Recent Advances in Autoimmune Liver Diseases

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Three diseases are regarded as autoimmune liver diseases, autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Major advances which have been achieved in this area are the molecular definition of autoantigens, a preliminary analysis of the T-cell response, the analysis of the immunogenetic background, a better distinction between autoimmune hepatitis and viral hepatitis and an improved strategy to treat these patients specifically either with interferons or corticosteroids.

The antigens in autoimmune liver diseases are now among the best characterized autoantigens in autoimmune diseases in general. The major antigens in primary biliary cirrhosis belong to the mitochondrial acyltransferases. The most prominent of all these antigens is the E2 subunit of pyruvate dehydrogenase. Anti-PDH-E2 antibodies inhibit enzyme function in vitro and T-lymphocytes were isolated from the liver which specifically respond to these proteins. Furthermore the bile duct epithelia of PBC patients express a structure that crossreacts with the autoepitope of PDH-E2. It is unknown whether this is PDH-E2 itself or a crossreacting infectious agent.

Primary biliary cirrhosis has also become a disease with a defined genetic background. Several studies have shown that HLA DR 8 is significantly increased. Furthermore complement genes which belong to the HLA class III genes due to their localization on the short arm of chromosome 6 have been linked to primary biliary cirrhosis. C4 B2 was found to be increased in British patients while C4 A Q0 alleles were found to be increased in German patients with PBC. This finding could hint to a viral etiology of PBC as complement factor C4 is involved in immune complex formation and viral clearance. Medical treatment of choice for PBC nowadays is ursodeoxycholic acid. Possibly the therapeutic effect of ursodeoxycholic acid is at least in part due to an interaction with the immune system. Finally orthotopic liver transplantation improves survival and quality of life for patients with end stage PBC.

Autoimmune hepatitis is also a disease of unknown cause. It has been redefined by an international group of experts. Autoimmune hepatitis is characterized by female sex, hypergammaglobulinemia, immunogenetic background, characteristic autoantibodies and response to immunosuppression. Immunogenetic background has been elucidated due to recent progress based on DNA based technology. After the demonstration of a link of autoimmune hepatitis type 1 with HLA haplotype AI-B8-DR 3, Japanese investigators found HLA DR 4 to be associated with their patients suffering from autoimmune hepatitis type 1. Therefore it became evident that there is a dual association of Caucasian patients with autoimmune hepatitis with either HLA DR 3 or HLA DR 4. Patients with HLA DR 3 are younger at onset of disease, disease progression is more severe, conse-
sequently the proportion of HLA DR3-positive patients has increased in the transplant population and relapse after treatment is frequent. Low serum levels of complement factor C4A in autoimmune hepatitis are due to gene deletions as demonstrated. Due to the application of molecular cloning techniques hepatocellular autoantigens became identified at their molecular level. There is a debate whether subgroups of autoimmune hepatitis may be defined by different patterns of circulating autoantibodies. Autoimmune hepatitis type I is serologically characterized by high titre antinuclear antibodies with or without smooth muscle antibodies directed against F actin. Autoimmune hepatitis type II is characterized by liver/kidney microsomal antibodies type I, while autoimmune hepatitis type III is associated with antibodies to cytosolic liver antigens called anti-SLA and anti-LP. Anti-SLA antibodies react with cytokeratins, while the molecular target of anti-LP antibodies has not yet been defined. There seem to be some characteristic clinical features of autoimmune hepatitis type II. This disease frequently starts in childhood and extrahepatic syndromes are frequent. The serological autoimmune response in autoimmune hepatitis type II is directed against microsomal antigens, in particular a short linear sequence of cytochrome P450 II D6. In general the immune response in autoimmune hepatitis type II is more homogeneous and more specific compared to the serological hallmarks of autoimmune hepatitis type I. Antinuclear antibodies (ANA) as detected by immunofluorescence on either tissue slices or Hep 2 cell cultures. The ANA antigens are very heterogeneous. So far neither a liver specific nor a disease specific nuclear antigen has been identified. Interestingly, nuclear autoantigens in hepatic and extrahepatic autoimmune disorders belong to functionally important families of proteins involved in cell division, RNA processing etc. Recently we added cyclin A to the list of nuclear antigens in autoimmune liver diseases. Another important group of autoantigens are the microsomal autoantigens which have been identified as members of the cytochrome P450 supergene family. The main antigen in autoimmune hepatitis type II is cytochrome P450 II D6. The core epitope is an 8 aminoacid peptide which shares sequence homology with the herpes simplex virus type 1 immediate early protein 175. These LKM-1 antibodies inhibit cytochrome P450 II D6 function in vitro but not in vivo. Patients with autoimmune hepatitis type II express the P450 II D6 protein in their livers. They are extensive metabolizers and usually carry one wild type and one mutant deficient allele of P450 II D6. 2–7% of patients with chronic hepatitis C have circulating LKM-1 antibodies as detected by immunofluorescence. The anti-LKM-1 response in chronic hepatitis C is much more heterogeneous than in autoimmune hepatitis type II. The autoepitope on cytochrome P450 II D6 is either larger or different from the 8 aminoacid epitope of autoimmune hepatitis type II. In addition LKM-1 antibodies in hepatitis C may react with either microsomal or conformational epitopes of P450 II D6. As the virus is not responsible, different host factors must be responsible for this type of autoimmunity observed in chronic hepatitis C. This could also explain the geographical difference observed for the occurrence of LKM-1 antibodies in chronic hepatitis C. Our latest discovery is the identification of family 1 UDP-glucuronosyl transferases (UGTs) as the major LKM-3 autoantigen in chronic hepatitis D and in a minority of patients with autoimmune hepatitis. The autoepitope is expressed on the constant region of exon 2–5 of UDP-glucuronosyl transferases. A minor additional epitope is expressed on UGT family type 2 proteins. Once again the autoepitope in autoimmune hepatitis is more homogeneous and the autoimmune response is much stronger than in viral hepatitis D. These studies will allow to distinguish between autoimmunity secondary to viral hepatitis and autoimmune genuine liver disease. This may help to treat these patients more specifically.
REFERENCES


5) Straßburg Ch., et al: submitted