

Has the time come to rethink the pathogenesis of asthma?

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Purpose of review

To explore new ground in asthma pathogenesis. Asthma is an inflammatory disorder of the airways that has strong association with allergy as characterized by a Th2-type T cell response. However, ranges of approaches that have targeted this immunological component have so far been disappointing. Most asthma therapy still relies on bronchodilators and corticosteroids rather than treating underlying disease mechanisms.

Recent findings

In this review, a case is made that asthma has its primary origin in the airways that involves defective behaviour of the epithelium in relation to environmental exposures. These include defects in barrier function and an impaired innate immunity to provide the substrate upon which allergic sensitization can occur. Once the airways are sensitized repeated allergen exposure leads to disease persistence. Such mechanisms could explain airway wall remodelling and the susceptibility of the asthmatic lung to exacerbations provoked by viruses, air pollution, certain drugs, and biologically active allergens.

Summary

Activation of the epithelial-mesenchymal trophic unit could be responsible for the emergence of different asthma phenotypes and direct a more targeted approach to treatment. There is also the possibility of developing treatments that increase the lung's resistance to the inhaled environment rather than focusing on the suppression of inflammation once established.

Keywords

allergens, asthma, epithelium, inflammation, mesenchyme, remodelling, virus infection

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Introduction

Asthma is an inflammatory disorder of the conducting airways that undergoes distinct structural and functional changes leading to nonspecific bronchial hyperresponsiveness (BHR) and airflow obstruction that fluctuates over time. It is amongst the most common chronic conditions in Western countries affecting one in seven children and one in 12 adults. A recent assessment of asthma across Europe (Brussels Declaration) has identified substantial unmet clinical need that, in the 10% of patients with severe disease, accounts for approximately 50% of the health costs [1•].

Shortfalls in current treatment approaches

Most, but not all, asthma is associated with atopy, a concept that has led to the condition being regarded primarily as an allergic disorder along with other atopic diseases. However, this conflicts with the findings that asthma prevention has not been achieved, once established there is no cure and there are currently no

medications that can alter the natural history of the disease [2].

Management is primarily directed towards suppressing airway inflammation with inhaled corticosteroids and relieving bronchoconstriction with bronchodilators. Apart from corticosteroids, the only oral medications in widespread use are cysteinyl leukotriene receptor 1 antagonists that inhibit the bronchoconstrictor and inflammatory actions of LTC₄, LTD₄ and LTE₄. All of these therapies exert their effect downstream of the origins of asthma. There is an urgent need to identify the underlying basis of asthma, understand the complex genetic and environmental influences, and develop appropriate treatment strategies. Although asthma may start at any time in life, the majority begins in early childhood [3], whereas it may spontaneously remit, longitudinal studies reveal that later relapses frequently occur [4]. The study by Sears *et al.* [4] is one of the few longitudinal cohort studies that track the life course of asthma. Severe, irreversible airflow obstruction may develop despite apparently appropriate use of controller

therapy as advocated by international and national disease management guidelines.

It is important to state at this point that widespread adherence to anti-inflammatory controller therapy as advocated in all Management Guidelines (especially inhaled corticosteroids) does have a major impact on national health outcomes of asthma such as deaths, hospital admissions and unscheduled medical interventions. Indeed, when treatment adherence is high as in Finland, asthma mortality and morbidity can be dramatically reduced. The problem is that in most countries of the world, treatment adherence is low especially when inhaled drugs are involved on account of perceived fear of systemic side effects, addiction and concerns over acquisition of drug resistance [5]. Many patients only take their anti-inflammatory treatment when they are symptomatic and stop when their symptoms abate [6]. Although there is some evidence that this approach might be effective in mild asthma [7], in more severe disease regular inhaled corticosteroids, often in large doses and in combination with long-acting β_2 -bronchodilators (LABAs), are required for disease control [8]. There is a new emphasis in Asthma Guidelines on gaining control over the disease rather than concentrating on steps of severity. In low-income and middle-income countries, inadequate diagnosis, the costs of drugs and poor education all contribute to poor disease management and over dependence on emergency interventions with the consequence of high mortality and morbidity [9].

A refocus on the underlying causes of asthma

The time has arrived to establish a new research approach that will provide greater insight into the initiation of the disease and its evolution over time into different subphenotypes and lead to treatments that are upstream of airway inflammation and its consequences. To achieve this 'high ground' rather than viewing asthma as a series of acute events, it is important to take a life-course view initially focusing on young children and the early life factors that drive the origins of the disease and then to track the structural changes and functional airway responses through childhood, adolescence into adults. On the basis of a large number of converging observations, it is becoming apparent that the lower airways epithelium in asthma is both structurally and functionally defective and that this may underlie the observed exaggerated and abnormal responses of the airways to the inhaled environment. The concept of persistent activation of the epithelium with signalling to the underlying structural cells has been called the epithelial-mesenchymal trophic unit (EMTU) that could promote a microenvironment that facilitates allergic sensitization, supports different types of inflammation and predisposes

the airways to exacerbations leading to persistence of asthma during childhood. Activation of the EMTU might also be responsible for driving tissue remodelling that progressively leads to loss of airways reversibility, reduced lung function and refractoriness to treatment in adults.

Asthma subphenotypes are now being recognized with differing pathology, clinical expression, response to treatment and long-term outcomes [10^{••}]. Although most asthma exhibits a Th-2-type inflammatory response with upregulation of cytokines of the interleukin (IL)-4 gene cluster linked to atopy, overinterpretation of this pathway has led to a simplified view that asthma results from allergen exposure alone. Both in adults and children the indistinguishable pathological features of nonallergic and allergic asthma emphasises that inflammation and remodelling can occur independently of atopy [11]. Atopy affects up to half of the adult population in developed countries; yet, the great majority do not progress to develop asthma [12]. Although in most patients allergen sensitization contributes to asthma, attempts to intervene using allergen reduction strategies [13] or allergen-specific immunotherapy [14] in moderate-severe asthma have on the whole been somewhat disappointing, despite clear efficacy in allergic rhinitis even if this is severe [15]. In severe asthma, activated T cells are present in abundance, but the initial promise of T-cell inhibitors (cyclosporine A, methotrexate, azathioprine, anti-CD4 or anti-CD25 blocking monoclonal antibodies) and blockade of Th-2 cytokines (IL-4, IL-5, IL-9 and IL-13) and anti-TNF α have so far failed to translate into clinical use [16].

However, at one time considered as a single-disease entity, asthma subphenotypes are now being recognized with differing pathology, clinical expression, responses to treatment, and long-term outcomes. Subphenotyping of asthma is well illustrated in relation to the use of an IL-5 blocking monoclonal antibody (mAb) directed to IL-5 (mepolizumab). Administration of this antibody in moderate-severe asthmatic patients had a clear effect in reducing circulating eosinophils but, surprisingly, had no effect on asthma outcomes [17]. The study of Flood-Page *et al.* [17] is a pivotal clinical trial of targeting eosinophils in asthma by blocking IL-5. The clinical outcomes are disappointing. In contrast, the same treatment of hyper-eosinophilic syndrome in both children [18] and adults [19] proved to be highly effective. Two recent clinical trials of mepolizumab in severe asthmatic patients requiring high dose corticosteroids but with persisting sputum eosinophilia have reported efficacy that includes eosinopenia and a marked reduction in asthma exacerbations, but no effect on airway hyperresponsiveness [20,21]. Nair *et al.* [20] and Halder *et al.* [21] show that blocking IL-5 in a selective severe asthma patient subgroup reveals

efficacy as examples of stratified medicine. A further development in relation to IL-5 as a target is the engineering of an antibody-dependent cell cytotoxic (ADCC) defucosylated IgG1 monoclonal antibody [22] that is directed to all cells expressing the IL-5 α (MEDI-563). Data from a completed Phase 1 study of MEDI-563 have demonstrated that the antibody is well tolerated and achieves substantial and prolonged depletion of blood eosinophils.

Improvements in inhaled bronchodilators and corticosteroids to enhance their efficacy, duration of action and safety have resulted in better and safer controller and reliever drugs but the discovery of entirely new anti-asthma drugs over the last 50 years has been disappointing, the only successful new treatments to emerge being leukotriene modifiers such as Montelukast and the anti-human IgE monoclonal antibody, omalizumab, both directed at asthma targets identified many years ago [23]. Thus, the view that chronic airway inflammation and remodelling in asthma are primarily caused by allergen sensitization and exposure is being challenged.

Holgate *et al.* [24] have provided a first description of the potential role of epithelial-mesenchymal communication as a driver for inflammation and remodelling of the asthmatic airways. This resulting alternative model implicates the EMTU in that epithelial damage by such environmental agents as viruses, air pollutants, environmental tobacco smoke (ETS), drugs and biologically active allergens resulting in signals to propagate and amplify inflammatory and remodelling responses in the submucosa [24,25]. Others and we have recently reported defective epithelial tight junction formation both in asthmatic biopsies and in the epithelium differentiated at an air-liquid interface *in vitro* in association with impaired barrier function [26]. The asthmatic epithelium is also functionally abnormal by being more sensitive to oxidant injury [27] and failing to generate interferon- β (IFN- β) and IFN- λ in response to common respiratory virus infection resulting in cytotoxic cell death and enhanced viral replication and shedding [28]. Wark *et al.*'s [28] description is the first description of defective interferon production by asthmatic epithelium underlying asthma exacerbations provoked by respiratory viruses. Thus, many of the chronic inflammatory and structural responses that occur in chronic asthma (including airway allergen sensitization) could follow from a defective epithelium leading to a chronic wound response to repeated environmental injury [29]. Swindle *et al.*, O'Regan *et al.*, Groschwitz and Hogan and Tieu *et al.* [29–32] give up-to-date reviews of the role of epithelial-barrier function defects as an underlying abnormality in the acquisition of allergy at epithelial surfaces. Similar mechanisms are now known to operate in other allergic diseases such as atopic dermatitis, where

loss-of-function polymorphisms in the flaggrin gene on chromosome 1q21 greatly reduce skin-barrier function [30], and in food allergy [31] and rhinosinusitis [32], are suggested as factors leading to enhanced allergen sensitization.

The finding that many novel asthma susceptibility genes identified through application of hypothesis independent approaches such as positional cloning and genome-wide association are expressed in the epithelium and mesenchyme adds to the evidence that places the EMTU at the centre of asthma pathogenesis [33,34]. Eder *et al.*'s [35] work is a comprehensive review of environmental factors that contribute to the rising trends of allergy and asthma worldwide. Further evidence for a critical role of the epithelium comes from showing that the most frequent risk factors for developing, exacerbating and prolonging asthma act through the EMTU including bacterial infection with *Chlamydia* and *Mycoplasma* [35,36].

Factors influencing the onset of asthma

Although asthma may begin at any time in life, most frequently it first expresses itself early in the first few years of life with suboptimal fetal growth, maternal micronutrient deficiencies and maternal smoking all being associated with impaired infant lung function and later asthma [37,38]. Both asthma and the subphenotype, airway hyperresponsiveness, have a strong genetic basis that is independent of atopy. For example, polymorphism of the asthma susceptibility gene, *ADAM33* is associated with reduced lung function in infants and the later development of bronchial hyperresponsiveness [39]. Birth cohort studies have also revealed that severe asthma is predicted by impaired infant lung function and BHR [40–42]; however, the role central of allergy *per se* as the initiator of asthma is being questioned. Illi *et al.* [43] did a pivotal birth cohort study in Germany showing the influence of atopy after the age but not before the age of 5 years in the persistence of asthma. Thus, in children who develop asthma, atopy has little influence on disease expression until 5 years of age, after which it predicts disease persistence [43,44], although those destined to acquire more severe disease becoming IgE-sensitized earlier [45]. This is in contrast to food allergy (e.g. peanut, milk and egg) where high exposure in early life induces immunological tolerance rather than sensitization [46]. In contrast to exposure via the gut, continued allergen exposure through the airways or skin facilitates sensitization [47,48].

Though allergen exposure is important as a driver of ongoing asthma in children, its role as a primary initiating factor is challenged by showing that prolonged suppression of inflammation by inhaled corticosteroids at the onset of disease in infants or later in childhood has little or

no influence over the natural history of asthma, despite effective control of symptoms while the treatment is given [49,50]. The study of Guilbert *et al.* [49] is one of the first to reveal that introduction of inhaled corticosteroids in genetically at risk babies does not influence the natural history of asthma. Other environmental factors are now emerging as being important in initiating asthma. A recent exciting discovery is that repeated infections with common cold rhinoviruses (RVs) during the first 3 years of life increases the risk of developing asthma by age 6 years 26-fold as compared with three-fold for allergen sensitization [51^{••}]. In a UK cohort study, the adjusted risk of asthma at age 10 years was four-fold in children who had recurrent chest infection before age 2 years [52,53]. The key role of early life virus infection also extends into adult asthma in the European Community Respiratory Health Survey [54]. In the United States 95 000 infant cohort study, the timing of birth in relationship to the winter virus season conferred a 30% increased risk of developing asthma by age 6 years [55], whereas in an Australian cohort, respiratory virus infection interacts with atopy to promote the development of asthma at age 5 years [11]. Importantly, the target for viruses and environmental stimuli such as ETS and other pollutants is the airway epithelium. Understanding why the airway epithelium of these children is so susceptible to these stimuli and how it affects allergic sensitization could provide a potential novel route to prevent asthma.

However, many children who wheeze with viral infections during infancy will not progress to asthma. Early life exposure to pollutants such as environmental tobacco smoke and atopy [53,54] are also risk factors for persistent asthma, suggesting a need for multiple environmental interactions interacting with susceptibility genes expressed in the airways. Antigen presenting cells especially airway dendritic cells (ADCs) play a centinel role in initiating and regulating the early inflammatory events that occur at epithelial surfaces. In the first year of life, infants do not exhibit ADCs in the absence of inflammation whereas severe respiratory infection is accompanied by the appearance mature ADCs [56]. Although the proteolytically active allergen *Der p1* can disrupt epithelial tight junctions to facilitate transport of allergen across the epithelium [57], it has been suggested that ADCs also need a 'danger signal' to activate T cells and avoid tolerance [58]. Respiratory virus infection of the preasthmatic epithelium may be the key factor that leads to ADC maturation with a bias towards a Th-2 response which is, in part, genetically determined. It follows that these events could promote a microenvironment that would facilitate allergic sensitization, support different types of inflammation and predispose the airways to development of asthma during childhood.

Asthma progression or remission

Bronchial biopsies obtained from very young children with early life virus-associated wheezing reveal little abnormal pathology, but by the time they reach 3 years of age, epithelial injury and thickening of the *lamina reticularis* is evident [59–61]. Although thickening of the *lamina reticularis* is diagnostic of asthma both in children and adults, there is some doubt being raised over its significance to airway remodelling since its extent does not relate to asthma duration [62], but may increase with disease severity [63]. Thickening and an increase in density of the *lamina reticularis* occur equally in atopic and nonatopic childhood asthma; indeed the airway pathology of these variants is identical [11]. On the basis of its unique presence in asthma and also its occurrence following lung transplantation [64], the deposition of new matrix in the *lamina reticularis* would seem to be indicative of a type of epithelial injury and abnormal repair. In adult and childhood asthma, epithelial over-expression of epidermal growth factor receptor, reduced markers of cell proliferation and increased nuclear translocation of the cell cycle inhibitors are consistent with impaired epithelial repair responses [65,66]. Most recently, airway epithelial cells cultured from atopic asthmatic compared with atopic normal children impaired wound repair responses following injury [67].

Conclusion

Asthma can no longer be considered simply in terms of a single cellular and mediator response to inhaled allergens but a complex interaction between the inhaled environment and the formed elements of the airways. The concept that the state of the airway epithelium and underlying mesenchyme (EMTU) may be important in translating the atopic phenotype into expression in the lower airways may give rise to different subphenotypes with differing responses to treatment and natural histories. A very recent publication by Woodruff *et al.* [68^{••}] using microarray and polymerase chain reaction analyses of airway epithelial brushings from 42 patients with mild-to-moderate asthma and 28 healthy control subjects classified subjects with asthma based on high or low expression of IL-13-inducible genes and validated this classification and investigated its clinical implications. Gene expression analyses identified two evenly sized, reproducible and distinct subgroups designated 'Th-2-high' and 'Th-2-low' asthma that differed significantly in their expression of IL-5 and IL-13 in bronchial biopsies, airway hyperresponsiveness, serum IgE, blood and airway eosinophilia, subepithelial fibrosis, and airway mucin gene expression. The lung function improvements with inhaled corticosteroids were restricted to Th-2-high asthma. The authors conclude that asthma can be divided into at least two distinct molecular phenotypes defined by

the degree of Th-2-driven inflammation and that current models failed to explain non-Th2-driven asthma, which represents up to 50% of asthmatic patients in their sample who responded poorly to inhaled corticosteroids. What is now needed is a greater focus on the origins of asthma especially early in life, new methods of subphenotyping including biomarker research and the connection of life-course epidemiological cohort studies with mechanistic research. A change in approach will provide a much needed insight into underlying disease mechanisms and hopefully lead to the identification of new therapeutic targets for disease prevention and treatment.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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