Meeting report

Leukocyte adhesion and recruitment, and alpha-1-antitrypsin deficiency: a report from ATS 2001, May 18–23, San Francisco

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Abstract

The program at this year's American Thoracic Society international conference included over 300 scientific and clinical symposia. In this report I have reviewed the data presented on two important areas of lung inflammation, namely leukocyte recruitment and alpha-1-antitrypsin deficiency. Highlights included work from a number of groups identifying the contribution of specific leukocyte adhesion molecules (CD18, CD11a and vascular cell adhesion molecule-1) which varied according to the site and nature of the initial inflammatory stimulus. In addition work was presented examining the contribution of various chemoattractants to the process of leukocyte recruitment in chronic obstructive pulmonary disease, with leukotriene B_4 in particular appearing to play a major role. In alpha-1-antitrypsin deficiency other molecules may also be important and work was presented demonstrating the pro-inflammatory potential of alpha-1-antitrypsin polymers in the lungs of these patients. These advances in the understanding of the basic mechanisms of inflammation will, in the future, allow the development of novel anti-inflammatory therapies for a variety of lung diseases.

Keywords: alpha-1-antitrypsin, chronic obstructive pulmonary disease, leukocyte, leukocyte adhesion molecule

Introduction

The American Thoracic Society international conference is the largest gathering of lung specialists in the world, attended by over 15,000 people from 80 countries. The meeting aims to offer the latest and most significant developments in clinical practice, and clinical and basic research to physicians, scientists and health care workers. The program this year was made up of more than 300 scientific and clinical symposia. In this report I will concentrate on two important aspects relating to the basic mechanisms of inflammation in lung disease, namely leukocyte recruitment and alpha-1-antitrypsin (A1AT) deficiency.

Review

Leukocyte adhesion and recruitment

Unique mechanisms of leukocyte migration from the blood-stream to the lung have been proposed with regard to the profile of the adhesion molecules, cytokines and chemokines involved, providing potential targets for pharmacological agents to control the inflammatory process. Data presented at this conference provided further insight into the mechanisms of leukocyte adhesion and recruitment into the lung and the potential effects of therapeutic agents on this process.

There is accumulating evidence that the mechanisms involved in leukocyte recruitment into the lung are depen-

A1AT = alpha-1-antitrypsin; COPD = chronic obstructive pulmonary disease; IL = interleukin; LTB_4 = leukotriene B_4

dent upon the stimulus and the site of migration. Data from SJ Hislip (University College, Ireland) demonstrated that the conversion from CD18-independent to CD18-dependent leukotriene B_4 (LTB_4)-induced and IL8-induced migration during acute inflammatory episodes may be due to n-formyl methionyl leucyl phenylalanine priming [1]. This effect was demonstrated using healthy neutrophils and antibodies to the CD11/18 integrin complex. In addition U Maus (Justus-Liebig-University, Germany) [2] reported that monocyte recruitment to mouse alveoli was dependent upon CD18, VLA-4 and intercellular adhesion molecule-1 under basal conditions, but following bacterial endotoxin stimulation CD11a and vascular cell adhesion molecule-1 were also involved, indicating a switch of mechanism. As well as bacterial endotoxin, cigarette smoke can also up-regulate adhesion molecule expression in the lung tissue. AJ Heires (University NE Medical Centre, USA) reported that cigarette smoke extract was able to up-regulate the expression of intercellular adhesion molecule-1 on human airway epithelial cells [3]. This effect could be abrogated by a C5a receptor antibody, implicating this molecule in the pathological process. AR Sousa (Guy's Hospital London, UK) presented data suggesting that the mechanisms controlling leukocyte influx also differed according to airway level and disease phenotype [4]. This group found that the expression of granulocyte/macrophage colony stimulating factor in the large airways was significantly higher in smokers compared to non-smokers, and in chronic obstructive pulmonary disease (COPD) patients with airflow obstruction compared to subjects with normal lung function. No differences, however, were found in the small airways.

Studies using airway secretions are now also providing some insight to the contribution of the various cytokines and chemoattractants to leukocyte recruitment into the lungs of patients with chronic lung diseases such as COPD. IS Woolhouse (Queen Elizabeth Hospital Birmingham, UK) and KM Beeh (University Hospital Mainz, Germany) demonstrated (using different methodologies) that the contribution of LTB_4 to the neutrophil chemotactic activity of sputum in COPD was significantly higher (30–50%) than that of IL-8 (16–30%) [5,6]. In addition DK Nelson (University of Arizona, USA) *et al*. were able to demonstrate that the increased chemotactic activity in exhaled breath condensate from smokers could be attenuated using an LTB_4 antagonist [7]. Taking these data together it would appear that LTB_4 is a particularly important neutrophil chemoattractant in smoking-induced lung disease.

In addition to the neutrophil, monocyte recruitment to the lungs is also likely to be important in COPD. SL Traves (National Heart and Lung Institute, London, UK) reported that in patients with COPD the migration of monocytes to growth-related protein α was significantly increased compared to monocytes from healthy volunteers [8]. This group also found that there were significantly higher levels of monocyte chemoattractant protein-1 and growth-related protein α in the sputum in COPD compared to healthy volunteers and smokers. Interestingly, KM Beeh (University Hospital Mainz, Germany) also found that monocyte migration in sputum from patients with lung cancer was increased, compared to smokers and healthy controls [9]. This effect appeared to be mediated by the CC chemokine, macrophage inflammatory protein-1α as chemotactic activity could be suppressed with an anti-macrophage inflammatory protein-1α antibody.

Finally three studies were presented showing how a number of COPD therapies, both in current use and potential agents for the future, may exert beneficial effects through the suppression of leukocyte migration. J Bishara (Southampton General Hospital, UK) studied the *in vitro* effects of fluticasone and salmeterol [10] and M Mikami (Tokyo Metropolitan Hiro-o General Hospital, Japan) studied the mucoactive agent s-carboxymethyl cysteine [11]. Both research groups were able to demonstrate significantly reduced transendothelial migration when neutrophils were incubated with these agents.

MP Pruniaux (Pfizer Laboratories, Fresnes, France) examined the effect of a novel phosphodiesterase 4 inhibitor on neutrophil numbers in bronchoalveolar lavage following lipopolysaccharide inhalation in rats [12]. This group found pre-treatment with this drug successfully inhibited neutrophil recruitment to the lungs of these animals and concluded that this therapeutic strategy may prove efficacious in the treatment of lung inflammation.

Alpha-1-antitrypsin deficiency

The early concept of the development of emphysema in patients with A1AT deficiency was based on a simple balance theory where the amount of neutrophil elastase released in the lung exceeded the amount of A1AT present. The net result was persistence of elastase activity leading to accelerated lung destruction. However it is now becoming clear that the pathogenic process is more complex than first believed.

A number of studies presented at the conference highlighted the influence of free elastase on aspects of host defences as well as connective tissue breakdown. T Spencer (University of Florida College of Medicine, USA) reported that alveolar macrophage function in patients with A1AT deficiency, as measured by lipopolysaccharide-stimulated IL-1β production, was significantly reduced compared to controls [13]. This appears to be an elastase-related effect given that IL-1β production was inhibited in control macrophages incubated with concentrations of elastase similar to that seen in A1AT deficiency. In addition, P Sivasothy (University of Cambridge, UK)

found that when A1AT was cleaved by free elastase in cystic fibrosis, it was unable to bind to human neutrophil defensin-1, a potent pro-inflammatory mediator released with elastase from the neutrophil azurophil granule [14].

Free elastase may also influence leukocyte recruitment in A1AT deficiency. IS Woolhouse (Queen Elizabeth Hospital Birmingham, UK) reported that the chemotactic activity of sputum from patients with A1AT deficiency is increased compared to matched control patients with COPD [5]. The major contribution to this chemotactic activity was from LTB_4, which has previously been shown to be produced by alveolar macrophages in response to free elastase [15]. Other molecules present in bronchial secretions may also be important in leukocyte recruitment. JS Parmar (Addenbrookes Hospital, Cambridge, UK) examined the pro-inflammatory properties of A1AT polymers, which can be detected in the lungs of some patients with A1AT deficiency [16]. He found that the polymers were able to induce neutrophil chemotaxis as well as shape change which may further compound the lung damage seen *in vivo*. H Parfrey (Cambridge Institute for Medical Research, UK) attempted to prevent this polymerisation by introducing mutations into an interhelical cavity on the surface of A1AT, however these mutations were ineffective [17].

Although the tissue damage seen in A1AT deficiency is thought to be predominantly neutrophil-mediated it is now becoming clear that the other cells may be involved. N. Kokturk (University of Florida College of Medicine, USA) reported that, despite the presence of increased levels of neutrophilic burden in bronchoalveolar fluid from subjects with A1AT deficiency, bronchial biopsy neutrophil counts were not raised [18]. This may be due to neutrophil migration into the airway lumen; however, M Hofer (University Hospital Zurich, Switzerland) found no difference in either intraluminal or intramural neutrophil counts in bronchiolar specimens from patients with A1AT deficiency and end-stage emphysema [19]. This group did, however, find significantly higher numbers of lymphocytes in the A1AT-deficient subjects, which may suggest a role for this cell in the pathogenesis of the disease.

The pathological and biochemical processes have been further studied in animal models of A1AT deficiency. These models also provide an opportunity to study the effects of A1AT augmentation therapy on these processes. G Lungarella (Sienna University, Italy) reported the pathological changes seen in the pallid mouse (which has a partial genetic deficiency of A1AT) following chronic cigarette exposure compared to room air exposed controls [20]. In the smoking mice he found that the emphysematous lesions were more severe and were associated with cellular infiltration and proliferation. In a similar study, Y Takubo (University of Utah, USA) compared the differences in smoke-induced emphysema between pallid and wild type mice [21]. This group found that the two types of mice developed different types of emphysema, with the pallid mouse resembling human panlobular emphysema and the wild type resembling human centrilobular emphysema. A Guerassimov (McGill University, Montreal, Canada) attempted to attenuate the smoking-induced emphysema in pallid mice by gene transfer of human A1AT [22]. There was no difference, however, in degree of emphysema following intramuscular injection of the human A1AT vector. Immunostaining of the vector-injected muscle suggested this lack of effect may be due to accumulation of the protein in the muscle.

Conclusion

The data presented at this conference highlight the considerable advances that have been made into the understanding of the basic mechanisms of inflammation in lung disease. We are now beginning to unravel the role of the individual adhesion molecules and cytokines in leukocyte recruitment into the lung with particular reference to the site and stimulus for migration, as well as disease phenotype. In alpha-1-antitrypsin deficiency the complex mechanisms of elastase-mediated lung destruction via effects on host defences are becoming clearer. In both of these areas this understanding should allow the development of specific novel anti-inflammatory therapies for acute and chronic lung diseases in the future.

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