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REVIEW

Viruses and auto-immune hepatitis

B. REHERMANN*, K. MICHITAKA†, M. DURAZZO‡, K. MERGENER*, P. VELEV§ & M. P. MANNS* *Abteilung Gastroenterologie und Hepatologie, Zentrum Innere Medizin und Dermatologie, Medizinische Hochschule Hannover; †Third Department of Internal Medicine, Ehime University, School of Medicine, Shizukawa, Japan; ‡Division of Gastroenterology, Institute di Medicina Interna, Universita di Torino, Torino, Italy and §Medical Academy, Institute of Gastroenterology and Nutrition, Sofia, Bulgaria

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Auto-immune disease and auto-immunity

Auto-immune disease is an aggressive and harmful immune reaction against autologous tissue. Both the humoral and the cellular part of the immune response are involved since auto-antibodies as well as auto-reactive T-cells are present. Auto-immune disease as a pathologic disorder has to be distinguished from auto-immunity which might serve physiologic functions: in fact, auto-antibodies as well as B- and T-lymphocytes bearing specific receptors for self-antigens are found in healthy individuals. Auto-reactive cells were fully capable of inducing experimental auto-immune disease in animals after *in vitro* clonal expansion, activation and adoptive transfer [1]. Surprisingly, the cells persisted after host's recovery from auto-immune disease and seemed to convey immune protection since then [2]. Whether an immune response stays protective or becomes auto-aggressive and harmful exacerbating in an auto-immune disease might depend on genetic predisposition, age, weakening of immunologic control mechanisms and environmental influences. Especially drugs, bacteria and viruses are discussed as triggering environmental agents. This review discusses the impact of hepatotropic viruses on a distinct form of auto-immune disease—auto-immune hepatitis.

Auto-immune hepatitis

Auto-immune hepatitis, first described by Waldenstrom in 1950 [3], is still a disease of unknown aetiology. It is characterized by histologic features as the occurrence of LE cells [4] and serologic findings as high titers of auto-antibodies. Antibodies against nuclear antigens (ANA) [5,6] and smooth muscles (SMA) [7,8] are present in type 1, antibodies against liver kidney microsomes (LKM-1) in type 2 [8] and antibodies against soluble liver antigen (SLA), i.e. cytokeratin type 8 and 18 [9] in type 3 of auto-immune hepatitis [10]. However, there are also antibody-negative forms of auto-immune hepatitis [11,12]. Very often the disease is associated with HLA antigens A1, B8, DR3 or DR4 [5] but all extensive genetic studies published so far are limited to auto-immune hepatitis type 1 (Table 2).

According to the consensus view of the International Autoimmune Hepatitis Group as elaborated at the last meeting in Brighton June 1992 [13] auto-immune hepatitis is most often found in women and defined an ANA, SMA or anti-LKM-1 titers greater than 1:80 and IgG greater than 1·5 of the normal (Table 1). Characteristics are increased transaminases and polyclonal hypergammaglobulinaemia. Liver biopsies show lymphoplasmacytic infiltrates and periportal piecemeal necrosis in presence or absence of lobular hepatitis. Biliary lesions, granulomatous siderosis, cuprinosis and other changes have to be excluded. HBsAg, IgM anti-HBc, IgM anti-HSV, anti-CMV, anti-EBV and IgM anti-HAV must be negative and HCV-RNA must not be detectable in serum. To exclude the possibility of any toxic liver damage the patient should not have taken any hepatotoxic drugs and no or only minimal amounts of alcohol. The disease responds to immunsuppressive therapy which is an accepted diagnostic criterium by itself.

Hepatotropic viruses in auto-immune hepatitis

Viruses are discussed as environmental agents triggering auto-immune disease in general and auto-immune hepatitis in particular. Potential mechanisms which viruses might use to induce self-perpetuating auto-immune reactions in susceptible individuals are disturbance of immunologic control mechanisms, modifica-

Correspondence: M. P. Manns MD, Professor and Chairman, Abt. Gastroenterologie und Hepatologie, Zentrum Innere Medizin und Dermatologie, Medizinische Hochschule Hannover, Konstanty-Gutschow-Strasse 8, Hannover, Germany.

Table 1. Definition of auto-immune hepatitis

Hypergammaglobulinaemia	+3
Auto-antibodies	
ANA, SMA, LKM-1	+3
SLA, ASGPR, LC, LP, HHPM	+2
AMA	−2
Female sex (80–90%)	+2
Benefit from immunosuppression	+2
Genetics	
B8-DR3 or DR4	+1
HBsAg, IgM anti HAV	−3

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tion of auto-antigens and molecular mimicry between self-antigens and viral sequences. Apart from the major hepatitis viruses A to E, herpes simplex virus type 1 (HSV-1) and measles virus (Table 3), several other hepatotropic viruses are under specific investigation: cytomegalovirus (CMV), Epstein-Barr virus (EBV), enteroviruses as coxsackie and arboviruses as dengue and yellow fever virus.

Hepatitis A

Hepatitis A runs an acute, self-limiting course, though rare cases show a prolonged course with one or more relapses. Proven chronic hepatitis is unknown [14,15]. Histologically, inflammation and piecemeal necrosis of hepatocytes dominate in the periportal fields [16]: characteristic histological changes that are usually found in chronic active, but not in acute hepatitis. Tissue destruction in hepatitis A seems to be mediated by immunologic mechanisms towards virus infected hepatocytes [17]: in fact, patients with acute hepatitis A show *in vitro* T-cell cytotoxicity against virus infected target cells [18]. High titers of auto-antibodies against smooth muscle antigens and liver components are present as well [19]. However, it seems to be difficult to explain why immunologically mediated liver destruction in hepatitis A is limited to the periportal region. One reason might be the expression of candidate self antigens such as the asialoglycoprotein receptor (ASGPR) on membranes of periportal hepatocytes

Table 3. Viruses and auto-immune hepatitis

Measle virus
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Hepatitis D virus
Herpes simplex virus

[20,26]. Many patients with acute hepatitis A synthesize antibodies against ASGPR [21,31] which might guide antibody dependent cytotoxic cells (ADCC) to the periportal region. Such an auto-immune reaction can even persist after clearance of the virus in susceptible individuals: two patients with a known defect of control mechanisms related to the ASGPR-immune response were described to develop auto-immune hepatitis following acute hepatitis A: After complete clinical recovery from acute hepatitis A anti-ASGPR-titers raised and chronic auto-immune hepatitis type I followed [22]. However, on the premise that auto-immune hepatitis could have developed accidentally after acute HAV infection in these few patients, it is still unknown how relevant hepatitis A virus is for the development of auto-immune disease in general.

Hepatitis B

It is well accepted that in hepatitis B (HBV) infection not the virus itself but the immune response of the host towards virus infected hepatocytes mediates tissue destruction. It is also speculated that humoral and cellular auto-immune reactions contribute to liver disease. Since many patients present with long standing disease or even liver cirrhosis it is difficult to differentiate whether a viral infection or an auto-immune disorder was present first [23] and whether HBV-infection may induce auto-immune hepatitis. However, a few case reports describe occurrence of auto-antibodies and chronic hepatitis half a year after complete clearance of hepatitis B virus [24]. These cases of apparently virus-induced auto-immune disease respond well to steroid treatment.

In chronic hepatitis B auto-antibodies are frequently observed in low titers and it is currently discussed

Table 2. Heterogeneity of HBsAg negative chronic hepatitis

	ANA	LKM-1	SLA	SMA	AMA	HCV-RNA	Therapy
Chronic hepatitis C	−	−	−	−	−	+	Interferon
Auto-immune hepatitis							
type 1	+	−	−	+	−	−	Immunosuppression
type 2a	−	+	−	−	−	−	Immunosuppression
type 2b	−	+	−	−	−	+	?
type 3	−	−	+	+/−	+/−	−	Immunosuppression
type 4	−	−	−	+	−	−	Immunosuppression
Primary biliary cirrhosis	−	−	−	−	+	−	UDCA etc.

whether they contribute directly to liver damage in chronic hepatitis B [25,26,27]. They can be divided into two groups according to their specificity: non-organ specific antibodies are directed against nuclear (ANA) and smooth muscle antigens (SMA). Liver-specific antibodies bind to the asialoglycoprotein-receptor (ASGPR), one of the many components of liver specific protein (LSP). LSP is a crude macromolecular mixture of proteins ($>4 \times 10^{-6}$) prepared by centrifugation of fresh normal liver homogenates and sepharose gel filtration of the supernatant [25]. While antibodies against LSP are frequently found in patients with auto-immune hepatitis, in approximately 50% of patients with viral hepatitis and also in other forms of liver disease, ASGPR antibodies seem to be closer associated with auto-immune hepatitis.

The production of these auto-antibodies might be virus-induced: though autoreactive B-cells are naturally occurring, they generally remain inactive without any specific stimulation. In chronic hepatitis B they become stimulated by virus-specific T-Helper-cells. The presence of autoantigen-specific T-Helper-clones [28] as well as polyclonal activation of autoreactive B-cells was excluded. Auto-antibodies produced by these B-cells then activate antibody-dependent cytotoxic cells (ADCC), i.e. non-T lymphocytes bearing Fc receptors [29]. These cells are identified in viral as well as in auto-immune hepatitis. Anti-ASGPR-antibodies, for example, may direct ADCC to the periportal regions where ASGP-receptors are expressed on almost all hepatocytes [27,30]. Afferent blood carrying more auto-antibodies into the periportal region could cause an additional coating of the surrounding cells with auto-antibodies.

According to this hypothesis, hepatocytes bearing the ASGPR on their cell surface are then lysed and periportal inflammation and piecemeal necrosis develops [27,31]. Since anti-ASGPR antibodies occur in viral hepatitis and in auto-immune hepatitis, humoral response to ASGPR may not be linked to a certain aetiology. However, recent data seem to indicate that the epitopes recognized by anti-ASGPR differ in liver disease of auto-immune and viral aetiology.

As far as cellular auto-immune reactions are concerned there is a major difference between viral and auto-immune liver disease: Cytotoxic T-lymphocytes dominate in viral hepatitis, but not in auto-immune liver disease [32]. In hepatitis B the major target antigen for cytotoxic T-cells is the HBV-core antigen expressed on the plasma membrane of infected hepatocytes [33,34,35]. These hepatocytes are then lysed by HBc-Ag-specific T-lymphocytes. Patients with self-limited acute hepatitis B have a strong lymphocytic response towards this epitope while patients developing chronic hepatitis B only show weak lymphocytic activation. Theoretically, the efficiency of this anti-viral-immune response might be decreased, when anti-HBc antibodies cover the cell-surface-antigens, when HBc-Ag is not expressed on the plasma membrane or when there is no sufficient HLA-co-expression. However, the actual mechanisms responsible for a weak cytotoxic response of lymphocytes in chronic hepatitis need to be further investigated.

Though cytotoxic lymphocytes are primarly targeted against viral antigens, they might also recognize auto-antigens under special conditions. HBV-polymerase shows an identical sequence of eight amino-acids with the encephalitogenic site of myelin basic protein. Autoreactivity in form of antiMBP antibodies, proliferation of MBP-specific lymphocytes and allergic encephalitis could be induced experimentally by immunizing rabbits with this epitope [36]. This kind of molecular mimicry between viral and auto-antigens seems to convey the missing link between viral and auto-antigen specific T-cell reactivity. However, encephalitis is not a frequent sequelae of HBV-infection.

Hepatitis C

Hepatitis C, the former nonA-nonB hepatitis, used to be distinguished from auto-immune hepatitis by the complete absence of auto-antibodies. This definition still provides the basis for different treatment: auto-antibody negative hepatitis C is treated with interferon while antiHCV- and HCV-RNA negative auto-immune hepatitis is treated with immunsuppressive agents (Table 2).

However, anti-HCV tests of first and second generation as well as polymerase chain reaction for HCV-RNA have revealed, that the dividing line between both entities is not that clear. In fact, hepatitis C virus infection is found in some patients with auto-immune hepatitis type 2 and in non-hepatic diseases with an unknown or presumably auto-immune aetiology. Among them are mixed cryoglobulinaemia [37], polyarthritis, polyarteritis nodosa [38] and Sjögren's syndrome [39]. Very recently, porphyria cutanea tarda [40] and glomerulonephritis [42] have been added to this list of diseases associated with HCV infection.

In auto-immune hepatitis type I, characterized by the presence of antinuclear antibodies, 44% of Spanish patients [43], 50% of Italian patients [44] and 60% of British patients [44] were positive for anti-HCV in first generation ELISA. However, these early tests were characterized by a high percentage of false positive results due to binding of antibodies to the test's superoxide dismutase [45] or to hypergammaglobulinaemia causing unspecific binding. For example, French children with auto-immune hepatitis who were positive for anti-HCV in first generation ELISA initially, were tested as negative when hypergammaglobulinaemia decreased under steroid treatment [46].

Tests became more reliable after the introduction of second generation ELISAs and recombinant immunoblot assay (RIBA) which are more specific due to the addition of several synthetic viral peptides and superoxide dismutase as a control. Later, polymerase chain reaction for the detection of HCV-RNA, i.e. the

replicating virus, became the gold standard. Testing the same patient population [43,44] revealed that 53% of Italian patients with auto-immune hepatitis type I and only 8% of British patients were positive for anti-HCV [44]. In general, there is striking difference between a low prevalance of hepatitis C in Caucasian patients with auto-immune hepatitis type 1 in Northern Europe and a high prevalence in the Mediterranean area [47].

Geographical as well as genetic differences might be responsible for this distribution. In Italy, for example [48], there is a high frequency of genuine exposure to hepatitis C. In patients with auto-immune hepatitis the prevalence of hepatitis C might even be higher due to immunosuppressive therapy. This hypothesis is confirmed by the fact that not only anti-HCV but also a variety of antibodies to other pathogens as rubella and measles virus can be detected [49]. Alternatively, the hepatitis C virus itself might be responsible for hepatitis C associated auto-immune hepatitis by triggering auto-antibody production. In Japan [50] and possibly in Africa (own unpublished data) HCV infection may lead to the induction of antinuclear antibodies.

Moreover, it is still an intriguing hypothesis that the hepatitis C virus might induce anti-LKM 1 antibodies in auto-immune hepatitis type 2. In auto-immune hepatitis type 2 the geographic distribution of anti-HCV-antibodies is similar to that of auto-immune hepatitis type 1. The overall prevalence of hepatitis C in auto-immune hepatitis type 2 is less than 10% in British patients [44] and approximately 50% in German [51] and French patients [52] as opposed to more than 90% in Italian [44], Spanish and Japanese patients [53]. The Caucasian population of North America represents the same pattern as in Northern Europe, i.e. a low association between auto-immune hepatitis and hepatitis C infection, while in Southern regions of the USA the situation is comparable to Southern Europe [54]. These results were confirmed by RIBA, anti-HCV ELISA of second generation and polymerase chain reaction for HCV-RNA.

Testing for HCV-RNA defines two clinically distinct subgroups of auto-immune hepatitis type 2: patients without hepatitis C infection (type 2a) present with the classical symptoms of auto-immune hepatitis (see above) while patients with hepatitis C infection (type 2b) are generally older, more often male and have lower anti-LKM titers [55]. While subgroup 2a responds well to therapy with steroids alone or in combination with azathioprin, subgroup 2b usually does not profit from any kind of immunosuppression (Table 5). Whether interferon is as effective in these patients as in patients with HCV-RNA positive chronic hepatitis C is not known yet; though a first response with normalization of transaminases is usually observed there seems to be an increased frequency of reactivation of the disease (Durazzo, Rizzetto *et al.*, personal communication).

Interestingly, differences in clinical presentation of both subgroups seem to correlate with differences in humoral immunology. There is evidence that the antigen specifically recognized by microsomal antibodies differs in patients with and without chronic hepatitis C infection [56]: in classical auto-immune hepatitis type 2a a 50 kd protein identified as cytochrome P450 IID6 [57,58] functions as the major target antigen for LKM-1 antibodies. The epitope recognized by LKM-1 antibodies consists of eight amino acids and shows sequence homology with the immediate early antigen of herpes simplex virus type I [59]. Our experience is that LKM antibodies in patients with HCV infection (AIH type 2b) may recognize other microsomal proteins in addition to the 50 kD P450 II D6 [60]. Those additional antigens were identified as 59 and 70 kD bands by immunoblotting. However, the analysis is not performed at a nuclear level yet.

Table 4. Hepatitis C virus and immune mediated disease

Auto-immune hepatitis type 1? (Japan, Africa)
Auto-immune hepatitis type 2
Mixed cryoglobulinaemia
Porphyria cutanea tarda
Sjögren's syndrome
Polyarthritis
Panarteritis nodosa
Membranoproliferative glomerulonephritis

Among the list of other diseases (Table 4) associated with HCV infection, mixed cryoglobulinaemia is one of the most important ones [61]. Two thirds of patients with mixed cryoglobulinaemia have abnormal liver function tests [62,63]. Whether viral or auto-immune hepatitis causes the deposition of immune complexes in the liver has not been evaluated so far. HCV-RNA was detected in serum of 90% of Italian [64], French [37] and American patients [65] with mixed cryoglobulinaemia and is a constituent of the cryoprecipitates. Interestingly, prevalence of anti-HCV was only around 42–70% and it has to be discussed whether other anti-HCV antibodies not detectable by currently available commercial ELISAs may exist and contribute to these cryoprecipitates. In most patients antinuclear and anti-smooth muscle antibodies but no LKM-antibodies are present (Ferri *et al.*, unpublished

Table 5. Heterogeneity of auto-immune hepatitis type 2

	Subgroup	
	Type 2a HCV− ($n=15$)	Type 2b HCV+ ($n=14$)
Anti-GOR	I	11
Sex (F/M)	12/3	8/6
Age (years)	19 (4–38)	46 (22–66)*
LKM 1-titre (RIA)	14823 (500–64000)	949 (10–800)*
AST ($U\ l^{-1}$)	440 (42–1425)	74 (19–362)*

Values expressed as medium (range); AST = aspartate aminotransferase. *$P<0.001$
According to reference 51.

data). There is also evidence that a monoclonal immunoglobulin might be involved in the aetiology of the disease; type 2 of mixed cryoglobulinaemia which shows the strongest correlation with hepatitis C infection, is characterized by the presence of this monoclonal immunoglobulin. A possible candidate is monoclonal IgM rheumatoid factor. It binds to the Fc portions of polyclonal IgG, e.g. anti-HCV, and thus may build the typical cryoprecipitates. In fact, treatment of cryoprecipitates with dithiothreitol to remove rheumatic factor led to an unmasking of anti-HCV [66]. Overproduction of rheumatoid factor as an example for a monoclonal immunoglobulin might occur by a B-cell clone stimulated by the hepatitis C virus. Similar mechanisms have already been shown in chronic EBV and HBV [67] infection where uncontrolled proliferation of a distinct B-cell-clone was induced by the virus. Whether this model might also apply to the hepatitis C virus still has to be studied.

If the hepatitis C virus contributes to the pathogenesis of mixed cryoglobulinaemia, inferferon seems to be a hopeful new therapeutic approach for this disease which has previously been treated with immunosuppressive agents. In a study of seven patients, all responded with reduction of circulating cryoglobulins, improvement of general conditions and systemic vasculitis [68]. However, the clinical effects of interferon treatment are still contradictory and need to be studied further: first, it has to be taken into account that interferon has a direct effect on cryoglobulin synthesis by inhibition of differentiation of immunocompetent B-cells [70,71]. In fact, one case with no improvement of liver function tests despite reduction of cryoglobulins is reported [69]. Second, two patients are known in which mixed cryoglobulinaemia developed at the same time as interferon therapy for haematologic tumours was started. After cessation of therapy mixed cryoglobulinaemia resolved [72].

Very recently, several patients with hepatitis C, mixed cryoglobulinaemia and glomerulonephritis have been described [73]. While the pathogenetic role of immunocomplexes forming subepithelial deposits in the renal glomerula is well accepted, the antigenic components of these complexes are still unknown. The new data suggest that hepatitis C virus might play a causal role, because HCV RNA and IgG anti-HCV antibodies to the nucleocapsid core antigen were detected in cryoprecipitates. Moreover, IgM rheumatoid factors binding to anti-HCV IgG were detected in these patients and could play a causal role in the induction of cryoprecipitates. Consequently, some of the patients were treated with alfa-interferon and responded with decreased HCV replication, improved renal function and reduced inflammatory activity of the liver disease [73].

Sjögren's syndrome and porphyria cutanea tarda shall be mentioned as candidates of non-hepatic disease that are associated with hepatitis C infection. Sjögren's syndrome is characterized by dry lacrimal and salivary glands. Demonstration of lymphocyte infiltration of salivary glands as well as antinuclear SSA/La antibodies in serum are diagnostic parameters [74]. As these antibodies indicate cell death due to auto-immune reactions, an immunologic reaction against antigenic targets of the glands seems to be possible. As EBV has been found in salivary glands of patients with Sjögren's syndrome [75] and HCV is also secreted by saliva, it is intriguing to speculate whether HCV proteins or HCV induced antigens are expressed on the epithelium of lacrimal and salivary glands. This hypothesis needs further evaluation by *in situ* hybridization and polymerase chain reaction. The detection of HCV minus strands would indicate HCV replication in these tissues.

As far as porphyria cutanea tarda is concerned, not much more than a strong association with HCV infection is known yet [40]. A recent Spanish study reported a prevalence of 62% of anti-HCV antibodies in patients with porphyria cutanea tarda [41]. Our own examinations resulting from a collaboration with an Italian group of investigators (Ferri *et al.*, unpublished data) identify a subgroup of patients positive for antiLKM-antibodies. This is earlier evidence for an assumed auto-immune background of porphyrea cutanea tarda and further investigation is required to understand the clinical relevance as well as pathogenesis in all these hepatitis C virus associated hepatic and non-hepatic diseases.

Whether hepatitis C virus induced auto-immunity really exists at the humoral and cellular level is one of the most interesting areas currently being investigated. There is increasing evidence that apart from cytopathic effects of the virus itself, immune reactions of the host towards virus-infected cells are present [76,77]. Liver lymphocytes are predominantly of the CD8+CD11− phenotype representing cytotoxic lymphocytes [78]. In mice infected with a recombinant vaccinia-HCV NS5 vector, CTL response has been demonstrated against a polymerase-like protein of the NS5 region [79]. In humans, HCV-specific HLA class I-restricted cytotoxic T-lymphocytes have been isolated from liver biopsies in chronic hepatitis C. Those cells lyse cells expressing either structural or non-structural proteins of HCV on the cell surface. In fact, two 8 and 11 aminoacids long T-cell epitopes were identified in variable regions of hepatitis C E1 and NS2 proteins [77]. Whether this virus specific immune response of the host contributes to the clearance of the virus or causes liver destruction is not yet known. However, sequence analysis revealed a great variation of the viral genome in the region covering the T-cell epitopes [80]. Therefore viral mutants that escape the immune response of the host and are responsible for the high percentage of chronic hepatitis C are probable.

By means of molecular mimicry between viral and host antigens, hepatitis C induced auto-immunity might become relevant. In this context it is important to mention that Mishiro [81] isolated a host nuclear antigen called GOR that shares part of its sequence with the HCV-core peptid. GOR is a 27 aminoacid

long antigen, over-expressed in the nucleolus of tumour cells. The epitope recognized by anti-GOR antibodies consists of 15 amino acids [82]. Anti-GOR antibodies are found in up to 60% of patients with hepatitis C for anti-HCV positive auto-immune hepatitis type 2b [51]. Their specificity to hepatitis C virus infection is corroborated by the fact that they are not found in anti-HCV negative auto-immune hepatitis type 2a and not in anti-HCV-negative hepatitis D infection. Moreover, anti-GOR titers decline similar to anti-HCV titers during effective interferon therapy of patients with chronic hepatitis C [83].

In summary, humoral immune reactions towards GOR-antigen could either reflect cross-reactivity of anti-GOR-antibodies with viral and self structures or represent true virus-induced auto-immunity. In fact, there is some, but not linear homology between a short sequence of aminoacids of the GOR epitope and the hepatitis C core peptide [82]. In this context it is of interest that we established GOR-specific T-cell clones from blood lymphocytes of a patient with chronic hepatitis C [84]. Whether they also recognize hepatitis C core peptide needs to be further analysed.

Hepatitis D

Auto-antibodies are found in one third of the cases with chronic hepatitis D infection [85,86,87]. All of them are organ-, but not liver-specific: antibodies against liver-kidney microsomes [88], against stellate thymic epithelial cells, reticular perithymic cells, basal cell layers in the thymus [89] and cytoskeleton antibodies, most often IgM-anti-intermediate filaments [90]. There is no difference between active and inactive disease [89,91] and the virus itself is known to be cytopathic [92]: therefore a pathogenetic role of these auto-antibodies may be doubted. Anti-GOR antibodies in chronic hepatitis D always indicate HCV-superinfection [93]. The major LKM-3 antigen characteristic for hepatitis D was located at 55 kD by immunoblotting; however this antigen has not been cloned yet.

Herpes simplex virus type I and other viruses

Antibodies to herpes simplex virus-1 proteins were detected in 17 of 20 LKM-1 positive human sera [94]. This is of special interest because the immediate-early protein IE 175 of HSV-1 shows some sequence homology to a short segment of P450 IID6, PAQPPR (Fig. 1). This protein is expressed during the early stages of HSV infection and neonatal patients with antibodies against it have a poor prognosis. In addition, there is sequence homology between a part of P450 IID6 and the HCV-protein c100-3. In an experimental approach to study molecular mimicry, the synthetic peptide DPAQPPRDC was used to purify LKM-1 antibodies and these affinity-purified antibodies reacted on immunoblots with a protein expressed by BHK cells after infection with HSV-1. However, they did not react with c100-3 [94]. Clinical relevance of molecular mimicry becomes evident from the following case: we recently treated a 7-year-old patient with chronic auto-immune hepatitis type 2 and fulminant liver failure. Signs of auto-immune disease were evident in form of vitiligo, nail dystrophie and alopecia areata. In addition to anti-LKM antibodies he developed high titers of IgM anti-HSV which decreased under immunosuppression. Sequence homology between LKM-1 antigen and HSV-1 antigen seems to be the basis for relevant molecular mimicry in this case.

Immunogenetics

In Caucasians auto-immune hepatitis type 1 is frequently associated with the HLA haplotype A1 B8 DR3 [95] and the immunoglobulin allotype Gm a+x+ [96,97]. Generally, DR4 is associated with later manifestation of the disease and a more favourable course (Table 6). In auto-immune hepatitis type 2 the situation is less clear. HLA DR3 seems to be increased in the whole group of auto-immune hepatitis type 2 in France [98]. In our German patients HLA DR3 is only increased in the HCV negative population of auto-immune hepatitis type 2 while in Italy HLA DR3 is

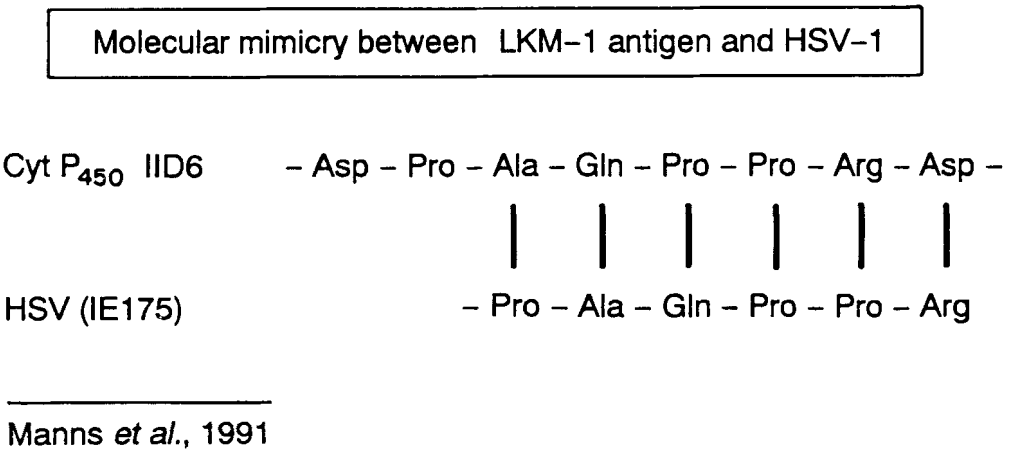

Figure 1.

long antigen, over-expressed in the nucleolus of tumour cells. The epitope recognized by anti-GOR antibodies consists of 15 amino acids [82]. Anti-GOR antibodies are found in up to 60% of patients with hepatitis C for anti-HCV positive auto-immune hepatitis type 2b [51]. Their specificity to hepatitis C virus infection is corroborated by the fact that they are not found in anti-HCV negative auto-immune hepatitis type 2a and not in anti-HCV-negative hepatitis D infection. Moreover, anti-GOR titers decline similar to anti-HCV titers during effective interferon therapy of patients with chronic hepatitis C [83].

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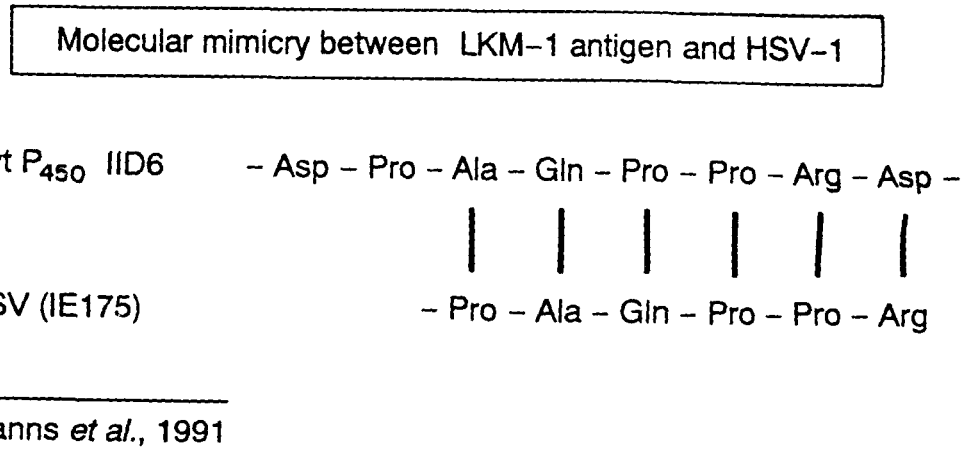

Figure 1.

Table 6. HLA DR3 and DR4 as markers of distinct subgroups of auto-immune hepatitis

	DR3	DR4
Age at onset	young	older
Disease activity	+++	+
Relapse after treatment	+++	+
Transplantation	+++	+
Extrahepatic syndromes	+	+++
C4A-deletion	+++	−

increased in all AIH type 2 patients [99]. Complement genes C2, C4 and Bf are localized on the short arm of chromosome 6 between HLA class 1 and 2 loci. They are therefore called HLA class 3 genes. The HLA class 3 allele C4A is often deleted in HLA-A1, B8, DR3 positive patients [100]. Consequences of C4A deficiencies are not clear yet: since C4 plays a crucial role in the classical pathway of complement activation, its deficiency might cause impaired clearance of immune complexes, viruses and other foreign antigens. Increased C4A-Q0 alleles are found in auto-immune hepatitis type 1 and 2.

So far no association between any viral hepatitis and HLA antigens has been found. However, HLA complexes bind small epitopes [101] of viral peptides and self and non-self are presented together to the effector cells. Genetic variety of HLA could change the HLA-specific binding motif and cause differences in the presentation of viral peptides and differences in the resulting immune response.

Clinical relevance and outlook

Understanding the mechanisms of immune response in viral hepatitis might clarify the differences between virus-associated immunologic epiphenomena, immunologic reactions necessary for viral clearance and immunologic disorders causing auto-immune hepatitis. Therefore more specific and effective therapies for viral and auto-immune hepatitis might become available. Treatment with interferon is of benefit to patients with chronic hepatitis B or C. At 5 million units interferon three times a week, 35% of patients lost the HBe antigen and HBV-DNA, 10% experienced permanent loss of HBs antigen [102]. In chronic hepatitis C 50% of patients treated with 3 million units interferon thrice weekly lost HCV-RNA and half of them stayed without relapse after the end of interferon therapy [103–106]. However, the same therapy might stimulate auto-immune responses and exert hazardous effects in auto-immune hepatitis since both disease entities might overlap. Since auto-immune hepatitis might deteriorate rapidly [11] it is crucial to apply criteria for immunosuppressive therapy. Corticosteroids and azathioprin are used successfully to maintain clinical symptoms, auto-antibody levels and histologic signs of inflammation at a low level. However, this therapy is still directed at an unspecific and global suppression of immune reactions. If our knowledge about lymphocyte stimulation and specificity increases, therapy might become more effective: currently investigated are the application of anti-CD4-antibodies and budenoside, a steroid with 90% first pass in the liver. On the other hand, new diagnostic tools may identify many diseases of auto-immune or unknown origin as virus-induced. One of the most relevant examples is mixed cryoglobulinaemia, especially type 2, which seems to be linked to the hepatitis C virus. Once the true pathogenesis of these diseases is revealed, more specific and causal therapies may become available.

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