

INVITED REVIEW

Lung damage and airway remodelling in severe asthma

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Summary

Severe asthma is a heterogeneous disease with substantial unmet clinical need. Airway damage and remodelling is a consequence of complex host–environment interactions and is considered to be the cardinal feature leading onto the development and persistence of airflow obstruction. In this review, we shall bring together recent insights into the causes of airway damage and remodelling that propose key roles for pathogens and mechanical damage in addition to allergens, underlying genetic susceptibility, inflammatory and structural cell interactions, and impaired resolution of damage. We shall consider the consequences of airway remodelling in terms of airway geometry, mechanics and clinical expression of disease. Understanding the causes and consequences of airway damage and remodelling will shed light upon the structure–function relationships required to begin to unravel the complexity of severe asthma and will enable us to target current and novel therapies as we begin to move towards realizing personalized medicine.

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Introduction

Asthma affects an estimated 300 million people worldwide and the burden is likely to rise substantially in the next few decades [1]. Approximately 5–10% of these asthmatics have severe asthma, whereby sufferers have persistent symptoms and exacerbations in spite of high dose standard therapy [2–6]. Patients with inadequately controlled severe persistent asthma are at particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life. Although this group represents a relatively small proportion of the asthma population they consume two thirds of the health care costs attributed to asthma. This disproportionate use of health care resources means there is a considerable unmet need to the individual patients, and to health care providers.

Asthma is a complex disease that encompasses several underlying pathological conditions that develop as a consequence of a variety of gene–environment interactions that give rise to a clinical phenotype. Clinically, asthma is characterized by typical symptoms of breathlessness, wheeze and cough together with episodes of marked worsening of symptoms known as exacerbations [6].

These symptoms occur on a background of disordered airway physiology characterized by variable airflow limitation, airway hyperresponsiveness (AHR) and in more severe disease persistent airflow obstruction. This decline in lung function and development of airflow obstruction is refractory to current therapy and is a consequence of airway damage, inflammation and remodelling.

To date, we do not have adequate tools to either predict disease progression or response to therapy. One of the major obstacles to progress has been our limited ability to assess the complexity of disease in large populations of patients with disease and appropriate controls, due in part to limitations in sample sizes, inadequate outcome measures and potential false positive findings with multiple comparisons. Novel developments in the measurement of airway inflammation, lung physiology and imaging, coupled with emerging data utilizing ‘omic’ technology and biostatistical modelling mean that we are now positioned to inform our understanding of the complexity of airways disease. This approach is perhaps particularly pertinent when considering lung damage and remodelling as this needs to be considered across multiple scales from tissue to organ, cell to tissue and molecules to cells. In this review, we will describe the current understanding of airway damage and remodelling in the context of these

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scales and the underlying host–environment interactions.

Tissue to organ: image functional modelling

Airflow obstruction and AHR in asthma is a consequence of both large and small airway disease. These changes in airway structure are largely due to airway damage and the consequent aberrant or exuberant repair known as airway remodelling [7]. Lung function decline is increased in asthma [8] and patients with severe airflow obstruction, as a consequence of remodelling, are also at increased risk of exacerbations [9]. Large airways account for the majority of airflow resistance, behaving effectively like resistors in series. In contrast, small airways (<2 mm diameter) provide parallel resistance pathways and contribute <10% of total airway resistance. Therefore, advanced small airway disease may be present before any detectable change in spirometry. A critical gap in improving our understanding of airway disease phenotypes is the ability to relate airway structure to important clinical outcomes and airway physiology. Recent developments in multi-detector CT scanning (MDCT), hyperpolarised helium MRI and small airway physiology mean that we are now able to bridge this gap [10].

Qualitative CT analysis has identified that airway wall thickening is typically observed in severe asthma, and bronchiectasis is reported in up to 40% of subjects [11]. Bronchiectasis in asthma is associated with longer disease duration [11–14] and poorer lung function [11, 15]. Whether or not bronchiectasis in severe asthma is a comorbidity resulting in ‘difficult’ to manage asthma or represents structural change or remodelling with natural progression of the disease [16] is not known, and longitudinal studies are required to ascertain this differentiation.

Quantitative CT analysis has revealed that the commonly observed bronchial wall thickening represents predominately airway luminal narrowing with minimal changes in the airway wall area or volume. Therefore, the increase in percentage wall area (wall area/total area%) reflects the decrease in luminal area more than an increase in wall area [17]. This is fundamentally important as it suggests that in airway remodelling the geometry and composition of the airway wall and its altered mechanics are likely to be more relevant in disease than the increase in wall area *per se*. For example, this altered airway geometry assessed by MDCT is related to changes in the airway wall composition observed in endobronchial biopsies [18]. The cause of this airway narrowing is uncertain. Intriguingly in subjects with chronic cough due to eosinophilic bronchitis there is a relative airway luminal dilatation compared to those subjects with asthma and a similar degree of airway inflammation [19]. This suggests this differential

airway geometry may be a consequence of repeated airway stretch due to cough in one group vs. repeated airway narrowing due to AHR in the other.

These measures of airway geometry can be further informed by functional imaging such as hyperpolarized helium magnetic resonance imaging to assess flow metrics (velocitometry) [20]. Smaller airways are beyond the conventional resolution of computed tomography and therefore a fingerprint of small airways disease can be derived only from fundamental properties, that is, abnormal ventilatory distribution, independence of maximal expiratory flow to gas density and air trapping. Ventilation and alveolar structure can be determined by MRI-derived apparent diffusion coefficient [21]. CT lung densitometry using inspiratory and expiratory scans provide a quantitative estimate of gas trapping. Severe asthma is associated with increased gas trapping demonstrated by CT due largely to airway closure [22], but rarely emphysema [17]. In combination with standard pulmonary function testing to measure spirometry, lung volumes and diffusion a variety of tools can now be employed to generate a small airway fingerprint. The impulse oscillation technique in the frequency range of 5–3 Hz (during tidal breathing) may allow partitioning of airway impedance between large and small airways [23]. In addition, oscillation of the airways during apnoea at frequencies between 0.1 and 5 Hz may allow for derivation of tissue impedance. Multiple breath inert gas wash-out has been developed to assess ventilation heterogeneity in the conductive (S_{cond}) and acinar (S_{acin}) zones of the airway [24], and washout markers correlate with AHR and response to ultra-fine particle inhaled corticosteroids. Image functional models integrating large and small airway behaviour, ventilation and impedance have demonstrated that large airway narrowing alone cannot account for the AHR seen in asthma [25]. We have recently applied the techniques of impulse oscillometry, multiple breath inert gas washout and MRI-derived apparent diffusion coefficient in concert in subjects with severe asthma compared to mild–moderate asthma and healthy controls. We found that in severe asthma, S_{acin} was increased without a difference between groups in the apparent diffusion coefficient determined by hyperpolarised helium MRI [26]. The reactance area determined by oscillometry was increased and was the only variable independently associated with airflow obstruction [27]. This suggests that severe asthma is characterized by proximal acinar disease with alveolar sparing, and that airflow obstruction is primarily associated with increased small airway elastance.

In summary, emerging evidence from integrating airway structure and function at an organ level suggests that in severe asthma the features of airway damage and remodelling are heterogeneous between patients

with, to a lesser extent, regional heterogeneity within individuals. Severe asthma is characterized by generalized airway luminal narrowing with minimal changes in wall volume, altered airway wall mechanics, increased airway closure, regional bronchiectasis in some asthmatics, and in contrast to chronic obstructive pulmonary disease minimal or no emphysema. These abnormalities are summarized in Fig. 1.

Cell to tissue: airway damage and remodelling

Host–environment interactions. The airway is exposed to a variety of pollutants, allergens, mechanical stress and pathogens. It is exposed to these insults continuously, and in health dynamic interactions between the environment and the host's innate and adaptive immune responses are critical to initiate and co-ordinate the cascade of immune, inflammatory and repair mechanisms required in response to an insult such as an acute infection, but also to prevent aberrant or over-exuberant inflammation or remodelling.

There is an increasing understanding of the role of pathogen and damage-associated molecular pattern receptors (PAMPS and DAMPS) in host defence and how alterations in the expression and function of these receptors and their ligands may play a role in airways disease. The receptor for advanced glycation end products (RAGE) is a pattern-recognition receptor which interacts with diverse endogenous ligands involved in the host response to injury, infection and inflammation. RAGE ligands include advanced glycation end products

and high-mobility group box-1 (HMGB1), which promote via RAGE activation of airway inflammation and tissue remodelling [28]. RAGE exists as both a membrane and soluble receptor. Soluble RAGE is a natural antagonist of RAGE [29]. A recent genome-wide association study identified RAGE as a genetic determinant of airflow obstruction [30, 31], and increased expression of RAGE and its ligand HMGB1 is observed in COPD [32]; increased HMGB1 levels are also observed in asthmatic sputum [33] and sRAGE in neutrophilic asthma [34].

In severe asthma, there is increasing evidence that there is an altered environment with a wider diversity of microbes, a higher bacterial DNA level [35, 36] and fungal colonization, in particular with *Aspergillus fumigatus* [37]. This exposure is related to airway damage, as fungal sensitisation and culture are correlated with the degree of airflow obstruction. Similarly, there is a strong association between the presence of fixed airflow limitation in severe asthma and positive serology for intracellular pathogens such as *Chlamydia pneumoniae* [38]. These data suggest that there is an abnormality in the innate immune response that promotes the persistence of pathogens. Indeed, mucociliary clearance is decreased in severe asthma as a consequence of abnormal ciliary beat frequency and beat pattern [39]. Whether these abnormalities are a cause or a consequence of an altered environment is uncertain. Furthermore, recurrent exacerbations are an important component of severe disease. In asthma, there is impaired secretion of type I and III interferons from the airway epithelium in response to human rhinovirus [40, 41]. This leads to decreased viral clearance and is associated with worsening symptoms at exacerbation. Thus, the role of pathogens in lung damage and remodelling is likely to be critical in persistent disease exacerbations and needs to be further assessed by microbiome analysis using multiplex and metagenomic techniques [36].

Exposure to tobacco smoke and other pollutants in asthma promotes a neutrophilic predominant response, [42] and importantly is related to poor corticosteroid response and airflow obstruction [43]. Differentiating between patients with severe asthma that smoke and smoking chronic obstructive pulmonary disease is complex. Emphysema is rarely observed in severe asthma and is probably confined to those that are exposed to pollutants.

In addition to the exposure to exogenous environmental agents, the airway is continuously exposed to mechanical stress in response to the normal breathing cycle, and requires periodical deep breaths to promote bronchodilatation and prevent airway closure [44]. In asthma, the loss of the normal response to deep inspiration, and indeed paradoxical bronchoconstriction, is likely to be due to changes in airway wall mechanics or as a consequence of an altered airway smooth muscle

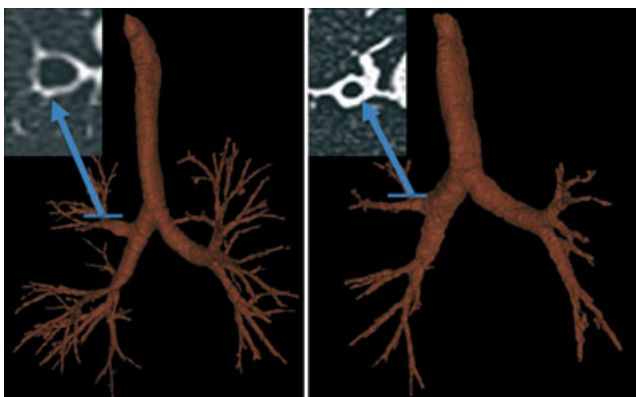


Fig. 1. Three-dimensional reconstruction of an airway tree from (a) a healthy control and (b) an asthmatic subject using VIDA software illustrating that in healthy subjects sub-segmental airways can be reconstructed to more generations than in asthma. This is due to increased airway narrowing and closure in asthma. The insets illustrate the cross-sectional area of RB1 in asthma and health and show that the lumen is narrowed in asthma with a decrease in total area and an increase in percentage wall area, but with a relatively preserved wall area.

response to stretch. This aberrant bronchoconstrictor response to deep inspiration is closely related to AHR, a hallmark of asthma which again exposes the asthmatic airway to repeated airway narrowing. Recent evidence has demonstrated that airway narrowing in response to repeated methacholine challenge can cause airway inflammation and remodelling, suggesting that mechanotransduction may play a hitherto poorly recognized role in airway damage and remodelling [45]. Therefore, increased matrix deposition in response to bronchial constriction and an abnormal response to airway stretch are likely to promote the luminal narrowing described above that is characteristic of severe asthma.

In summary, the airway in severe asthma is exposed to a variety of environmental exposures beyond the classical exposure to allergen in a sensitized individual. These environmental exposures may exert effects upon structural and inflammatory cells, via a broad spectrum of mechanisms including but not restricted to DAMPS and PAMPS. Whether there is an altered level of expression or activation of these receptors or whether there are specific or generalized abnormalities in the response of cells in disease is poorly understood and requires further study. Importantly, the inflammatory and remodelling processes need to be considered in the broader context of the multiplicity of the environmental challenges and their potential consequences to the airway.

Airway inflammation in severe asthma. Atopic asthma has classically been associated with an increased expression of Th2 cytokines, which are increased in

sputum [46] bronchoalveolar T cells [47] and bronchial biopsies [48]. A major effector axis resulting in induction of Th2 polarization is the recognition of allergen presented by dendritic cells in local lymph nodes to CD4⁺ T cell. The differentiation of naïve T cells or reactivation of memory T cells depends on various co-stimulatory molecules primarily expressed on the surface of T cell, and their cognate ligands such as OX40 and OX40 ligand. OX40L is directly mediated by thymic stromal lymphopoietin (TSLP), which is produced by epithelial cells [49], mast cells [50], airway smooth muscle [51], and dendritic cells [52], which are all involved in Th2 responses. In severe asthma, TSLP but not OX40/OX40L is up-regulated [53–55]. Interestingly, there is emerging evidence that Th1/Tc1 pathways with activation of neutrophils may play a role in asthma [56–59]. The Th1/Th2 mediated cellular interactions that drive airway damage and remodelling are summarized in Fig. 2. Importantly, these inflammatory profiles do not necessarily occur independently but may co-exist to varying degrees within an individual.

Critically, there is no clear pathological definition that distinguishes severe asthma from asthma in general. However, a number of studies have suggested some features that are more prominent in severe disease. The analysis of the type and magnitude of airway inflammation in severe asthma has proven to be helpful in distinguishing clinical phenotypes, especially the analysis of sputum inflammatory cells [60, 61]. Studies addressing cytokines and chemokines in severe asthma have also shown that severe asthma is not a classical

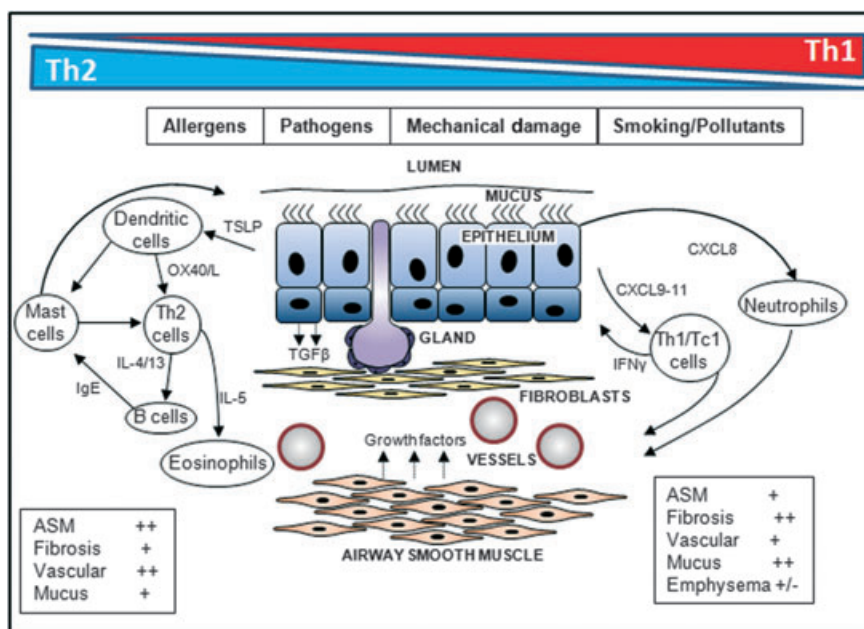


Fig. 2. Schematic diagram of the immunopathogenesis of asthma illustrating the interaction between the Th1/Th2 inflammatory cells and the structural components of the airway and the consequent development of airway remodelling.

Th2 inflammatory disease and that both Th1 and Th2 cytokines can be expressed and the Th17 axis is up-regulated [62, 63]. In biopsies, the quantification of neutrophils and eosinophils in the airway mucosa and structural changes of the airways such as the thickening of the reticular basement membrane and lamina reticularis has suggested different clinical phenotypes [57]. Some patients with severe refractory asthma have persistent eosinophilia of the airways, whereas others are neutrophil predominant [56, 57]. The eosinophil number is related to the severity of asthma, is associated with increased risk of exacerbations [64] and is related to persistent airflow limitation [65]. Although the presence of neutrophils in severe asthma may be attributed to the use of corticosteroids, which cause increased neutrophil survival, they may also be central in the pathogenesis, as neutrophilic inflammation is associated with chronic airway narrowing in asthma [66, 67]. LTB₄, IL-8, MIP-1 α and TNF α are increased in severe asthma [68], and can induce neutrophil chemotaxis. Mast cells are in an activated state in asthma, particularly in severe disease [48, 69]. In the healthy lung, the predominant mast cell phenotype is tryptase⁺ chymase⁻, but in severe disease there is a tryptase⁺ chymase⁺ MC (TC) predominance in the lamina propria and within airway structures such as the epithelium. These MC(TC) are also an important source of PGD₂ which is increased in bronchoalveolar lavage in severe asthma [69]. In severe asthma, MC(TC) are increased in the smaller airways and intriguingly are positively correlated with lung function suggesting that they may be protective for lung function in this site [70].

Airway remodelling in severe asthma. Structural cells of the airways, such as epithelial cells and airway smooth muscle cells, contribute to the inflammatory response and are capable of producing a number of inflammatory mediators such as chemokines, cytokines and growth factors. Epidermal growth factor receptor, as a marker of epithelial stress/damage, is increased in severe asthma, suggestive of ongoing epithelial cell activation [71]. The activated epithelium releases several pro-angiogenic and growth factors such as transforming growth factor- β (TGF- β) [72] and vascular endothelial growth factor [73]. In concert with pro-inflammatory cells, TGF- β activates sub-epithelial mesenchymal cells to release matrix and proliferate [74]. In addition, TGF- β may promote epithelial mesenchymal transition perhaps through an autocrine mechanism. The epithelium in severe asthma has distinct features and has been reported to be thicker compared to that of patients with mild asthma [75]. Epithelial cells from severe asthmatics secrete a number of chemokines, in particular IL-8, which is an important neutrophil chemoattractant [76]. Airway smooth muscle mass is

increased in severe asthma compared to mild-moderate asthma or chronic bronchitis [77–80]. The strongest predictors of airflow obstruction are airway smooth muscle mass, smooth muscle hypertrophy and sub-epithelial fibroblasts [77]; whether this increase in airway smooth muscle mass is due to hyperplasia [81], hypertrophy or both remains uncertain.

Interactions between structural and infiltrating cells are likely to play an important role in the development and persistence of airway dysfunction. The activated airway smooth muscle releases chemotactic factors to recruit mast cells in asthma, which interact with the airway smooth muscle to promote further recruitment of myofibroblasts [82]. Microlocalisation of mast cells to the airway smooth muscle-bundle is related to the degree of AHR across the severity of disease [83, 84] and to the loss of the bronchodilator response to deep breath [44]. These mast cells are predominately MC(TC) and express Th2 cytokines such as IL-4 and IL-13 [81, 85]. Mesenchymal progenitors, fibrocytes, also infiltrate the airway smooth muscle-bundle in severe disease [86], are increased in peripheral blood [83, 84] and are related to airflow obstruction [87]. Airway smooth muscle also releases matrix proteins, which further alter the airway geometry and biomechanical properties [88]. In addition to the epithelium, angiogenic factors released by the airway smooth muscle promote neovascularisation to further increase the sub-epithelial vascularity and MC(TC) are associated with areas of increased vascularity [89–91]. Importantly, neutrophils and mast cells localize to glands and are associated with increased mucus plugging in fatal asthma [88, 89].

Increased production and deposition of the extracellular matrix is a characteristic of severe asthma [88]. Thickening of the reticular basement membrane due to extracellular matrix deposition has been extensively studied in asthma as a marker of remodelling. The results are not always consistent, but the majority of studies showed that severe asthmatics have thicker sub-epithelial layers [75, 83, 84, 92–97] compared to those with mild disease together with evidence of epithelial proliferation in some [75]. Indeed, in one study thickening of the reticular basement membrane was the most discriminate feature of severe asthma [97]. Fibrosis may also contribute to fixed airway obstruction in severe asthmatic individuals [98]. Involvement of the small airways in asthma has been related to disease severity, as suggested by functional and radiological studies as described above [25, 99, 100]. However, it is not clear whether severe asthmatics have more small airways involvement compared to mild or moderate asthma. It is difficult to conduct invasive bronchoscopy in these patients, and thus most of the information to date on the involvement of small airways in severe asthma is based upon autopsy studies [101, 102]. Studies of fatal

asthma have found decreased elastic fibre content in the periphery with abnormal alveolar attachments. These features would promote the abnormalities in airway elastance, loss of compliance and promote airway closure [103, 104]. In contrast, changes in the more proximal airways may contribute to airway wall stiffness and oppose airway narrowing in response to airway smooth muscle contraction. For example, sub-epithelial fibrosis might also prevent airway narrowing, increase airway wall stiffness and resistance to compression and tension. In severe and fatal asthma, the proteoglycans versican, biglycan and lumican are increased in the lamina propria and around the airway smooth muscle [104–106], although they are not increased within the airway smooth muscle-bundle [105]. The increased elastic fibres in the airway smooth muscle-bundle and the distribution of proteoglycans may increase resistance to airway wall deformation and provide a preload to the airway smooth muscle that opposes its shortening and therefore airway narrowing. The potential physiological consequences of these changes are summarized in Fig. 3. Fibrosis in the airways is generally irreversible, and treatment has little effect on this feature. In stable disease, inhaled corticosteroid therapy for 6 weeks did not affect collagen III expression [107] and following allergen challenge extracellular matrix increased and was augmented by corticosteroids [106] suggesting that corticosteroids may promote rather than attenuate the deposition of certain matrix proteins.

Taken together, structural and cellular changes within the airway wall in asthma, notably increased airway

smooth muscle mass [108], vascular remodelling, thickening of the reticular basement membrane and increased fibroblast numbers in the lamina propria have been shown to correlate with airflow limitation. Furthermore, cellular infiltration of the airway wall in asthma is related to decline in lung function [109]. The association of structural change in the airway wall in asthma with AHR is much more tenuous. A number of reports have drawn conflicting conclusions about the association of AHR with epithelial desquamation/loss of tight junctions [77, 93, 98–100], reticular basement membrane thickening [110–112], vascular remodelling [73, 89, 113] and airway smooth muscle mass [114].

Resolution of inflammation and remodelling in severe asthma. Transcellular eicosanoid metabolism in the airway occurs during cell–cell interactions leading to generation of bioactive lipid mediators known as lipoxins, which can regulate inflammation and functional responses. A lower biosynthetic capacity for these potentially anti-inflammatory mediators has been linked to severe asthma [115, 116]. Development of small molecule mimetics of these pro-resolving mediators will enable further investigation of the impact of these compounds on severe asthma [117].

In summary, the consequent airway inflammation in response to the impaired innate immunity and altered airway environment is diverse, but results in a common pathway of airway wall remodelling with alterations in geometry and biomechanical properties, with mucus plugging and small airway closure which result in the development and persistence of airflow obstruction.

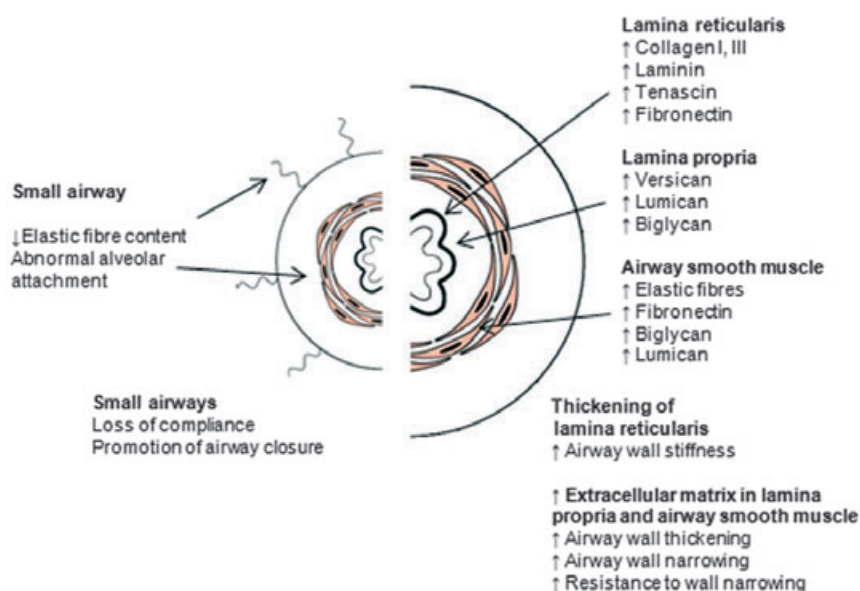


Fig. 3. Illustration of the changes in matrix and alveolar attachments in the large and small airway and their potential functional consequences.

Molecules to cells: functional 'omics'

Genome-wide association studies have begun to identify key single nucleotide polymorphisms (SNPs) associated with asthma, and severe asthma specifically [118–127]. Recent genome-wide association studies have identified a number of genes implicated in modulating the response of the epithelial repair following epithelial damage as a consequence of trauma, exposure to pollutants such as smoking, allergens and infections in asthma, such as IL-33 and IL-18 receptor [126, 127]. In addition, SNPs associated with airflow obstruction and lung function impairment have been recently elucidated [30]. SNPs in the IL-4 receptor have been associated with persistent airways inflammation and severe asthma exacerbations, [128] suggesting alterations in the IL-4 pathway in allergic inflammation in some severe asthmatics. This altered genetic background in combination with environmental exposures is likely to drive the over-exuberant repair mechanism characterized by remodelling and persistent inflammation described above. Validation of these new discoveries is underway with the application of functional genomics.

Statistical modelling: phenotyping the heterogeneity of severe asthma

Early observational studies have identified clinical and pathological features associated with persistent airflow obstruction and exacerbation frequency using multiple regression [129]. The integration of data derived from non-invasive markers of airway inflammation have provided new inflammatory phenotypes of eosinophilic and non-eosinophilic asthma [28–30], and further statistical modelling using factor and cluster analysis has provided further insight into the complexity of asthma phenotypes [48, 130].

These approaches have indeed demonstrated that they add value to our current disease definitions [131], which have hitherto hampered development of some novel therapies, as they have not considered the group of patients most likely to respond. This is perhaps best exemplified by anti-IL5. IL-5 is required for eosinophil maturation and survival, and anti-IL-5 attenuates peripheral blood and sputum eosinophilia [132]. Early studies did not demonstrate clinical efficacy [132], but did not preselect patients that had an eosinophilic phenotype. Recent studies that have selected severe asthmatics with evidence of eosinophilic inflammation have demonstrated marked reduction in exacerbation events [64, 133], but with no effect upon day-to-day symptoms or lung function, and a small effect upon airway geometry. Anti-IL5 reduces sub-epithelial fibrosis, possibly due to decreased matrix deposition from fibroblasts partly activated by eosinophils. In contrast,

anti-IL-13 has recently demonstrated benefits in lung function, suggesting that this cytokine may be involved directly in airway smooth muscle function, or indirectly via other features of airway remodelling. Importantly, this highlights the need to consider the subgroups of patients most likely to respond to a given therapy and the outcome most likely to be modified by the intervention.

The integration of data now available from multiple scales can be used to develop statistical models of future risk of developing frequent exacerbations or lung function decline, or the likelihood of responding to therapy. Using a variety of data reduction methods, panels of biomarkers will be identified as 'fingerprints' of specific airway disease sub-phenotypes. To date, these statistical approaches have been largely restricted to cross-sectional observations and have used tools such as cluster analysis, which lack mathematical inference [48, 130]. Hence, the generalizability of these findings beyond the cohorts studied, or phenotypic stability within these cohorts is unknown. Therefore, these statistical approaches remain limited in their ability to predict response to therapies and disease progression. Computational models of the respiratory system in health have begun to be established. Some airways disease-specific models exist at the tissue–organ level of large and small airways disease [134], and at the molecular–cellular level for airway smooth muscle contraction [135]. The challenge is therefore to extend and integrate these existing models so that the relative importance of the airway inflammation and remodelling within an individual can be understood so as to provide an insight into structure–function relationships, and predict future risk and response to therapy and is the ambition of several large consortia such as AirPROM [136].

Conclusion

Severe asthma presents an enormous unmet clinical need. There is increasing recognition of the heterogeneity of the disease across multiple scales. With respect to airway damage and remodelling, we now have the tools to determine their relative contributions towards airway function within an individual asthmatic and to assess the underlying structural and inflammatory cell interactions, as well as the genetic background and the environmental exposure to allergens, pollutants and pathogens. By extending the existing approaches to defining the heterogeneity of severe asthma sub-phenotypes towards a systems biology approach [137] we shall be able to integrate clinical, physiological, structural, inflammatory, genotype and environmental data to develop both statistical and computational models. These models will need to be rigorously tested with

experimental validation and proof-of-concept studies designed to carefully select the right therapeutic approach in the right patient, and to measure the right outcome. This will become particularly important with the emergence of thermoplasty [138–140] and highly specific monoclonal therapy such as anti-IL-5 [64, 133] and anti-IL-13 [141] as new therapies for severe asthma. There is real promise that this approach will inform our understanding of the role of airway damage and remodelling in severe asthma and underpin the move towards personalized healthcare.

Conflict of interest

Christopher Brightling has received consultancy and research funding from AZ, MedImmune, GSK, Novartis, and Chiesi, and support to travel to international meetings from Boehringer-Ingelheim. Salman Siddiqui has received research funding from Chiesi. Sumit Gupta and Sherif Gonem have no conflict of interest.

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