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Editorial

Genetics of tumour necrosis factor (TNF) in autoimmune liver diseases: red hot or red herring?

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A MAJOR THRUST of medical research at present involves the localisation and characterisation of those genetic variants that contribute to the development of common diseases. A large number of diseases have a multifactorial basis, with both environmental and genetic factors being important in the aetiology and/or clinical severity. For many of these diseases multiple genetic variants are believed to contribute, with a threshold number of variants possibly being required. Localisation of this relatively small number of variants, among the total of around 100 000 genes contained within the 3 billion bases that make up the human genome, is a major task.

Two approaches have been used: whole genome or candidate gene scans. The former relies on identification based on position, and generally involves typing of 200–300 polymorphic markers scattered across the genome, frequently at 10–20-million base (mb) intervals. Initial genome scans have been reported in a number of polygenic diseases such as insulin-dependent diabetes mellitus and rheumatoid arthritis (1,2). These studies have mainly involved large numbers of sib pairs concordant for disease. The second approach, the candidate gene approach, involves genetic screening of a gene whose encoded protein has been implicated in the pathogenesis of the disease under study. In diseases with a significant inflammatory component potential candidates genes are those encoding cytokines, adhesion molecules and apoptotic factors.

The gene for tumour necrosis factor alpha (TNFA) has attracted much attention as a possible contributor in autoimmune diseases because of the activities of the encoded protein and because TNFA lies within the human major histocompatibility complex. This is a 4 mb stretch of DNA on chromosome 6 that encodes over 200 genes, many of which are immunologically relevant (Fig. 1). Of the large number of diseases with an autoimmune component, most show genetic association with MHC alleles, with most studies implicating the class II loci HLA-DR and -DQ (3). TNFA lies less than 1 mb from the DR locus, which is, in genetic terms, very close.

A number of polymorphisms within TNFA have been described. Four polymorphisms lie in the promoter region and a fifth is located within the first exon (4). Most interest has centred on position −308, which contains a biallelic variant; the common allele is designated TNF-308G (TNF1) and the uncommon allele TNF-308A (TNF2) (5). Genetic studies have shown that TNF2 lies on the HLA A1-B8-DR3-DR2 haplotype (6). This is of interest for a number of reasons: individuals with this haplotype produce high levels of TNFα and are more susceptible to a range of autoimmune diseases (3).

Several studies have addressed the functional significance of this polymorphism using reporter gene constructs. While not all studies are in agreement, the majority have shown that the TNF2 promoter fragment is a more powerful transcriptional activator (7–9), possibly due to the differential binding of a nuclear protein to this allele (7,10).

These results have led to extensive investigation into the importance of TNFA genetics in autoimmune and

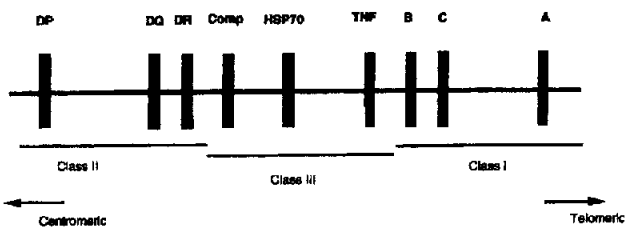

Fig. 1. Structure of the human MHC. This region is 4 million bases in length and lies on the short arm of chromosome 6.

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infectious diseases (see (11)). The most significant findings have been in infectious diseases, such as malaria (12), leishmaniasis (13) and trachoma (14), in which carriage of TNF2 is associated with a poorer prognosis. Studies in autoimmune diseases have been less convincing, although there is evidence in several autoimmune rheumatic diseases of a genetic contribution from the TNF locus (15–17).

A number of studies published in this journal have investigated the role of TNFA polymorphism in autoimmune hepatic diseases. Primary biliary cirrhosis (PBC) is associated with HLA-DR8. Two groups have examined TNFA genotypes in PBC patients and controls. Interestingly, one concluded that TNF2 was under-represented in patients compared with healthy controls, suggesting protection against disease susceptibility (18), while another found under-representation in patients with severe disease, suggesting a modulating effect on disease severity (19). It may, at first, seem surprising that carriage of a high TNFα-producing allele should be protective against an autoimmune disease. However, a similar association has been described in human systemic lupus erythematosus (20), and administration of recombinant TNFα to an animal model of lupus protects against a severe phenotype (21). A recent study has suggested a possible mechanism for these observations: chronic administration of TNFα to T cell receptor transgenic mice suppressed T cell responsiveness and function, so perhaps in PBC higher TNFα levels may downmodulate the immune activity that is directed against the liver (22). Primary sclerosing cholangitis shows a strong association with the HLA A1-B8-DR3-DQ2 haplotype, with the telomeric limit of the MHC-encoded susceptibility lying in the vicinity of the HLA C locus (23). A report in this journal has now localised the region containing the disease-related genetic variant to the region containing TNF and HLA B (24).

The rapid accumulation of the genomic sequence and large number of well-characterised polymorphic markers within this region of the genome will be key to further genetic studies (25,26). The localisation of the MHC disease-related variants in autoimmune liver disease will be greatly facilitated by this information. Future studies, using a dense array of polymorphic markers in this region of the MHC, should give a clearer indication if genetic variation within TNFA, rather than a nearby linked gene, is the reason for the genetic association of this region with autoimmune hepatic diseases.

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