Review

Focusing on diffuse (interstitial) lung disease: a rapidly evolving field

Roland M du Bois

Royal Brompton Hospital, London, UK

Correspondence: Roland M du Bois, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK. Tel: +44 20 7351 8327; fax: +44 20 7351 8336; e-mail: r.dubois@rbh.nthames.nhs.uk

Received: 14 January 2002
Accepted: 15 January 2002
Published: 19 February 2002

Respir Res 2002, **3**:16

(Print ISSN 1465-9921; Online ISSN 1465-993X)

The diffuse (interstitial) lung diseases have attracted an unprecedented level of interest over the past 5 years. Statements from the American Thoracic Society/European Respiratory Society committees on idiopathic pulmonary fibrosis (IPF), sarcoidosis and the idiopathic interstitial pneumonias, and from the British Thoracic Society on diffuse parenchymal lung diseases [1–3] have defined the phenotype of the idiopathic interstitial pneumonias more tightly than was previously the case. Much of the credit for this lies in the exploitation of high-resolution computed tomography to provide a three-dimensional anatomical display, with great precision, of the patterns of abnormality that occur in diffuse lung diseases [4]. Such precision has reinvigorated a molecular scientific approach, including molecular genetics, to gain an understanding of disease causation and progression.

With a more precisely defined diffuse lung disease phenotype, it is now possible to apply high throughput, moderately fine mapping technologies to define genetic predisposition to disease and severity of disease. The more precise phenotype has also stimulated scientists to rethink concepts of pathogenesis, particularly with regard to IPF, and to re-explore the relative contributions of inflammation and fibrogenesis to this disease. This renaissance in scientific interest has stimulated the pharmaceutical industry into an unprecedented level of activity with regard to these diseases, with investment in phase II and phase III studies of novel therapeutic approaches in an attempt to improve the appalling outcome for the most lethal of the diffuse lung diseases – IPF. At least seven studies of IPF therapy have been completed, are proceeding or are at the planning stages. In this series of articles in volume 3 of *Respiratory Research*, we address a number of key areas of development, with a specific focus on genetic predisposition and the fibrogenesis versus inflammation debate in IPF.

Iannuzzi *et al.* [5] discuss the power of genetic polymorphism analysis. They stress the number of pitfalls that can be encountered and the need for careful study design, using clearly defined populations, appropriate controls and a judicious combination of family-based association studies (generally using genome marker strategies) with case–control candidate gene studies. With this approach, important strides can be taken in our understanding of a variety of lung diseases, particularly chronic beryllium disease, sarcoidosis and IPF.

Seitzer *et al.* [6] and Pantelidis *et al.* [7] provide reviews of specific genetic targets. Seitzer *et al.* [6] discuss the loci on the short arm of chromosome 6, most specifically the class II human leucocyte antigen (HLA)-DR and tumour necrosis factor (TNF) loci, and the concept of a complex haplotype of major histocompatibility complex alleles with TNF-α and lymphotoxin-α genes. Defining genotype not just in terms of polymorphisms at one region (in this instance HLA-DR) but also in terms of those at a second region (specifically TNF-α in that review) provides evidence that this co-association of polymorphisms at different regions of the genome is important in identifying both disease susceptibility and progression markers. In this regard, a co-association of HLA-DR3 with TNF-A2 is associated with the less severe form of sarcoidosis – Löfgren's syndrome [8]. Seitzer *et al*. conclude that it was difficult to determine whether the TNF or the HLA-DR allele (which are in linkage disequilibrium) confers the greater risk, and that other element(s) in linkage disequilibrium are more likely to convey susceptibility.

Pantelidis *et al.* [7] review surfactant polymorphisms in the light of the recent observation by Nogee *et al.* [9] of a polymorphism in the surfactant protein C gene that

HLA=human leucocyte antigen; IPF=idiopathic pulmonary disease; TNF=tumour necrosis factor.

occurred in a mother and daughter, both of whom suffered from (different) diffuse lung diseases. The importance of surfactant in normal lung homeostasis and the association with abnormalities in surfactant in diffuse lung diseases is outlined. These abnormalities are most typically found in IPF, but also in sarcoidosis and hypersensitivity pneumonitis. Pantelidis *et al.* point out that a number of mutations have now been identified in association with hereditary surfactant deficiencies, and that all surfactant protein genes are polymorphic, but associations with diffuse lung disease have only been described for surfactant protein C thus far. Since the report by Nogee *et al.* [9] was published, a further series of surfactant protein C mutations have been identified in 34 infants with non-familial chronic lung disease (presented at the Thomas L Petty Aspen Lung Conference; Aspen, CO, USA; June 6–9 2001).

The application of immunogenetic predisposition to the diffuse lung diseases is an exciting development, and one that is matched by the intensity and quality of the debate surrounding the relative contributions of aberrant wound repair and inflammation to the pathogenesis of IPF. In a comprehensive commentary based on a recent review article by Selman *et al.* [10], Gauldie *et al.* [11] explore the concept that IPF is more due to an abnormal wound healing response than to inflammation-induced injury. They conclude (citing evidence from their own work and that of others) that inflammation may be necessary for the evolution of IPF, but it is insufficient alone to account for the histopathological and clinical response observations [12]. They suggest that a modulation of the normal interactions between alveolar epithelial cells and mesenchymal cells are critical determinants in the evolving disease process.

This issue is debated further in a comprehensive review by Selman and Pardo [13]. They present an elegantly logical argument, the central tenet of which is that damage to or stimulation of the epithelial cell (by cause or causes unknown) results in triggering of a mesenchymal response with a perpetuation of fibrogenesis, the trademark fibroblastic focus of which is among the more striking consequences of the interaction. Other factors that are probably involved in the dysregulation of repair include most notably those involved in coagulation (the balance between procoagulant and anticoagulant effects) and in collagen turnover (profibrotic and antifibrotic mechanisms).

The importance and interaction of growth factors in the new paradigm is reviewed by Allen and Spiteri [14]. They highlight the relative contributions of the key growth factors and the importance of the emergence and persistence of myofibroblasts, together with regulatory factors including apoptosis.

Keane and Strieter [15] review the role of the balance of T-helper-1 and T-helper-2 cytokines and chemokines in fibrosing lung disease, and emphasize the importance of the concept of balance in biosystems. They 'rein back' the momentum of conceptualizing IPF as a pure injury/response disease and highlight a variety of inflammatory responses that must not be minimized in terms of their role in modifying the pathogenesis of this disease.

The study of diffuse lung disease is in a golden era of rapid molecular science advances, which are being integrated into the design of new highly targeted therapeutic strategies. The reviews in this series illustrate the considerable knowledge that has been acquired over recent years and signposts future goals and targets. In particular, an increased understanding of the genetic control of (aberrant) responses to injury, inflammation and fibrosis, and the relative contributions made by positive and negative controls in these processes augers well for future and rapid advances in diffuse lung disease.

References

1. American Thoracic Society: **Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS).** *Am J Respir Crit Care Med* 2000, **161**:646-664.
2. **The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults.** *Thorax* 1999, **54(suppl 1)**: S1-S28.
3. Anonymous: **Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999.** *Am J Respir Crit Care Med* 1999; **160**:736-755.
4. Hansell DM: **High-resolution computed tomography and diffuse lung disease.** *J R Coll Physicians Lond* 1999, **33**:525-531.
5. Iannuzzi MC, Maliarik M, Rybicki B: **Genetic polymorphisms in lung disease: bandwagon or breakthrough?** *Respir Res* 2002, **3**:15.
6. Seitzer U, Gerdes J, Müller-Quernheim J: **Genotyping in the MHC locus: potential for defining predictive markers in sarcoidosis.** *Respir Res* 2002, **3**:6.
7. Pantelidis P, Veeraraghavan S, du Bois RM: **Surfactant gene polymorphisms and interstitial lung diseases.** *Respir Res* 2002, **3**:14.
8. Swider C, Schnittger L, Bogunia-Kubik K, Gerdes J, Flad H, Lange A, Seitzer U: **TNF-alpha and HLA-DR genotyping as potential prognostic markers in pulmonary sarcoidosis.** *Eur Cytokine Netw* 1999, **10**:143-146.
9. Nogee LM, Dunbar AE III, Wert SE, Askin F, Hamvas A, Whitsett JA: **A mutation in the surfactant protein C gene associated with familial interstitial lung disease.** *N Engl J Med* 2001, **344**: 573-579.
10. Selman M, King TE, Pardo A: **Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy.** *Ann Intern Med* 2001, **134**:136-151.
11. Gauldie J, Kolb M, Sime PJ: **A new direction in the pathogenesis of idiopathic pulmonary fibrosis?** *Respir Res* 2002, **3**:1.
12. Sime PJ, Xing Z, Graham FL, Csaky KG, Gauldie J: **Adenovector-mediated gene transfer of active transforming growth factor-beta1 induces prolonged severe fibrosis in rat lung.** *J Clin Invest* 1997, **100**:768-776.
13. Selman M, Pardo A: **Idiopathic pulmonary fibrosis: an epithelial/fibroblastic cross-talk disorder.** *Respir Res* 2002, **3**:3.
14. Allen JT, Spiteri MA: **Growth factors in idiopathic pulmonary fibrosis: relative roles.** *Respir Res* 2002, **3**:13.
15. Keane MP, Strieter RM: **The importance of balanced pro-inflammatory and anti-inflammatory mechanisms in diffuse lung disease.** *Respir Res* 2002, **3**:5.