

Mechanisms of severe asthma

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Summary

The mechanisms behind the development of severe asthma are poorly understood. However, these patients disproportionately consume healthcare resources related to asthma. Severe asthma may develop over time, or may develop shortly after onset of the disease. The genetic and environmental elements that may be most important in the development of severe disease are poorly understood. Physiologically, these patients often have air trapping and airway collapsibility. The pathology demonstrates a heterogeneity of findings, including continued eosinophilic inflammation, an apparently different pathology, structural changes likely to be remodelling related, and predominant distal disease. Treatment remains problematic and likely will remain so until a better understanding of this disease develops.

Keywords: asthma, inflammation, phenotypes, physiology, remodelling, treatment

Introduction

Severe or refractory asthma afflicts a small percentage (likely <5%) of the asthma population. However, as these patients remain difficult to treat and prone to severe exacerbations, they contribute disproportionately to the overall costs of asthma. The introduction of high-potency inhaled corticosteroids (CS) had a marked impact on the numbers of patients dependent on oral CS. However, beyond these medications, more research is needed to expand the understanding of the disease or diseases that make up severe asthma, and eventually in improving its treatment.

Definitions

Severe persistent asthma has been defined in recent guidelines, but the definitions have been somewhat limited in scope and difficult to apply. Severe or 'refractory' asthma was given a working definition by the American Thoracic Society-sponsored workshop, the proceedings of which were published in 2000 [1]. This definition included one of two major criteria (continuous high-dose inhaled CS or oral CS for >50% of the previous year), with two of seven additional minor criteria required. The minor criteria included aspects of lung function, exacerbations, disease stability and amount of additional medications. Patients must also have had compliance and exacerbating factors fully addressed. Although these definitions are a start (the author of this paper was chair of that workshop), it is likely they will need to be updated as investigators develop more experience with this group of

patients. For instance, it is not clear whether a patient with stable symptoms on a fluticasone/salmeterol combination (500/50), who has a forced expiratory volume in 1 s (FEV₁) of 78% predicted, truly meets the definition of 'refractory asthma'. Yet, the current definition would include that patient. It is likely that expanding the minor criteria requirements to three would improve the capture of those who fulfil the 'spirit' of the definition rather than the 'letter' of the definition.

Epidemiology

Surprisingly, little is known about the development of severe asthma. Do most severe asthmatics have a life-altering event in childhood that irreversibly remodels their lungs and from which they will never recover, or do they slowly but steadily decline over the years? Did those with a history of 'adult-onset' disease actually have some level of asthma as children that was ignored, or did they develop the disease *de novo* in adulthood? None of these questions has been satisfactorily answered. Some helpful information comes from the large cohort of asthmatics and control subjects from Melbourne, Australia, which has been followed for 35 years [2]. These data suggest that if one has reduced lung function in childhood, one is likely to have reduced lung function in adulthood as well, but that there is little 'progressive decline', at least when the data are evaluated using the means. This is in contrast to the data of Lange et al. [3], which suggested that a more rapid decrease in FEV₁ occurred in asthmatics than in controls. However, no attempt was made to break out the asthmatics by severity groups. Interestingly, two studies from Europe suggest that late-onset asthma is associated with a more rapid decline in lung function [4, 5]. In the database of over 100 severe asthmatics seen at National Jewish,

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approximately two-thirds had onset in childhood, the remaining one-third after the age of 20 years [6]. The subject/patients with late-onset disease have an FEV₁ that is lower than the childhood onset group, despite the fact that the adult onset group had the disease for substantially fewer years [7]. This would also imply that late-onset disease is associated with a more rapid decline in lung function, but longitudinal studies are required to verify this.

Risk factors

As for many diseases, risk factors can be divided into genetic and environmental. Unfortunately, asthma itself is a disease involving multiple genes. Severe asthma is not likely to be different and is less well studied. There are reports of relevant mutations in both the IL-4 gene and the IL-4 receptor, some of which have been linked to a loss of lung function and others to near-fatal events [8, 9]. Interestingly, two 'non-Th2' factors have also been associated with severity of asthma – transforming growth factor (TGF)- β 1 and monocyte chemoattractant protein (MCP)-1 – both of which can promote fibrotic reactions [10, 11]. Whether mutations of the receptors for the primary treatments for asthma (β_2 and glucocorticoid receptors) decrease responsiveness to medications and influence outcomes is controversial.

Environmental factors include both allergen and tobacco exposure, with the strongest data for house dust mite, cockroach and alternaria exposures [12–14]. Additionally, many patients will continue to smoke or own a cat despite being aware of the negative effects [15]. Infection may also contribute to severe disease, with respiratory syncytial virus infections implicated in childhood, while pathogens like mycoplasma and chlamydia may play a role in adults [5, 16, 17]. Although not precisely 'environmental', additional 'lung-external' factors likely include obesity, gastro-oesophageal reflux disease (GERD) and chronic sinusitis. A recent large-scale epidemiologic study of severe/difficult-to-treat asthmatics suggests that the body mass index (BMI) increases with increasing severity of disease and that 76% of that severe cohort were either overweight or obese [18]. It is not clear whether the increased BMI contributes to the development of severe disease, or whether it is a consequence of severe disease. Similar to GERD and chronic sinusitis, the relationship of effective treatment of obesity to the severity of disease is not clear.

Certainly another 'external factor' related to severity is compliance/adherence to medications. Studies have suggested that in children and adolescents, instability of disease is related to adherence to CS therapy [19]. However, there are other patients in whom current medications do not effectively treat the disease. Recent studies have suggested that even CS therapy is only clinically effective in 70% of the asthma population [20]. In those patients, adherence to medication may be influenced by a lack of responsiveness to medication, but further study is required in the severe population to determine the proportions of each. If the patient is on oral CS, an early morning cortisol level can be helpful in determining compliance. If concern remains, then treatment trials with injectable long-acting steroids, such as depomethylprednisolone or triamcinolone, can be informative [21].

Physiologic aspects

Although the classic measure of airflow limitation, FEV₁, has been used to indicate the presence of 'severe' disease, it is becoming clear that the correlation between FEV₁ and disease symptoms is poor, at best [22]. While airflow limitation is clearly a component of the physiologic changes of severe asthma, it is likely to be only part of the picture. One prevalent theory regarding severe asthma is that it develops due to a progressive increase in airflow limitation, which is often presumed to be 'irreversible'. Although this may be true in some patients, others may have severe airflow limitation at presentation, while others, primarily adults, may develop a more rapid decline in lung function over a 10-year (or less) period of time [5]. Finally, it is not clear whether these changes are truly 'irreversible'. There may be irreversibility to current aggressive medical management, but that does not necessarily mean the lungs are in a fixed fibrotic state.

Changes in airway reactivity also play a role in the severity of asthma, but the correlations of PC20 with disease severity, although present, are poor as well [23]. Increased airway reactivity likely relates to the stability of airflow, and hence variability in peak flow/FEV₁. This 'instability' may be an important aspect of the symptomatology of a subgroup of severe asthmatics, where continuous airflow limitation may play a more minor role [24].

As FEV₁ and airway reactivity changes do not adequately explain disease severity, it is conceivable that other physiologic factors, such as changes in elastic recoil/collapsibility and/or small airway physiology, are also important. It has long been observed that the elastic recoil properties of the lung in asthma are not normal [25, 26]. It was recently reported that general compliance is increased in patients with moderate persistent asthma [27]. However, the precise pathologic mechanism behind the change is not clear. There are also suggestions that the airways (in addition to parenchyma) may be more collapsible than normal. The forced vital capacity to slow vital capacity ratio appears to be decreased in a group of severe asthmatics with persistent eosinophilia [28]. These asthmatics also appear to be at a higher risk of near-fatal events than those with a more normal (1:1) ratio. Whether a relationship exists between airway collapsibility and loss of elastic recoil is not clear.

Various measures of small airway physiology have been developed. Unfortunately, there are no comprehensive studies of small airway physiology in patients with severe asthma. However, there is considerable evidence for air trapping in severe asthma, without associated hyperinflation. Residual volumes are routinely over 200% predicted in severe asthma, with only modestly increased thoracic gas volumes [28]. Whether this increase in residual volume is reflective of small airway disease is not known. Other than FEV₁, few attempts have been made to correlate physiologic measures with inflammatory or structural changes.

Pathology of severe asthma

Unlike many diseases, the pathology of asthma itself remains only partially understood, primarily due to limitations in

tissue availability. With that in mind, the pathology of severe asthma is more limited, especially with regard to the distal lung and disease heterogeneity. As heterogeneity is apparent regarding both presentation and the physiology, it is not surprising that heterogeneity exists at the pathologic level as well.

Multiple different pathologic explanations for severe asthma likely exist. In this regard, it is possible to generalize these explanations into four different areas. These four areas include (1) continuous, ongoing inflammation despite appropriate therapy, (2) a different underlying pathology, (3) alterations in lung structure (remodelling), and (4) a different distribution of the disease. It is obvious that, although different, there are considerable ways in which these explanations may overlap as well.

Continuous, ongoing inflammation despite appropriate therapy

Pathologic studies of severe asthma suggest that one-half to two-thirds of severe asthmatics have persistent large airway tissue eosinophils, despite continued high-dose systemic steroids (Fig. 1). In addition to high numbers of eosinophils, there are associated increases in T-lymphocytes and markers for the activation of a Th2-type of pathway [28]. Severe asthmatics with persistent eosinophils also have increased levels of the mast cell mediator tryptase in bronchoalveolar lavage (BAL) fluid, the innate response factor, TGF- β (specifically TGF- β 2) in tissue, and both 5- and 15-lipoxygenase (LO) enzymes and their products (cysteinyl leukotrienes and 15-hydroxyeicosatetraenoic acid (HETE)) [28–30]. Certain structural changes, such as a thicker subepithelial basement membrane (SBM), also appear to be associated with a persistence of eosinophilic inflammation [28].

Although Th2 processes have been associated with fibrosis, the connection of the eosinophilic process to a Th2 immune process in severe asthma is not yet clear. The 15-LO enzyme is strongly up-regulated by the Th2 cytokines, IL-4 and IL-13. Its product, 15-HETE, has been described to be increased in eosinophil (+) asthma, in comparison with those severe asthmatics without eosinophils [30]. However, neither IL-4 nor IL-13 have been definitively shown to increase in relation to disease severity. Additionally, no differences in IgE levels or skin test positivity were seen between severe asthmatics, with or without eosinophils [28]. Interestingly, although severe asthmatics with early onset of disease (<10 years old) are more likely to be allergic and have a family history of allergies and asthma, they are generally less likely to have persistent tissue eosinophilia than those severe asthmatics with onset of disease later in life [7, 31]. These observations are consistent with those from the ENFUMOSA group, a recently formed European network to understand mechanisms of severe asthma. The data from the ENFUMOSA group suggest that although eosinophils may persist in severe asthma (by sputum analysis), the presence of atopy is less in severe asthma than in a milder control group [32]. Similarly, there appeared to be a higher percentage of aspirin-sensitive asthmatics than in the milder control group. Aspirin-sensitive

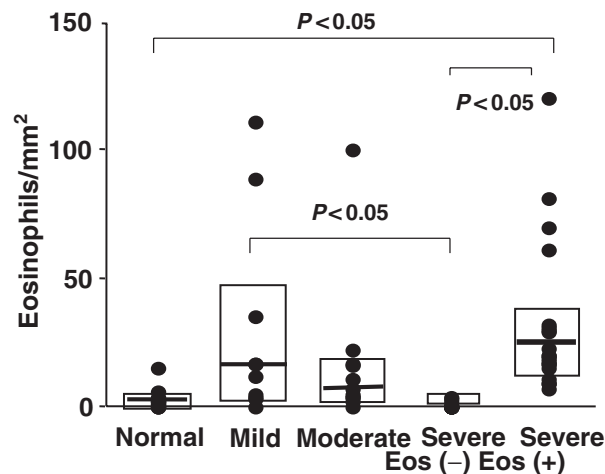


Fig. 1. Initial description of the two inflammatory phenotypes of severe asthma (with and without eosinophils), in relation to mild and moderate asthma, and normal controls. (Reprinted with permission from Am J Respir Crit Care Med 1999.)

asthma is typically considered to be a highly eosinophilic process, with lesser association with atopy. Therefore, the relationship of persistent eosinophilic inflammation to a Th2 process is not well understood.

A different underlying pathology

A second inflammatory/pathologic phenotype of severe asthma has also been described. In this group, neutrophils appear to be increased. The increase in neutrophils is sometimes seen in isolation, but sometimes in the presence of persistent eosinophils [28, 33]. (Intriguingly, occasionally there is no evidence for any type of tissue inflammation.) This increase in neutrophils has also been seen in studies of sputum in severe/difficult asthmatics on high doses of inhaled/oral steroids [34, 35]. It is not clear what the mechanism or the clinical implications are of this different 'type' of inflammation. It is possible that this represents a 'different disease' such as a variant of bronchiolitis obliterans (BO) [32, 36]. Interestingly, a recent comparison study of computer tomography (CT) scans in patients with severe asthma vs. BO, another disease with severe airflow limitation, showed that there were no changes on CT that convincingly discriminated BO vs. asthma [36].

It is also possible that this represents a subtype of general asthma, in which the high doses of steroids have generally decreased the eosinophils, while leaving or even augmenting the neutrophil [37]. It is likely that if this second hypothesis is correct, the absence of the eosinophil, with a continued neutrophilic presence, alters the repair process as well. Eosinophils have been associated with a more fibrotic repair process [38], while the presence of the neutrophil may suggest a more limited ability to establish a fibrotic response. In this regard, the absence of the eosinophil in severe asthma is associated with a thinner SBM than that seen when eosinophils are present [28]. The presence of neutrophils, in contrast, was associated with an increase in BAL fluid and

tissue (SBM) matrix metalloproteinase (MMP)-9, as well as the worst lung function [39]. Which of these explanations is correct is not yet clear. However, a close evaluation is likely to eventually detect distinct clinical and physiologic differences between those patients with a predominant eosinophil or neutrophil process. Finally, it is likely that implications for treatment will also emerge. A recent study suggested that differences in steroid responsiveness may exist between moderate-to-severe asthmatics with a neutrophilic process and those with persistent eosinophils. The neutrophil predominant pattern was associated with a much less robust response to steroids than those with eosinophilic inflammation [40]. A similar study, specifically looking at the predictive value of eosinophils with regard to treatment, has also been reported with regard to severe childhood asthma [41].

As noted above, there remains a group of severe asthmatics where virtually no inflammation of the classic cellular variety is present on endobronchial biopsy. Very little is understood about the pathogenesis of the disease in this group, but it is possible that inflammation remains in the distal portion of the lung, not usually accessible to bronchoscopic studies. It is also possible that the lungs have been structurally altered such that inflammation of the classic sense is no longer necessary. For a summary of pathologic and physiologic differences between eosinophil (+) and eosinophil (–) severe asthmatics, see Table 1.

Although for years, steroid 'resistance' has focused on the lymphocyte as the 'target cell' for the resistant pathways, it is now clear that steroid resistance could occur at many levels. As noted above, one possibility is that steroid resistance exists because in some cases the underlying pathologic process – perhaps neutrophilic or mast cell in nature – is generally poorly responsive to steroids. Another possibility is that in severe asthma, the damage has 'already been done', such that there is nothing further for steroids to treat. Finally, the classic version of steroid resistance also remains an eventuality. Numerous laboratories are working on the mechanisms underlying the potential lack of effect of steroids in patients with persistent eosinophilic/lymphocytic inflammation. Possibilities include high levels of pro-inflammatory mediators sequestering the glucocorticoid receptor (GR), diminished binding of the GR to the genome, or increased levels of an alternatively spliced GR (GR- β) that has lessened inhibitory capabilities [42–44]. A recent study reported abnormalities in the balance of the histone acetylation and deacetylation pathways in asthma, which contribute to inflammatory gene transcription. Normally, these pathways appear to be well modified by glucocorticoids. It is conceivable that in steroid-unresponsive patients, this pathway is also poorly inhibited by steroids [45]. However, even in

patients with persistent eosinophilic inflammation, it is possible that other, non-Th2 pro-eosinophilic factors are playing a role in the process, through cell types such as fibroblasts or epithelial cells.

Airway/parenchymal remodelling

In the last 5 years, it has been suggested that the apparent progressive loss of lung function in more severe forms of asthma is due to structural or remodelling changes in the airways and perhaps parenchyma. However, what the precise changes are remains unclear. Numerous structures have been implicated, including the SBM, epithelium, smooth muscle, nerves and blood vessels. In general, there is a paucity of data on any of these structures in relation to disease severity.

The SBM has been the most extensively studied structure associated with lung remodelling in asthma. Although it has been reported to be thickened in asthma, the relationship to disease severity is unclear. Severe asthmatics with persistent eosinophils had the thickest SBM when compared with normal controls, milder asthmatics and those without eosinophils [28]. Interestingly, this thickened SBM was seen in association with high numbers of TGF- β positive cells in the submucosa [28, 46]. Just underneath the SBM lies a band of fibroblasts [47]. These fibroblasts are likely to be stimulated by the TGF- β to increase collagen production, which could then contribute to increased thickness of the SBM [48]. When an airway fibroblast is stimulated with the combination of a Th2 cytokine, such as IL-4 or IL-13, and TGF- β , there is an additive effect on the production of pro-collagen I [48]. At the same time, however, there is a profound increase in the production of eotaxin, a potent eosinophil chemoattractant [49]. It is possible that the fibroblast serves to perpetuate both the eosinophilia seen in asthma, as well as the associated fibrotic response.

Interestingly, there also appears to be an increase in MMP-9 in the SBM of severe asthmatics [39]. Although the function of the MMP-9 in the SBM is not clear, it could contribute to a continuous 'remodelling' of the SBM itself. In that case, TGF- β could increase collagen deposition, while MMP-9 (and perhaps other MMPs) serves to help break it down. This cycling may also explain why the absolute increase in thickness is small and not likely to explain the increase in airflow limitation. Rather, the dynamic nature of the SBM may be a sign of disease activity. Additionally, it may be a marker for abnormalities in composition, distribution or quantity of extracellular matrix elements in other regions of the airway or parenchyma, which are not as easily identified [50].

The epithelium is almost certainly abnormal in asthma. In asthmatics, there appears to be an increase in the goblet to ciliated epithelial cell ratio. Mucus plugging of the small and medium airways may contribute to airflow limitation and air trapping in severe asthma. Early studies suggest that two pathways – epidermal growth factor (EGF) receptor and TGF- β 2 – may be altered in asthma and contribute to an inappropriate and inadequate repair process, augmenting goblet cell metaplasia and mucus production [51–53]. A schematic of some of the possible interactions of inflamma-

Table 1. Characteristics of eosinophil (+) and eosinophil (–) severe asthma

Severe asthma group	EOS	PMNs	Lymphs	SBM	FVC/SVC	Near fatal events
Eosinophil (+)	+++	++	+++	++++	Low	+++
Eosinophil (–)	0	++	+	+	Normal	+

EOS: eosinophil; PMN: polymorphonuclear leucocyte; SBM: subepithelial basement membrane; FVC: forced vital capacity; SVC: slow vital capacity.

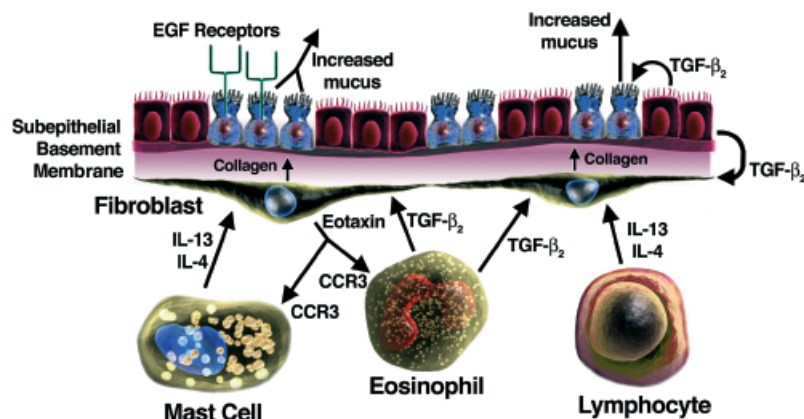


Fig. 2. Interactions of inflammatory cells, fibroblasts and epithelia that could contribute to the remodelling seen in some severe asthmatics.

tion and remodelling at the mucosal and submucosal region is represented in Fig. 2.

The amount (and perhaps phenotypes) of smooth muscle in the airways of severe asthmatics has also been reported to be increased. Patients dying of status asthmaticus were reported to have increased smooth muscle mass in the airways from the largest airways to nearly the smallest [54]. Although a relationship of increased airway smooth muscle to severity of disease would seem to be logical, there are no studies that have specifically addressed this question. The mechanisms driving the increased smooth muscle are not clear.

Relating any of these structural changes to functional changes has been difficult. As noted earlier, in addition to airflow limitation, air trapping and hyper-responsiveness, loss of elastic recoil/collapsibility may also be important. It is likely that alterations in the alveolar attachments to the airways, and the airways themselves, play a role in collapsibility, but issues of recoil remain less clear. Elastin has been shown to be abnormal (decreased or disordered) in patients who died of asthma [55, 56]. Further, proteolytic enzymes that alter elastin composition (MMP-2, MMP-9) have been shown to be increased in several instances in asthma, but perhaps most importantly in cases of status asthmaticus [57, 58]. It may be that changes in elastin composition, secondary to chronic inflammatory elements, also contribute to the unique structural/functional relationships of severe asthma.

Altered location of disease

Physiologic and pathologic data suggest that inflammatory changes exist in the lung periphery. Although the relationship to severity of disease remains unclear, autopsy studies have suggested that both increased inflammation and wall thickness exist in patients who died of asthma, as opposed to milder asthmatic and normal controls [59, 60]. However, there is a paucity of data available to describe the type and amount of inflammation and structural changes present in the periphery, or the relationship to clinical and physiological changes. Recent studies of living asthmatics have suggested that distal lung inflammation may be as or more important than proximal inflammation [61, 62]. The distribution of inflammatory cells may also be different in the distal lung,

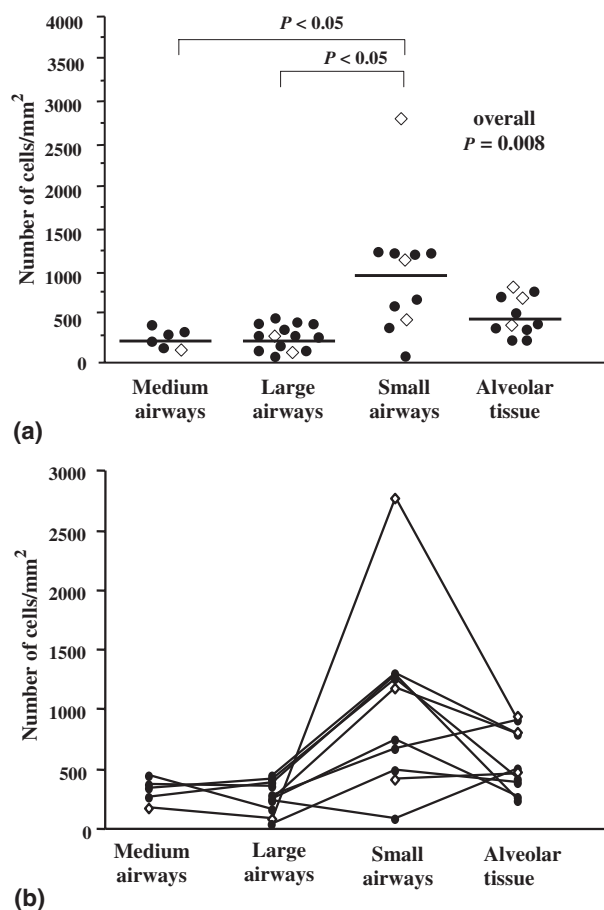


Fig. 3. Increase in inflammatory cell numbers in the distal airways, as compared with the large airways in patients with severe asthma. (Reprinted with permission from Eur Respir J 2002.)

with greater numbers and percentages of neutrophils in the small airway inner wall, while mast cells are increased in the small airway outer wall and alveolar attachments (Fig. 3) [60]. The mast cells in the small airways appeared to be the only cell type strongly related to pulmonary function changes [63]. Similarly, distal lung fibroblasts (likely primarily from the parenchyma), obtained from the same donor as proximal airway fibroblasts, also appear to be phenotypically different

from large airway fibroblasts. Large airway fibroblasts appear to be larger and more synthetically active than fibroblasts from the distal lung [64]. Unfortunately, until further studies are performed, it will be impossible to know the clinical relevance of these 'different' inflammatory or structural elements. However, these data could have considerable implications for current drug therapy of asthma, and severe asthma in particular, as most inhaled medications are unlikely to reach the lung periphery in high amounts [65]. Finally, structural and inflammatory changes in the small airway and parenchyma may interact to a greater degree in the small airways than the larger ones due to the smaller general mass of the airway structure.

Conclusions

The basic understanding of the mechanisms behind the development of asthma is only beginning to be elucidated. It is likely that there is a considerable overlap between the development of asthma and severe asthma, with many of the differences being an element of degree. However, the development of severe asthma is also likely to be more complicated and requires several combined insults, including genetic, structural, environmental, infectious and perhaps also responses to medications. These complex and interacting mechanisms are also likely to contribute to the heterogeneity of the disease that continues to make the understanding of this syndrome a challenge.

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