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EDITORIAL

Airway remodelling: the future

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The research of structural changes in airway diseases is relatively recent compared with studies on physiological or inflammatory features. In airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), structural alterations have been observed, such as: epithelial desquamation or hyperplasia; increases in smooth muscle mass; angiogenesis; increases in subepithelial collagen deposition, proteoglycans and elastin content; cartilage changes; and goblet cell and glandular hyperplasia, in addition to increased airway wall thickening [1].

During the past months, the *European Respiratory Journal* has published a series on airway remodelling in order to review the state of knowledge in this increasingly important domain [2–6]. We learnt from this series that airway remodelling is by no means a single entity. It is a complex and dynamic process with multiple components, evolving differently in various conditions, according to the type and extent of the structural responses to inflammatory or physical stimuli, probably under genetic influences modulating host response to the latter. The various *in vitro* and animal models developed to study the pathways involved in the changes in the bronchial structure induced by airways allergic reactions or other stimuli confirm this vast heterogeneity. The possible clinical significance of these structural changes and the effects of treatment are even more diverse. Hence, at this stage we will need to further elaborate on the main challenges for research in this field in order to help better understand the mechanisms of airway remodelling and to decide if, how and when to intervene on this process.

WHAT ARE THE REMAINING QUESTIONS?

Some of the key questions on airway remodelling are itemised in table 1. Here are some of what we consider to be the vital remaining domains of research in this field.

What is the time-course of the various remodelling changes?

Animal models and studies of groups such as asymptomatic subjects with airway hyperresponsiveness (AHR) show that the various elements of the remodelling process evolve with time, not only with regard to the quantity of the various elements but also in type and airway distribution, possibly under the influence of epithelial cells, and particularly when there is a significant ongoing inflammatory process [3, 7–9]. However, the specific time-course of these various changes is still to be explored. The initial insult to the airways generates a fibroblastic response and other changes involved in the restitution *ad integro* of the structure; although in some predisposed subjects this process may lead to permanent remodelling [10, 11]. Increased deposition of elements such as proteoglycans in the airway wall can then occur, followed by the less reversible collagen deposition. Whether these events happen sequentially or simultaneously remains to be determined [12].

This has clinical relevance, particularly if there is a stage of the process at which these changes could be more easily reversible. In this regard, however, even in mild recently diagnosed asthma or in childhood asthma, significant airway remodelling can already be observed, although more needs to be known with regard to the reversibility of some of the changes at this early stage [13–15].

Which aspects of airway remodelling are detrimental or beneficial?

Observations reported in many studies suggest a relationship between the development of airway remodelling and the progressive increase in airway responsiveness, impaired pulmonary function and development of fixed airway obstruction [5, 16]. However, increased bronchial extracellular matrix deposition may also have protective effects against excessive bronchoconstriction and limit the detrimental effects of inflammation [17].

What is the influence of the various aspects of airway remodelling on airway function and clinical outcome?

It is probable that the establishment of a certain magnitude and type of airway remodelling will contribute to AHR and symptomatic airway obstruction, in addition to playing a role in the development of fixed airway obstruction and excessive airway narrowing. With regard to the clinical expression of airway diseases, increases in airway wall thickness, collagen content and airway smooth muscle mass have been associated, although inconsistently, with asthma severity [18–21]. Subepithelial fibrosis may be involved in the decline in lung function, but this could not be confirmed in a recent longitudinal study [22]. The possibility that remodelling can contribute significantly to fixed airways obstruction is supported by the persistence of the latter in some (but not all) patients with severe asthma under maximal treatment that results in the elimination of airway inflammation [23].

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TABLE 1 Remaining questions on airway remodelling

What is the time-course of the various remodelling changes described?
Which aspects of airway remodelling are detrimental and which ones are beneficial?
What is the influence of the various aspects of airway remodelling on airway function and clinical outcome? (What are the mechanisms by which such changes translate into modifications of airway responsiveness and symptomatic airway obstruction?)
How can the methods used to analyse structural changes influence these measurements and which are the best to use? Can surrogate markers or noninvasive methods of airway remodelling be useful?
Is airway remodelling reversible, and to what extent? If so, what are the effects of treatments used for airways diseases and how long and at which dose should they be used to influence this process?
Can we prevent remodelling and, in doing so, can we prevent the development of conditions such as asthma or chronic obstructive pulmonary disease?
Should airway remodelling be considered as a therapeutic target when determining a therapeutic strategy for diseases such as asthma?
Can remodelling modulate the airway inflammatory response and contribute to its chronicity?
Could the treatment of allergic rhinitis help prevent the development of asthma with airway remodelling?

However, it cannot be excluded that thickening [24] and/or stiffening [25] of the airway wall provides functional protection against airway narrowing in asthma. Therefore, the respective structural determinants of the presence and absence of excessive airway narrowing have to be established. This introduces significant dilemmas when it comes to deciding whether or not to treat airway remodelling.

How can the methods used to analyse structural changes influence such assessment and which are the best to use?

Endobronchial biopsies are currently the gold standard of airway remodelling studies [26]. However, in addition to requiring an invasive procedure that is not always easily repeatable, they have their limitations, as they sample a superficial and limited area of the bronchial wall. Imaging techniques such as high-resolution computed tomography (HRCT) scanning may help to assess airway wall thickness, but they do not, as yet, provide information on the various constituents of the airways, and radiation exposure limits their frequency of use [27]. Innovative bidimensional models of tissue engineering using cultured cells from bronchial biopsies from normal or diseased airways, in order to study structural cell interactions and function changes, may provide another means to explore the mechanisms acting in the establishment of the remodelling process [28].

What else have we got? Surrogate markers of remodelling, such as various mediators and growth factors, cytokines, or other measures, such as the ratio of tissue inhibitor of matrix metalloproteinase/matrix metalloproteinase-9 in the blood or induced sputum, may provide information about the repair process, but how they relate to the overall remodelling process remains to be established [29, 30]. ''Physiological surrogates'', such as the ratio of forced expiratory volume in one second/forced vital capacity [31], is probably one bridge too far, even though recent studies are showing that the correlations between spirometry and airway dimensions, as measured by HRCT, are surprisingly good in asthma [32], as well as in COPD [33].

Is airway remodelling reversible and to what extent?

There is evidence both from animal models and human clinical trials that environmental or pharmacological interventions may reduce various aspects of airway remodelling [6, 34, 35]. Again, however, anti-inflammatory intervention can also increase the deposition of extracellular matrix [36], which may or may not be of functional benefit in asthma. Therefore, the type of drug, its dose and duration of treatment may all have differential effects on components of airway remodelling, and this aspect deserves explicit studies. A recently described nonpharmacological intervention, bronchial thermoplasty, considered to act through a reduction in airway smooth muscle, or at least ''disconnecting'' the circular smooth muscle airway bundles, resulted in a reduction in airway responsiveness and in clinical improvement in asthmatic subjects [37, 38]. This is an example of an innovative method that could improve clinical features by interventions on airway structure. We look forward to the results of studies on the effects of thermoplasty on airway structure.

Hopefully, in the near future, we will able to more effectively reduce or prevent the detrimental effects of airway remodelling, either by using specific therapeutic regimens, including currently used medications, or with new agents targeting various parts of the process [39]. Initial phenomena, such as airway inflammation, will continue to be an important target for therapy, but we will possibly only be successful in reducing the severity of airway diseases or preventing disease progression by helping to restore the structural integrity of the airway wall. Finally, gene therapy is currently progressing and should provide a new means of influencing end-organ responses to external or ''internal'' aggressions [40]. Cystic fibrosis is presently a priority target of gene therapy, but these findings will help progress in the treatment and prevention of other respiratory conditions. In this regard, many genes have been linked to the risk of developing asthma (some being related to remodelling processes) and research on which of these are more relevant to the pathophysiology of the disease should be soon determined [41, 42].

Can we prevent remodelling and, in doing so, prevent the development of airway diseases?

We should certainly aim at reducing the severity of airway diseases, but the best approach is obviously prevention. Influencing pathophysiological processes leading to uncontrolled or too intense inflammatory processes and blocking their translation into structural changes possesses a high potential for reducing the manifestations of frequent diseases

and their high burden. Lifestyle changes, such as smoking cessation, prevention of infections or modulating immune responses, as well as reduction of exposure to potential environmental hazards, such as allergens and pollutants, both at home or at the workplace, may help to reduce airway remodelling but are often difficult to achieve [6, 34, 35]. Animal models showed that early interventions, such as with inhaled corticosteroids or leukotriene receptor antagonists, may prevent many aspects of airway remodelling, at least partly [3, 7, 8]. We still do not know whether this can prevent remodelling in humans at current or higher doses of these agents. It is possible that new molecules, such as T-helper type 2 cytokine inhibitors, anti-tumour necrosis factor-α, monoclonal antibodies or other types of agents acting on various mechanisms involved in tissue repair, may become added tools for the prevention of remodelling [39].

We may also propose that the notion of ''airway epithelial protection'', as used for the gastric mucosa, may apply to airways diseases, in order to reduce the possibility for various aggressions on the bronchial epithelium to translate into remodelling. However, we should first determine which the best agents are for this purpose and what will be the result in terms of inhibition of the process. Finally, the possibility of modulating fibroblast function may have protective effects on airway diseases additional to those conditions involving the lung parenchyma, such as pulmonary fibrosis [43].

Should airway remodelling be considered as a therapeutic target when determining a therapeutic strategy for diseases such as asthma?

Currently, asthma guidelines base their treatment needs on the assessment of clinical criteria, although airway inflammation has also shown to be a highly successful marker for the guidance of asthma therapy [44, 45]. Airway remodelling has recently been suggested as another potential therapeutic target [46]. However, before we understand how the various structural changes affect airway function and clinical features in acting on the most relevant components, in addition to how the various medications influence these processes, it may be too early to settle treatment goals on airway remodelling. Current knowledge could possibly be better applied to the prevention of airway structural changes by controlling triggering mechanisms of the disease at an early stage (*e.g.* inflammation and epithelial damage), or maybe for treating conditions associated with an increased risk of developing an airway disease (*e.g.* rhinitis in regard to asthma).

CONCLUSIONS

Although its clinical consequences are still controversial, current evidence suggests that airway remodelling can be responsible for persistent increases in airway responsiveness and mucus production, variable or fixed airflow limitation, and perhaps even decline in pulmonary function. Airway remodelling is not a single entity, and seems to be due to an exaggerated or uncontrolled injury repair process, probably related to the type or intensity of the stimulus and modulated by host factors under genetic control. Therefore, better understanding of the complex relationship between changes in airway structure and airway function is a prerequisite for developing therapeutic interventions that are aimed at targeting airway remodelling in asthma.

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