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REVIEW ARTICLE

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Autoimmune hepatitis

Definition – classification – histopathology – immunopathogenesis

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Abstract Autoimmune hepatitis (AIH) is a distinct form of acute and chronic inflammatory liver disease in which immune reactions against host antigens are found to be the major pathological mechanism. If left untreated it carries an unfavourable prognosis, and the diagnosis should be made as soon as possible. The diagnostic approach has been greatly facilitated by the establishment of a panel of marker autoantibodies, which do not define distinct therapeutic groups of AIH, but do allow a subgrouping based on differences in patient populations, some clinical features and prognosis. The characterization of organ-specific components of the liver cell surface as targets of cellular and humoral autoimmune reactions give new insights into the pathogenesis of the disease, even though the primary event triggering the disease remains to be defined. The most important disease-promoting factor seems to be a genetically determined background for autoimmunity. Without this different environmental factors, including viruses, toxins, cytokines and drugs, are only able to induce transient autoimmune phenomena and not autoimmune disease. The histopathology of AIH is in keeping with the present pathogenetic concept. Although there is no pathognomonic feature distinguishing this type of hepatitis from virus-induced forms, some distinct morphological lesions are regarded as characteristic. Clinical research on AIH has benefited greatly from observations of experimental AIH in mice. Recognition of the critical role of autoreactive T-lymphocytes in the pathogenesis and the observation of spontaneous recovery from AIH in the animal model associated with antigen-specific and antigen-non-specific T-cell suppression have made basic contributions to our improved understanding of the natural course of AIH in humans.

Key words Autoimmune hepatitis · Characterization · Histopathology · Immunopathogenesis

This article is dedicated to Prof. Dr. Dr. h.c. Paul Schölmerich on the occasion of his 80th birthday

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Definition

Acute and chronic inflammatory liver diseases resulting from autoimmunity are distinct entities in which immune reactions against host antigens are believed to be the major pathogenetic mechanism [80]. The clinical characteristics of these forms of inflammatory liver disease were first described by Waldenström in 1950 [113], and later by Kunkel et al. in 1951 [42]. In 1955 Joske and King [36] observed the lupus erythematosus (LE) cell phenomenon in such patients. Mackay et al. [60] confirmed this finding in a larger number of patients and created the term lupoid hepatitis.

Today autoimmune hepatitis (AIH), like other autoimmune disorders (Table 1) is regarded as a clinical syndrome occurring in both sexes and all age groups, with a marked female predominance. Familial occurrence has also been described. Most patients present with typical clinical manifestations. Hepatomegaly and splenomegaly are the most common abnormal physical findings. AIH is frequently associated with other autoimmune disorders [23, 102]. The abnormalities of the immune system include autoantibodies [25, 35, 60, 64, 93], hypergammaglobulinaemia, associations [22, 42, 111] with typical HLA class I and class II antigens [17, 59, 62], and an increased CD4/CD8 ratio in peripheral blood and liver tissue [80]. Epidemiological and virological studies suggest that autoimmune hepatitis cannot be attributed to the presence of hepatitis viruses A–E [34, 57]. It is important to exclude drug-induced or toxic liver disease in the diagnosis. Some drugs are implicated in the development of clinical disorders and immune abnormalities that are similar to AIH [80, 102]. Early observations of the

Table 1 Profile of autoimmune diseases

Female predominance
Autoantibodies
Chronic inflammatory disease
Immunogenetic background: HLA association
Associated immune disease
Therapy: immunosuppression

Table 2 Definition of autoimmune hepatitis [34]

Hypergammaglobulinaemia		+3
Autoantibodies	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 and HAV		−3

Table 3 Hepatitis C virus (HCV) in autoimmune hepatitis type 2

	HCV ∅	HCV ⊕
Age	Young	Older
Sex	Female	No predominance
SGPT	↑↑↑	↑
LKM-1 titre	+++	+
Immunosuppression	+++	?
IFN	∅	(+)
DR3	++	+
C4A-Q0	+	+

natural course of AIH stress the serious nature of the disease and the poor prognosis [4].

About 40% of the patients present with acute hepatitis, some of them with fulminant liver failure or rapid progression to cirrhosis. These results have been confirmed in controlled trials and support the view that AIH is an aetiologically, histologically and clinically distinct subgroup of acute and chronic hepatitis that benefits from immunosuppressive therapy [34, 39].

The last decade has seen significant advances in clinical research into autoimmune liver diseases thanks to contributions from basic immunology and from molecular and cell biology. In this article the data on classification, immunopathogenesis and histopathology of AIH are reviewed.

Classification

The availability of precise and specific techniques for the detection of the hepatitis viruses A, B, C, D and E has led to a more definitive characterization of AIH [34, 51]. Clinical, biochemical, and histological features and the specificity of circulating autoantibodies were used in the development of diagnostic criteria by a panel of experts (International Autoimmune Hepatits Group) during the meeting of the International Association for the study of the liver in Brighton, UK, 1992 [34] (Table 2). Although the panel voted against the subdivision of AIH based on marker autoantibodies (autoantibodies do not define distinct therapeutic groups of AIH), it is reasonable to distinguish between AIH type I, characterized by antinuclear antibodies (ANA) and smooth-muscle antibodies (SMA, anti-actin) and AIH type II, defined by liver-kidney microsomal antibodies (LKM_1) [1]. The subgrouping is justified by differences in patient populations, some clinical features, and prognosis [34].

AIH type I is the most common type of AIH, accounting for about 60–70% of patients [23]. Low-titre anti-mitochondrial antibodies (AMA] are found in about 20% of this group without biliary changes when they are investigated by histopathology or cholangiography [38], but biliary lesions, which are typical for primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) with a positive test for ANA or SMA should not be regarded as criteria for the diagnosis of AIH, even when there is a good response to immunosuppressive therapy [1].

AIH type II characterized by autoantibodies against microsomal antigens of liver and kidney (LKM_1) [10, 25] and absence of ANA and SMA is a rare disease, accounting for only 5% of patients with AIH (Table 3). Seventy percent of the patients are young, between 2 and 14 years, at onset, and an association with concurrent immunological disorders is found in about 50% of them [1]. AIH type II frequently starts with acute onset, severe course, and quick progression to liver failure or cirrhosis. Diagnostically it may sometimes be difficult to distinguish LKM_1 autoantibodies from AMA by immunofluorescence using kidney tissue sections. Nowadays an enzyme immunoassay is available, which is more specific in the detection of LKM_1 autoantibodies. As target autoantigen the cytochrome P450 IID6 has been identified (Table 4). Molecular cloning of human LKM_1 antigen has enabled the production of recombinant LKM_1 antigen as a diagnostic reagent [58, 62, 65].

LKM autoantibodies can be induced not only by autoimmune mechanisms but also by drugs, such as tieniec acid [24], dihydralazine, halothane, phenytoin, phenobarbital and carbamazepine) (for references see [61]) and the hepatitis C and D viruses (for references see [70, 109]). Low-titre LKM_1 autoantibodies have been observed in less than 5% of patients with hepatitis C virus infections. A good response to α-interferon suggests a viral and not an autoimmune aetiology. The course of hepatitis C virus-induced, LKM_1 autoantibody-positive disease is usually mild, with sluggish progression to cirrhosis of the liver. The patients are significantly older and more frequently male than those with AIH type II [10, 47] (Table 3). The so-called LKM_2 autoantibodies observed in drug-induced liver diseases react with different cytochrome P450 epitopes (Table 4; see also [61]). The target antigen of LKM_3 antibodies occurring in about 10–15% of patients with delta hepatitis is an enzyme of the endoplasmatic reticulum, UDP glucuronosyl *S*-transferase or UDP-GT (Table 4) [89].

Table 4 Microsomal autoantigens in liver diseases

Nomenclature	MW (kDa)	Biochemical definition	Association with disease
LKM-1	50	P450 II D 6	Autoimmune hepatitis type II
LKM-1	64	?	Chronic hepatitis C
LKM-1	50	P450 II D 6	Chronic hepatitis C
LKM-1	59	?	Chronic hepatitis C
LKM-1	70	?	Chronic hepatitis C
			Drug-induced hepatitis
LKM-2	50	P450 II C 9	Tienilic acid
LKM-2	52	P450 I A 2	Dihydralazine
LKM-2	57	P450 II C	Halothane
LKM-2		P 450 II C 11	Anticonvulsants
LKM-2		P 450 III A 1	Anticonvulsants
LKM-3	55	UDP-GT	Hepatitis D

Only 70% of patients with AIH have one of the classic autoantibody markers, such as ANA and/or SMA or LKM_1. Tests for autoantibodies to a soluble liver antigen (SLA) [64], liver cytosolic antigen (LC_1) [66], an antigen of liver and pancreas (LP) [61], and the asialoglycoprotein receptor (ASGPR) [68, 91, 107] can help to identify AIH in most cases, especially patients with hypergammaglobulinaemia and a selective increase of serum IgG levels. Unfortunately, assays for anti-SLA, anti-LC_1, anti-LP, and anti-ASGPR are restricted to very few laboratories, a problem that has to be solved in the near future [74]. In addition to testing these autoantibodies, HLA-typing should be performed, since most AIH patients are positive for HLA A1, B8, DR3 or DR4 [17, 62]. If the findings are suggestive but not definitive, a prompt complete response to immunosuppressive drugs may help to confirm the diagnosis. The clinical course of patients with anti-SLA, anti-LC_1, anti-LP, or anti-ASGPR autoantibodies is similar to that seen in patients with AIH type I. At the moment it is important to note that the absence of autoantibodies at presentation should not exclude the diagnosis of AIH [1, 74]. This still holds true for about 30% of the patients whose diagnosis may be missed because of incomplete autoantibody testing as mentioned above [74].

Application of the entire panel of autoantibodies reduces the number of autoantibody-negative AIH patients to less than 10% in our experience.

Histopathology

The histopathology of AIH is in keeping with the present pathogenetic concept that it is a genuine immune disorder with target antigens on hepatocytes and an effector response, mainly of cell-mediated pathways, dominated by lymphocytes. Although there is no pathognomonic feature distinguishing this type of hepatitis from the virally induced forms – virus-containing hepatocytes are also killed by immune mechanisms – distinct morphological lesions regarded as characteristic for this type of hepatitis have been evaluated by some groups [3, 14, 43, 98]. The spectrum of histopathology is reviewed under the aspect of a morphological substrate induced by distinct immune mechanisms.

Hepatocellular necrosis in the lobule is quite conspicuous and is generally more prominent than in viral hepatitis [3]. Ballooning degeneration is the cardinal feature (Fig. 1) presaging lytic necrosis. The confluence of lytic necroses may produce bridging necrosis, which can extend to centrolobular areas, especially in acute disease [43, 84, 99] or in acute flare-ups during a chronic course. Apoptosis is less frequent, and correspondingly the eosinophilic shrinkage of hepatocytes seen in this type of necrosis is less conspicuous. The necrosis in AIH shows a zonal preference with periportal predominance, which differs from virus-induced tissue damage even though immune mechanisms are also involved. However, viral replication in the liver has a focal distribution. The regeneration of hepatocytes is an integral part of the typical histopathology, and there are numerous pale-staining hepatocytes especially in the periportal region.

The hallmark of AIH is the infiltration by *lymphocytes* that seem to spill over from portal tracts, as tertiary lymphoid sites, into the lobules (Fig. 1A). Lymphocytes are the predominant cells of the inflammatory infiltrate and frequently induce the phenomenon of emperipolesis, which is an important feature of AIH. The presence of plasma cells is variable, although in earlier reports AIH has been termed plasma cell hepatitis [22, 87] and in individual cases plasma cells may be abundant. However, our own observations [14] and data from other authors [82] show that the plasma cells are not a constituent feature of AIH. Eosinophils may be present in some cases, and a picture similar to that in AIH has been observed in the hypereosinophilic syndrome.

Portal tracts (Fig. 1A) are expanded and display dense infiltration by mononuclear cells, mainly lymphocytes though monocytes are also seen. Genuine lymphoid follicles may develop, but they are less frequent than in chronic hepatitis C [3, 12]. Bile ducts are involved in the inflammatory process in about 30–40% of cases [3].

The lesions may overlap with those seen in PBC, consisting of epithelial necrosis, nuclear pyknosis and infiltration by lymphocytes [84]. However, there are significant differences in that there are no basement membrane disruption and no granuloma formation in AIH. Small bile ducts are more often affected than the larger interlobular ducts [84, 117]. As in the lobule, the presence of

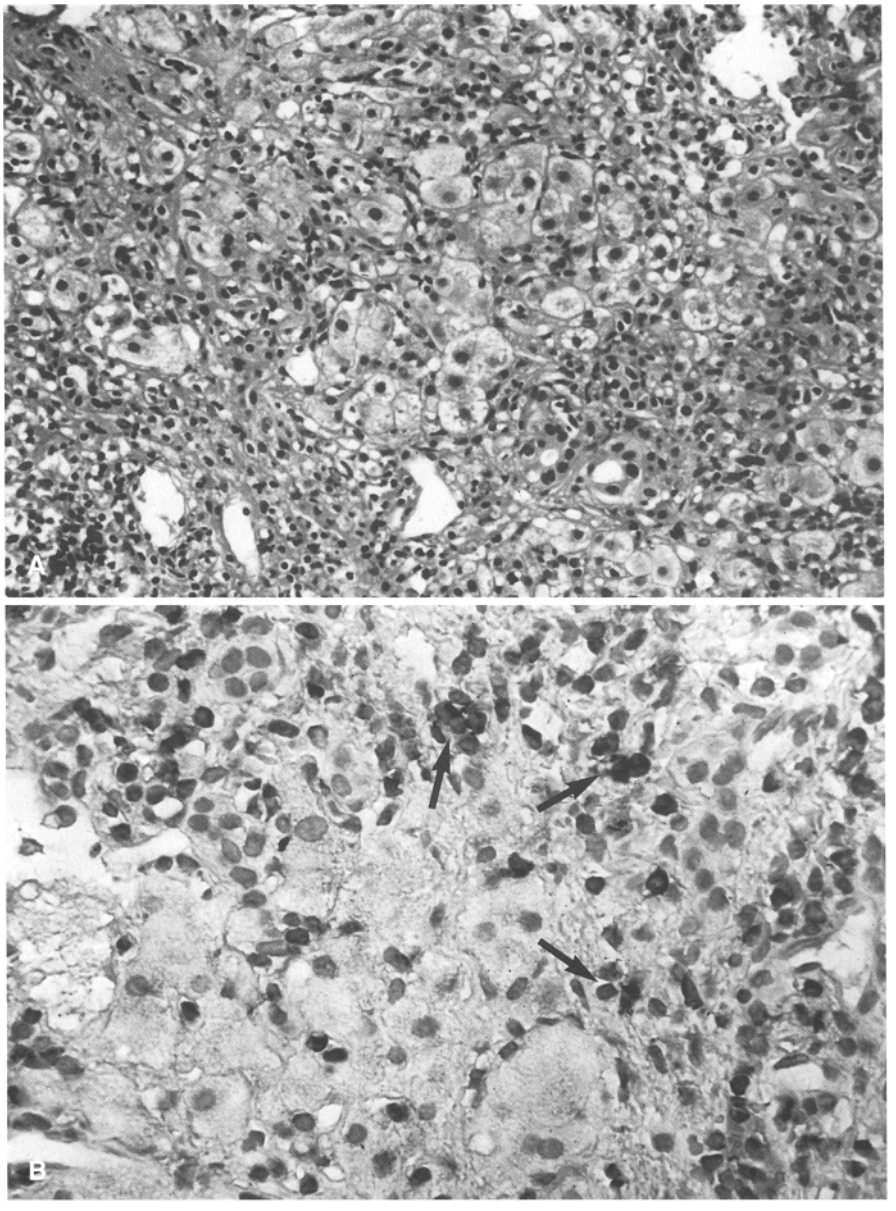


Fig. 1 **A** Autoimmune hepatitis with severe activity: periportal area with a dense lymphocytic infiltrate, parenchymal collapse owing to confluent piecemeal necrosis and microacinar array of hepatocytes. H&E, ×320. **B** The same biopsy specimen as in **A**. Staining for CD4 lymphocytes within a portal tract shows that most of the mononuclear cells are positive (*arrows*). mAb-ati-CD4, ×400. **C** Neuroinflammatory activity in the lobule: hepatocellular ballooning with emperipolesis of lymphocytes is evident. Few plasma cells are present. H&E, ×480. **D** Autoimmune hepatitis with mild activity. H&E, ×320

plasma cells is a variable and inconstant finding. The most severe and impressive lesions are found at the portal lobular interface. The severity of piecemeal necroses as an indicative histological feature has been stressed by some authors [3, 14, 84]. The confluence of piecemeal necroses results in parenchymal collapse in the periportal area, leading the surviving hepatocytes into a microacinar array. The parenchymal collapse can extend as far as the centrilobular region in the fashion of bridging necrosis.

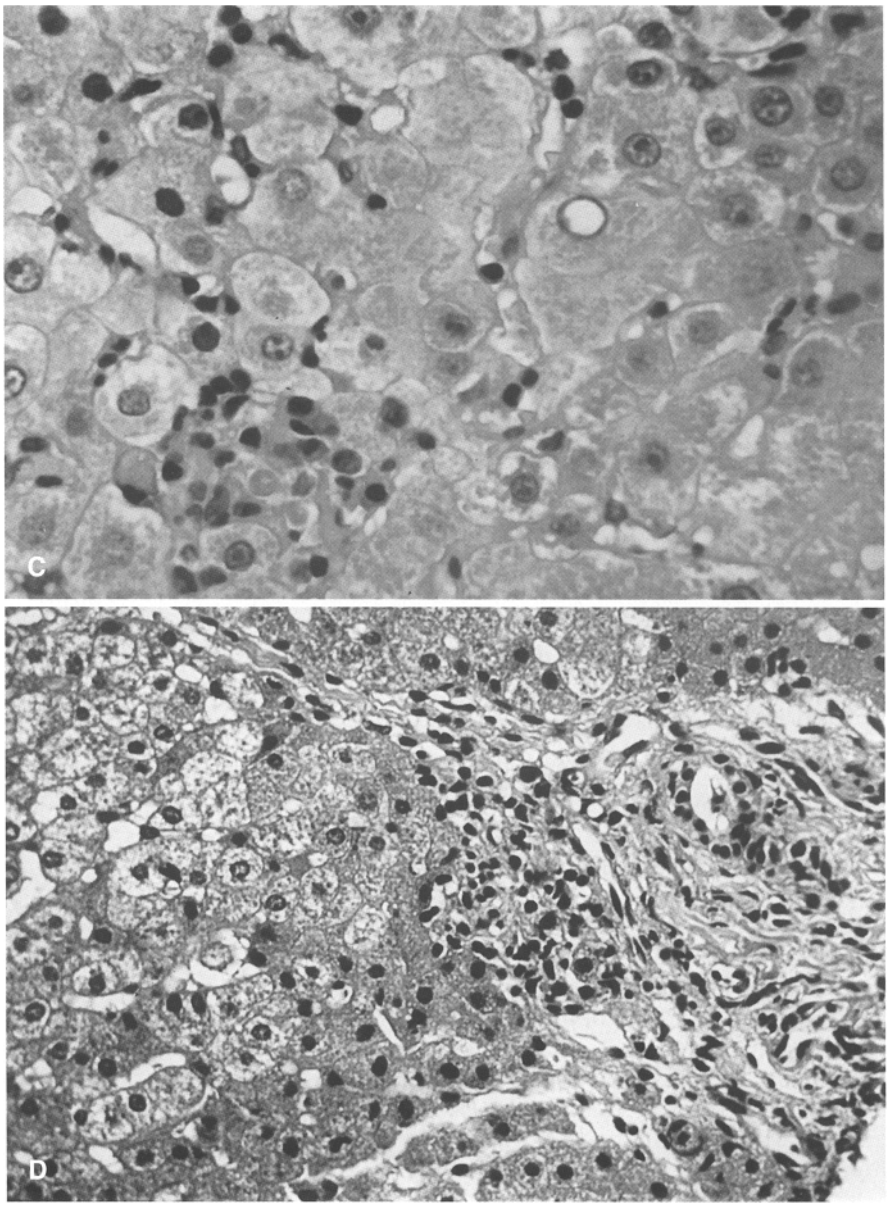
The pattern of fibrosis does not differ from that in viral hepatitis and fails to give diagnostic clues, as is the case in toxic lesions. Collagen fibres are produced in portal tracts and in areas of necrosis that have been scavenged. Thus, a portal and septal distribution emerges during the course of the disease. Perivenular fibrosis must be expected and may occur after long-standing necrosis in that area [84]. Pericellular fibrosis with deposits of collagen fibres in the space of Dissé does not occur.

The disease is considered chronic a priori; however, it can start as acute hepatitis, as described in case reports [44, 47].

Histopathology in these cases is characterized by acute necroinflammatory lesions with centrilobular predominance mimicking acute hepatitis B [99] or drug-induced injury. Most cases that present as acute illness in AIH are characterized by histopathology of an acute flare-up of *chronic* hepatitis (Fig. 1A) or cirrhosis.

The mild form of chronic hepatitis (formerly known as chronic persistent hepatitis) is also seen in a certain percentage of patients (15%; unpublished observations) (Fig. 1D) and may be diagnosed incidentally by the detection of elevated serum transaminases.

Fig. 1 C, D



Electron microscopy

The contribution of electron microscopy to the diagnosis or to the understanding of pathogenesis is of minor importance. Ultrastructural analysis allows the initial cell damage of ballooning and lytic necrosis to be appreciated more readily than does light microscopy. However, no specific features have been described. It is noteworthy that microacinar transformation in the periportal area as a typical feature of AIH is associated with basement membrane formation in the space of Dissé [1].

By electron microscopy the phenomenon of emperipolesis can be analysed in greater detail and changes in the hepatocellular membrane with flattening of the microvilli and submembranous oedema are readily seen.

At the ultrastructural level the contribution of Kupffer cells to the immune response in the tissue is clear. It is uncertain whether this cell, making up almost 40% of the inflammatory infiltrate [1, 6] exerts a scavenger function only or whether it acts as a cytotoxic effector.

Typing the inflammatory infiltrate

The dense lymphocytic infiltrate in the portal tracts and periportal areas are a hallmark of chronic AIH. Subtyping the lymphocyte by monoclonal antibodies against specific epitopes revealed a majority of T-lymphocytes [18]; B-lymphocytes make up only 20% of the total. Further subdivision of the T-cells shows a predominance of CD4 (Fig. 1B) over CD8, with a ratio up to 2:1, which is in contrast to viral hepatitis, typically characterized by a preponderance of CD8 lyphocytes [1]. NK-cells (CD56+) seem not to play a significant part, by analogy with other autoimmune diseases [13, 18].

The application of immunoelectron microscopy demonstrates that lymphocytes exhibiting large dense cytoplasmic granules as a substrate for the cytolytic tools may also be positive for CD4 [18].

Extensive immunohistology in AIH has revealed that the immunological microenvironment for T-cell-mediated killing of hepatocytes as target cells is created in the active phase of the disease. The liver cells display an increased expression of aberrant HLA molecules class I and, especially, of class II as ligands for the CD4+ lymphocytes. Furthermore, *de novo expression* of CD58 and ICAM 1 on hepatocytes as ligands for CD2 and LFA1 on the effector lymphocytes can be regarded as significant constituents of the steps of adhesion, recognition and activation in the sequence of T-cell-mediated killing [2]. Additional adhesion molecules such as E selectin and ICAM 1, directing the T-lymphocytes to the site of inflammation, have also been described as integral part of chronic active hepatitis [112]. The patterns of cytokines regulating the immunological machinery (IL2, IFNγ), and especially TNF, seem to play the predominant part in the tissue when analysed by immunohistology and by secretory assays of isolated lymphocytes from the liver [15, 51].

Immunopathogenesis

Liver membrane autoantigen – autoantibody systems

Marker autoantibodies are the hallmark of autoimmune liver diseases (AILD); however, their target antigens are mainly located intracellularly and lack organ specificity. This fact makes it difficult to understand their origin and immune pathogenetic role [1]. Little is known about the physiological expression of cytosolic antigens on the surface of hepatocytes [61]. In the case of LKM_1 antigens membrane expression has been studied intensively, but it remains questionable in amount and may exist only at a very low level [49, 53, 61, 95].

The lack of membrane expression of target antigens of marker autoantibodies has stimulated investigations to identify those autoantigens expressed on the plasma membrane of hepatocytes since the 1960s [76]. At that time a crude plasma membrane preparation with organ-specific components, later named liver-specific membrane lipoprotein (LSP) [75], received clinical and experimental attention. It was possible to induce an autoimmune-type liver disease in experimental models, first in rabbits [26, 40, 73, 77] and later in mice [54, 56]. Furthermore T-cell reactivity to LSP and its components have been described in AIH but also, to a lesser extent in other inflammatory liver diseases, in particular PBC [78] (for references see [80]). In addition, several groups detected autoantibodies against LSP, more frequently in sera of patients with AIH [33, 37, 63]. In follow-up-studies anti-LSP antibodies could predict the clinical outcome of AIH in men and received clinical relevance [72]. On the basis of clinical and experimental data a further search for the relevant target antigens in LSP preparation has been started, which led to the detection of LM Ag [79] and the ASGPR as part of LSP [71] and its identification as autoantigen [68]. Meanwhile, several studies have demonstrated the clinical relevance of anti-ASGPR autoantibodies for both diagnosis and prognosis in AIH [106, 107]. In addition to the ASGPR, several other liver-membrane autoantigens have been identified by autoantibodies, but their clinical relevance remains questionable. Of special interest for further studies are a 43-kDa protein [90], located on the basolateral membrane of hepatocytes, a 26-kDa liver-membrane antigen (LMA) [28, 29], and a partialy liver-specific 60-kDa membrane antigen [104] (Table 5). Further studies are needed to characterize the epitopes, to determine their usefulness as diagnostic factors and, more importantly, to characterize their role as pathogens for AIH. The binding of liver-membrane autoantibodies to hepatocellular membrane antigens in vivo suggests that these antibodies may be involved in the pathogenesis of AIH [26, 27].

Mechanisms of autoimmune mediated hepatocellular injury

Theoretically, either of the cellular and humoral autoimmune reactions described above has the capability of

Table 5 Critical characteristics of autoantibodies

Autoantibody	Autoantigen(s)	Clinical association(s)/ clinical utility (prevalence in specific diseases)	Preferred detection method(s)	Other important characteristics (genetic association, pathogenetic importance, etc.)
Anti-LSP	Liver-specific protein (LSP), 43-kDa protein	Up to 100% in autoimmune hepatitis, 50% in chronic viral hepatitis	Indirect RIA (indirect ELISA)	Proved to be pathogenic in animal models, linked to inflammatory activity
Anti-LMA	Liver membrane antibodies (LMA), 26-kDa protein	Up to 100% in autoimmune hepatitis, 90% in viral hepatitis C	Immunofluorescence	
Anti-PM	Hepatocyte plasma membrane (PM)	Autoimmune hepatitis	Immunoblot	
Anti-ASGPR	Asialoglycoprotein receptor (ASGPR)	80% in autoimmune hepatitis	Indirect ELISA, indirect RIA, immunoblot	Linked to inflammatory activity

causing hepatocellular damage. The direct cytotoxicity of T-cells reacting with organ-specific antigens expressed in the liver membranes is probably the most important mechanism in the initial phase of liver injury [19, 116]. Evidence for this comes from the murine model of AIH [56]. The essential role of T-cell recognition of liver antigens has been shown by a passive transfer of the disease by CD4-positive T-cells in syngeneic mice. In this model autoantibodies appear at the time of spontaneous recovery from the disease [58].

In human disease an acute onset and spontaneous recovery have rarely been observed, and immunological studies need to be done in such patients. The most usual clinical picture is that of an acute or chronic progressive inflammatory course with cell-mediated autoreactivity, autoantibodies, hypergammaglobulinaemia and the histopathological features described above. Keeping in mind the monophasic course of experimental AIH, it is clear that there must be additional factors causing the chronic fluctuating self-perpetuating disease.

There is increasing evidence that in the chronic phase of the disease liver-membrane autoantibodies are involved. The first hint of this was the in vivo binding of IgG in a linear pattern to the surface of isolated hepatocytes taken from liver biopsies in AIH [27]. The essential role of the humoral autoimmune response in AIH received further support from an experimental rabbit model. A monoclonal antibody against the 43-kDa liver-surface antigen was able to induce acute liver injury and lysis of hepatocytes in vivo, but also in vitro in the absence of serum or T-cell components of the immune system [90]. It is likely that in vivo the monoclonal antibodies cooperate with K-cells via antibody-mediated cellular cytotoxicity (ADCC). Additional information from liver-perfusion studies using Anti-ASGPR antibodies has shown that anti-ASGPR antibodies bind or are consumed predominantly in the periportal zone of the hepatic lobule [69]. Since periportal inflammatory infiltrates predominate and are characteristic of AIH, ADCC may be responsible in part for the destruction of periportal hepatocytes. This notion is further supported by in vitro studies showing that non-T-lymphocytes (K-cells) from the peripheral blood have cytotoxic activity to autologous hepatocytes isolated from liver biopsies in AIH. Again it is likely that K-cells may have induced liver cell lysis via in vivo-bound auto antibodies to the surface of hepatocytes [82].

These close correlations of anti-LSP and anti-ASGPR autoantibodies to disease activity and the disappearance of these autoantibodies under immunosuppression [106, 107] further support their pathogenetic role in vivo. In contrast, antinuclear and anticytosolic autoantibodies are detectable in AIH after many years in remission.

When the clinical and experimental observations are considered together, we recognize that there is increasing evidence that autoimmune diseases are partially regulated by each patient's own immune system [9]. This is also true for AIH [55, 58]. In most cases, AIH runs a subacute or a chronic course with intermittent phases of acute disease exacerbation and recovery. This clinical pattern can only be explained by an active interplay between disease-promoting factors (genetic predisposition and/or environmental factors) and counterregulatory elements of the immune system [58]. The experimental data discussed above give accumulating evidence that T-cell-mediated cytotoxicity may be the primary event of liver injury in AIH. The quality of downregulation of T-cell response involving antigen-specific and, to a lesser extent, -nonspecific suppression is the course-determining factor. In most cases of human AIH the natural control and downregulation of a liver-specific T-cell response may be not strong enough to control the autoimmune process. This may lead to the various courses seen in many autoimmune mediated disorders. In the chronic self-perpetuating phase of AIH, both cellular and humoral autoimmune reactions may shape the inflammatory picture then probably dominated by autoantibody mediated cytotoxicity.

T-cell autoreactivity to liver membrane antigens

Studies of cell-mediated immunity against LSP were extended to the ASGPR in the 1980s (for references see [70, 91]). Circulating T-lymphocytes that were sensitized against ASGPR in patients with AIH were described [86]. Using a different method, Löhr et al. [48] were able to confirm the presence of T-cells with specific reactivity to the human asialoglycoprotein receptor in AIH. All patients showing T-cell reactivity against human ASGPR had signs of active disease at the time of study.

We established T-cell clones from liver biopsies taken from patients with AIH. Approximately 10% of the clones responded specifically to human ASGPR. The response was restricted to autologous antigen-presenting cells and HLA class II recognition [48]. The majority of the T-cell clones exhibited the CD4-positive, CD8-negative phenotype. The T-cells were able to stimulate B-cells in an antigen-specific manner to produce autoantibodies against the ASGPR [50]. Furthermore it could be shown that the liver-infiltrating T-cell clones produced more IL_4 than did liver-infiltrating lymphocytes from patients with non-AIH showing a dominance of CD8- and CD4-positive cells producing significantly less IL_4 [51, 100]. These data indicate that the liver-infiltrating T-cells from patients with AIH and non-AIH belong to different functional T-cell subsets. The predominance of CD4-positive T-cells among the T-cell clones from liver biopsies is in accordance with findings obtained from peripheral blood and in situ phenotyping of liver-infiltrating lymphocytes on tissue sections [1].

Immunopathological findings in AIH concerning the ASGPR resemble observations in other autoimmune disorders where immune reactions to organ-specific receptor molecules mediate the disease process, especially in thyroid diseases and myasthenia gravis [7, 85].

In the murine model of experimental AIH it has been shown that the autoreactivity of T-cells is strongest against smaller soluble liver antigens obtained from LSP preparations [54]. Studies with these antigen fractions in patients with AIH provide support for further T-cell-tar-

get antigens and T-cell autoreactivity in the majority of patients with AIH, but not in patients with PBC or in other liver diseases or autoimmune disorders. The reactivity was almost exclusively confined to patients with active and progressive disease [58].

Further evidence for the critical role of autoreactive T-cell lymphocytes in the pathogenesis of AIH was provided by observations of the murine model of AIH. Spontaneous recovery of experimental AIH was associated with antigen-specific and antigen-non-specific T-cell suppression [55]. A similar immunoregulatory phenomenon was seen in patients with AIH [58]. The presence of active suppression of T-cell auto-reactivity in vitro in AIH and marked nonresponsiveness to in vivo challenges with an unrelated antigen (tetanus toxoid) suggest generalized spontaneous immunosuppression that is more pronounced in vivo than can be measured in vitro.

The results contribute to our understanding of the natural course of AIH. Initially the disease may run a mild spontaneous course, followed by fluctuating elevations of transaminase levels prior to diagnosis and initiation of immunosuppressive therapy. The clinical observations are likely to be the expression of a relevant imbalance between autoreactive and counterregulatory force. It may be, then, that in patients with AIH the immune system tries to downregulate its aberrant autoimmune response in an attempt at spontaneous immunosuppression.

In this context a very interesting model of a T-cell-mediated liver injury in mice, induced by concanavalin A, will be discussed [105]. Although not autoimmune mediated, it seems to be an ideal system to study the induction of a liver injury by a lectin via CD_4-positive T-cells in a dose-dependant manner. T-cell-deficient mice, T-cell depletion, anti-CD4 monoclonal antibodies or immunosuppressive drugs can prevent the disease, even in doses that lead usually to death of the control mice within 24 h. There seems to be a strain-dependent susceptibility. Locally adherent lymphocytes to sinusoidal endothelial cells and hepatocytes have been observed. Pretreatment destruction of Kupffer cells and hepatic endothelial cells can prevent ConA-induced liver injury. It can be concluded that an intact liver-related immune system is a prerequisite for induction of ConA-hepatitis. The animal strain and the injected ConA doses then determine the outcome of the disease. It is most likely that the induction of a pathogenic T-cell response is the consequence of a locally activated immune system and a destroyed physiological interplay between hepatocytes and nonparenchymal liver cells by cytokines. Further studies are needed to analyse the CD_4-positive T-cell subsets involved. Th_1-cells have a higher cytotoxic capacity than TH_2-cells and secrete IL-2, interferon-γ and tumour necrosis factor (TNF)α, cytokines than can affect synthesis, function, and structure of liver-membrane antigens, especially of the ASGPR [103, 108]. Recent publication suggest TNF as a key cytokine [20, 45, 46]. The roles of nonparenchymal liver cells and of factors responsible for susceptibility and resistance require more detailed study.

Disease-promoting factors

Viruses

Several studies have failed to show any significant associations between infection with hepatitis A, B, C and D-viruses and autoimmune liver diseases [47, 57, 83]. The coexistence of viral hepatitis and AIH is a rare event and appears to be due to chance. Hepatitis B, D and C, however, are able to induce autoantibodies in a significant number of patients, most commonly ANA and/or SMA but also anti-LSP and anti-ASGPR and to a lesser extent LKM autoantibodies in hepatitis C, and more frequently in hepatitis D (for references see [48]). These autoantibodies usually tend to be low in titre and the patients mainly have one autoantibody subtype. SLA autoantibodies are found to be specific for AIH [57]. Interferon alpha therapy can induce a transient appearance of autoantibodies in viral liver diseases [67]. A special autoantibody observed in about 50% of patients with chronic hepatitis C, named anti-Gor [48, 81], is a rare finding in AIH or other liver diseases. In hepatitis-C anti-Gor correlates with disease-activity [42] (Fig. 2).

In this context it is of special interest that anti-ASGPR autoantibodies are induced at high titres of between 1:600 and 1:1600 in patients with acute virus hepatitis A (68%), B (60%), C (53%) and NA-NB-NC-ND in 48% [110], but so far only three cases with AIH after acute hepatitis A [30, 92] and one following acute hepatitis B [43] have been reported, suggesting a pathogen-non-specific or -unrelated induction of anti-ASGPR. Similar data have previously been described for anti-LSP. The viral trigger mechanism is of special interest pathophysiologically. Autoimmune reactions against membrane antigens of hepatocytes can be induced by all hepatitis viruses, but do not usually run to self-perpetuating autoimmune liver disease. The same may be true for some nonhepatotropic viruses, such as Epstein Barr virus and measles virus [56, 94].

Cytokines and lectins

Circulating cytokine and cytokine receptor levels are high in AIH [31]. As viruses and viral antigens are un-

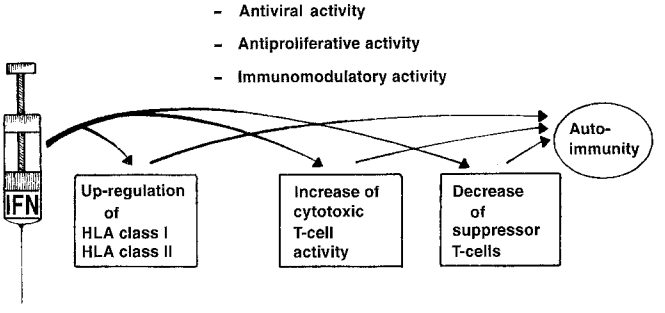


Fig. 2 Modes of action of interferon

likely to be pathogens inducing AIH in man via mimicry or cross-reactive mechanisms, it has been suspected that the cytokine release during acute virus infection or in the presence of other environmental factors, in particular toxins and lectins, may stimulate or alter the liver-associated immune system made up of lymphocytes and nonparenchymal liver cells, particularly in patients who are susceptible to autoimmune disorders [21, 111]. Cytokines may affect synthesis, function and membrane expression of hepatocellular membrane glycoproteins such as the ASGPR. ASGPR dysfunction has been reported in chronic active hepatitis and cirrhosis of the liver [41]. This can be explained by a loss of ASGPR as a consequence of a reduced liver parenchyma, but should perhaps be more properly interpreted as an alteration of the actual ASGPR during inflammation. Weiss and Ashwell speculated that a neuraminidase-producing pathogen might lead to an accumulation of desialysated lymphocytes in the liver which, after binding to the ASGPR, proliferate and mount a cytotoxic response against hepatocytes [115]. The immunogenicity of liver-membrane lipoproteins might also be increased by way of dysfunction or alteration of the ASGPR itself by excess ligands or desialysation by neuraminidases, that is by producing hyperasialoglycoproteinaemia [97] or defects of resialysation by liver-specific enzymes [89, 115].

We were interested in cytokines as critical mediators of the immune response TNFα, interferon (IFT)α and γ, or interleukin-2 (IL2) may have a direct effect on the expression and/or function of ASGPR [108]. Our data clearly show an inhibitory effect on binding and uptake of asialoglycoproteins by human hepatoma cells (HepG2) and freshly isolated rat hepatocytes. This effect was reversible for up to 4 h of exposure and was accompanied by selctive phosphorylization of the cell-surface receptor. The downregulation of ASGPR expression was due to reduced synthesis as a result of reduced receptor transcript levels. Since surface-associated receptor protein is not lost after 24 h of IL2 incubation, cytokine-induced phosphorylization may constitute a mechanism designed to regulate receptor activity. The basic physiological levels of cytokines in vivo are difficult to determine, but preliminary data concerning TNFα and IL2 that are consistent with those used in our study may explain in part some clinically observed hepatocytotoxicity in cytokine-treated patients [8, 96, 114].

Immunogenetics

Most autoimmune disorders involve a genetic predisposition (Table 1), as has been shown in human diseases and experimental models of autoimmune disorders. Recently published review reports by Manns and Krueger [62] and Donaldson et al. [17] on immune genetics in chronic liver diseases discuss the genetic background of AIH and the increasing clinical relevance of HLA-typing in detail. It has become clear that AIH is characterized by a dual association with HLA-A1-B8-DR3 or -DR4 in Caucasians [11, 17, 59]. In Japan AIH is mainly associated with DR4 [32, 101]. The associations are confirmed at DNA level.

Most autoimmune disorders show a multiple allelic association, coding for antigens belonging to more than one class of HLA molecules. The specificity of antigen recognition by T-cells and the variability in response to self- and foreign antigens depends on the polymorphism at some amino-acid positions of HLA antigens. The role of genetically polymorphic T-cell-receptor molecules, but also of critical autoantigens as the third member of the effector–target cell binding complex requires more attention to help us extend our understanding of susceptibility and resistance to autoimmunity. In this context, findings of Doherty et al. [16] are particularly promising. The aminoacid sequence Leu-Leu-Glu-GLn-Lys-Arg at position 67–72 on the DR polypeptide was found in 94% of patients with AIH, regardless of whether they were DR_3 or DR_4 positive [16, 17]. It has to be confirmed whether this motif is specific for AIH or a possible trigger of immune manipulation. Keeping in mind the AIH-promoting factors in human and animal AIH discussed above, there seems to be no doubt that different environmental factors, such as viruses, toxins, drugs, and cytokines, are frequently able to induce transient autoimmune phenomena, but not autoimmune disease if distinct from a disease-promoting genetically determined background for autoimmunity. Further advances in immunogenetic studies may have a key role in extending our knowledge on the immune pathogenesis of autoimmune liver diseases.

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