

EDITORIAL

Clinical & Experimental Allergy

Localization of pathology in asthma

This editorial discusses the findings of the paper by Shiang et al. [12]

A. L. James

Department of Pulmonary Physiology, West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Nedlands, WA, Australia

One of the intriguing aspects of asthma is the confinement of its pathophysiology to the conducting airways. Although there are data to show that there may be inflammation in the parenchyma in 'nocturnal asthma' and there are changes observed in the mechanical properties of the lung in some patients with asthma, the overwhelming site of pathological change in people who have variable airway excessive airway narrowing associated with variable chest tightness, cough, wheeze and shortness of breath, is in the conducting airways. This localization suggests that the interaction of the external environment with the body's immune system at this site, in susceptible individuals, results in airway injury, persistent inflammation and remodelling, and altered function.

The best characterized risk factors for asthma include the development of IgE-mediated sensitization to food and aeroallergens [1] in childhood and non-IgE-mediated sensitization to inhaled immune stimulants in occupational asthma in adults. Therefore, inhaled environmental stimuli appear to be required for the development of asthma. But not all inhalational injuries cause localized airway disease or the clinical syndrome of asthma. The inhalation of cigarette smoke results in injury, not only in the large and small airways [2], but also in the lung parenchyma, in the form of emphysema [3]. Inhalation of a large number of inorganic and organic compounds results in interstitial lung disease with relative preservation of airway structure and function. One might ask, why is the pathology of asthma confined mainly to the conducting airways? Clearly there are factors related to the properties of the inhaled material, including aerodynamic properties and interactions with the innate and adaptive immune systems. Even in allergen inhalation, the inhaled dose will alter the pattern of tissue inflammation

[4]. But are there local host airway factors that might result in the local airway pathology observed in asthma?

Much attention has focused on the epithelium as the site of primary abnormality in asthma [5]. Possible mechanisms include impaired integrity of the epithelium, resulting in increased access of allergen to the immune system, repeated injury resulting in epithelial–mesenchymal transformation and remodelling, altered function of the epithelium that leads to persistent immune responses to allergen or abnormal healing associated with abnormal and pro-proliferative matrix deposition.

The airway smooth muscle is uniquely distributed along the conducting airways, and in asthma, the increased area of airway smooth muscle is most the obvious structural change that contributes to remodelling and probably to abnormal airway function. Although it is increased in volume, the smooth muscle layer has few of the increased numbers of inflammatory cells that are observed elsewhere in the airway wall, other than increased numbers of mast cells [6]. The airway smooth muscle from cases of asthma shows numerous secretory and proliferative changes compared with that from non-asthmatic subjects [7]. It is interesting to note that the smooth muscle of the bronchi may have different contractile responses from those of the tracheal smooth muscle [8]. Therefore, there is considerable evidence that the smooth muscle in asthma behaves differently from that of non-asthmatic individuals. It remains to be seen if this difference occurs before or after the onset of airway inflammation. The recent finding that the thickness of the smooth muscle layer is related to the severity of asthma, but not its duration, raises the possibility that changes in the smooth muscle occur very early in the course of asthma [9].

The bronchial circulation, a systemic circulation, is also unique to the conducting airways [10]. The bronchial arteries arise from the aorta and intercostal arteries, join the main bronchi at the hila and follow the branching airway tree. Although a fraction of the bronchial circulation drains to the true bronchial veins, more than 85% returns to the left ventricle via anastomoses with the

Correspondence:

Prof. Alan James, Department of Pulmonary Physiology/West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Nedlands, WA, Australia.

E-mail: Alan.james.scgh@health.wa.gov.au

pulmonary circulation. Small arterial branches give rise to plexuses inside and outside the layer of smooth muscle. The small arterioles, capillaries and venules that arise from the pulmonary circulation are increased in area and number within the airway wall of patients with asthma, compared with non-asthmatic controls. This is associated with increased levels of vascular endothelial growth factor in the broncho-alveolar lavage fluid of patients with asthma and the increased vascularity responds to treatment with inhaled corticosteroids, which suggests a relation to airway inflammation [10]. The increased area of the bronchial circulation is likely to contribute to inflammation through trafficking of inflammatory cells and increased capillary permeability to fluid and plasma proteins. Changes in the bronchial circulation might also alter the metabolism or removal of bronchoconstrictor agents or other inflammatory mediators within the airway wall [11].

In this issue of the journal, Shiang et al. [12] have focused attention on another structural compartment of the airways, the pulmonary circulation, in particular the pulmonary arterioles. They studied the peri-arterial region of small pulmonary arteries in 22 cases of fatal asthma and characterized the inflammatory cells that were present. Compared with 10 control subjects (death from non-respiratory causes) they found increased area densities of mast cells, eosinophils and neutrophils but no differences in B lymphocytes or T lymphocytes or the ratio of chymase vs. chymotrypsin positive mast cells. Interestingly, they found that the increased number of inflammatory cells occurred around the entire circumference of the vessel and not just in the vessel wall adjacent to the bronchiole. They found no inflammatory cells within the arterial media or intima.

Early studies of fatal asthma noted the involvement of the pulmonary circulation in the inflammatory and remodelling process in asthma, and reported thickening of the pulmonary (and bronchial) vessels. These reports were from cases of fatal asthma, that had been clinically very severe and who had often died of asthma after a protracted increase in severity. These cases occurred before the invention of inhaled corticosteroids, and of antibiotics, so that the effects of infection, right heart failure and pulmonary hypertension cannot be excluded. Subsequently, Saetta et al. [13] showed that, in cases of fatal asthma, the pulmonary vessels that accompany small intrapulmonary airways were inflamed and that the inflammation was mainly confined to the region of the vessel wall that was adjacent to the airway. This finding suggested that the pulmonary vessel was involved as an 'innocent bystander' to airway inflammation in asthma. Green et al. [14] reported increased thickness of the intima of small pulmonary arteries, not only in cases of fatal asthma, but also in cases of non-fatal asthma, of mild to moderate clinical severity, compared with non-asthmatic

control subjects. Intimal thickness was also increased in smokers, in males and in older cases, and resulted in reduced lumen area. Associated lesions included reduplication, fenestration, fragmentation, calcification, smooth muscle 'proliferation' and collagen deposition. These observations suggested more than just an innocent bystander effect and since they were also seen in less severe cases of asthma that secondary changes due to pulmonary hypertension were unlikely.

On each transverse section of arterial wall, Shiang et al. [12] divided the adventitia into quadrants in relation to the adjacent airway, and the area density of each inflammatory cell type in each quadrant was measured. Specific histochemical and immuno-histochemical markers were used to identify cell types (B lymphocytes and T lymphocytes, neutrophils, eosinophils and mast cells). The authors found no consistent differences in the density of inflammatory cells between the quadrants in either the cases of fatal asthma or the control subjects. These findings suggest that the inflammation observed within the pulmonary arteries in asthma arises locally and does not 'spread' from the nearby airway. This is in keeping with the findings of Green et al. [14] and those from animal models of airway inflammation where it is hypothesized that peri-arterial capillaries may be the site of inflammatory cell accumulation from the circulation [15].

Inflammatory cells get into lung tissue from the pulmonary and bronchial circulations in a number of ways [16]. In the lung parenchyma, neutrophils and other cells in the pulmonary circulation must traverse between 40 and 100 capillary segments to pass from an arteriole to a venule. Neutrophils have a diameter that is, on average, larger than that of a capillary segment, so they must deform to some degree to pass through. This size mismatch and the subsequent slow transition of neutrophils through the lung results in a margined pool that assists the initial stages of sequestration in the lung. Adhesion and emigration of neutrophils from the capillary segment requires the interaction of adhesion molecules such as intercellular adhesion molecule (ICAM)-1, L-selectin and P-selectin on the endothelial surface and CD11/CD18 adhesion molecules on the neutrophil cell membrane. The type of molecule expressed is dependent upon the nature of the inflammatory stimulus. Neutrophils leave the capillaries through specific junctions, after which their passage through the tissue is guided by fibroblasts.

In the bronchial circulation, there is probably less of a margined pool. In normal bronchial vessels, there is expression of P-selectin, E-selectin, VCAM-1 and ICAM-1 and some, or all, are up-regulated in response to inflammatory stimuli. It has been shown *in vitro* that endothelial expression of ICAM-1, P-selectin and L-selectin, but not E-selectin is associated with binding of lymphocytes [17]. The authors of that study incubated unstimulated peripheral blood lymphocytes with sections of medium and large

bronchial segments obtained from lung resection specimens so that these observations would have been on capillaries of the bronchial circulation.

The origin of inflammatory cells seen around the pulmonary arteries by Shiang *et al.* [12] is not clear. Although small arterioles arising from the bronchial circulation supply the vasa vasorum of the large pulmonary arteries, it is not known whether small branches of the pulmonary arteries may be specific sites of inflammatory cell migration into the tissue or if there are specific adhesion molecules that control this process. Recent attention has been drawn to the potential role of the perivascular space as a site of inflammatory cell migration from the circulation to the lung tissues, including the airways. In a mouse model of lung inflammation induced by lipopolysaccharide, Tschernig *et al.* [15] showed that the accumulation of neutrophils and mononuclear cells in the perivascular space was associated with the increased expression of the chemokine monocyte chemoattractant protein-1. However, the authors did not identify the origin of the capillaries from which these cells arose. The cell surface and endothelial adhesion molecules confer specificity to the homing of inflammatory cells to target tissues, including the lung and serve to re-unite activated immune cells with their specific target antigens. Differences in cell trafficking between central and peripheral airways have been observed [18]. It remains to be determined whether these differences are due to variations in adhesion molecule expression, or if there is regional specificity related to the pulmonary and bronchial circulation within the conducting airways.

Finally, the functional effects of the pulmonary artery inflammation observed by Shiang *et al.* [12] and the remodelling observed by Green *et al.* [14] remain to be determined. Shiang *et al.* [12] suggest some interesting possibilities including alterations in regional blood flow secondary to bronchoconstriction, contributing to hypoxia and pulmonary hypertension, and fluid extravasation. These effects remain hypothetical for now. However, their study adds further evidence that the pulmonary arteries are independently involved in inflammation and remodelling in asthma, and as such, consideration of their role in the pathophysiology of the disease deserves further attention.

References

- 1 Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; **368**:763–70.
- 2 Hogg JC, Chu F, Utokaparch S *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; **350**:2645–53.
- 3 Cosio MG, Guerassimov A. Chronic obstructive pulmonary disease. Inflammation of small airways and lung parenchyma. *Am J Respir Crit Care Med* 1999; **160** (Part 2):S21–5.
- 4 Temelkovski J, Hogan SP, Shepherd DP, Foster PS, Kumar RK. An improved murine model of asthma: selective airway inflammation, epithelial lesions and increased methacholine responsiveness following chronic exposure to aerosolised allergen. *Thorax* 1998; **53**:849–56.
- 5 Holgate ST, Davies DE, Lackie PM, Wilson SJ, Puddicombe SM, Lordan JL. Epithelial–mesenchymal interactions in the pathogenesis of asthma. *J Allergy Clin Immunol* 2000; **105** (Part 1): 193–204.
- 6 Siddiqui S, Sutcliffe A, Shikotra A *et al.* Vascular remodeling is a feature of asthma and nonasthmatic eosinophilic bronchitis. *J Allergy Clin Immunol* 2007; **120**:813–9.
- 7 Black JL, Roth M, Lee J, Carlin S, Johnson PR. Mechanisms of airway remodeling. Airway smooth muscle. *Am J Respir Crit Care Med* 2001; **164** (Part 2):S63–6.
- 8 Bai TR. Abnormalities in airway smooth muscle in fatal asthma. A comparison between trachea and bronchus. *Am Rev Respir Dis* 1991; **143**:441–3.
- 9 James AL, Bai TR, Mauad T *et al.* Airway smooth muscle thickness in asthma is related to severity but not duration of asthma. *Eur Respir J* 2009, in press.
- 10 Paredi P, Barnes PJ. The airway vasculature: recent advances and clinical implications. *Thorax* 2009; **64**:444–50.
- 11 Wagner EM, Mitzner WA. Bronchial circulatory reversal of methacholine-induced airway constriction. *J Appl Physiol* 1990; **69**:1220–4.
- 12 Shiang C, Mauad T, Senhorini A *et al.* Pulmonary periarterial inflammation in fatal asthma. *Clin Exp Allergy* 2009; **39**, doi: 10.1111/j.1365-2222.2009.03281.x.
- 13 Saetta M, Di Stefano A, Rosina C, Thiene G, Fabbri LM. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *Am Rev Respir Dis* 1991; **143**: 138–43.
- 14 Green FH, Butt JC, James AL, Carroll NG. Abnormalities of the bronchial arteries in asthma. *Chest* 2006; **130**:1025–33.
- 15 Tschernig T, Janardhan KS, Pabst R, Singh B. Lipopolysaccharide induced inflammation in the perivascular space in lungs. *J Occup Med Toxicol* 2008; **3**:17. Available at <http://www.occup-med.com/content/3/1/17>
- 16 Doerschuk CM. Leukocyte trafficking in alveoli and airway passages. *Respir Res* 2000; **1**:136–40.
- 17 Ainslie MP, McNulty CA, Huynh T, Symon FA, Wardlaw AJ. Characterisation of adhesion receptors mediating lymphocyte adhesion to bronchial endothelium provides evidence for a distinct lung homing pathway. *Thorax* 2002; **57**:1054–9.
- 18 Miller LA, Hurst SD, Coffman RL *et al.* Airway generation-specific differences in the spatial distribution of immune cells and cytokines in allergen-challenged rhesus monkeys. *Clin Exp Allergy* 2005; **35**:894–906.