

Diffuse lung disease: product of genetic susceptibility and environmental encounters

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Abstract

Diffuse (interstitial) lung disease comprises a wide variety of conditions, individually relatively uncommon but collectively being found in approximately 50 per 100 000 population. Some of these diseases are of known aetiology but others are not. It has been suggested that the environment is a major contributory factor in this group of diseases. However, since not all individuals exposed to a common environment develop interstitial diseases, it can be hypothesised that there is a genetic predisposition to their development. These diseases cause major morbidity and mortality due to lung injury and fibrosis. It follows that, if individuals who are genetically predisposed to develop diseases characterised by lung injury and fibrosis can be identified, then management strategies can be designed which will attempt to identify and treat early disease and, in the longer term, to develop targeted genetic interventional approaches to treatment.

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Diffuse lung diseases may be triggered by known or unknown factors. Environmental risk factors include occupational exposure to beryllium, cobalt or asbestos, therapeutic drugs, and radiation. Risk factors also include gender, age, and race. For example, systemic sclerosis occurs predominantly in women (male:female ratio 9:1) whereas sarcoidosis occurs predominantly in those in the 30-40 year age range and is a more aggressive disease in patients of Afro-Caribbean descent than in Caucasians.

Exposure to similar amounts of environmental agent does not induce disease in all individuals and apparently trivial exposure can result in disease, suggesting that genetic predisposition may be important in disease development. Complex diffuse lung diseases are the product of genetic factors, which do not exhibit Mendelian characteristics, and environmental exposure. Linkage and population studies are among the means used to identify genetic predisposition.¹ Most studies of diffuse

lung disease have used a population study approach with genes of interest, or candidate genes, identified prospectively by a knowledge of the pathophysiology of the disease.

Scientific basis

The principal candidate genes that have been studied in diffuse lung disease have been those encoded by the major histocompatibility complex (MHC) classes I, II, and III. Genes within the MHC region encode cell surface glycoproteins known as the human leucocyte antigens (HLA) which present processed antigens to T cells and are highly polymorphic. Immune responses are principally driven by T cell receptor (TcR) activation resulting from recognition of peptides which are presented as a complex with HLA molecules on the surface of antigen presenting cells.

GRANULOMATOUS DISEASES

Immune granulomas result from specific cell mediated immune mechanisms, although the triggering event is not always clearly identified. Chronic beryllium disease (berylliosis) is an antigen driven disease in which sarcoid-like granulomas are formed in the lungs following inhalation of beryllium salts. Not all individuals exposed to beryllium develop the disease and exposure to relatively small amounts of antigen can cause disease in some individuals. There is an association between HLA-DPB alleles with a glutamate residue at position 69 of the β chain (Glu 69) and development of berylliosis.² HLA-DPB proteins are encoded by genes within the MHC and are involved in presenting foreign antigens to CD4+ T lymphocytes. The amino acid residue 69 is situated within the binding cleft of the HLA-DPB protein (fig 1) and is involved in antigen binding and recognition by the TcR. This suggests that the immune response seen in chronic beryllium disease is at least partially controlled by the presentation and binding of the antigen.

Sarcoidosis is a chronic granulomatous disorder of unknown aetiology. Some evidence suggests that sarcoid granulomas are formed in response to a persistent and poorly degraded antigenic stimulus and that there is likely to be some form of genetic predisposition to the disease related to antigen presentation. Genes

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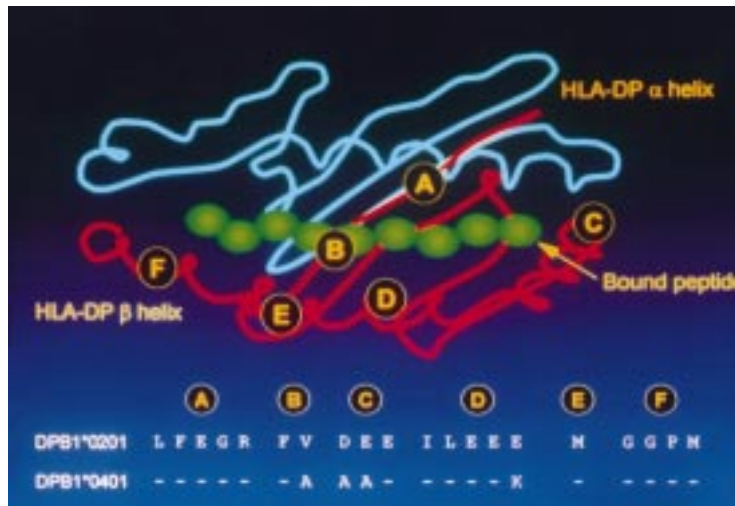


Figure 1 Antigen binding cleft of the DP molecule showing polymorphic sites which are thought to influence antigen binding and recognition by the T cell receptor.

within the MHC region are the most likely candidates for this predisposition, although studies of the association between these genes and sarcoidosis have produced disparate results.³ This discrepancy may be attributed to a number of factors including obvious ethnic differences and disease diagnosis or staging. We have recently shown a significant association between HLA-DPB Glu 69+ alleles and sarcoidosis in a carefully defined population of Caucasian patients with sarcoidosis when compared with an ethnically matched control population.⁴ This suggests that there may be a common gene or set of genes involved in the formation of granulomas.

Generally, the reported MHC associations have not been absolute, suggesting that other genes may also be involved. Accumulation of activated T cells at disease sites in sarcoidosis, and the functional relationship between the MHC and the TcR, support the hypothesis that the genes encoding the TcR are good candidates to influence the development of diffuse lung disease. There is discordance in the results of studies of the clonality of TcR variable (V) chain families found in diffuse lung disease, which is possibly due to differences in the MHC phenotype of the patients studied. This hypothesis has been tested in a study which used a combined MHC, TcR approach in sarcoidosis and showed a very strong concordance between HLA-DR3, DQ2, and the TcR V α 2.3 chain.⁵

FIBROSING LUNG DISEASE

Diffuse lung disease is one of the most common features of systemic sclerosis and some degree of fibrosing alveolitis is found in most patients at post mortem examination. Systemic sclerosis is considered to be an autoimmune disease and population studies have reported conflicting and often relatively weak associations of MHC with the disease, possibly due to geographical, environmental, and ethnic variability or clinical heterogeneity. Environmental variability may be important since different causal antigens

may trigger the same disease in different patients. Additionally, environmental triggers may be refractory to digestion by macrophages and may therefore induce prolonged release of inflammatory mediators which perpetuate the T cell response. Geographical variability may result in the presence of different environmental triggers but also differences in linkage disequilibrium between HLA antigens. There may also be heterogeneity in disease diagnosis resulting in a lack of consistency in terms of disease subsetting.

In a study of patients with systemic sclerosis in association with pulmonary fibrosis it was shown that the presence of the HLA-DR3/DR52a alleles and/or the anti-Scl-70 autoantibody was a risk factor for the development of pulmonary fibrosis.⁶ Similar findings have subsequently been reported in other racial groups and suggest that HLA alleles may be important in identifying specific disease subtypes.⁷⁻⁹

Therapeutic potential

One of the more exciting potential benefits of defining genetic susceptibility to diffuse lung disease is the identification of patients who are more likely to develop lung disease, especially fibrosis. Early clinical intervention in such cases could be of considerable benefit for the patient. A good example is the identification and assessment of disease progression in diffuse lung disease found in systemic sclerosis. Autoantibodies to critical cell antigens are common in systemic sclerosis and the presence of certain autoantibodies has been linked with clinical subsets or racial subgroups of patients with systemic sclerosis.¹⁰ This association probably occurs because the disease subsets result from activation of distinct subpopulations of T cells and stimulate the production of different autoantibodies. This is supported by data that show that certain MHC alleles are associated with the development of certain autoantibodies.¹¹ It is therefore reasonable to suppose that identification of a disease subset may be important in the instigation of careful monitoring and potentially more effective treatment. Ultimately, genetic transfer technologies may reverse the biological consequences of the genetic predisposition.¹²

Conclusions

In the past decade there have been considerable advances in the assessment of genetic susceptibility to diffuse lung disease. We are now able to identify genetic polymorphisms and to perform functional studies related to polymorphisms found in these regions. Consequently, we are in a strong position to identify and define disease susceptibility in genetic terms, although this clearly requires further study and confirmation from different research groups. In addition, the identification of risk factors has important implications for the initiation of close disease monitoring and for the initiation of appropriate therapy at an early

stage of disease when this would be most effective.

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