normal lung function to age six years.[22] Thereafter, from age six to sixteen years, lung function tracks.[24] In contrast, the Perth group found evidence of impaired lung function even at birth in the future persistent wheezer.[23] What does seem clear, from a series of overlapping cohort studies,[25,26] is that lung function tracks from about 3–5 years of age until nearly 50; in other words, lung function until late middle age is predetermined in the preschool years, and therefore it is at this time that the roots of inflammation and remodelling should be sought.

ANTENATAL REMODELLING

What is clear from epidemiology is that there are at least some structural changes are determined antenatally. Whether this is termed remodelling is a matter of definition, but it is useful briefly to focus on them, because their effects are long-lasting (above), and they may in the future provide an opportunity for future therapeutic intervention. Airway branching is pattern is determined in the first half of pregnancy, and thereafter, antenatal influences can affect airway calibre. There are a number of antenatal determinants of airway anatomy. These include genes, of which the best characterised is *ADAM33*, which is important in antenatal lung development,[27] in particular branching morphogenesis, and polymorphisms of which also affect airway calibre at age 3 and 5 years.[28] Interestingly, however, the *ADAM33* null mouse has no pulmonary phenotype at all,[29] so there must be considerable redundancy in the system. The most obvious intrauterine environmental effect is maternal smoking, which is associated with airflow obstruction shortly after birth in the fetus. There are important gene-environment interactions; maternal and fetal glutathione metabolising enzyme phenotype both interact with environmental smoke; the fetal exposure to maternal smoke is greater if the mother carries null polymorphisms, and the consequences are greater for the null child.[30,31]

The knowledge of the effects of the mother smoking on the development of the foetal lungs has come from animal and human work. Pregnant guinea pigs exposed to tobacco smoke gave birth to pups with a greater than normal distance between alveolar attachment points, due both to an increase in the outer perimeter of the airway, and a reduction in the number of attachments. There were also non-significant trends for inner and outer airway wall area, and ASM area to be increased compared with controls.[32] Nicotine given by subcutaneous infusion to pregnant baboons caused airway remodelling in the pups.[33] There was increased airway wall area per mm of epithelium, and upregulation of mRNA for Types 1 and 111 collagen, confirmed by immunostaining, in the airway and alveolar walls. There were also increases in elastin mRNA, but if anything, elastin protein was decreased, not increased; this counter-intuitive result did not reach statistical significance. The mechanism is probably via the reaction of nicotine with the $\alpha 7$ nicotinic acetyl choline receptor. These changes were not reported to be associated with inflammation, establishing proof of concept that inflammation is not a pre-requisite for airway remodelling.

The most extensive human studies have come from autopsy data from Melbourne, Australia.[34-36] In the first study, the lungs of infant victims of sudden infant death syndrome (SIDS) whose mothers did and did not smoke in pregnancy were compared.[34] Of course, it could be argued that the best control group would be trauma victims, because it could be argued that some changes may have been related to a genetic or other predisposition to SIDS, independent of maternal smoking. In the first study, inner airway wall thickness relative to the basement membrane perimeter was found to be greater in the large airways of the SIDS infants whose mothers smoked in pregnancy. In a subsequent study, the controls were non-SIDS related deaths, the SIDS victims had increased ASM, but epithelial and wall thicknesses were similar in the two groups.[35] However, pregnancy smoking history did not affect airway ASM content. The final study,[36] this time without non-SIDS controls, showed an increased distance between alveolar attachment points in those with a history of antenatal smoke exposure, similar to the findings in guinea pigs (above). They confirmed that there was no difference in airway or parenchymal elastin content in either group. Postnatal smoke exposure had no effect on alveolar attachment points. The thickness of the inner airway wall was greater in the ante-natal smoke exposure group. Taken together, these animal and human data suggest that antenatal smoke exposure can cause a form of remodelling characterized by increased types 1 and 111 collagen, increased inner airway wall thickness, and an increased distance between alveolar attachment points. The functional consequences might be to alter airway wall compliance, a consequence supported by complex mathematical modeling based on physiological observations in humans.[37]

There are other maternal factors known to be associated with airflow obstruction in the antenatal period, although the pathology in the neonatal airway has not been characterized, and thus whether they also cause remodelling is not known. Maternal atopy has also been associated with impaired lung function in the newborn, although the precise mechanisms are not clear.[38,39] Other factors include maternal hypertension or pre-eclampsia, which is associated with an increased risk of transient early wheezing, persistent wheezing and late-onset wheezing. Use of antibiotics for urinary tract infections was associated with transient early wheezing, and antibiotic administration at delivery was associated with both transient early wheezing and persistent wheezing.[40] Children who had a mother with diabetes were more likely to have persistent wheezing.[40] Finally, amniocentesis or chorionic villus sampling was associated with the subsequent development of wheezing.[40] Further mechanistic studies are needed in babies with these pregnancy histories.

A WINDOW OF OPPORTUNITY? BRONCHIAL BIOPSY STUDIES IN YOUNG CHILDREN

Two studies from our group have established the pathological counterpart of the epidemiological find-

ings of changes in lung function between birth and age six years.[41,42] In the first,[41] infants, median age 12 months were investigated for persistent respiratory symptoms in Helsinki. As part of the investigations, bronchoscopy and endobronchial biopsy were performed. The infants were divided into three groups, (A) those with airflow obstruction, responsive to acute administration of bronchodilators; (B) a group with airflow obstruction, non-responsive to bronchodilators; and (C) the group with normal lung function. Group C was the nearest equivalent to normal controls that could be obtained, given the ethics of bronchoscopy in young children. There was no difference in rbm thickness, or any inflammatory cell, in any group. Nor was there any difference between the group at highest risk for persistent wheeze (atopic children in Group A) and the others or any subgroup thereof. The biopsies all looked entirely normal and featureless, despite the presence of symptoms of a severity and duration to provoke referral to a specialist centre. It will be of interest to re-analyse the data when the infants are age 6 years, and can be rephenotyped by the Tucson criteria ([22] and see above). It would of course have been of interest to perform follow up biopsies, but this is not ethical.

We also performed a second, cross-sectional study in a different group of pre-school children, referred to The Royal Brompton for investigation of really severe wheeze. They were divided into confirmed wheezers (using a videoquestionnaire[43]) and unconfirmed wheezers, a group in whom parents identified a different noise on the questionnaire. Control children were those being investigated for stridor, other upper airway problems, and hemoptysis, who had never wheezed. The confirmed wheeze group had rbm thickening, and eosinophilic airway inflammation on endobronchial biopsy, with a good correlation between the two. Of course, correlation does not prove causation, or even association. In a post-hoc analysis, there was a marked trend for the changes to be more marked after rather than before the second birthday. These children are currently being followed up and rephenotyped at school age, when the data can be reanalysed by retrospective phenotype. Thus these two studies suggest that there may be a window between the onset of symptoms, and two years of age, during which time the airway pathology of asthma develops in those who will turn out to have persistent wheeze.

In terms of the nature of the rbm changes, we compared the fibrillary structure using electron microscopy, in these infants, and older children and adults with asthma.[44] The fibrillary structure was identical, implying that the changes seen were due to an increase in the normal content of the RBM, and not a fundamental change in structure, which would have implied the laying down of new components beneath the normal rbm.

SUPPORTIVE EVIDENCE: OTHER STUDIES IN YOUNG CHILDREN

The concept we propose, namely that there is a window between the onset of symptoms, and the establishment of eosinophilic airway inflammation receives support from other studies of pre-school wheeze. The initial pattern of inflammation would appear to be intermittent and acute neutrophilic, rather than eosinophilic. In acute preschool presumed viral induced wheeze, serum soluble L-selectin was increased, and membrane bound L-selectin (CD61) was reduced, implying neutrophil activation.[45] BAL studies have shown that preschool wheeze is associated with a neutrophilic cytology, similar to cystic fibrosis, rather than the typical eosinophilic pattern seen in atopic asthmatics.[46,47] This was confirmed by a non-bronchoscopic BAL study, which showed that viral associated wheezers had no eosinophilic airway inflammation.[48] Treatment with oral and inhaled steroids is very effective in atopic, eosinophilic asthma, but has minimal if any benefits in pre-school viral associated wheeze,[49-51] again implying a lack of eosinophilic involvement. Finally, in a natural experiment, young children with autoimmune neutropaenia were matched with a control group with the same number of atopic first degree relatives; none of the neutropaenic group developed asthma, significantly different from the control group.[52] Thus eosinophilic involvement is not early in the evolution of wheeze in the pre-school child.

IMPLICATIONS FOR TREATMENT

It is when considering treatment that the importance of the different paradigms is most obvious. If remodelling leads to progressive airflow obstruction, then preventive treatment is appropriate. However, there is at least some evidence that rbm thickening may be protective, and intuitively, if it stiffens the airway and prevents constriction this might protect long term lung function. We showed that rbm thickening appeared to be associated with *better* lung function ([18], and see above). However, an adult study[53] showed the reverse. A physiological study suggested that rbm thickening may be protective against BHR.[54] Thus the data as to benefit or otherwise for rbm thickening is unclear. There are even fewer data for other components of remodelling, although one study showed a correlation between worse lung function and greater ASM thickening.[55] It is possible that some components of remodelling are protective, whereas others are adverse. Therefore caution should be employed before attempting to modulate remodelling, and more data are needed.

FUTURE WORK

Ideally, we need techniques by which we can directly measure the separate components of inflammation

and airway remodelling non-invasively, reliably and repeatably. None exist. High resolution CT scanning (HRCT) in adults has shown that there are good correlations between spirometric indices of airflow obstruction, rbm thickening and HRCT measurements of airway wall thickness.[53] In our hands, the use of qualitative or quantitative measurements of airway wall thickness on HRCT did not correlate with rbm thickness.[56] De Blic *et al* have found some weak correlations,[57] but the spread of the data is such that it is difficult to believe they would be of use in individuals.[58] They also partitioned nitric oxide (NO) production into airway wall (J_{NO}) and alveolar (C_{alv}) by measuring NO production at different flow rates.[59] They reported a weak correlation between HRCT measurements and J_{NO}.[57] However, since J_{NO} correlates with $FeNO_{50}$ (NO measured at an expiratory flow rate of 50 ml/sec,[59] and $FeNO_{50}$ is a marker of eosinophilic airway wall inflammation, it is more likely that their results reflect a relationship between inflammation and airway thickening, rather than airway thickening itself. In a separate paper,[60] they reported further correlations, C_{alv} with BAL TGF-β and J_{NO} with rbm thickness and TIMP1: MMP9. However, the complex interdependence of these factors makes interpretation difficult, and it is difficult to believe that partitioning NO production will help monitor airway remodelling. In any case, the technique is not appropriate to the age group of interest, namely preschool children (above).

Other possibilities include exhaled breath condensate (EBC), and sputum induction. EBC is non-invasive, which is attractive, but as yet no useful biomarkers for remodelling have been identified. It may seem paradoxical to suggest induced sputum as a technique in an age group which do not spontaneously expectorate sputum, but the technique has been used even in babies to diagnose tuberculosis,[61] so in principle this technique could be used to study inflammation and remodelling. Urine is a very attractive source of biomarkers. Desmosine (DES) and isodesmosine (IDES) are amino acids derived exclusively from cross-linked elastin. Hydroxylysylpyridinoline (HP) and lysylpyridinoline (LP) are amino acids derived exclusively from cross-linked collagen. All have been measured in urine, but there are no data correlating them with endobronchial biopsy in children. Adult studies suggest that they may be useful markers of tissue destruction.[62-66] They are not specific to the lung, but in the absence of important systemic disease, an elevation in levels is most likely attributable to some event within the lungs. However, remodelling is not the same as tissue destruction. More data are needed to determine if there is a role for these biomarkers.

In adults, the relationship between allergens, inflammation and remodelling has been studied using a model of acute endobronchial allergen challenge.[67] This model has shown myofibroblast differentiation and airway deposition of matrix components such as tenascin in response to acute allergen challenge, which would appear to contradict the concept of remodelling being an early and non-progressive phenomenon. However, at least some of the changes regress after the challenge, if a later bronchoscopy is performed (for example, changes in tenascin were no longer significantly different over baseline; and it would have been of interest to repeat the bronchoscopy a few eeks after the challenge),[68] and it is difficult to determine the relationship between acute endobronchial challenge, and the more physiological, low dose exposures seen in real life. If each allergen exposure lead to the cumulative deposition of matrix components in the airway, then the airway would surely rapidly become obliterated, which simply does not happen. Furthermore, ethical constraints preclude the application of these techniques in young children.

If human studies fail, can animal models help? There are numerous studies in the very unphysiological adult mouse model, in which 'asthma' is induced by convoluted procedures including intraperitoneal ovalbumen injection. We need to develop animal models which more closely mimic real life—these will need to be in neonatal animals, with inhalational (and in particular, viral) challenges. The adult animal, with fully developed airways and a mature immune system, cannot possibly mimic the newborn situation. More satisfactory animal models will allow us to generate hypotheses, which will then be tested in preschool children. It is quite clear that disease modifying interventions are only likely to work in the preschool years. In the human, by school age, the disease is established, and probably not modifiable.

The really relevant question is, what will be the disease modifying therapies? Inhaled corticosteroids are definitely not the answer.[49,50,69-71] Could it be that macrolides, with their ubiquitous effects,[72,73] might modify remodelling,[74] and thus the natural history of asthma, as they have of diffuse panbronchiolitis? That would be another tremendous benefit of East meeting West!

SUMMARY AND CONCLUSIONS

The whole area of early inflammation and remodelling is still controversial. It is clear that some structural changes take place antenatally, and these are likely (but not proven) independant of inflammation. Biopsy of the airways of the very young infant with symptoms, the only real way of studying early disease, reveals no inflammation or remodelling. The absence of eosinophilic inflammation at least is supported by studies showing that the neutrophil appears to be the key effector cell in pre-school wheeze, and also by the at best weak effects of corticosteroids in early life. There are at least four possible models

which could describe the relationship between inflammation and remodelling:

Eosinophilic inflammation is the primary event, and leads to remodelling as a secondary event, which itself results in progressive airflow obstruction. In this case, treatment of eosinophilic inflammation would be expected to be disease modifying. This is completely against the observation of the failure of inhaled corticosteroid to be disease modifying, and this model is in my view the least likely.

Eosinophilic inflammation is the primary event, but remodelling is protective, preventing worsening AHR. In this case, the concept of preventing remodelling pharmaceutically is misplaced, and possible we should even be trying to enhance it. It should be noted that 1. and 2. are not mutually exclusive; rbm thickening may be protective, but other components, for example increased ASM, may have adverse effects.

Eosinophilic inflammation and airway remodelling are parallel processes, driven by some underlying 'asthma factor', perhaps via a CD4 lymphocytic bronchitis.

The primary abnormality is not airway inflammation at all, but some form of airway remodelling, perhaps related in some way to the EMTU. In this model, airway inflammation is a secondary problem, and treating it will not modify the disease process.

Unravelling these hypotheses, or producing newer and better ones, will require new strategies. Bronchoscopic biopsy can only provide tiny and very precious pieces of tissue, and can never be applied to longitudinal studies. At best, the tissue can be used to confirm hypotheses. There is an urgent need for biomarkers that can be utilised in preschool wheezers. Urine is an obvious possibility; induced sputum might be used to demonstrate airway cellularity; and exhaled breath condensate might also have a role. Animal models have been severely criticised, and it is difficult to see the physiological relevance to early disease of an adult mouse model that needs an intraperitoneal allergen injection to make it work. However, increasingly models requiring merely inhalational challenge, and models of asthma in the newborn airway, are being devised. These are ideal for hypothesis generation. Ultimately, a portfolio of techniques will be needed to determine how and why the pattern of intermittent, neutrophilic inflammation, with complete resolution, switches to chronic eosinophilic inflammation and structural airway wall changes, and thus how long term lung health can be modulated in early life, with preservation of airway function into adult life.

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