Remodeling in small airways of asthma

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Summary
Airway inflammatory processes are pivotal as the pathological features of bronchial asthma. Standard therapy with inhaled corticosteroids markedly suppresses such inflammatory changes, resulting in clinical beneficial effects. However, it is now clear that several histological changes including goblet cell hyperplasia, subepithelial collagen deposits, increased capillary networks and smooth muscle hypertrophy can occur as a chronic consequence of this airway disorder even when asthma is treated with inhaled or oral steroids. These pathologic changes, the so-called remodeling, play an important role in increased airway obstruction, increased clinical severity and difficulty in controlling asthma, and eventually in the development of irreversible respiratory failure. Targeting these remodeling changes may become a new specific therapeutic strategy for controlling asthma.

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Introduction
Asthma is characterized by allergic inflammatory responses associated with airway hyper-responsiveness, and is increasing in prevalence and sociomedical burden in many countries. Both clinical and experimental studies suggest that eosinophils and T cells play a key role in the induction of airway inflammation and mucosal injury, which closely links to non-specific airway hyper-responsiveness in asthma. Inhaled corticosteroids markedly suppress the airway hyper-responsiveness and asthma symptoms along with decreased eosinophil infiltration in the airways. More targeted types of anti-inflammatory therapy such as anti-IL-5 antibody, however, have failed to show clinical improvement, despite apparent decrease in eosinophils in the peripheral blood, and hence posed some doubt about the critical role of this inflammatory cell. It is now believed that asthma is a
Asthma. The inflammation in these more distal airways recognized as a predominant site of airflow obstruction in the lung parenchyma. In fact, the small peripheral airways, those that are less than 2 mm in diameter, are recognized as a predominant site of airflow obstruction in asthma. Most of the previous reports regarding the allergic inflammatory processes in asthma have been focused on the large airways. Pathological as well as physiological findings reported during the past few years, however, suggest that the inflammatory processes involve not only the large airways but also the smaller peripheral airways and the lung parenchyma. In the small peripheral airways, those that are less than 2 mm in diameter, are recognized as a predominant site of airflow obstruction in asthma. The inflammation in these more distal airways has been described as more severe than large airway inflammation associated with the remodeling processes. Therefore, the peripheral airways should be considered a prime target in therapeutic strategies for treatment of asthma.

**Are small airways involved in asthma?**

Considerable information about the existence of small airway involvement in asthma has first come from post-mortem studies. Haley et al. performed a morphometric analysis of postmortem lung specimens from patients who succumbed to asthma. They found that the inflammatory processes in distal airways appeared to be qualitatively different from that in large airways with different distributions of cellular infiltrates within the walls of large and small airways. In large airways with cartilaginous layers, relatively more T cells and eosinophils were found in the inner region of the airway wall (between basement membrane and smooth muscle), compared with the outer region (between smooth muscle and alveolar attachments). In the small airways, however, the pattern was reversed, with CD45+ T cells and eosinophils more abundant in the outer region.

Faul et al. studied inflammatory changes among patients with fatal asthma with sudden death. Large numbers of T cells and activated eosinophils were found in both proximal and distal lung tissue. In contrast to individuals with stable asthma, larger numbers of CD8+ T cells were found in those with fatal asthma.

Surgically obtained lung specimens from thoracic surgery on people with and without clinically defined asthma allow us to study larger samples than the specimens obtained during bronchoscopic procedures. Using these larger samples, Hamid et al. were able to evaluate the inflammatory process throughout the entire length of the airways. They showed that increased numbers of T cells (CD3+), total eosinophils (major basic protein positive) and activated eosinophils (EG2 positive) were found in both the small (<2 mm internal diameter) and the large (>2 mm internal diameter) airways of sample taken from people with asthma compared to those without asthma. When comparing the large and small airways in those with asthma, there were an increased number of activated eosinophils (EG2 positive) in small airways, suggesting that a similar but more severe inflammatory process is present in the peripheral airways.

The inflammatory processes in the distal airways of patients with asthma have also been studied by using bronchoscopic techniques. Inflammatory infiltrates were observed in the airways of both untreated and patients receiving intensive steroid treatment, but with lesser inflammation in patients with mild-to-moderate asthma. Evidence of distal lung inflammation was also reported by Vignola et al. who compared several markers of inflammation in mucosal biopsy specimens and BAL fluid from healthy control subjects, patients with intermittent asthma, and patients with mild-to-moderate persistent asthma. They found that alveolar macrophage activation was significantly increased in patients with asthma compared with control patients.

Kraft et al. studied biopsy samples from distal and proximal lung tissue, and found that the inflammatory changes that accompanied nocturnal asthma were more prominent in the alveolar tissue area and the number of inflammatory cells, especially eosinophils and macrophages, increased at night in the alveolar tissue area of patients with nocturnal asthma, whereas the number of inflammatory cells found in the proximal airways was similar in patients with asthma who did or did not experience nocturnal worsening. Specifically, they further found that the presence and extent of alveolar tissue eosinophils were correlated with nighttime decline in lung function, especially the nighttime decline in FEV1. Taken together, this information shows that small airway involvement plays an important role in determining clinical features and severity of asthma.

**Airway remodeling in small airways of asthma: pathological evidence**

Asthma-related airway remodeling has been found to occur in both large small airways. From autopsy studies, Carroll et al. found thickening of the inner wall of distal airways in individuals who died as a result of asthma as well as in people with asthma who died of nonrespiratory causes compared with airway measurements in nonasthmatic control subjects. The increased smooth muscle mass found in those with asthma suggests a mechanism for heightened response to broncho-constricting stimuli. Interestingly, the structural changes implicated in airway hyper-responsive-ness were predominantly found in the distal airways of nonfatal asthma cases but were also found in both large and small airways in fatal asthma cases. These structural changes were not focal in their distribution but were observed throughout the distal lung. In specimens from individuals who died of asthma, the adventitial,
submucosal and muscle areas of the distal airways were greater than those measured in patients with chronic obstructive pulmonary disease (COPD) and control subjects. The smooth muscle layer in patients with asthma was 2 to 3 times thicker than that in control subjects and COPD, and was associated with disease severity. Muscle thickness was, in general, greater in patients with fatal asthma compared with those with nonfatal asthma.

Autopsy studies strongly support the existence of a degree of small airway remodeling in severe and fatal asthma, but did not provide clear evidence of whether or how often such structural changes were found in milder, well-controlled asthma. Recently, evidence of remodeling in peripheral airways of patients with mild-to-moderate asthma has been demonstrated by Bergeron et al. Transbronchial and endobronchial biopsies were obtained from 12 patients with mild-to-moderate asthma before and after a 6-week course of small particle hydrofluoralkane (HFA)-inhaled corticosteroid. Total collagen occupied 37.7% of the wall area of peripheral airways, compared with 54.5% of the wall area of central airways \( (P = .04) \). After inhaled corticosteroids therapy, there was no significant difference in central vs. peripheral airways for collagen III or \( \alpha \)-smooth muscle actin immunoreactivity and in the number of TGF-\( \beta \)+ cells in the submucosa. The only significant effect of HFA-flunisolide was a decrease in \( \alpha \)-smooth muscle actin area in peripheral airways that correlated with the percentage increase in forced expiratory flow at 25–75% of vital capacity. The researchers concluded that there is a considerable degree of airway remodeling in peripheral airways in patients with even mild asthma and that inhaled corticosteroid do not modulate collagen deposition and TGF-\( \beta \) expression. However, the treatment is associated with a significant decrease in the expression of \( \alpha \)-smooth muscle actin in peripheral airways, which correlated with the improvement in peripheral airway function.

**Airway remodeling in the peripheral airways of asthma: clinical implications**

**Physiologic consequences of small airway involvement in asthma**

Since the volume and surface area of the lungs increases with increasing airway generations, the contribution of peripheral resistance to the total lung resistance was originally believed to be minimal. Ohru et al. demonstrated that there was a dose-dependent increase in both central and peripheral airway resistance in response to inhaled methacholine in patients with asymptomatic asthma using a catheter-tipped micromanometer wedged into the lower lobe of the bronchus in order to partition central and peripheral airway resistance. Wagner et al. used the wedged bronchoscopic technique to measure airway resistance in the peripheral lung of patients with asymptomatic asthma who had normal spirometric values. Patients with asthma had significantly increased peripheral airway resistance compared with control subjects; there was more than a 7-fold increase in peripheral lung resistance in the asthma group. In addition, computational analyses based on quantitative histology have shown the peripheral airways to account for the majority of airway hyper-responsiveness among asthmatic persons. Noninvasive methodologies for separating airway and parenchymal mechanics have been developed using the low-frequency forced oscillation technique in humans. Hall et al. showed the contribution of the small airways to the total lung resistance by this technique. These observations strongly suggest that contribution of the small airways to the total lung resistance has thus far been grossly underestimated.

**Pathology-physiology correlations**

Numerous studies have attempted to correlate clinical measures of standard lung function with the presence and degree of distal airway involvement. Those study suggest that it is likely that small airway involvement contributes to hyper-responsiveness by amplifying the effect of even slight amounts of muscle shortening or contraction. For example, the amount of airway smooth muscle shortening or contraction required for occluding an airway lumen is shown to be less in asthmatic than nonasthmatic airways. Wagner et al. examined the hyper-responsiveness in small airways by measuring changes in peripheral resistance after a histamine challenge by using a wedged bronchoscopic technique. Peripheral resistance doubled at lower average concentrations of histamine in patients with asthma compared with healthy control subjects, indicating an increased sensitivity to the provoking agent. Loss of lung elasticity is an overlooked, yet potentially significant, factor in the loss of lung function in asthma. Although the mechanism is unclear, the loss of elasticity is likely to reflect distal airway abnormalities, especially at the alveolar–lung parenchymal interface.

Taken together, evidence from histologic as well as physiologic studies indicates that distal airways of individuals with asthma undergo pronounced and, perhaps, permanent structural changes along with long-standing inflammation that appears to affect coarse measures of lung performance. Structural changes, with wall thickening being the most pronounced, are likely to contribute to hyper-responsiveness. These structural changes in distal airways were observed even in patients receiving corticosteroid therapy, suggesting that this therapy did not completely control distal airway inflammation.

**Assessment of small airway changes in asthma**

As described, the small airways were once called the “silent zone of the lung”. It is not easy to assess the disease processes of this area in clinical practice. While classic spirometry and flow-volume curves are routinely evaluated in daily practice, application of parameters of small airways, such as V25 or V50/V25, has been limited because of their lack of reproducibility. Low-frequency forced oscillation technique might be an alternative. In addition, several research methods including CT, ultrathin bronchoscopy or microsampling have been proposed for evaluation of small airways in asthma. To date none of these are feasible for primary care or many non-academic specialty practices.
High-resolution CT

High-resolution CT (HRCT) studies can reveal anatomic details of the lung only as small as 200–300 μm, corresponding to wall thickness in airways 2 mm in diameter or larger. At present, therefore, this method is inadequate for directly visualizing small airways. Alternatively, HRCT has proved to be useful to detect functional changes in the small airways by indirectly monitoring air trapping at distal sites. Air trapped in the mid-zone airways at residual lung volume after methacholine challenge can be indirectly detected by HRCT, appearing as regions of decreased signal attenuation. Patients with moderate asthma exhibit an aberrant “mosaic” pattern of pulmonary perfusion, which is correlated with small airway obstruction as indicated by air trapping on HRCT and may therefore be useful for the evaluation of therapeutic effects (see below).

Other potentially available tools

As described above, application of fibroptic bronchoscopy in asthma has greatly facilitated understanding of the airway changes by obtaining biopsy samples from the large airways in patients with asthma. We successfully harvested living epithelial cells by brushing the small airway mucosa under direct vision by using a newly developed ultrathin bronchoscopy BF-2.8 T (the outer diameter: 2.7 mm with a biopsy channel of 0.8 mm in diameter). It is well known that airway epithelial cells are potent sources of profibrotic growth factors and inflammatory cytokines. We recruited healthy non-smokers (n = 8) and mild asthmatics (n = 8), and recovered peripheral airway epithelial cells after informed consent. Among the factors studied, TGF-β-1 mRNA levels significantly increased and showed a significant inverse correlation with percent V25 and V50/V25 after bronchodilator treatment. These findings may highlight the role of airway epithelium-derived TGF-β-1 in the irreversible small airway obstruction found in chronic asthma, frequently observed as airway remodeling (manuscript in preparation).

Small airways as a therapeutic target in asthma

Although inhaled corticosteroids reduce airway inflammation in patients with asthma, prolonged courses of inhaled steroids do not normalize hyper-responsiveness. Furthermore, it was demonstrated in deposition studies that most of the currently used inhaled corticosteroids are predominantly deposited in the large airways and not in the lung periphery. Therefore, therapeutic actions of inhaled corticosteroids at sites of small airway involvement must be improved.

Metered-dose inhaler (MDI) corticosteroids

Aerosol particle size is a key element in determining lung deposition and the regional distribution of inhaled medication within the lung. In general, smaller aerosol particles are more likely to be deposited in the lung. The fraction of particles emitted by a pressurized MDI is closely related to the percent of deposition in the lung; aerosol particles with a mass median of approximately 4.7 μm are respirable. In the lung, the smaller and less dense the particle, the more likely it is to reach the distal regions. However, particles between 0.6 and 0.3 μm mass median aerodynamic diameter are often exhaled.

Deposition studies by scintigraphic techniques with technetium Tc 99m-radiolabeled HFA-beclomethasone (BDP) (mean diameter:1.1 μm) and classical chlorofluorocarbon (CFC)-BDP (mean diameter:3.5 μm) clearly showed that BDP in HFA showed an increased deposition compared with BDP with CFC (55–60% vs. 4–7%). In addition to increasing lung deposition, the reduction in oropharyngeal deposition with HFA formulation can minimize local side effects.

Goldin et al. used HRCT and regional air trapping to compare the efficacy of HFA– and CFC–corticosteroid formulations in corticosteroid-naive patients with mild-to-moderate asthma. Pretreatment functional CT studies before and after a methacholine challenge were performed at baseline and after 4 weeks of treatment. Post-treatment scanning indicated significant improvement in air trapping for both groups. However, after challenge with equal constrictor stimuli, smaller increases in air trapping were observed for subjects treated with the HFA formulation. Corren et al. showed comparable efficacy between flunisolide HFA at one-third the dose of its CFC counterpart. However, trends favored flunisolide HFA on several parameters, including 40.4% fewer asthma exacerbations. Similar efficacy at lower doses was reported for HFA-BDP compared with CFC-BDP in a 6-week study by Busse et al. Ciclesonide is delivered as a small-particle inhaled corticosteroid with HFA and improves lung function and airway hyper-responsiveness. Cohen et al. assessed whether ciclesonide can significantly improve small airway function in asthma. Sixteen mild-to-moderate asthma patients (7 males, median age 39 (range 19–56) years, FEV1 predicted 89% (range 62–120) were randomized to a 5-week treatment with placebo or 320 μg ciclesonide once daily. Both CT measurements of expiratory lung volume after methacholine challenge and alveolar eNO decreased significantly more with ciclesonide than with placebo. Ciclesonide did not significantly improve other small airways parameters such as FEF25–75%, percentage fall in FVC at PC20adenosine-5′-monophosphate (AMP) and at PC20methacholine. This recent report suggests that ciclesonide in HFA exerts anti-inflammatory effects on small airways. However, longer-term efficacy especially on small airway remodeling remains to be studied.

Dry powder inhalers

Dry powder inhalers (DPIs) represent another alternative to HFA-pMDIs. Data on regional lung deposition and distal lung access by DPI-delivered corticosteroids are limited. It has been demonstrated that deposition with DPIs is dependent on inspiratory flow rates (IFRs), with faster flow rates seeming to increase lung deposition. For example, scintigraphic imaging of budesonide delivered by DPI in healthy volunteers showed an overall pulmonary deposition of 14.8% and 27.7% at slower and faster IFRs, respectively.
Oral agents: an alternative route to the distal lung?

Oral agents would be other candidates that have access to this area of the lung through the circulation (Figure 2). The leukotriene receptor antagonists are oral anti-inflammatory agents with bronchodilating activity.\(^4\)\(^1\) They are efficacious and safe for the treatment of asthma in adults and children.\(^1\),\(^4\)\(^1\) In animal models of asthma, these agents are reported to prevent airway remodeling processes.\(^4\)\(^2\) There is one clinical study which supports potential benefit of this class of agent.\(^4\)\(^3\) However, specific studies are needed to define the potential action of anti-leukotrienes on distal airway inflammation and remodeling. Treatment of asthma as a systemic disease could become a new paradigm, and systemic anti-inflammatory and anti-remodeling therapy might be necessary for the complete control of this disease.\(^4\)\(^4\),\(^4\)\(^5\)

Practice points: importance of small airway involvement in asthma

- Difficult to detect: limitation of techniques, the so-called Silent Zone
- Easy to be targeted: noxious agents such as tobacco, air pollutants, viruses, etc.
- Difficult to defend: lack of effective defense
- Disturbed lung function: remodeling causing irreversible obstructive changes
- Difficult to treat: needs strategy to drug treatment

Conclusion

There is accumulating evidence to suggest that small airway involvement plays a crucial role in the disease processes in asthma. It is anticipated that poorly controlled inflammation in small airways may contribute to accelerated decline in lung function and airway remodeling. The application of HRCT appears to allow indirect assessment of the morphological changes (resulting from air trapping and regional hyperinflation) in the small airways, still remains research tools. Less-invasive and concise techniques would be necessary for clinical evaluation of the disease at this site. Remodeling processes in this site would become important new therapeutic target in asthma.

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Educational questions

Answer true or false to the following statements:

1. Asthma is an inflammatory disease that affects only large airways.
2. Airway inflammations show different patterns in large and small airways.
3. Airway remodeling is associated with increased smooth muscle thickness in both large and small airways.
4. Treatment with inhaled corticosteroids clear all findings of airway remodeling in patients with milder asthma.
5. In asthma airway resistance is not influenced by the smaller more peripheral airways.
6. HRCT scans can directly assess small airway remodeling.

References