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Etiopathogenesis of autoimmune hepatitis

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ABSTRACT

Autoimmune hepatitis is a chronic inflammatory liver disease characterized by hypergammaglobulinemia, the presence of autoantibodies, and inflammation within the liver, including lymphocytic infiltrates and interface hepatitis. Autoimmune hepatitis shows a female predominance and can present at any age and in any ethnicity. The disease is thought to be a consequence of a break of immune tolerance leading to an autoimmune process that induces liver injury. The self-attack is triggered by T-helper cell-mediated liver autoantigen recognition and B-cell production of autoantibodies, and is sustained by impaired regulatory T cells number and function. Superimposed on a genetic predisposition, infections and environmental factors have been studied as triggering factors for the disease. Allelic variants in the HLA locus have been associated with susceptibility; associations with single nucleotide polymorphisms within non-HLA genes have also been assessed. Several factors have been described as triggers of autoimmune responses in predisposed individuals, including infections, alcohol, vitamin D deficiency, and an altered composition of the intestinal microbiome. Importantly, drugs and herbal agents may trigger classical autoimmune hepatitis, or may induce a liver disease with autoimmune features. Interactions between female hormones and genetic factors have been hypothesized to play a role in autoimmunity, although the exact role for these factors has not been fully established. Herein we present a review of the etiology of autoimmune hepatitis including *de novo* autoimmune hepatitis post-liver transplantation as well as animal models for its study.

1. Introduction

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease first described by Waldenström as a chronic hepatitis of young women with hypergammaglobulineamia [1]. AIH is characterized histologically by interface hepatitis and lymphocytic infiltration of the liver and, serologically by high levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), immunoglobulin G (IgG), and the presence of autoantibodies [2,3]. The association of AIH with the presence of anti-nuclear antibodies (ANAs) led to coining the term "lupoid hepatitis", now obsolete [3,4]. AIH affects mainly women, although 25–30% of patients are male [3,5,6]. AIH shows a bimodal age of onset with a peak in children and teens and another in the fourth to sixth decade of life [6] and can present across different ethnic groups [3,5,6]. AIH may start as an episode of acute hepatitis or more indolently and in some cases progresses to cirrhosis, hepatocellular carcinoma, or death [3,7,8].

AIH occurs worldwide; however, as the diagnosis is often overlooked, epidemiological data vary [9]. As reviewed by Czaja et al. [5], the annual incidence in the adult general population ranges between 0.67 and 2 per 100,000 persons depending on the geographical location. Among children, the annual incidence of AIH has been reported at 0.23 and 0.4 cases per 100,000 persons in Canadian and American children, respectively [5]. Prevalence rates for AIH range from 2.4 cases per 100,000 persons in children in Canada to 42.9 cases per 100,000 persons in native Alaskans. Similar rates of AIH have been noted in Asia

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Abbreviations

AD	autoimmune disease
AIH	autoimmune hepatitis
AIH-1	type 1 autoimmune hepatitis
AIH-2	type 2 autoimmune hepatitis
AIRE	autoimmune regulator
AITD	autoimmune thyroid disease
ALT	alanine aminotransferase
AMAs	anti-mitochondrial antibodies
ANAs	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
APC	antigen-presenting cell
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
ConA	concanavalin A
CTLA4	cytotoxic T lymphocyte antigen-4 gene
CYP2D6	cytochrome P4502D6
DAMPs	damage-associated molecular patterns
DC	dendritic cell
DILI	drug-induced liver injury
EBV	Epstein-Barr virus
ELISA	Enzyme-linked immunoabsorbent assay
FTCD	formiminotransferase cyclodeaminase
GSTT1	glutathione-*s*-transferase T1
GWAS	genome-wide association study
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HLA	human leucocyte antigen
HSV-1	herpes simplex virus type 1
IAIHG	International Autoimmune Hepatitis Group
LC1	anti-liver-cytosol type 1 antibody
LKM1	anti-liver-kidney microsomal antibody type 1
LKM2	anti-liver-kidney microsomal antibody type 2
LKM3	anti-liver-kidney microsomal antibody type 3
LPS	lipopolysaccharides
LSP	liver-specific membrane lipoprotein
MAPK	mitogen-activated protein kinase
MHC	major histocompatibility complex
MIF	macrophage migration inhibitory factor
miRNA	microRNAs
MMA	malondialdehyde
MS	multiple sclerosis
NASH	nonalcoholic steatohepatitis
NK	natural killer cells
NKT	natural killer T-cells
PAMPs	pathogen-associated molecular patterns
pANNA	peripheral anti-nuclear neutrophil antibody
PBC	primary biliary cholangitis
PRMD1	PR domain zinc finger protein 1
RA	rheumatoid arthritis
SLA/LP	soluble liver antigen/liver-pancreas antibodies
SLE	systemic lupus erythematosus
SMA	smooth muscle antibodies
SS	Sjögren's syndrome
SSc	systemic sclerosis
TCR	T-cell receptor
TGF-β1	transforming growth factor β1
Th0	T-helper cells
TLR	Toll-like receptor
TNFA	tumor necrosis factor-α gene
TNFAIP3	TNFA-induced protein 3 gene
Tregs	regulatory T-cells
T1DM	type 1 diabetes mellitus
VD	vitamin D
VDBP	vitamin D-binding protein
VDR	vitamin D receptor

as well. In Singapore the prevalence was 4 per 100,000 [10], while in Japan during 2014, the incidence was 2.23 with a prevalence of 23.4 per 100,000 [11]. In South Korea the incidence and prevalence are reported as 1.07 per 100,000 person-years and 4.82 per 100,000, respectively [12].

The etiology of AIH is unknown, however, genetic and environmental factors are likely to play an important role [3]. Genes from the human leucocyte antigen (HLA) have shown a strong association with AIH [3]. According to the antibody profile, AIH can be classified in two subtypes, type one AIH (AIH-1) is characterized by the presence of ANAs and/or anti-smooth muscle antibodies (SMA) while in type two AIH (AIH-2) anti-liver-kidney microsomal antibody type one (LKM1), anti-LKM3 and/or anti-liver cytosol type 1 antibody (LC1) are the markers of the disease [3].

Several factors, including genetic background, viruses, xenobiotics and drugs have been associated with AIH [3,13]. Herein we review and summarize them as they relate to the autoimmune etiology of AIH.

2. Autoimmune mechanisms

Due to its location and function, the liver is continually exposed to pathogenic antigens, toxins, malignant cells and food antigens to which the hepatic immune system must be tolerant or able to respond [14,15]. In the liver, immunosuppressive cells, cytokines and ligands provide tolerance. The hepatic sinusoids allow the transmigration of these cells and immune mediators towards the hepatic parenchyma [14,15]. Chronic inflammation in the liver is a consequence of the retention of lymphocytes, macrophages and stromal cells that secrete IFNγ, TNFα and other pro-inflammatory cytokines. The process of recruitment of effector and regulatory T-cells (Tregs) is mediated by the interaction of lymphocytes with endothelial cell surface molecules [16]. Chemokines play a critical role in the process of retention of lymphocytes as they trigger integrin-mediated stable adhesions and direct migration [16,17]. Antigenic uptake by resident immature dendritic cells (DC) of the liver promotes their maturation and migration to peripheral lymph nodes where they act as antigen-presenting cells (APC) [14,16]. In the liver, Tregs secrete immunosuppressive cytokines, IL-10 and TGFβ, to suppress proliferation and function of effector cells [14]. DCs secrete IL-12, IL-18 and IL-23 that promote the differentiation of effector cells [14]. The interaction between APC and natural killer T-cells (NKT) mediates the expression of regulatory cytokines from a Th2 response and a pro-inflammatory cytokine profile characterized by IFNγ, TNFα and IL-4 secreted by NKT cells [16]. Besides DC, hepatocytes, Kupffer cells and liver sinusoidal endothelial cells can present antigens to $CD8^+$ T-cells [15,16].

The pathophysiology of autoimmune liver diseases is thought to be based on T-lymphocyte-mediated cell destruction, imbalance in the regulation of immune cells, and a defective immune response to foreign antigens caused by the loss of tolerance to immune stimulants [18–22]. As discussed by Arndtz et al. [18], evidence of loss of central tolerance in murine models and predominance of T-lymphocytes in areas of interface hepatitis has been described as a pathophysiological pathway in AIH.

The inflammatory process in the liver is thought to be initiated by the presentation of self-antigenic peptides to the T-cell receptor (TCR) of T-helper cells (Th0) by APC, DC and other cells capable of presenting

antigens. Antigen presentation may take place in the liver as well, which is a peculiar feature of liver immunology [23]. This event leads to the recruitment of Th1, Th2 and Th17 cells to the tissue [18,24,25]. These effector cells initiate a cascade of immune reactions depending on the cytokines they release. Th1 cells secrete IL-2 and IFNγ stimulating $CD8^+$ cells, expression of HLA class I, expression of HLA class II on hepatocytes and mediating the activation of macrophages which release IL-1 and TNFα [6,24,25]. Th2 cells produce IL-4, IL-10 and IL-13 inducing maturation of B-cells into plasma cells responsible for the production of autoantibodies that are involved in antibody-mediated cellular cytotoxicity and complement activation [24,25]. Th17 cells produce IL-17, IL-22, TNFα and a chemokine ligand (CCL-20) [6,18,25]. Localized T reg cells in the liver control the effector cells limiting hepatic injury as they mediate the action of cytotoxic T-lymphocytes, Th1, Th17, macrophages, natural killer (NK) cells and complement activation [18,25]. As in other autoimmune liver diseases, AIH has been linked to abnormalities in the Th17 pathway finding higher frequency of Th17, IL-17 and IL-23 in liver and serum [18,25]. As reviewed by Liberal et al. [25], the hypothesis of numerically defective Tregs in AIH patients has been assessed and it is thought that this could be associated with lower expression of forkhead box P3 (FOXP3). Other differences have been described between Tregs from healthy subjects and treated and untreated AIH patients, interpreted as an impaired ability to suppress the proliferation of certain cell populations and the inability to suppress the production of IFNγ by $CD8^+$ T-cells [25]. One additional mechanism is the response of effector T cells to Tregs which is probably impaired in AIH [26].

Several autoantibodies have been postulated as contributing to the pathogenesis of AIH. Titers of anti-liver-specific membrane lipoprotein (LSP), and anti-asialoglycoprotein receptor (ASGPR) have been correlated with disease severity [27]. Anti-soluble liver antigen/liver-pancreas antibodies (SLA/LP) are present in around 50% of AIH-1 and AIH-2 patients and anti-LKM1 are frequent in AIH-2 which recognize autoepitopes of cytochrome P4502D6 (CYP2D6) of hepatocytes [27].

Molecular mimicry has been implicated in the pathogenesis of many autoimmune diseases (AD) and is hypothesized as a possible mechanism behind AIH [6,28,29]. Initially, T-cell recognition was thought to be highly specific but further studies found that the structure of peptide binding by major histocompatibility complex (MHC) class II molecules was based on amino acid properties [30]. Amino acids sharing similar chemical structures were able to bind at the same place in the MHC showing that cross reactivity is not as rare as previously thought, and that TCRs showed polyspecificity [30]. It has been hypothesized that, besides similarities of the amino acid sequence, self-reactive immune cells are primed by molecular mimicry and bystander activation, thereby opening the possibility for environmental insults to induce these sensitized autoreactive cells to generate an AD [30]. Molecular mimicry presumably initiates the immune process and sustains the autoreactive response [31].

A study evaluating the role of molecular mimicry in a murine model of AIH, found that transfection with adenovirus delivering the major human autoantigen CYP2D6 into the mouse liver resulted in the development of AIH [28]. Molecular mimicry, rather than identity, was thought to induce a greater T-cell response [28].

Cross-reactivity between hepatitis C virus (HCV) components and AIH-2 autoantigens has been described [28]. During chronic hepatitis B virus (HBV) infection and HCV infection, around 50% of patients develop autoantibodies such as ANA and SMA, and about 10% of the patients with chronic HCV are positive for LKM1, suggesting that molecular mimicry could be an important factor [27]. Multiple viruses have been implicated in the pathogenesis of AIH, including hepatitis A virus (HAV), HBV, HCV, measles virus, varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) [6,31]. Fig. 1 outlines the natural history of the disease.

3. Genetic factors

The understanding of the genes that may predispose to ADs has increased over the last years [32,33]. Genome-wide association studies have been implemented, demonstrating that most of the associations are specifically with the HLA region, although several non-HLA loci have been identified [32]. Autoimmune liver diseases have shown a clear genetic component based on the observations made on twin pairs, family studies and population-based studies [34,35]. As reviewed by Webb and Hirschfield [34], no genetic concordance has been found between twins, and, although the estimates of familial risk for AIH are lacking, about 40% of AIH patients have a family history of autoimmunity. Furthermore, extrahepatic autoimmune conditions are often observed in AIH patients [36].

3.1. HLA genes

Genetic predisposition to AIH has been linked to genes within the

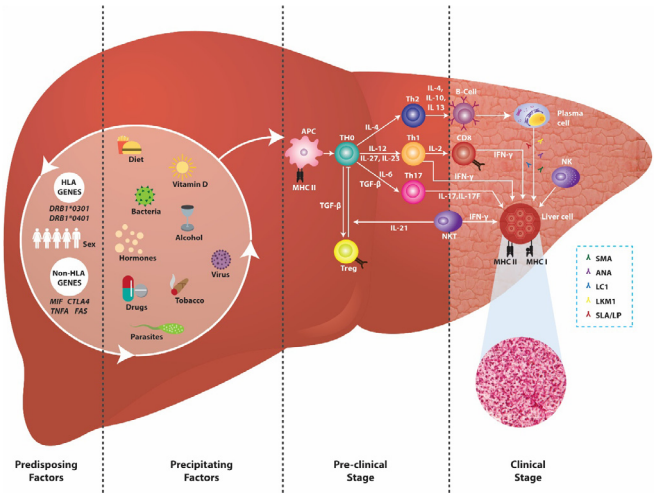

Fig. 1. Natural history of autoimmune hepatitis. HLA: human leucocyte antigen; MIF: macrophage migration inhibitory factor; CTLA4: cytotoxic T lymphocyte antigen-4 gene: TNFA: tumor necrosis factor; APC: antigen-presenting cell; MHC: major histocompatibility complex; TH: T-helper cell; Treg: T-regulatory cell; NKT: natural killer T-cell; NK: natural killer cell; SMA: smooth muscle antibody; ANA: anti-nuclear antibody; LC1: liver-cytosol-1 antibody; LKM1: anti liver-kidney antibody; SLA/LP: soluble-liver antigen/liver-pancreas antibody. The figure shows the natural history of AIH. Although the exact etiology of AIH is still unknown, genetic and environmental factors are supposed to play a role in the pathogenesis of the disease. Among the predisposing factors, the figure shows the influence of gender on the development of AIH, which presents a female-to-male ratio of 4:1 and the influence of HLA and non-HLA genes in the pathogenesis of the disease (the most important HLA genes have been noted, however others have been associated with AIH). The precipitating factors include several environmental exposures that are described as either protective factors, as tobacco, alcohol and vitamin D, or as risk factors as exposure to drugs, hormones, diet and pathogens as viruses, parasites and bacteria. The influence of precipitating factors on susceptible individuals (predisposing factors) leads to the pre-clinical stage in which APCs recognizing antigens or self-antigens activate Th0 cells who give rise to Th1, Th2 or Th17 cells depending on the cytokine environment. Th2 cells secrete IL-4, IL-10 and IL-13 which stimulate the maturation of B-cells into antibody producing plasma cells which produce autoantibodies SMA, ANA, LC1, LKM1 or SLA/LP depending on the subtype of AIH. Antibodies bind to liver cells and contribute to NK and complement-mediated cytotoxicity. Th1 cells secrete IL-2 and IFNγ stimulating $CD8^+$ cells, expression of HLA class I, expression of HLA class II on hepatocytes. Th17 cells secrete proinflammatory cytokines. Th0 cells differentiate into Treg cells under the stimulus of TGF-β, this process is mediated by IL-21 secreted by NKT cells. The histological plaque shows an inflammatory cell infiltrate, mainly cytotoxic T-cells and plasma cells, around the portal tracts characteristic of interface hepatitis in AIH [16].

HLA region on the short arm of chromosome 6, particularly to allelic variants of DRB1, and most of the confirmed associations come from candidate gene approaches in small study populations [9,37,38]. Type 1 AIH has a strong association within the HLA loci, Table 1 [37–48] shows the frequency of HLA alleles in American, European and Asiatic studies. In Northern and Central America, an association with *DRB1*0301* and *DRB1*0401* alleles has been described, while in Brazilians, *DRB1*13* and *DRB1*03* seem to be the more prevalent [37]. In Northern Europe there is a strong association with the ancestral 8.1 haplotype (HLA A1-B8-DR3-DQ2) [43–45]. In Asiatic studies, both *DRB1*0405* and *DRB1*0401* have been described to increase the susceptibility of AIH [46–48]. Some studies have also analyzed the protective role associated with some alleles. For example, *DRB1**1501 has been described as a protective factor against AIH in North America and Japan [39,48]. De Boer et al. [38] performed the first genome-wide association study (GWAS) in AIH in the Netherlands. In their study they found a strong association between *DRB1*0301* and *DRB1*0401* with AIH-1, similar to previous reports in Caucasian patients. In addition, they found an association with the *rs3184504*A* allele in the non-HLA gene *SH2B3*, and, although it did not exceed the stringent threshold for genome-wide significance, they suggest a possible true association due to the consistent results they obtained in their replication analysis in German cases and controls [38].

A meta-analysis in the Latin American population including 694 cases and 1769 controls found that in this region of the world the serological group *DQ2* is associated with an increased risk of AIH, whereas *DR5* and *DQ3* are protective factors [49]. As far as the allelic analysis is concerned, *DQB1*02, DQB1*0603, DRB1*0405*, and *DRB1*1301* are risk factors, whereas *DRB1*1302* and *DQB1*0301* are protective [49]. Besides some geographical variations, it should be noted that GWAS have been performed in a few cohort studies [38,50].

The association between AIH-2 and HLA genes has been studied only partially because of its low prevalence. However, an association with *HLA-DRB1*0701, -DRB1*0301,* and *-DQB1**0201 has been suggested [51,52]. Moreover, a more aggressive disease with severe prognosis has been associated with *DRB1*0701* and *DRB1*03-DRB1*04* [18,52].

3.2. Non-HLA genes

Genetic studies performed looking outside the HLA have found polymorphisms of cytotoxic T lymphocyte antigen-4 gene (*CTLA4*), TNFα gene (*TNFA*) and *FAS* as potential susceptibility genes for AIH-1 [53]. The TNFA-induced protein 3 (*TNFAIP3*) gene encodes for an ubiquitin-modifying enzyme that has been associated with the development of autoimmune disorders [53]. A study in Chinese population evaluating five *TNFAIP3* polymorphisms found that rs10499194 T allele and CT genotype were significantly associated with an increased risk of developing AIH [53]. This association has been found positive for other ADs such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and multiple sclerosis (MS) [53]. The association between *CTLA4* and AIH-1 was assessed in a meta-analysis that included seven studies with a total of 1270 patients and 1614 controls [54]. Of the included studies, only one showed a positive association between *CTLA4* and AIH-1, however, the meta-analysis showed no significant association.

Macrophage migration inhibitory factor (*MIF*) is a pro-inflammatory cytokine that mediates both innate and adaptive immunity and has been associated with disease severity in ADs such as SLE, RA, systemic sclerosis (SSc) and inflammatory bowel disease (IBD) [55]. The *MIF* gene has been associated with an earlier onset and an increased severity of ADs as well as with higher steroid requirements [55]. A recent study suggested that *MIF* polymorphism (173C) in AIH patients might be a biomarker of increased disease activity [55].

A study comparing the serum profile of microRNAs (miRNA) among liver diseases found significant differences between healthy individuals and subjects with HBV, HCV, AIH, PBC, drug-induced liver injury (DILI) and nonalcoholic steatohepatitis (NASH) [56]. The principal component analysis demonstrated that the profiling of 37 miRNAs in sera could be used to help in the diagnosis of various liver diseases [56]. In summary, there are HLA and non-HLA polymorphisms associated with AIH, most of them shared with others ADs as part of the common mechanisms of these conditions (i.e., the autoimmune tautology) [57].

4. Autoimmune ecology

Autoimmune diseases represent a heterogeneous group of disorders that affect specific target organs or multiple organ systems. As mentioned, these conditions share common immunopathogenic mechanisms (i.e., the autoimmune tautology), which explain the clinical similarities they have among them as well as their familial clustering (i.e., coaggregation). As part of the autoimmune tautology, the influence of environmental exposure on the risk of developing ADs is paramount (i.e., the autoimmune ecology) [58,59]. In fact, environment, more than genetics, shapes immune system. Autoimmune ecology is akin to exposome, which is all the exposures – internal and external – across the lifespan, interacting with hereditary factors (both genetics and epigenetics) to favor or protect against autoimmunity and its outcomes. Next, we discuss the main environmental factors associated with AIH.

4.1. Viruses

Several viruses, such as HAV, HCV, HBV, measles virus, VZV, CMV and EBV have been linked to the development of AIH, supporting the hypothesis of molecular mimicry between components of these viruses and components of the host [6,27,28,31,60–62]. Molecular mimicry contributes to humoral and cellular manifestations of the disease, and sustains and extends the autoreactive process [31]. Viruses with hepatic tropism have a great potential to induce liver ADs due to the local inflammatory reaction and, in most cases, the generated cytotoxic immune response to eradicate a pathogen [63]. A significant proportion of patients infected with HBV or HCV become autoantibody-positive and, in some cases, the level of autoantibodies correlates with the severity of the disease [64]. Cross-reaction of anti-LKM1 antibodies with homologous regions of HCV, HSV-1 and CMV has been described [64], and

Table 1
HLA alleles frequency in type 1 AIH.

Author	Year	Country	Associated risk	Protection risk
American studies				
Strettell MD [39]	1997	North America	DRB1*0301 DRB1*0401	DRB5*001 DRB1*1501
Czaja AJ [40]	1997	US	DRB1*0301 DRB1*0401	–
Vazquez-Garcia MN [41]	1998	Mexico	DRB1*0404	–
Bittencourt PL [37]	1999	Brazil	DRB1*13 DRB1*03	DRB1*0301
Fortes Mdel P [42]	2007	Venezuela (Mestizo population)	DRB1*0301 DRB1*1301	DQB1*04
European studies				
Muratori P [43]	2005	Italy	B8-DR3-DQ2	–
Teufel A [44]	2006	Germany	B8-DR3-DQ2	–
Al-Chalabi T [45]	2006	UK	B8-DR3/DR4	–
de Boer YS [38]	2014	The Netherland	DRB1*0301 DRB1*0401	–
Asiatic studies				
Lim YS [46]	2008	Korea	DRB1*0405 DQB1*0401	–
Umemura T [47]	2014	Japan	DRB1*0405 DQB1*0401	DRB1*1501 DQB2*0602
Oka S [48]	2017	Japan	DRB1*0401 DRB1*0405 DQB1*0401	DRB1*1302

LKM1 antibodies against CYP2D6 have been found in HCV infection [65,66].

Organ and non-organ specific autoantibodies have been described in chronic HCV infection [66]. The most frequent autoantibody encountered is anti-SMA in around 66% of patients, followed by ANAs and anti-LKM1 in 41% and 11% of patients, respectively [66]. As reviewed by Vergani et al. [66], the development of autoantibodies with HCV infection has been associated to the genetic background of the subject. ANA, identified in immunofluorescence, usually gives a speckled pattern in HCV infection, whereas SMA is usually limited to the vessels [65]. The presence of SMA and ANAs has been described for HBV and hepatitis D virus (HDV) infections with a similar immunofluorescent pattern to that of HCV infection, but at a lower frequency [66]. Anti-LKM1 appears to act as a danger marker and should be measured in all HCV-positive patients, while LKM1-positive subjects without HCV markers probably represent a true autoimmune group, including children who respond to immunosuppressive treatment [65].

The first observation on the role of HAV triggering AIH came from Vento et al. [67] who followed-up three cases of subclinical acute HAV infection. Two of the three subjects had a defect in suppressor-inducer T lymphocytes specifically controlling immune responses to the ASGPR, an antigen expressed on the hepatocyte surface, before the HAV infection. These subjects developed AIH-1 within 5 months after the acute episode of HAV infection [67]. Table 2 [68–75] shows four further cases of AIH triggered by an acute episode of HAV infection.

A recent review described the results of a Brazilian study that evaluated the frequency of AIH in patients with chronic HCV infection [63]. Biopsies from 1759 patients were analyzed; 92 of them showed interface hepatitis compatible with AIH. Other reports indicate that around 66% and 41% of patients with HCV develop SMA and LKM antibodies, respectively, in conjunction with positive ANAs [63]. HCV infection has been associated epidemiologically With AIH and has been considered a triggering factor as well [63].

Another viral candidate, EBV, has been associated with the development of various ADs such as SLE, MS, autoimmune thyroid disease (AITD), RA, IBD, type 1 diabetes mellitus (T1DM) and Sjögren's syndrome (SS), among others [63]. The authors described studies that showed a temporal association between EBV infection and the development of AIH indicating that EBV infection could promote a pre-existing autoimmune process that could progress to an AD [63]. In fact, EBV is a common environmental factor for several ADs as part of the autoimmune tautology [57]. Finally, hepatitis E virus (HEV) might trigger AIH. In fact, non specific autoantibodies are frequently present during acute HEV infection, thus clinicians should exclude acute HEV infection before diagnosing and treating AIH [76].

4.2. Bacteria

The hypothesis of molecular mimicry between a protein from *Rickettsia* spp. and SLA/LP was evaluated in a recent study [77]. The results suggest that a highly significant sequence similarity between SLA/LP and a non-homologous protein from *Rickettsia* spp. might drive an autoimmune response mediated by $CD4^+$ T-cell recognizing self-antigens with the concomitant humoral response. *HLA-DRB1*0301* allele confers a high risk for this cross reaction contrary to the protective role observed in the presence of *HLA-DRB1*1501* [77]. However, more studies are needed to make strong conclusions and to evaluate other possible bacteria that may be associated with AIH.

4.3. Parasites

Christen and Hintermann [63] reviewed pathogen infections as possible causes of AIH and described a case report of a female who presented with anorexia, malaise, weight loss, joint swelling and fever. Her serum aminotransferases were elevated and she was positive for ANA, SMA and anti-mitochondrial antibodies (AMA) and negative for LKM. The liver biopsy showed an infiltrate of plasma cells and lymphocytes in an interface hepatitis pattern. Fina *Leishmania* were detected and she received specific treatment for this parasite. They concluded that the observed features of AIH could have been caused by the release of auto-antigens during the tissue destruction caused by *Leishmania* [63].

4.4. Alcohol

Products of alcohol metabolism, acetaldehyde, alcohol dehydrogenase, and malondialdehyde (MMA), can induce autoantibodies in either humans or experimental models [78,79]. Additionally, alcohol-fed rats have generated antibodies that respond to unmodified liver-self proteins, suggesting that MMA adducts induce an anti-self-immune response [80]. MMA adducts have been shown to contribute to the onset of an autoimmune-like disease in murine models [81].

A population-based case-control study performed in New Zealand evaluated the role of environmental exposures on the risk of developing AIH [82]. Results from the univariate analysis showed that alcohol consumption lowered the risk of being diagnosed with AIH (OR: 0.34, 95%CI: 0.19–0.61); when they graded alcohol consumption in less than 50 g per week, 51–100 g per week or more than 100 g per week, results maintained statistical significance [82]. This results coincide with observations in other ADs where low-to-moderate alcohol consumption is a protective factor for the development of the diseases [59].

In the univariate analysis of the New Zealand study, positive significant associations were found for a vegetarian diet and antibiotic use prior to the diagnosis of AIH [82]. Results for tobacco use showed no significant association for risk reduction of AIH [82] even though it has been proposed as a risk factor for PBC [82] and other ADs [59,82]. Although a vegetarian diet was shown to be a risk factor for AIH, the results could have been confounded by a lower alcohol intake in vegetarians [82].

4.5. Vitamin D

The effect of vitamin D (VD) has been evaluated in various ADs. A recent literature review describes evidence suggesting that VD deficiency is associated with a higher risk of developing T1DM, SS, MS, SLE and RA among others [59,83]. High levels of VD have also been associated as a protective factor for MS [59].

Vitamin D is produced as a result of cholesterol metabolism that leads to the production of pro-vitamin D which is transformed into pre-vitamin D after UV-B radiation exposure in the skin [84]. Pre-vitamin D sustains reorganization of its double bonds and converts into inactive vitamin D. This molecule is transported to the liver by the vitamin D-binding protein (VDBP) where the first hydroxylation occurs resulting in 25-hydroxyvitamin D,m which is transported to the kidney where a second hydroxylation occurs producing 1,25 dihydroxyvitamin D, the bioactive form of VD [84]. Vitamin D plays an important role in the

Table 2
AIH triggered by HAV infection.

Author	Year	Country	Gender	Age	Time onset from acute hepatitis
Huppertz H [68]	1995	Germany	F	45	6 months
Hilzenrat N [69]	1999	Israel	F	55	Convalescence
Skoog SM [70]	2002	USA	F	24	3 weeks
Grunhage F [71]	2004	Germany	F	75	2 weeks
Tanaka H [72]	2005	Japan	F	57	concomitant
Tabak F [73]	2008	Turkey	F	21	19 months
Kim YD [74]	2011	Korea	F	57	15 months
Hussain S [75]	2013	India	F	45	6 months

regulation of the immune system as it induces downregulation of Th1 and Th17 lymphocytes and upregulation of Th2 and Tregs, stimulates the production of cathelicidin in monocytes, pulmonary, intestinal and epithelial cells and increases the production of reactive oxygen species [59,84]. The immunomodulatory effect of VD is mediated by the expression of vitamin D receptors (VDR) on immune cells and the regulation it exerts over these immune cells [59,85,86].

The immunomodulatory effect of VD in the liver is attributed to the locally produced 1,25 dihydroxyvitamin D that creates a negative feedback for liver inflammation and the expression of VDR in bile duct cells [85]. Two gene polymorphisms of VDR have been associated with autoimmune liver diseases, *Bsm*I and *Taq*I; these and the *Fok*I polymorphism have been associated with AIH, as reviewed by Luong and Nguyen [86]. The non-genetic role of VD in AIH is related to the mitogen-activated protein kinase (MAPK) pathway, which is upregulated by the inhibition that VD exerts over cytokine production in monocytes and macrophages by lipopolysaccharide (LPS) and to the regulatory effect of VD on the production of IFNγ and reactive oxygen species [86].

A case-control study of 68 patients and 34 age-and-sex matched controls evaluated the association of low VD levels with histological features and poor response to therapy in patients with AIH [87]. The results showed significantly lower VD levels in AIH when compared to controls. Interface hepatitis and fibrosis scores showed a positive association with low VD levels, and patients with low VD levels were more likely to have a poor response to treatment [87].

4.6. Microbiome

The composition of a microbiome is influenced by diverse environmental factors including water sources, sanitation, pollution and exposure to residues, and by host-related variables such as genetic background, delivery method, age, diet, personal habits and antibiotic exposure [88,89]. The intestinal microbiome is a key factor for the development of intestinal immune responses and it is thought to influence systemic immune responses. Molecular mimicry is posed as a possible mechanism for the induction of autoimmunity in the relationship of the microbiome and immunity [88,89]. Toll-like receptors (TLR) in the intestine are key to identifying molecular patterns of pathogens, microbes and damaging stimulants. Inflammasomes are multimeric protein complexes that assemble in the cytosol in response to the stimulus by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and are responsible of driving the inflammatory response through active caspase-1 that cleaves precursor cytokines into active pro-inflammatory cytokines [90]. In AIH, the interaction of TLRs and the inflammasome has not been clearly defined [88]. Variations in intestinal microbiomes have been associated with the development of some ADs and, vice-versa, certain autoimmune and non-autoimmune diseases have been associated with changes in gut microbiomes [88]. Other variations in the microbiome have been associated with sex-related differences, attributed to habits, and the effect of sex hormones, and may be responsible, in part, for the increased female propensity for ADs [88]. Disruption of the gut barrier is a key event in the role of microbiomes on the development of autoimmunity [91]. The mechanisms proposed for this event are translocation of gut derived products by weakened tight junctions, increased intestinal permeability or paracellular migration and increased mucosal permeability in the intestine or active transport of bacterial antigens across the intestinal barrier [88]. Any of the mentioned pathways can lead bacteria or bacterial products into the portal circulation in the liver where they generate an immune stimulus that initiates liver inflammation [91]. A case control study evaluating 24 AIH patients and 6 healthy controls [91] found altered intestinal tight junctions with inflammatory infiltrates in the lamina propria in a group of patients, while normal structures were observed in healthy controls [91]. Evaluation of the intestinal microbiome found a reduced number of anaerobes, *Bifidobacterium* and *Lactobacillus*, with normal counts of aerobes, *Escherichia coli* and *Enterococcus*, when compared to healthy controls. Compared to healthy controls, AIH patients also had higher serum levels of LPS suggesting bacterial translocation [91]. The authors concluded that an association might exist between a “leaky gut” and dysbiosis, with the development of AIH [91]. A recent study in HLA-DR3 mouse models of AIH found that gut microbiota differed from those in healthy mice [92].

AIH is a progressive disease but generally an adequate response to conventional treatment with corticosteroids [16]. Around 90% of treated patients achieve remission after treatment with prednisolone and/or azathioprine [16]. The intestinal microbiome is thought to serve as a continuous reservoir of antigens that can initiate, maintain and/or perpetuate the autoimmune response in AIH [88]. Additional integrative studies on the microbiome and epigenomics are probably required to unveil the role of the microbiome on the pathogenesis of autoimmunity [93].

4.7. Sex and hormones

One hallmark of autoimmunity is the dominance of female gender for most ADs [90]. AIH has a strong female predominance; AIH-1 has a female to male ratio of 3–4:1; AIH-2 affecting mainly children has a female to male ratio of 9:1 [24,94]. However, it is uncertain if this effect is due to regulatory mechanisms due to sex-linked genes or if it is attributable to gender-specific hormones [95]. Higher serum levels of immunoglobulins after antigenic exposures, more frequent expression of autoantibodies and a more marked cell-mediated immunity after immunizations characterize the immune response of women [95,96]. Estrogens play an important role in immunologic behavior and high estrogen levels have been shown to inhibit a Th1 response and promote a Th2 response, favoring antibody production and antibody-dependent pathways. [95,96]; low estrogen levels favor the Th1 response thus promoting cell-mediated pathways [90,95,96]. Other hormones such as prolactin, growth hormone, progesterone and testosterone regulate the immune response by altering the cytokine secretion and the expression of the estrogen receptor [95,96]. Prolactin stimulates both cellular and humoral immune responses [90]. Various transcription factors have been shown to regulate immune tolerance mechanisms, including the immune regulator (AIRE) which displays gender-biased thymic expression [97]. The consequence is that females show a lower expression of transcription modulators than males in mice and humans [97]. In addition, estrogens and androgens modulate the expression rate of AIRE and PR domain zinc finger protein 1 (PRMD1) [97]; women with AIH are more frequently *HLA-DRB1*04* than men, and also a greater diversity of *HLA-DRB1*04* alleles than men [95]. The effect of sex hormones cannot solely explain the predominance of AIH in women as this predominance is observed among children and elderly populations The female predominance of AIH may be also explained by gender-related characteristics in antigenic presentation and T-cell activation [95].

Other mechanisms proposed to explain the susceptibility of women to ADs are the interactions between sex hormones and genetic factors as in the hypotheses of the skewed X chromosome activation, X monosomy and microchimerism [90,95,98–100]. The X inactivation process occurs in early embryonic development and leads to females being mosaics for two different lines of cells: cells with the maternal and cells with the paternal X chromosome as the active X [90,98]. The frequency of skewed X inactivation varies and increases with advancing age. This inactivation process is a potential mechanism whereby X-linked self-antigens may escape presentation in the thymus or in peripheral sites involved in tolerance induction [98]. Studies have assessed the association between ADs and defects in X chromosome and several reports have found the rate of X monosomy to be significantly increased in peripheral blood cells in patients with PBC and SSc [99] as well as a higher prevalence of skewed inactivation in patients with ADs [90]. It has been suggested that X monosomy may cause haploinsufficiency in X-linked genes that escape X chromosome inactivation [100].

Consequently, autoreactive T-cells are not exposed to self-antigens encoded by one of the two X chromosomes, perpetuating the autoimmune response [100]. Fetal-maternal microchimerism is defined as the movement of hematopoietic stem cells from fetal to maternal circulation during pregnancy [90,95]. These cells have been proposed to influence the pathogenesis of ADs if they are targeted as foreign [90]. Microchimerism can persist for years and can compromise self-tolerance, however, the exact role in AIH has not been fully established [95].

4.8. Drugs

Acute liver failure attributed to drugs, one of the primary causes of liver failure, can show autoimmune manifestations similar to idiopathic AIH [31,101]. Drug-induced AIH is classified separately from idiopathic AIH, however, drugs cannot be completely ruled out as possible causative agents of AIH even in the absence of a clear relationship with drug intake [31]. Unrecognized previous exposure and sensitization to drugs could be responsible for the initiation or maintenance of liver disease based on the hypothesis of genetic predisposition and molecular mimicry as factors contributing to the development of AIH [31]. However, it is important to take into account that drugs implicated in triggering AIH may also be causative agents of DILI with autoimmune features and that old case-reports in the literature are described as AIH without distinguishing the pathogenic mechanism [101]. Several drug compounds are being studied to determine possible associations with drug-induced AIH, among them, minocycline and nitrofurantoin have been proved to be associated with the disease [31].

Assessment of the role and interaction of drugs and autoimmune features in the development of liver disease is complex [102]. Drug-induced autoimmune liver disease can be classified as: a) AIH with DILI, in patients with known AIH in whom reactivation of AIH occurs after the introduction of a new drug; b) drug-induced AIH, in patients with no previously diagnosed low grade AIH or predisposition to AIH in whom a drug produces an autoimmune chronic process; c) immune-mediated-DILI, in patients who present with symptoms of an autoimmune hypersensitivity that remits after drug cessation; d) mixed autoimmune type DILI with positive autoantibodies [102].

The mechanisms by which drugs may induce AIH include the production of drug metabolites that bind to proteins and act as antigenic complexes stimulating the production of autoantibodies, principally CYP1A2 and CYP2A6, and the sensitization of lymphocytes [31]. Weiler-Normann and Schramm established a classification of DILI with autoimmune features and AIH [101]. They suggest that the main characteristics that favor the diagnosis of drug-induced AIH are genetic predisposition with the presence of haplotype HLA-B8-DR3, hypergammaglobulinemia, severe fibrosis or cirrhosis on liver histology, need for immunosuppression without withdrawal after remission and frequent association with another extra-hepatic autoimmune condition [101]. DILI is a different entity from drug-induced AIH however, the fact that a second episode of liver injury can occur in cases of re-exposure to proven drugs suggests an immune-mediated response [101,103].

DILI with autoimmune features is a syndrome characterized by biochemical and histological features of AIH following the ingestion of a drug or a herbal product [104]. Compared to drug-induced AIH, DILI with autoimmune features has a short incubation process and usually presents with jaundice and symptoms of liver injury; the liver biopsy shows inflammatory changes with predominance of lymphocytic and/or eosinophilic infiltrates. Improvement after drug withdrawal is often slow and recurrence is common if the drug is re-administered [104]. Metabolic and immunological factors have been identified as responsible for DILI with autoimmune features. It has been hypothesized that toxic agents are metabolized leading to the formation of a neoantigen and presented to T-cells with consequent immune activation process involving binding to T-cell receptors or the MHC which mediates the antigenic presentation [104].

DILI with autoimmune features has been described for nitrofurantoin, minocycline, hydralazine, procainamide, methyldopa, statins, interferons and anti-TNF agents (infliximab, adalimumab, etanercept) [103–105]. The anti-TNF agents are thus suggested as agents both capable of inducing AIH as well as immunosuppressing AIH in refractory disease. A cohort study in Holland [103] analyzed 88 cases of DILI attributed to nitrofurantoin, minocycline, methyldopa or hydralazine found an autoimmune phenotype in 72% of cases. The analysis of HLA alleles showed no association between HLA-DRB1*03:01 or DRB1*04:01 with an increased risk of developing autoimmune features [103].

The status of checkpoint inhibitors in use in cancer therapy today, which are reported as causing hepatitis with immune features, is not clear at this time.

5. Autoimmune hepatitis post-liver transplantation

Autoimmune hepatitis can recur or appear *de novo* after liver transplantation [16,106]. Around 8–12% of patients develop AIH one year after transplantation with an increasing incidence reaching 36–68% at five years [106]. In patients who were transplanted because of AIH, recurrence may be asymptomatic and is usually characterized by similar features as the initial presentation of the disease with elevated transaminases, positive autoantibodies, hypergammaglobulinemia including elevated IgG levels and similar histologic findings [16]. The term "*de novo* AIH" was first used to describe pediatric patients, and later adult patients, who developed AIH after liver transplantation for other diseases [106,107].

Although the exact pathophysiology of *de novo* AIH remains unknown, the possible mechanisms include damage to the graft by ischemia-reperfusion injury, infections and exposure to antigens, similar mechanisms to those proposed for AIH [106,107]. Presentation of antigens or autoantigens by APCs, either from the donor or the recipient, stimulates the memory T-cells from the host's immune system leading to a self-directed immune response [106,107]. It is thought that calcineurin inhibitors have an important role as they reduce the production of IL-2, a cytokine needed for the proliferation and survival of Tregs [106]. Additionally the role of molecular mimicry between infectious agents and the host supports the possibility that previous viral infections could be a potential cause of *de novo* AIH [106,107].

Glutathione-*s*-transferase T1 (*GSTT1*) which has been identified as a risk factor for *de novo* AIH [106,108], although other reports suggest that *de novo* AIH occurs in the absence of these antibodies [109]. As reviewed by Vukotic et al. [107], epidemiological data on *de novo* AIH describes an incidence of 5–10% in pediatric patients and around 1–2% in adult patients. Viral molecular mimicry is thought to participate in the pathogenesis of this condition, especially viruses such as CMV, EBV and parvovirus that often affect immunosuppressed individuals [107].

As reviewed by Faisal et al. [110] and Kerkar et al. [106], patients with recurrent AIH have a good prognosis; survival rates are around 90% and 86% at 1 and 5 years, respectively. Recurrence of AIH after liver transplantation ranges from 15% to 40% [106,110]. Although AIH-2 is known to have a more aggressive course, AIH-1 has a higher rate of recurrence after liver transplantation [111]. Recurrence is diagnosed based on the reappearance of symptoms and clinical signs of AIH, elevated transaminases, positive autoantibodies, elevated IgG levels, a biopsy showing interface hepatitis and a response to corticosteroid therapy with exclusion of graft rejection [110,111]. The pathogenic mechanisms of recurrence are not fully understood but cellular and antibody-mediated cytotoxicity are thought to be involved [106]. Evidence of the role of HLA *DR3* and *DR4* as risk factors for the recurrence of AIH is controversial [110,112] as well as is the role of an *HLA-DR3*-negative donor and *HLA-DR3* or *DR4*-positive recipient. Tacrolimus therapy and severe initial disease have been suggested as possible prognostic factors [106,108,110,111]. High levels of transaminases and IgG as well as necroinflammatory activity in the liver

appear to increase the risk for AIH recurrence [110]. The pathophysiological mechanism of the disease is similar to that of *de novo* AIH in relation to the antigenic presentation by APCs that mediate re-stimulation and re-expansion of sensitized cells to species-specific antigens that invade the graft and start an autoimmune process [106].

6. Animal models for autoimmune hepatitis

The search for appropriate animal models which mirror human AIH, in order to better understand the complex mechanisms that underlie the onset and the pathophysiology of the disease, and to identify new, specific and efficient therapeutic agents has been sought over many years [113]. Several strategies have been used to reproduce an immune-mediated hepatitis in mice, which comprise concanavalin A (ConA) treatment, immunization approaches and transgenic and knock-out mice models. Detailed reviews of the experimental AIH models described over time have been published in the last decade [113,114].

6.1. ConA-induced hepatitis

A single intravenous injection of the plant lectin ConA is a reliable strategy to induce an acute and severe liver injury in mice [115,116]. ConA, by cross-linking TCRs with surface glycoproteins on sinusoidal endothelial cells and MHC-II on Kupffer cells, drives the recruitment of $CD4^+$ T-cells and NKT cells in the liver leading to their activation and to a massive cytokine release. IFNγ and TNF-α are the major cytokines responsible for ConA-induced liver damage [115,116]. Although circulating autoantibodies are not produced, parenchymal cell apoptosis, together with the increase of serum transaminases, are rapidly induced within few hours upon a single-dose injection of ConA [117]. The development of tolerance mechanisms to ConA-mediated damage impairs reproduction of chronic hepatitis in mice [118]. Genetic background influences the outcome of the treatment as Th1-biased C57BL/6 and C3H mice are most susceptible to ConA-induced liver injury [115].

6.2. TGF-$\beta_1^{-/-}$ and NTx-PD-$1^{-/-}$ knock-out mouse models

The depletion of genes associated with anti-inflammatory activity and self-tolerance is one of the strategies aimed at inducing an immune-mediated hepatitis in mice [119]. The significant role of transforming growth factor β1 (TGF-β1) in immune homeostasis has been widely described since gene disruption in mice results in multi-organ inflammatory lesions and early death [119]. Balb/c TGF-$\beta_1^{-/-}$ mice are particularly prone to spontaneously develop extensive liver inflammation and hepatocyte necrosis associated with elevated plasma ALT levels [120]. Necroinflammatory liver disease in Balb/c TGF-$\beta_1^{-/-}$ mice has been attributed to $CD4^+$ Th1 cells and its IFNγ-mediated immune modulation, which seems to resemble human conditions [120,121].

Spontaneous and fatal fulminant hepatitis was observed in programmed death (PD-1) deficient mice subjected to neonatal thymectomy (NTx-PD-$1^{-/-}$). In these mice, immunological tolerance failure occurred through the loss of PD-1 signaling and the deficit in T-cells [122]. Mice showed progressive mononuclear cell infiltration and massive hepatocyte degeneration in the histopathology and an increase in serum aminotransferases and total bilirubin. Notably, circulating antinuclear antibodies were also detectable [122]. Although both TGF-$\beta_1^{-/-}$ and NTx-PD-$1^{-/-}$ mice mirror features of acute human AIH, their shortened postnatal survival limits their potential use as preclinical models [122].

6.3. Immunization with liver homogenates

During the course of 1980, immunization protocols through injection of syngeneic liver homogenates were developed to induce the loss of hepatic tolerance in mice [123–125]. Syngeneic homogenates or their supernatant fraction S-100, administered together with complete Freund's adjuvant or LPS, developed persistent hepatitis with autoantibodies production, mild to severe periportal inflammatory cell infiltration and focal necrosis. The grade of injury varied according to the protocol of immunization and the mouse strain used [123–125].

6.4. Transgenic mouse models

Over the years, researchers aimed at replacing the use of undefined antigens of hepatic homogenates with a stable expression of specific neoantigens in the liver through transgenic technology [125,126]. However, as transgenic mice need to be infected with liver-specific pathogens or with antigen-specific T-cells, this strategy failed to establish a chronic hepatitis although it induced a short-lived hepatitis, due to central host tolerance. Detailed descriptions of the evolution of such tempted models were recently reviewed [125,126]. In 2010, the group of Zierden et al. [127] generated the Alb-HA/CL4-TCR double transgenic Balb/c mice that spontaneously developed chronic autoimmune-mediated liver inflammation. The fusion of influenza virus hemagglutinin (HA) gene under the control of albumin promoter (Alb-HA) directed liver-specific neoantigen expression in addition to an HA-specific CL4-TCR expression on $CD8^+$ T-cells. From the histological point of view, Alb-HA/CL4-TCR mice liver tissues displayed necro-inflammatory lesions, fibrosis and increased serum ALT although severe disease was prevented by peripheral tolerance mechanisms [127].

6.5. Humanized mouse models

The identification of CYP2D6 and FTCD as the targets of anti-LKM1 and anti LC1, respectively, has led to the generation of AIH-2 models through cross-species immunization with human liver antigens. This strategy exploits the viral mechanism of molecular mimicry [114]. Adenovirus-vector expressing human CYP2D6 or FTCD and plasmids containing cDNA for a human CYP2D6/FTCD chimeric protein have been used to infect mice and induce a break in immune tolerance [128,129]. FVB/N mice injected with human CYP2D6-adenovirus developed chronic hepatitis with subcapsular and/or parenchymal fibrosis, circulating anti-CYP2D6 antibodies and increased serum aminotransferase [128,129]. Similarly, intravenous injection of NOD mice with human FTDC-adenoviral vector induced chronic AIH-2 with hypergammaglobulinemia, anti- FTCD and ANAs antibodies and, in some cases, portal and lobular fibrosis [130]. Through DNA vaccination of C57BL/6 female mice with CYP2D67/FTCD-plasmid, Lapierre et al. [131] generated a murine model of AIH-2 characterized by a mild increase in serum ALT and circulating anti-LKM1 and anti-LC1 autoantibodies. Histologically, the livers had periportal and portal inflammatory infiltrates (predominantly $CD4^+$ T cells), interface hepatitis and necrosis, but no signs of fibrosis [131] Using the same xenoimmunization protocol, Yuksel et al. [92] were recently able to mirror human AIH in *HLA-DR3* transgenic NOD mice. Immunization with autoantigens triggered a sustained ALT elevation, production of anti-LKM1 and anti-LC1 autoantibodies as well as ANA and chronic immune cell infiltration. In addition, half the mice developed F1/F2 mild liver fibrosis [92].

In conclusion, the feasibility of animal models of AIH is somewhat questionable. Several models aim to investigate the immune mechanisms, or to assay new treatments. The novel humanized mouse models are similar to the human AIH, displaying autoantibodies, hypergammaglobulinemia, and lymphocytic infiltrate in the liver, representing a powerful tool for the study of autoimmune-mediated liver inflammation and fibrogenesis and for the preclinical testing of new immunotherapies [92].

7. Conclusions

Although the etiology of AIH is not fully understood, several studies have addressed the importance of genetics and environmental factors in

the pathophysiology of this condition. Genetic studies have found strong associations with HLA genes, and weaker associations with non-HLA genes for predisposition, severity and response to therapy. Presumed triggering agents, particularly infectious agents with hepatic tropism including viruses, bacteria and parasites have been proposed to function in the immunopathophysiological paradigm of AIH. Moreover, data for the roles of alcohol and its metabolites, vitamin D, the microbiome, gender, estrogens, drugs and vaccines as environmental factors contributing to the development of AIH-1, AIH-2 and post-transplant AIH have accumulated. An animal model which faithfully recapitulates human AIH is still being sought.

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