The Role of Inflammation in Airway Disease
Remodeling

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WHAT DO WE KNOW?

Chronic airway inflammation is a general feature of some types of asthma, cystic fibrosis (CF), bronchopulmonary dysplasia (BPD), and chronic obstructive pulmonary disease (COPD). This chronic inflammation is associated with structural changes in the airway wall and parenchyma, which affect the functional properties of these tissues. It is these changes that are defined as remodeling. However, association between inflammation and remodeling cannot be regarded as proof of causality. These airway changes should not be considered as fixed; there is a dynamic state of cell and matrix protein turnover in both diseased and healthy airways. Knowledge of the type and distribution of morphological changes that can (ir)reversibly impair lung function may potentially lead to the development of more effective treatment. Unfortunately, virtually all our knowledge comes from studies of the mature airway. We do not know whether in children the response of cells to inflammatory stimuli is greater or less than in adults, or the capacity of the developing airway to restore itself to normality.

Lung Morphology

The morphological development of the lungs from the simple outgrowths of the primitive foregut to the mature adult structures is well described (1). The mechanisms controlling these processes and the growth factors involved are less well characterized, and in general a reductionist approach to describe single processes rather than synthesis of a complex whole is all that has been attempted. The context of lung development is an important one. It should be noted that many growth factors play an important part in the inflammatory and remodeling process (2). Furthermore, steroid treatment, which may have a beneficial effect on airway remodeling (3), may have an adverse effect on the developing lung. The profound morphological changes that occur during development have important functional consequences. Since airway mechanics change with growth and development, the functional consequences of remodeling will be age dependent (4).

The morphology of the airways and parenchyma has been established in normal lungs, in the lungs of patients with airway disease, and in animal models of airway disease. For this review, nomenclature is used to quantify subdivisions of the bronchial wall as seen in histological cross-sections (5) (Figure 1 [6]). Changes in various components of the bronchial wall in asthma, CF, BPD, and COPD will be addressed, going from the epithelium to the outer wall area and parenchyma.

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Epithelium

The surface area of the airway is covered with pseudostratified ciliated epithelium. The respiratory epithelial forms an interactive interface between the external and the internal environment and has many important functions, which include (7) the following:

- Formation of a natural barrier to invasion and injury by bacteria, viruses, and toxic inhaled molecules
- Contribution to the mucociliary clearance of inhaled matter
- Formation of a barrier against leakage of solutes in the airways
- Modulation of bronchial smooth muscle tone by production of mediators and neurotransmitters that reduce smooth muscle tone, and by inactivation of factors that increase this tonus

In asthma, shedding of epithelium is seen in bronchoalveolar lavage (BAL) fluid of children and adults (8, 9). Damage of the airway surface epithelium is prominent in biopsies of adults with (mild) asthma (10). The importance of epithelial loss and its distribution in the bronchial tree in children with asthma are unknown. Twenty-three percent of the airway surface area was not covered by epithelium in patients with CF who underwent lung transplantation (11). It has been shown that *Pseudomonas aeruginosa* preferentially adheres to regenerating respiratory epithelium (12). The large airways of infants with BPD who have died show substantial loss of epithelium, up to 50% of the surface area (13). The loss in smaller airways varies between 1 and 25% (14, 15). Increased shedding of the epithelium in BAL fluid has been described for patients with COPD. However, lobectomy specimens from these patients show only 9% loss of epithelium (11). The height of the epithelium in the smaller airways of patients with CF and patients with BPD is increased, which is likely to increase the resistance of the peripheral airways.

Basement Membrane

The epithelial layer rests on the basement membrane, which consists of two layers (16): the basal lamina, which can be seen only by electron microscopy, and the lamina reticularis, which can be seen by light microscope and consists of a loose array of collagen fibrils that are connected to the smooth muscle and adventitial layer. The mechanical properties of the basement membrane are thought to be an important determinant for the stiffness and folding pattern of the mucosa during contraction of bronchial smooth muscle (17, 18). Extensive thickening of the basement membrane has been described in asthma and can be seen in early stages of the disease (3, 19–21). Bronchial myofibroblasts are thought to be responsible for this thickening (22). In CF subepithelial fibrosis of central airways has been described in biopsy and lobectomy material (23). Whether the basement membrane is thickened by BPD has not been systematically investigated to our knowledge.

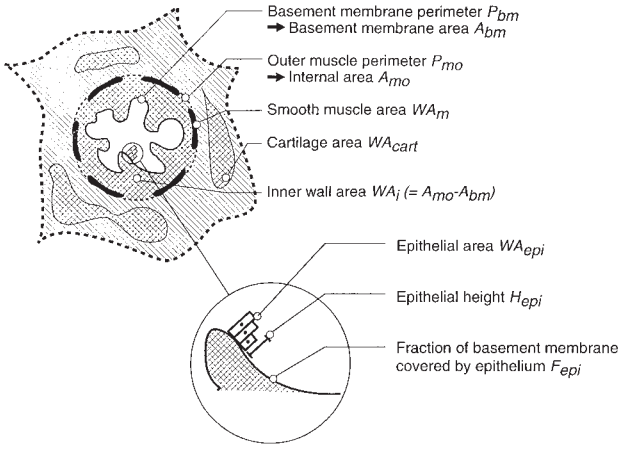

Figure 1. Diagram of airway wall dimensions (6). [Reproduced with permission from Tiddens, H. A. W. M., P. D. Paré, J. C. Hogg, W. C. J. Hop, R. Lambert, and J. C. de Jongste. *Am. J. Respir. Crit. Care Med.* 152:260–266.]

Inner Airway Wall

The tissue between the basement membrane and smooth muscle layer contains a dense microvascular network that occupies 4 to 10% of the inner wall, and that is embedded in fibrous tissue (24). Thickening of the inner airway wall is a common feature of asthma, CF, BPD, and COPD (6, 11, 14, 25). The magnitude of the thickening is greatest in patients with asthma or CF (11). In COPD, the thickening of the inner airway wall area is in proportion to the inflammatory changes and is correlated with the level of airflow obstruction (6). In asthma, CF, and COPD, thickening is more severe in peripheral compared with more central airways (6, 11, 25). Increased microvascular permeability and plasma exudation are likely to contribute to this airway wall thickening (26–28). The absolute number of blood vessels in patients who have died from or with asthma is increased in proportion to the increase in airway wall area (29).

Smooth Muscle

The smooth muscle layer runs down from the trachea to the smallest bronchioles. Smooth muscle makes up 5 to 10% of the bronchial wall of the small airways and only 1 to 2% of the more central airways (6, 30). The amount of smooth muscle in adults with (fatal) asthma is increased (25, 31). However, it is not clear whether the increased smooth muscle mass is accompanied by an increase in force (32). The effect of an increase in smooth muscle force is further amplified by airway wall thickening (11, 31). The amount of bronchial smooth muscle is increased in CF, BPD, and in the small airways of patients with COPD (11, 14, 25, 33). The proportional increase in bronchial smooth muscle is higher in more peripheral airways compared with central airways.

Cartilage

Airway cartilage is a prominent component of the outer wall area and makes up 25 to 63% of the total wall in large airways and 4 to 10% in smaller airways. This cartilage is an important structural contributor to the ability of the airway wall to resist deformation during forced expiration. The biochemical composition and biomechanical properties of cartilage change with age (34, 35). Some studies of patients with COPD have suggested that inflammation reduces cartilage volume and, therefore, contributes to increased airflow obstruction (36, 37). This was not confirmed in other studies (38, 39). In patients with CF the cartilage volume is reduced in comparison with patients with COPD (11). Patients with asthma and COPD show more degeneration and perichondrial fibrosis compared with control subjects (39).

Outer Wall

The outer wall area is the tissue between the outer edge of the smooth muscle layer and the parenchyma, with which it forms a continuum. This area is, therefore, difficult to measure. Inflammatory thickening of the outer wall area can theoretically uncouple airway smooth muscle from the tethering forces of the parenchyma and thus contribute to airway narrowing (32). Little is known about the changes in the outer wall in relation to chronic airway inflammation. Probably, the outer wall area is thickened in severe asthma (25) and BPD (14). For COPD this is less clear (6, 30).

Parenchyma

There is a strong functional interdependence between lung parenchyma and airways. Alveolar walls attach to the outside of the intraparenchymal airways and contain elastic fibers that resist deformation and provide radial traction on the airway wall. Loss of this functional interdependence can lead to abnormal smooth muscle mechanics (32, 40). In adults with asthma it has been shown that considerable alveolar tissue inflammation is present that contributes to lung function abnormalities in these patients (41). In patients with COPD severe airflow obstruction is related to destruction of peribronchial alveoli (42), reduced density of the lung parenchyma (43), and a larger distance between alveolar attachments (44). It is likely that airways in emphysematous lungs are irregular and distorted (45, 46). A reduction in the number of alveoli is a possible feature of CF (47) and is a common feature in BPD (48, 49).

WHAT DO WE NEED TO KNOW?

1. What structural abnormalities are present in the lungs of children in different age groups?

2. Lung growth is a highly complex process. Depending on the severity and timing of disturbances in lung growth, a variety of permanent or transient pathological conditions may result. However, little is known about how airway inflammation interferes with lung growth (1) or whether the morphological changes are secondary to inflammation. Using available data, it is not possible to ascertain whether inflammation precedes the airway structural features conventionally labeled as remodeling, or whether in fact some or all of the airway structural changes are independent of, or even precede, inflammation. Therefore, we need to know whether prenatal pulmonary inflammation, which is usually associated with infection or amnionitis, is important in any subsequent airway changes (50).

3. Most of the literature on airway remodeling is based on adult patients with COPD since lung tissue from patients operated on for a lung tumor is relatively easily available. Considerably less is known about remodeling in the lungs of patients with asthma, CF, or BPD since the lung tissue of these patients is difficult to obtain. Morphometric studies should include the whole range from large airways and parenchyma. Data obtained from central airways may have only little relevance for disease processes in more peripheral airways (6, 51). Treatment of chronic airway disease in children should primarily prevent or reduce remodeling in those areas of the lung responsible for impairment of lung function. Identification of this area enables us to select the most effective aerosol characteristics of the drug of choice. For example, an aerosol with a small median particle size is likely to be more effective in

small airways than an aerosol with larger particles. To date it is still difficult to define the most important target area of the bronchial tree for more selective treatment for a number of reasons. First, for children only limited data are available on the distribution of morphological abnormalities along the bronchial tree (11, 14). Second, although morphological changes of airways and parenchyma have been described, little is known about how these changes affect their mechanical properties and lead to lung function abnormalities (52). Third, little is known about the (ir)reversibility of various morphological changes. For example, thickening of the basement membrane might be reversible, as was suggested by biopsy findings of a prospective study of patients with asthma treated with inhaled corticosteroids for 2 yr (3). To date, we do not know the extent of the reversibility of any structural changes in children.

HOW DO WE ACHIEVE THIS?

1. To define structural abnormalities in the lungs of patients in different age groups, comparison with normal tissue is crucial. Furthermore, morphometric data on normal lungs are essential to study the effect of structural and functional changes of airways and parenchyma on lung function in computer models (6, 11, 53). Such models are available for adults based on "normal" lung geometry derived from cast studies (54). These models can be modified for children when pediatric lung geometry data are available.

2. The normal geometry of the lung should be described using post-mortem casts and modern imaging techniques, such as three-dimensional computer tomography and magnetic resonance imaging, in healthy and diseased children in different age groups (55–60).

3. Animal models of chronic airway inflammation during growth can be used to determine how airway inflammation interferes with lung growth (61, 62).

4. Lung function measurements could be used to study the relationship between chronic inflammation and airway mechanics in a noninvasive fashion in children. For example, high-frequency respiratory input impedance measurements (63) could be used to estimate airway compliance, or the effect of deep breaths on flow volume estimates of airway obstruction could be used to detect abnormal parenchyma–airway interdependence (64, 65).

5. We need imaging techniques that do not use ionizing radiation and that can be applied serially to measure lung growth. These techniques are essential if we are to follow the structural outcomes of interventions, particularly in a context where intervention could harm other parts of the growing lung.

6. Systematic collection of autopsy material and from children who have had a lobar resection or pneumonectomy in designated centers is needed to obtain further knowledge of the morphology of diseased lungs.

7. Wherever possible, indirect techniques should be validated against biopsy information on structure. Every ethical opportunity to obtain biopsy material from young children should be sought.

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