Inflammation and remodelling in the ageing airway

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In asthma, there is an influx of inflammatory cells, including eosinophils and mast cells, and activated T-lymphocytes (predominantly reflected in the Th2 phenotype), into the airway, as well as the production of multiple cytokines, growth factors and inflammatory mediators.[1] Together with these typical acute and chronic inflammatory cellular findings, there are specific structural changes resulting from airway remodelling. These include epithelial shedding, subepithelial reticular basement membrane thickening, submucosal collagen deposition, and submucosal angiogenesis, with increased vascularity and smooth muscle hyperplasia.

This architectural reassignment is thought to be a consequence of persisting stimulation by local microenvironmental growth factors. Thickening of the airway wall is associated with increased bronchial hyperreactivity, lack of normal distensibility and reduced responsiveness to β_2-adrenergic agonist bronchodilators.[2]

Understanding the basis of structural change in the airway is essential for developing therapeutic strategies that might limit the progressive decline in lung function associated with asthma. Longitudinal surveys have clearly shown that the onset of airflow limitation during childhood predicts airflow limitation in later life.[3] In addition, children with mild symptoms frequently become disease-free and maintain normal lung function in adult life.[4] Large population studies have identified that the rate of decline in forced expiratory volume in 1 second (FEV_1) is substantially increased in people with asthma (38 mL/year) compared with matched controls (22 mL/year).[5] Cigarette smoking is also clearly associated with further decline in lung function, and the relatively high incidence of smoking means that many people with asthma may be losing lung function at an accelerated rate. Clearly, differentiating the aetiologies of this fall in lung function may prove difficult in older subjects (ie, those over 60 years of age), with a considerable number showing features attributable to both asthma and chronic obstructive pulmonary disease ("overlap syndrome"). The reduction in FEV_1 is likely to be multifactorial and is probably due to loss of elastic recoil, as well as to long-standing airway changes. Interestingly, neither α_1-antitrypsin nor elastase levels in sputum from people with asthma were found to vary with age, reinforcing the view that the lung is not necessarily subject to enhanced tissue degradation with age.[6]

Once established, airway changes as a result of remodelling are unlikely to be progressive over time. Analysis of airway sections from autopsy series indicate that bronchial wall morphology is not affected by age, suggesting that loss of elastic recoil may be a dominant factor in loss of airway patency. The bronchial vasculature may assume a more important role in elderly subjects with "cardiac asthma", because of the increased likelihood of a congested bronchial circulation, leading to increased bronchial reactivity.[7,8]

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ABSTRACT

What we need to know

- What changes occur in atopic and non-atopic airway inflammation in asthma with increasing age?
- What is the relationship between wound healing and airway remodelling in older subjects?
- What is the response to anti-inflammatory therapy in older subjects?
- What is the basis of the "overlap syndrome" with chronic obstructive pulmonary disease in older people with asthma, in whom smoking contributes to airway disease?

What we need to do

- Identify the contribution of immunological mechanisms to asthma in ageing.
- Determine the extent to which airway remodelling plays a role in airflow obstruction in older people, specifically reversible components.
- Reduce the impact of smoking in young people with asthma.

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Atopic response

There is evidence that some impairment of allergic immune responses occurs with ageing. Decreased expression of Th2 cytokines occurs in animal models of inflammation with ageing, exhibited as a failure to induce eosinophilic airway inflammation and produce airway hyperresponsiveness after allergen exposure.[9] A defect in eosinophil accumulation occurs, associated with reduced chemotaxis to interleukin-5 (IL-5).[10] In this model, both old and young rats were capable of ovalbumin sensitisation; however, the elevation in IgE was greater in younger animals. Serum eosinophil cationic protein (ECP) levels are less likely to be elevated in older subjects during acute asthma, possibly due to the role of remodelling rather than acute inflammatory cellular events,[10] although ECP levels are frequently raised in children with acute wheeze.[11] Despite this evidence for an impaired cellular response, eosinophil counts have still been closely correlated with bronchial responsiveness and asthma symptoms in older men.[12,13]

Response to remodelling

The response to injury involves fibroblast migration into the zone of tissue damage, and the activation of collagen genes to produce scar-type collagens III and V. In studies on older rats, incorporation of ^{3}H-thymidine and ^{3}H-proline were significantly reduced, indicating an age-dependent loss of tissue repair capacity. These findings also indicate a reduced turnover of collagen and likely reduced ability to resolve deposition of scar tissue.[14] In humans, similar observations apply to donors of skin fibroblasts that show a reduction in ability to synthesise collagen VII when stimulated by IL-1 and tumour necrosis factor α (TNF-α) with age.[15] A lack of observed deficiency in healing in older subjects is likely to be due

to an excessive ability to mount a repair response to injury, masking any particular deficit at the cellular level.[16] Unfortunately, slower rates of collagen turnover may be reflected in persisting airway remodelling abnormalities in older people with asthma.

Response to infection

Many studies on the ability of older subjects to respond to antigenic challenge have given insight into innate and acquired immune responses.

In a rabbit model of sepsis examining neutrophil and corticosterone levels, no significant differences in age response were identified.[17] Alveolar macrophages from senescent animals capable of generating reactive oxygen species and nitric oxide showed a significantly impaired response to lipopolysaccharide (LPS) stimulation compared with healthy adult controls.[18] The senescent phenotype is characterised by impairment of response to stressful stimuli, with apparent prolongation of the inflammatory response.[19] This may be due to a decreased responsiveness to stimulation by regulating factors at the cellular level.[20] An impaired response to infection may therefore predispose older people to more severe and prolonged airway infections, leading to secondary chronic inflammatory and remodelling sequelae.

What we need to know

There is a substantial body of evidence relating airway inflammation to airway remodelling and bronchial hyperreactivity in asthma, but little evidence on changes in immune function, healing processes and airway function to clinical asthma in the ageing population.

Provided patients with cardiac failure are excluded, standard bronchial provocation and/or bronchodilator testing, as well as skin prick testing, remain valid diagnostic tests in older patients with asthma. The decline in FEV_1 seen with age does not appear to accelerate and may be related to a combination of airway remodelling and loss of elastic recoil in the ageing lung. Non-allergic factors are more likely to contribute to airway symptoms and loss of lung function than atopic asthma.[21] Bronchial hyperresponsiveness in older people remains dependent on serum IgE level and eosinophil count.[22] We must identify the specific changes that occur with ageing in both atopic and non-atopic airway inflammation in asthma, and we need to better understand the relationship between wound healing and airway remodelling with ageing. There is much to be gained by understanding steroid-responsive and steroid-resistant mechanisms in older patients.

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