Review

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Autoimmune hepatitis – Update 2015

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Introduction and history

Autoimmune hepatitis (AIH) was first described in 1951 [1] as a chronic hepatitis of young women with hypergammaglobulinemia in the absence of cirrhosis, which responds well to adrenocorticotrophic therapy (ACTH). Shortly thereafter this syndrome was described and characterized in the USA. In 1956 the association with anti-nuclear antibodies (ANA) was discovered and the term "lupoid hepatitis" was created [2]. AIH and systemic lupus erythematosus (SLE) are distinct autoimmune disorders. However, they may occur together in a given patient. Between 1960 and 1980 several prospective trials were published demonstrating the benefits of corticosteroids alone or in combination with azathioprine in severe cases of AIH. AIH became the first liver disease in which medical therapy improved survival [3]. The advent of immunofluorescence, thereafter radio, as well as enzyme-linked immunosorbent (EIA) assay technology, in addition to molecular cloning techniques allowed a molecular identification and characterization of the hepatocellular autoantigens involved in AIH (Table 1). Characterization of the humoral and cellular immune system in patients and several animal models significantly improved our knowledge of this still poorly understood autoimmune liver disease (Fig. 1). Immunosuppression and liver transplantation are our therapeutic weapons. While corticosteroids alone or in combination with azathioprine are effective and prolong survival, treatment failures to this standard of care (SOC) are still a challenge. This review on the occasion of the 30 year anniversary of the *Journal of Hepatology* and the 50 year anniversary of the European Association for the Study of the Liver (EASL) summarizes the developments over the past 50 years in AIH. We will also give an outlook on how our progress in the understanding of the molecular and cellular pathogenesis of AIH will pave the way for future therapies specifically targeting the underlying disease progress and eventually avoiding liver transplantation.

Key Points

- Autoimmune hepatitis (AIH) is a chronic self-perpetuating inflammatory disease with a female predominance occurring in all ages and races that may start with an episode of acute hepatitis and may lead to liver cirrhosis, liver cancer, liver transplantation or death
- Over the last decades molecular targets of the most relevant disease associated autoantibodies were identified and characterized. Recent investigations on the immunopathogenesis concentrated on regulatory T cells and the complex genetic background of AIH via GWAS analyses
- Immunosuppressive therapy in severe cases of AIH prolongs survival
- Standard of care includes corticosteroids alone or in combination with azathioprine to achieve normalization of transaminases and immunoglobulin G levels in serum. The topical steroid budesonide can be used in non-cirrhotic patients instead of predniso(lo)ne to reduce steroid specific side effects.
- In treatment failures mycophenolate mofetil, cyclosporine A, tacrolimus and lately anti TNF or anti CD20 monoclonal antibodies can be used as second line treatment based on a careful individual risk evaluation and should be done in experienced centers

Aetiology and pathogenesis

AIH is divided in two main types: AIH type 1 (AIH-1), positive for anti-nuclear (ANA) and/or anti-smooth muscle (SMA) antibodies, and AIH type 2 (AIH-2), positive for anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-LKM3 and/or anti-liver cytosol type 1 antibody (anti-LC1) (Figs. 2 and 3). Whether specific

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Abbreviations: AIH, Autoimmune hepatitis; AMA, Anti-mitochondrial antibody; ANA, Anti-nuclear antibodies; APC, Antigen-presenting cell; APECED, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CTL, Cytotoxic T lymphocytes; DIL, Drug-induced liver injury; GWAS, Genome-wide association; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HLA, Human leukocyte antigen; HSV, Herpes simplex virus; IE, Immediate early; NK, Natural killer; PBC, Primary biliary cirrhosis; PSC, Primary sclerosing cholangitis; SLE, Systemic lupus erythematosus; SMA, Smooth muscle antibody; SOC, Standard of care; SSSE, Steroid specific side effects.

Table 1. Molecular targets and disease associations for autoantibodies in liver diseases.

Autoantibodies	Target	Disease association
ANA	Multiple nuclear antigens	AIH, SLE, MTCD etc.
AMA	2-oxo-acid-dehydrogenase complex	PBC
pANCA	h-Lamp-2, proteinase 3	AIH, PSC, PBC
SMA	Actin, troponin, tropomyosin	AIH I
LKM 1	CYP 2D6	AIH II, HCV
LKM 2	CYP 2C9	Tienilic acid-induced hepatitis
LKM 3	UGT1A	AIH, hepatitis D
LM	CYP 2A6	APECED, hepatitis C
LC1	FTCD	AIH II
SLA/LP	tRNP$^{(Ser)Sec}$	AIH III?
LM	CYP 1A2	Dihydralzine-induced hepatitis, APECED
ASGP-R	Asialoglycoprotein receptor	Autoimmune liver disease, HCV

ANA, anti-nuclear antibodies; AMA, anti-mitochondrial antibodies; ANCA, antineutrophilic cytoplasmatic antibodies; SMA, smooth muscle antibodies; LKM, liver kidney microsomal antibodies; LM, liver microsomal antibodies; LC1, liver cytosolic antibodies type 1; SLA/LP, soluble liver antigen/liver pancreas antibodies; ASGPR-R, asialoglycoprotein receptor antibodies; UGT1A, UDP glucuronosyltransferase family 1 A; FTCD, formimino-transferase cyclodeaminase; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; HCV, hepatitis C virus; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.

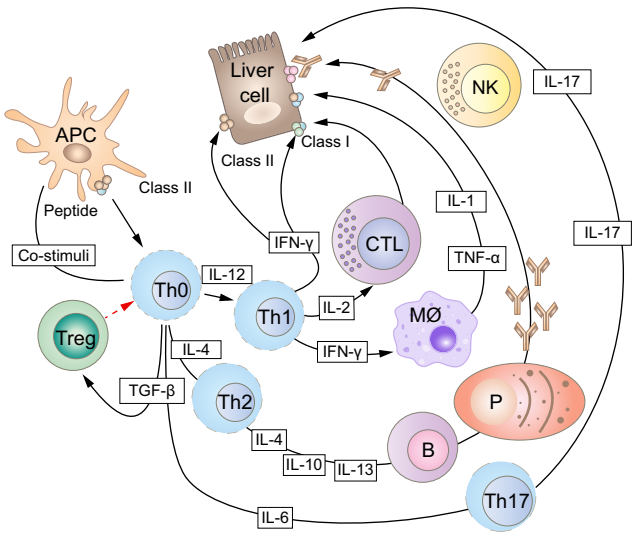

Fig. 1. Molecular pathogenesis of autoimmune hepatitis. An autoantigenic peptide is presented to an uncommitted T helper (Th0) lymphocyte within the HLA class II molecule of an antigen-presenting cell (APC). Th0 cells become activated and, according to the cytokines present in the microenvironment and the nature of the antigen, differentiate into Th1, Th2, or Th17 cells, initiating a series of immune reactions determined by the cytokines they produce: Th2 secrete mainly IL-4, IL-10, and IL-13, and direct autoantibody production by B lymphocytes; Th1 secrete IL-2 and IFN-γ, which stimulate cytotoxic T lymphocytes (CTL), enhance expression of class I and induce expression of class II HLA molecules on hepatocytes and activate macrophages; activated macrophages (MØ) release IL-1 and tumour necrosis factor alpha (TNF-α). Regulatory T cells (Treg) are derived from Th0 in the presence of transforming growth factor (TGF-β). If Tregs do not oppose, a variety of effector mechanisms can be activated: liver cell destruction could derive from the action of CTL; cytokines released by Th1 and recruited macrophages; complement activation or engagement of Fc receptor-bearing cells such as natural killer (NK) lymphocytes by the autoantibody bound to the hepatocyte surface. The role of the recently described Th17 cells, which arise in the presence of TGF-β transforming growth factor beta (TGF-β) and IL-6, is under investigation. Of note, TGF-β is highly expressed in the inflamed liver, dwindling during remission [67].

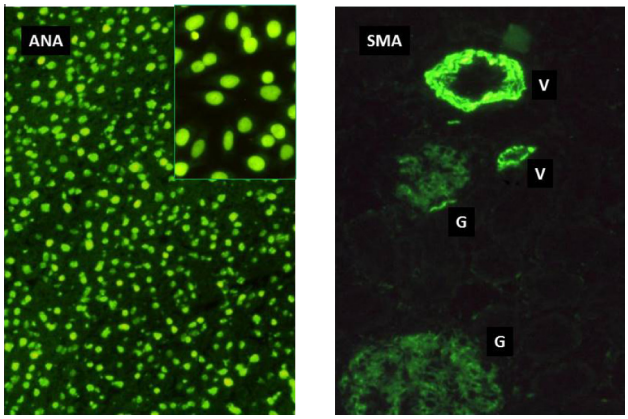

Fig. 2. Indirect immunofluorescence pattern of anti-nuclear (ANA) (left panel) and smooth muscle (SMA) (right panel) autoantibodies. Immunofluorescence pattern of anti-nuclear autoantibody (ANA) on rodent liver and Hep2 cells (inset), which, having a large nucleus, allow pattern recognition. The homogeneous pattern is the most common in autoimmune hepatitis. Immunofluorescence pattern of smooth muscle (SMA) autoantibody on rodent kidney. SMA stains the smooth muscle of arterial vessels (V) and the glomeruli (G).

autoantibody profiles determine aetiologically distinct entities of AIH remains to be proven [4].

The aetiology of autoimmune hepatitis is unknown, though both genetic and environmental factors are likely to be involved. An immune response targeting liver autoantigens is thought to initiate and perpetuate the liver damage. Several genetic factors interact to influence susceptibility to AIH, clinical manifestations, response to treatment and overall prognosis.

The strongest genetic associations are found within genes of the human leukocyte antigen (HLA) region (the human major histocompatibility complex, MHC) – located on the short arm of chromosome 6 – which are involved in the presentation of antigenic peptides to T cells, and are therefore implicated in the initiation of an adaptive immune response [5].