

OPINIONS IN ALLERGY

Non-atopic intrinsic asthma and the 'family tree' of chronic respiratory disease syndromes

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Summary

We present a scheme below in which the most common forms of inflammatory diseases of the respiratory tract, notably atopic and non-atopic asthma and COPD, are depicted as separate offshoots from a common 'at-risk' pathway underpinned by genotypes related to aberrations in control of host defence and tissue repair mechanisms. We propose that entrance into this pathway is initially programmed by environmental experience during infancy and early childhood, in particular by severe lower respiratory tract infection, and that further progression towards expression of specific disease phenotype(s) is determined by the nature, timing and frequency of additional environmental insults subsequently encountered. At the one extreme, early sensitization of at-risk subjects to aeroallergens can potentially drive rapid progression towards expression of the atopic asthmatic phenotype under the dual onslaught of inflammatory responses to allergens/pathogens. At the opposite end of the spectrum the drip-feed effects of occasional infections on respiratory function(s) are amplified over a longer time frame by inflammation resulting from exposure to tobacco smoke and/or related chemical pollutants. Non-atopic asthma is envisaged to fit between these two extremes, being driven essentially by the downstream effects of respiratory infections alone in at-risk subjects. An important common factor in all three disease phenotypes is that acute exacerbations are typically driven by infections, the host responses to which display a characteristic T-helper type 2-like footprint, which in our view points to underlying genotype(s) which result in unbalanced host responses to respiratory pathogens.

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Introduction

The issue of the role of atopy-associated inflammatory mechanisms in the aetiology and pathogenesis of asthma-like diseases has been debated vigorously for many years. The spectrum of opinions to an extent mirrors the age range of the patient population under discussion viz. acceptance of the likelihood of a positive role for atopy in this context is most common at the pediatric end of the spectrum. It is clear from the epidemiological literature that the prevalence of asthma in non-atopics increases beyond the teen years, the age range identified in cross-sectional studies as showing the stronger association between atopy and asthma [1]. However, the link by no means disappears, particularly at the severe end of the adult asthma spectrum, but precisely how atopy contributes to chronic asthma in adulthood, and how asthma pathogenesis differs between atopics and non-atopics, remains in contention.

Research in our group approaches these issues from the developmental standpoint, and is driven by the underlying philosophy that the ultimate solution to the asthma problem will be via primary and/or secondary prevention as opposed to development of more effective treatments for established disease. This will require a more detailed understanding of the causal pathways and associated inflammatory mechanisms driving the early phase of asthma induction, in order to identify potential targets for intervention aimed at halting disease development in the early stages [2].

The approach which is proving to be most productive in regard to unravelling relevant pathogenic mechanisms involves prospectively tracking large birth cohorts of children over periods of years and studying the development of wheezing phenotypes across different ages. Findings from the major cohort studies which have contributed much of current knowledge have been recently reviewed in detail [3], and for the purposes of this discussion only a brief synopsis is merited.

The key findings derive from the observation that while wheeze that manifests in early childhood is frequently transient, it is much more likely to develop into severe asthma if it is associated with early [4–8] and persistent [6, 7, 9] atopic sensitization. Moreover, it is also clear that while atopy can act as an independent risk factor in this regard, it can also interact with other asthmagenic environmental factors [3]. In particular, early respiratory tract infections and atopic sensitization during the pre-school years are both independently associated with risk for asthma development, but the highest risk for persistent asthma is observed in children who experience both. These and related findings have given rise to a general working model for the aetiology of atopic asthma (AA) in childhood, the 'two hit' hypothesis, which envisages synergistic interactions between host inflammatory pathways targeted at respiratory pathogens and aeroallergens as the principal driving force for development of the persistent asthma phenotype during early childhood [10].

The crucial life phase in this context is the preschool years, during which postnatal lung growth and differentiation is most vigorous, leading to the establishment of structure/function relationships which are central to normal respiratory function in later life. Prospective studies indicate that lung function in individual children 'tracks' over time during early childhood [10–12], and in particular low lung function in infancy is a recognized risk factor for increased airway responsiveness [13] and persistent respiratory symptoms [14] in the later school years. Moreover, lung function can continue to track on the same trajectories into adulthood [15]. The implication from these findings is that acute and/or persistent inflammatory stimuli (in this case respiratory pathogens and aeroallergens) which have the capability to perturb early postnatal lung tissue growth and differentiation, may have very long term deleterious effects on lung function, and in the context of this discussion may contribute to development of the AA phenotype.

At the severe end of the AA spectrum is a small subset of sufferers who are subject to high-intensity virus-induced acute exacerbations which require hospitalization. The trigger for these events appears to be infection-induced acute airways inflammation acting against a background of pre-existing atopy [3]. Atopic asthmatics appear also to manifest increased susceptibility to infection spread to the lower airways [16], which may be related to attenuation of T-helper type 1 (Th1)-polarized anti-viral defense mechanisms via immune deviation resulting from the Th2 bias in overall immune function in atopics [17, 18].

How does this relate, if at all, to non-atopic asthma (NAA)? Firstly, the tracking phenomenon described above also appears applicable here, given that low lung function [19, 20] and bronchial hyperresponsiveness [20] in childhood are independent risk factors for adult NAA. Addi-

tionally, significant parallels are evident in findings related to the comparative pathology of acute severe AA and NAA. In particular, Th2-associated markers, including relevant cytokines and their receptors as well as eosinophils are prominent in *both* groups [21–23], despite the lack of a concomitant IgE component in NAA. Severe exacerbations of NAA, similar to the situation in AA, are almost invariably triggered by virus infection, and these findings suggest that the host response to the virus in NAA also contains a significant Th2 component. As noted above in relation to AA, the efficient operation of antiviral immunity can potentially be compromised via the activities of Th1-antagonistic Th2 cytokines. The intrusion of IgE-independent Th2 effector responses into airway host defense in these subjects may also add to the sum of 'bystander' tissue damage that is an inevitable consequence of infection spread to the lower airways. It is noteworthy that Th2 effector responses extrinsic to classical IgE-associated reactions are believed to play a central role in driving the tissue remodelling process which underpins the progressive deterioration of lung function in AA [24, 25]. It is conceivable that the covert operation of these same processes in the background of NAA at a lower but nevertheless biologically significant level may play a similar pathogenic role, but requiring a longer time scale to reach a similar clinical end point.

Does a similar analogy apply to other chronic inflammatory diseases in the respiratory tract? We suggest that a comparable argument can be made in relation to COPD pathogenesis. Prospective evidence comparable to that in asthma for progression from reduced lung function in infancy to eventual chronic disease in later life is not yet available for COPD. However it is noteworthy that lung function itself is heritable [26] and inheritance of reduced lung function is a risk factor for severe, early onset COPD [27]. Moreover, as above, further clues are again provided by the pathology of disease exacerbations. The major focus of cellular studies on inflammatory mechanisms driving disease pathogenesis in COPD has been on macrophages and neutrophils, and observations concerning the presence of eosinophils have not attracted comparable attention. However, recent findings on these cells are becoming increasingly difficult to ignore. In particular, large increases in the number of airway wall eosinophils have been observed in COPD exacerbations [28], and in stable COPD high eosinophil numbers are associated with more serious airway obstruction [29]. Additionally, positive responsiveness to corticosteroids among COPD sufferers is reflected by reductions in sputum eosinophil numbers [30].

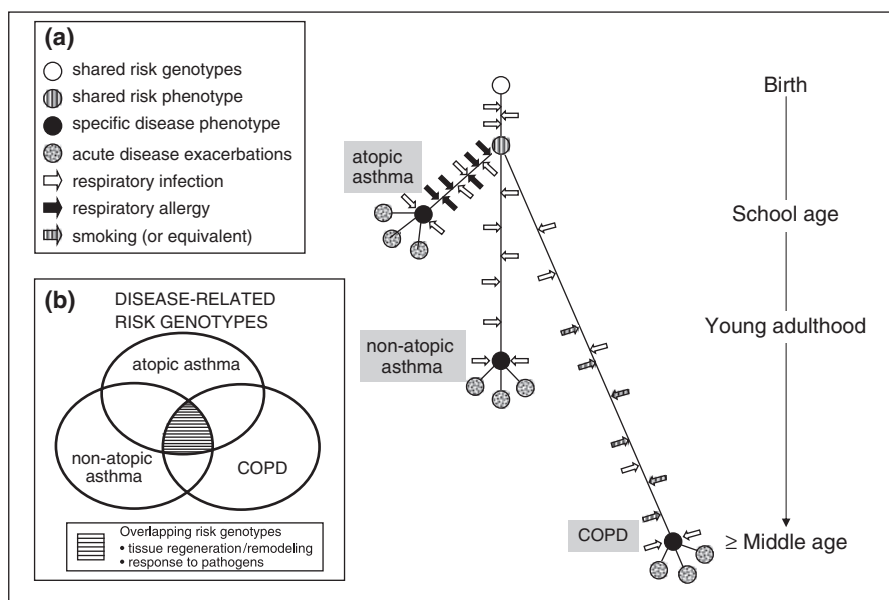
It is conceivable that these responses in COPD patients may arise via direct effects of bacterial products on eosinophils themselves, which express a range of Toll-like receptors capable of recognizing microbial motifs [31]. However, it is equally plausible that in COPD patients the

mechanisms controlling qualitative aspects of host defense responses against pathogens operate at suboptimal efficiency, permitting incursion of a significant Th2 component (in this instance eosinophil-trophic factors such as IL-5) into what is normally a strongly Th2-polarized response profile. The recent identification of a Th2 'footprint' in the form of IL-4/IL-13-dependent alternatively activated macrophages in lungs of both chronic asthmatics and COPD patients [32] is consistent with this possibility. Accordingly, inappropriate contributions from Th2-associated immune mechanisms triggered by microbial stimuli are potential contributors to the pathology of underlying acute COPD exacerbations, and by inference may also contribute towards driving overall disease pathogenesis.

The scheme in Fig. 1 provides a framework for integrating these related respiratory disease mechanisms into a contiguous causal pathway for progression to chronicity and expression of acute symptomatology. At the core of the pathway is a common stem in the form of overlapping 'risk genotypes' (Fig. 1; Inset B), interaction of which with appropriate exogenous trigger factors (especially severe infections) during early life leads to development of a 'risk phenotype', defined by heightened susceptibility to the effects of pro-inflammatory airborne environmental irritants. As described above in the context of AA, the primary target(s) for these interactions are proposed to reside within the differentiation programs that control lung growth and remodelling during the preschool years. Multiple genes may be involved, an archetypical example being ADAM33, polymorphisms in which are associated with accelerated lung function decline in

asthma and COPD patients [33, 34] and in the population at large [35]. However, we propose that another class of risk genes are of equivalent importance, notably those that regulate the responses of the innate and adaptive arms of the immune system to pro-inflammatory environmental stimuli. A likely contributor to this 'immunogenotype' is the Th2 gene IL-13 which has been identified as a candidate risk gene in both asthma and COPD [36]. We propose that variations in other genes directly associated with Th2 effector functions, and genes which modulate cell types within the innate immune system that exert *qualitative* control over adaptive immune responses, may also contribute to this overlapping risk genotype. In this context it is pertinent to note that the ultimate control of the Th-cell balance in immune responses to respiratory pathogens is vested in the network of dendritic cells (DC) first described here by us in human airway mucosal tissues [37]. A key function of these cells in the lung and in other tissues is to guide compartmentalization of adaptive immune responses to ensure that defense mechanisms are optimally tailored to the relevant challenge antigens. Dysregulation of this key cellular network leading to inappropriately balanced immune responses is central to the immunopathology in a range of infectious and inflammatory respiratory diseases [38], and as such is a likely contributor to the 'at risk' phenotype in Fig. 1.

Given the clear epidemiological link between the frequency and severity of early-life respiratory infections and likelihood of development of persistent asthma [3], the level of risk is likely to be directly related to the frequency and intensity of early infections. However,



Inset A : Key

Inset B : Proposed partial overlap between disease risk genotypes

Fig. 1. Chronic respiratory inflammatory diseases – a 'family tree'.

progression beyond the 'risk phenotype' stage illustrated in Fig. 1 and thence down any of the three causal pathways shown, and the speed with which this progression occurs, is proposed to be determined by a second tier of environmental irritants. Based again on a solid body of epidemiological evidence, the most rapid track to full expression of persistent respiratory disease phenotype is the AA pathway, in which atopic sensitization to indoor allergens provides a virtually continuous drip-feed of Th2-mediated airways inflammation. In the most susceptible children who manifest very early and intense/persistent sensitization³, cumulative damage to the airways can commonly exceed the threshold required to establish the persistent asthma phenotype by as early as age 4–5 years. In the absence of atopic sensitization the accumulation of airway damage over time is restricted to inflammation stemming from the less intense Th2-associated aberrations in host responses to respiratory infection in non-sensitized subjects, and progression to the equivalent clinical endpoint (in this case NAA) takes much longer compared to the AA pathway [19, 20]. In this regard the degree of Th2 bias in this NAA subgroup may be similar to that frequently observed towards the lower end of the atopy spectrum, where low level sensitization and accompanying enhanced Th2 cytokine production commonly occurs in the absence of significant allergy symptoms.

In the COPD branch of this tree, it is envisaged that infection mediated damage *per se* is insufficient to drive disease pathogenesis. This may be due to a lower frequency of infections over time in these subjects, and/or to subtle variations in their immunophenotypes resulting in a less marked distortion in their anti-microbial defenses relative to AA/NAA. However in the scheme illustrated, if beyond late school age these subjects commence smoking, this can create an additional and qualitatively distinct tier of inflammatory damage in the airways, leading over a longer timeframe to the pathology of COPD.

The factor common to each branch of this family tree of respiratory syndromes is that once respective persistent clinical phenotypes are established, acute bursts of high-intensity inflammation triggered by spread of infection to the lower respiratory tract can induce severe disease exacerbations. As noted above, underpinning this susceptibility is the incursion of Th2-associated elements into the pathogen-specific immune responses of these at risk subjects, which can delay clearance and introduce additional (e.g. eosinophil-mediated) damage.

The scheme illustrated in Fig. 1 can be considered as an extension of the *Dutch Hypothesis* first outlined in the 1960s [39], but it places the relevant observations into a novel developmental context which emphasizes the importance of risk factors for chronic respiratory disease that are operative years in advance of disease onset. As such it may prove useful in the formulation of new approaches to the study of the pathogenesis of this family of respiratory

diseases, in particular approaches that are targeted at disease prevention via early intervention.

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