HCV, HDV and autoimmunity

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Autoimmunity may be observed in chronic viral hepatitis, in particular hepatitis C and D. The hepatitis C virus (HCV) displays numerous interactions with the immune system. Hepatitis C virus induces a number of diseases of presumed autoimmune background, like mixed cryoglobulinemia, glomerulonephritis, panarthritis, arthritis, thyroiditis and skin lesions. On the other hand a number of autoantibodies are observed during the course of hepatitis C. Of particular interest are liver/kidney microsomal antibodies (LKM). Their occurrence in viral hepatitis may indicate an increased risk for treatment with interferons. LKM antibodies in chronic hepatitis C recognise several autoepitopes differing from those in autoimmune hepatitis. Hepatitis C-associated LKM antibodies are more heterogeneous. They recognise either conformational or several distinct linear autoepitopes on cytochrome P450 2D6, they may also react with other microsomal proteins. Apart from their molecular weight at 59 and 70 kD these microsomal antigens are not yet identified. LKM-1 antibodies in hepatitis C recognise one conformational epitope that is common to hepatitis C and autoimmune hepatitis sera. Specific linear epitopes are associated with autoimmune hepatitis, one of them has sequence homology with the immediate early protein of the herpes simplex virus type 1.

Another model of virus-induced autoimmunity in man is chronic hepatitis D which always requires co-infection with hepatitis B. Hepatitis D is known to be associated with a number of autoantibodies, amongst them basal cell layer antibodies (BCLA), thymic stellate antibodies and liver kidney microsomal antibodies type 3 (LKM-3). LKM-3 antibodies have recently been shown to react with proteins of the UDP glucuronosyl transferase family (UGT). The main antigen is an autoepitope expressed on exon 2-5 of family 1 UGTs. Some hepatitis D sera recognise a minor second epitope on family 2 UGTs. It is interesting that hepatitis C patients recognise proteins of the cytochrome P450 family while hepatitis D sera react with UGTs. There seems to be little overlap between autoimmunity seen in hepatitis C and D as far as autoepitopes are concerned. LKM-3 antibodies against UGT 1 are also seen in a minority of patients with autoimmune hepatitis type 2. However, the autoimmune response against UGTs seen in autoimmune hepatitis differs from that observed in viral hepatitis. Autoantibodies in autoimmune liver disease are usually more homogeneous and are directed against precise linear epitopes. Autoepitopes in autoimmune hepatitis usually represent conserved regions of these proteins, the antibody usually is inhibitory and antibody titres are very high. In contrast autoantibodies in viral hepatitis are more heterogeneous, recognise several linear and conformational epitopes ; antibody titres are much lower. However, the major LKM autoantigen in chronic hepatitis C also is P450 2D6. A minority of hepatitis C sera recognise cytochrome P450 2A6 which is a major autoantigen in the autoimmune polyendocrine syndrome type 1. A hepatitis C virus core CTL-epitope shares sequence homology with cytochrome P450 2A6 and P450 2A7. However, this CTL-epitope is also recognised by lymphocytes from healthy controls. A sequence homology between hepatitis C core and cytochrome P450 2D6, the major autoantigen in hepatitis C and autoimmune hepatitis type 2 has been described before, however, a crossreactivity at the T-cell level has not been demonstrated so far. Autoimmune hepatitis and autoimmunity in viral hepatitis must be distinguished clinically by all means due to the need for specific therapeutic interventions. These liver diseases may serve as models to study virus induced autoimmunity and autoimmune disease in man.

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