

Commentary

Autoantibodies in cryptogenic fibrosing alveolitis

Suveer Singh and Ron du Bois

Royal Brompton Hospital, Sydney Street, London, UK

Correspondence: Ron 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

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Abstract

The pathogenesis of cryptogenic fibrosing alveolitis (CFA) involves injury, an immune/inflammatory response and fibrosis. The cause of the injury is unknown, but the identification of serum autoantibodies makes an autoimmune aetiology attractive. The core study on which this commentary is based used novel cloning and serum screening technologies in order to identify new public and private autoantibodies in sera from 12 patients with CFA. Largely negative conclusions were drawn from that study. However, we suggest that the prevalence of autoantibodies may have been underestimated, that the study was timely and that this approach is worth pursuing further.

Keywords: autoantibodies, cryptogenic fibrosing alveolitis, expression libraries, idiopathic pulmonary fibrosis, pathogenesis

Introduction

CFA is associated with inflammation and fibrosis of the pulmonary interstitium and peripheral air spaces, and is of unknown cause [1]. It is synonymous with the term 'idiopathic pulmonary fibrosis', which is employed in the USA. Recent international consensus [2] defined this entity more specifically, on the basis of the histopathological appearances of a usual interstitial pneumonia pattern of idiopathic nature, thus distinguishing it from usual interstitial pneumonia of known cause and from idiopathic interstitial pneumonias with different histopathological patterns.

Prevalence and incidence

The incidence has been estimated at 10.7 and 7.4 cases per 100,000 for males and females, respectively, on the basis of US registry data, whereas population-based studies put the prevalence at between 3 and 20 cases per 100,000 [3]. Prognosis is generally poor, with mean survival from diagnosis of 3.2–5 years [4].

Aetiology

Potential aetiological risk factors for CFA include cigarette smoking, and exposure to metal and wood dust [5–7]. Infectious agents, in particular Epstein–Barr virus, have been implicated in case referent data that demonstrated increased antibody titres to Epstein–Barr virus in CFA as compared with pulmonary fibrosis of known causes [8], although recent gene amplification studies [9,10] have been equivocal. There is some evidence for hereditary factors in descriptions of familial cases of CFA, although these are infrequent, and there has been no clear demonstration of an association with the major histocompatibility complex loci or other candidate genes.

Pathogenesis

The pathogenesis of CFA involves alveolar injury from an unknown trigger, a persistent or repeated immuno-inflammatory phase, and dysregulated tissue repair, with exaggerated angiogenesis and fibroproliferation in susceptible individuals. This results in progressive deposition of extra-

cellular matrix, pulmonary fibrosis and lung destruction [11]. These processes may run in parallel rather than sequentially. Hence, the temporal pathological heterogeneity is reflected in the spatial heterogeneity of histopathological appearances [12].

T-helper-1/T-helper-2 balance

The mechanisms that underlie the immunopathological process are being elucidated. The balance of T-helper (Th) lymphocyte subsets (Th1/Th2) appears important in this respect. A Th2 response predominates in the pulmonary interstitium of CFA. By contrast, Th1 and Th2 are equally expressed in the lung of fibrosing alveolitis associated with systemic sclerosis [13]. This may promote a profibrogenic state, through the actions of fibroproliferative mediators such as transforming growth factor- β , which is preferentially expressed in the pulmonary epithelium and interstitium of patients with CFA [14]. Moreover, the finding of reduced expression of the Th1-derived cytokine interferon- γ , which may activate cell-mediated mechanisms for removal of cellular antigens and restoration of normal tissue, led to a recent pilot study of interferon- γ 1b in idiopathic pulmonary fibrosis [15], with some reported outcome benefit. Thus, fibrosis is believed to result from an imbalance between proinflammatory and anti-inflammatory cytokines, fibrogenic and antifibrogenic polypeptides, and angiogenic/angiostatic molecules.

Autoantibodies

In CFA, polyclonal B-lymphocyte stimulation results in increased peripheral blood immunoglobulin concentrations. Non-organ-specific circulating autoantibodies have been found in approximately 40% of patients with CFA [16]. These include antinuclear antibodies, anti-DNA topoisomerase II antibodies and antibodies to cytokeratin 8 [17–19]. Moreover, immune complexes are present in blood, lung lavage fluid and tissue of CFA patients [20,21]. In seeking an explanation for the presence of autoantibodies in CFA, it has been suggested that they are unlikely to be a primary cause of tissue damage, although they may augment the inflammatory process. It is possible that they may represent a nonspecific consequence of lung inflammation and injury, thereby providing some explanation for their variable expression. More specific immunohistochemical data [22,23] have demonstrated the presence of circulating IgG autoantibodies to pulmonary epithelial cells in CFA patients, thus implicating the putative autoantigen as endogenous and specific to the lung.

Public and private specificities: the core article

In the present issue of *Respiratory Research*, the interesting report of Robinson *et al* [24] adds weight to the circumstantial evidence for an association between autoantigens and CFA. Through the use of a cDNA library derived from a tumour cell line, proteins were expressed, and those recognized by antibodies that were present in

the serum of an index case were used to screen sera from 12 other patients with CFA. Three such autoantigens were identified, of which alanyl tRNA synthetase has previously been associated with pulmonary fibrosis in the context of polymyositis, but not CFA. The absence of individual antibody specificities in more than one patient led to a conclusion that these antibodies with so-called private specificities in CFA sera are an epiphenomenon rather than a potential cause of alveolar damage. The same group used the serologic identification by recombinant expression cloning (SEREX) technique to identify the public antibody specificities that were present in patients with malignant mesothelioma [25].

With regard to the study of Robinson *et al* [24] presented in this issue, it is debatable whether a cloned malignant-cell derived cDNA library can provide appropriate antigen specificities to enable adequate identification of autoantigens that are specifically relevant to CFA. Furthermore, a single patient's serum was used as the probe for the expressed library, which makes subsequent screening very dependent on the epitopic specificities of that individual's (auto)immune response and of the origins of the cloned library. Thus, there may be a potential under-representation of autoantigens and their associated antibodies. Therefore, although the private specificities identified in the study of Robinson *et al* do not provide sufficient evidence for a causative role in CFA, neither can this possibility be ruled out on the basis of the small number of patients screened and potential under-representation of antigens from the cDNA library.

Conclusion

In conclusion, the pathogenesis of CFA remains unclear, but involves a fibroblastic process that is coexistent with or consequent upon a parenchymal injurious process. The exact role of the autoantigen specificities that are identifiable in the sera of such patients is elusive. Do such autoantibodies represent evidence of ongoing injury, or could they be initiating the damaging process? Furthermore, could their presence amplify an already established cycle of inflammation/fibrogenesis?

The presence of private specificities, which are frequently associated with certain connective tissue/rheumatological diseases, in serum from CFA (without clinical manifestations of an overlap state) is intriguing. Could CFA be a 'local' autoimmune process, and what additional molecular process(es) is necessary for linking these autoantigens/antibody complexes to a pulmonary inflammatory process and the clinical manifestations of CFA/overlap syndromes.

With the use of new molecular techniques, including SEREX, and with progress in well-defined cDNA library technology, it is now possible to screen large numbers of CFA sera. Perhaps the central 'cause or effect' question

may then be addressed more rigorously. Genetic predisposition and host susceptibility factor(s) that determine the phenotypic expression of autoantibodies (as with Scl-70 in systemic sclerosis) and clinical manifestations of CFA remain unknown, and molecular genetic studies such as that by Robinson *et al* are a welcome addition to our present knowledge and must be commended. That report points the way forward.

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