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Autoimmune liver disease, autoimmunity and liver transplantation

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Summary

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) represent the three major autoimmune liver diseases (AILD). PBC, PSC, and AIH are all complex disorders in that they result from the effects of multiple genes in combination with as yet unidentified environmental factors. Recent genome-wide association studies have identified numerous risk loci for PBC and PSC that host genes involved in innate or acquired immune responses. These loci may provide a clue as to the immune-based pathogenesis of AILD. Moreover, many significant risk loci for PBC and PSC are also risk loci for other autoimmune disorders, such type I diabetes, multiple sclerosis and rheumatoid arthritis, suggesting a shared genetic basis and possibly similar molecular pathways for diverse autoimmune conditions. There is no curative treatment for all three disorders, and a significant number of patients eventually progress to end-stage liver disease requiring liver transplantation (LT). LT in this context has a favourable overall outcome with current patient and graft survival exceeding 80% at 5 years. Indications are as for other chronic liver disease although recent data suggest that while lethargy improves after transplantation, the effect is modest and variable so lethargy alone is not an indication. In contrast, pruritus rapidly responds. Cholangiocarcinoma, except under rigorous selection criteria, excludes LT because of the high risk of recurrence. All three conditions may recur after transplantation and are associated with a greater risk of both acute cellular and chronic ductopenic rejection. It is possible that a crosstalk between alloimmune and autoimmune response perpetuate each other. An immunological response toward self- or alloantigens is well recognised after LT in patients transplanted for non-autoimmune indications and sometimes termed "de novo autoimmune hepatitis". Whether this is part of the spectrum of rejection or an autoimmune process is not clear.

In this manuscript, we review novel findings about disease processes and mechanisms that lead to autoimmunity in the liver and their possible involvement in the immune response *vs.* the graft after LT.

Keywords: Autoimmunity; Primary biliary cirrhosis; Primary sclerosing cholangitis; Autoimmune hepatitis; Genome-wide association studies; Recurrence; Rejection; *De novo* autoimmune hepatitis.

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Introduction

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the tree major forms of autoimmune liver disease, which differ according to the focus of autoimmune injury, the pattern of inflammation and the clinical phenotype.

In AIH, the autoimmune injury affects the hepatocytes, leading to the histological picture of interface hepatitis. In PBC, the autoimmune injury affects the small, interlobular bile ducts, causing the typical appearance of non-suppurative, destructive cholangitis. In PSC, autoimmune or immune-mediated injury affects the medium-sized intra- and extrahepatic bile ducts, causing concentric and obliterative fibrosis and multifocal bile duct stricturing.

AIH, PBC, and PSC represent complex disorders, in that they result from the interaction between genetic and environmental factors (Fig. 1). In recent years, there have been major efforts to delineate the genetic architecture of these conditions. Recent genome-wide association studies (GWAS) and iCHIP-association studies [1–8] identified numerous risk loci for PBC and PSC that host genes involved in innate or acquired immune responses. These findings have resulted in a better understanding of the pathogenic mechanisms underlying these immune-mediated conditions, highlighting common immune pathways between clinically associated disorders and explaining the tendency for patients and their families to suffer from multiple autoimmune conditions. This translates in the possibility of unique immunologic pathways for therapeutic intervention. The implication is that biological processes involved in loss of immune tolerance to one self-antigen (such as CYP2D6 in the case of some models of AIH or PDC-E2 in PBC) might be the same for other self-antigens (such as thyroid peroxidase in thyroid disease).

All three disorders have a progressive course that, if untreated, develop into liver failure requiring liver transplantation (LT). The aim of treatment is to abolish or reduce inflammation, cholestasis and progression of fibrosis. Standard therapy in AIH consists of a combination of corticosteroids and azathioprine, which is effective in 80% of patients; however progression may occur despite seemingly effective treatment. Other immunosuppressive agents such as mycophenolate mofetil, d-penicillamine, sirolimus and anti-T cell therapies have been tried in refractory cases with limited success [9]. The only licensed therapy for PBC and PSC is ursodeoxycholic acid (UDCA) [10]. In PBC, response to UDCA has a favourable effect on long-term survival

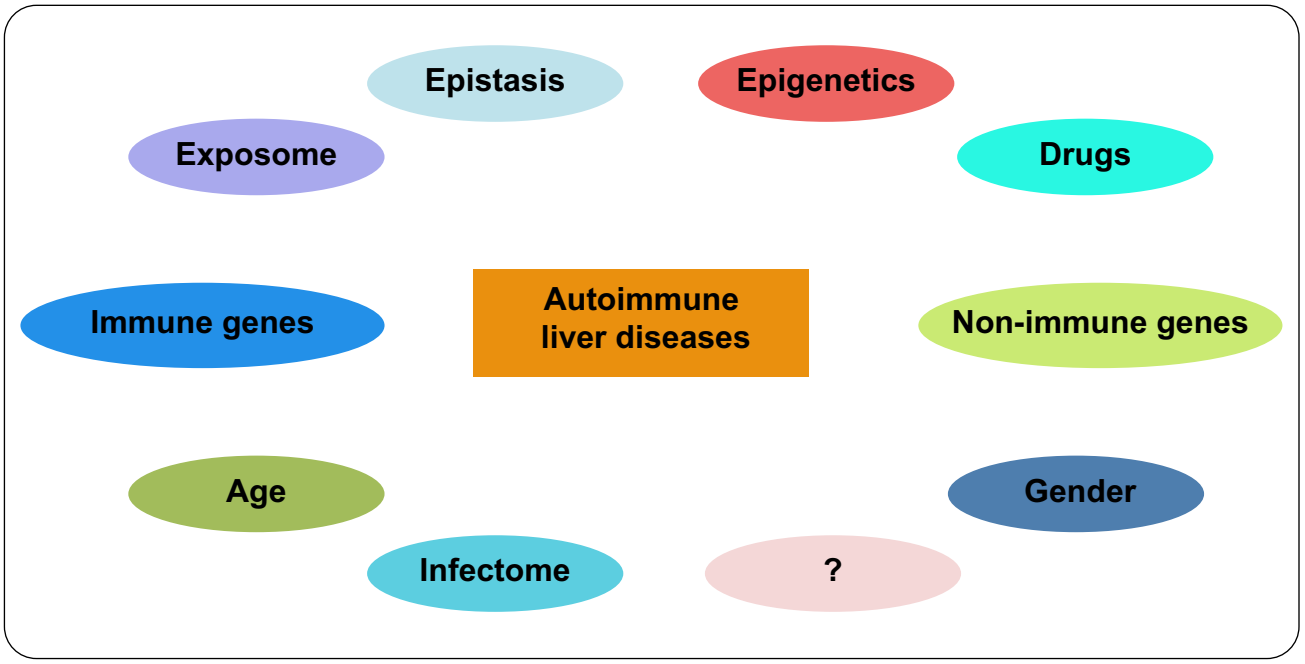

Fig. 1. AIH, PBC, and PSC are complex disorders meaning they are likely associated with the effects of multiple genes in combination with environmental factors.

and progression of fibrosis; those who do not respond to UDCA have a poor survival (10-year survival is >95% and <80% in responders and non-responders to UDCA, respectively) [11]. Other drugs including methotrexate, colchicine and fibrates, have been tested in combination with UDCA but none has been found to be of benefit [12–18]. A promising agent, under investigation is Obeticholic acid (OCA); this is a novel bile acid, which is an agonist of the Farsenoid X receptor implicated in the metabolism and enterohepatic circulation of bile acids [19].

In PSC, treatment with UDCA improves serum liver tests but does not improve survival; indeed, higher doses (17–23 mg/kg/day) are associated with high rates of serious adverse events [20]. Although some units no longer routinely advise their patients with PSC to take UDCA, recent data from the analysis of the UK-PSC cohort [21] of around 700 patients, have shown a dose dependent effect of UDCA on LT-free survival (*UK-PSC – unpublished data*). Thus, for these autoimmune liver diseases there is a subgroup of patients who are non-responders to current treatments and have a poor prognosis, for whom new therapeutic options are warranted. However, development of novel agents is currently hindered by inadequate understanding of the aetiology and pathogenesis of these autoimmune conditions.

Clinical phenotypes of autoimmune liver disease

Clinical and immunological features suggest that AIH is an archetypal autoimmune condition. It is characterized by a strong female preponderance (F:M ratio 7:1); hypergammaglobulinaemia; seropositivity for autoantibodies and a good clinical, serological and histological response to corticosteroids. Furthermore, in AIH concurrent autoimmune disorders occur in approximately 40% of patients, particularly autoimmune thyroid disorder (AITD). Two types of AIH are recognised: type 1 (AIH-1), characterised by antinuclear antibodies (ANA) and/or anti-smooth muscle antibody (SMA), and type 2 (AIH-2), characterised by anti-liver kidney microsomal type 1 antibody (anti-LKM-1) or for anti-liver cytosol type 1 antibody (anti-LC-1) [22].

PBC also exhibits a number of autoimmune features, including the presence of autoreactive T cell and B cell responses against mitochondrial self-antigens, in particular the E2-domain of pyruvate dehydrogenase complex (PDC-E2); the almost universal presence of auto-antibodies reactive with mitochondrial self-antigens; a strong female predominance (F:M ratio, 10:1) and an association with other autoimmune diseases in the same individual and their close family. A concurrent autoimmune disorder occurs in between 32% and 53% of patients, most notably AITD, systemic lupus erythematosus (SLE) or systemic sclerosis (SSc) [23,24]. Autoimmunity is also common in families of PBC patients, with an estimated 14–20% of first degree relatives of PBC probands having an autoimmune disease other than PBC [25,26]. However, unlike AIH, no immunosuppressive agent to date has been shown to be effective in PBC.

PSC is considered an 'autoimmune disease with atypical features' because it displays several differences when compared with the classical autoimmune diseases: these include male predominance (M:F ratio, 2:1), the absence of disease-specific autoantibodies, and the poor response to immunosuppression. However, features that suggest an immune-mediated origin include the major contribution of risk variants within the human leukocyte antigen (HLA) complex, the presence of non-specific autoantibodies, including atypical anti-neutrophil cytoplasmic antibodies (ANCA) [27], the preferential usage of specific T cell receptor variable chains implying the presence of a specific (self)-antigen [28], and a strong association with other autoimmune or immune-mediated disorders which occur in approximately 70% of patients. Most notable is a form of inflammatory bowel disease (IBD), sometimes termed IBD-PSC, which affects up to 90% of patients [29,30]. IBD without any sign of PSC occurs more frequently among first degree relatives of patients with PSC.

IBD in those with PSC tends to have a different phenotype compared with IBD alone. Approximately 25% of PSC patients have an autoimmune condition outside of the gastrointestinal tract, most commonly type I diabetes mellitus (T1DM) or AITD [31].

Shared serological, immunological and histological patterns exist across the spectrum of AIH, PBC, and PSC. Conditions exhibiting features of two different autoimmune liver diseases are commonly designated 'overlap syndromes'. These are represented by variant forms of AIH, in which there are characteristics of both AIH and PBC ('AIH/PBC overlap') or AIH and PSC ('AIH/PSC overlap'). Whether these represent distinct entities or part of a disease spectrum ranging from pure PBC'/'pure PSC at one extreme to 'pure AIH' at the other, is not clear. Despite genetic susceptibility loci for these diseases being strongly linked to the HLA region, these are generally distinct across all three disease entities. Intriguingly, there is barely any significant genetic overlap between PBC and PSC. Indeed, clinical overlap of PBC and PSC is not a well-recognized entity.

Recent highlights from high-throughput genetic studies of autoimmune liver disease

In the last decade, there have been major efforts in Europe, North America and Japan to establish large, well-characterised patient cohorts for high-throughput genetic studies of PBC and PSC, and to a lesser extent, AIH. Four GWAS [1–4] and two iCHIP-association [5,6] studies of PBC have been published; and two GWAS of PSC followed by a number of replication studies, and a recent iCHIP association study of PSC [7,8,21,32–35]. High-throughput genetic studies have revolutionized the study of complex diseases, changed the genetic landscape of autoimmune liver disease and highlight the shared genetic basis of diverse autoimmune conditions. Risk loci for PBC and PSC appear to be enriched for gene products involved in innate or acquired immune responses, consistent with an autoimmune component to pathogenesis. However, more work is required to confirm candidate genes, to evaluate the functional consequences of risk variants and to understand how functional changes contribute to disease-specific pathologies.

GWAS have clearly demonstrated that the major component of the genetic architecture of PBC and PSC is within the HLA region. As expected in a genetically complex disease, GWAS also identified several novel non-HLA variants, but all lie in immune-related genes. In PBC, candidate genes are potentially involved in regulation of the immune system, from the development and differentiation of the myeloid cell compartment (*SPIB, IRF5, IRF8,* and *IL-7R*) to antigen presentation and T cell differentiation (class II *HLA, CD80, IL12, IL12R, TYK2, STAT4, SOCS1*) up to B cell function (*SPIB, IRF8, PLC-L2, SPIB, PLC-L2, IKZF3, CXCR5*). In PSC, there is an overwhelming contribution to disease risk by the HLA (in particular HLA class I genes HLA-B and HLA-C). The immunological implications of the PSC associated HLA variants are not entirely clear. It is possible there is a protective effect of the HLA-C2 killer immunoglobulin receptors (KIRs) ligand variant on PSC development [36]. The non-HLA findings in PSC to some extent indicate that the proposed hypotheses on PSC pathogenesis related to autoimmune mechanisms (*IL2* and *IL2RA*), bile acid toxicity (*GPBAR1*), and mechanisms related to the concomitant IBD (*IL2/IL21, IL2RA, REL etc.*) might operate in concert to cause the disease.

However, more work is required to confirm candidate genes, to evaluate the functional consequences of risk variants and to understand how functional changes contribute to disease-specific pathologies.

A GWAS of AIH in European and Japanese cohorts are underway and results from these studies will be reported by 2014.

GWAS typically identify common genetic variants with small effect sizes, leading to incomplete tagging of rarer variants with a potentially higher phenotypic impact. Also, GWAS have identified only a small number of the causal variants for recently identified genetic loci (mainly intronic and intergenic) which, in turn, interpret only a small part of the genetic contribution to these diseases (i.e., 'missing heritability'). To identify the rare genetic variants and explain the missing heritability sequencing the use of emerging platform is required. Whole-genome and whole-exome sequencing (which focuses on the protein-coding exons and exon/intron boundaries containing splicing signals) are becoming increasingly available but present significant challenges with respect to data analysis, interpretation, and display. Integration of the other comprehensive "-omics" methodologies into the analysis of genetic variants may help to explain their potential effects. Transcriptomics aims to elucidate the transcripts of the genome or gene expression levels on the RNA level under varying conditions; genomics/transcriptomics screens can yield information on both gene expression and alternative splicing and can help to identify previously unknown genes. Finally, proteomics studies the proteome in a cell compartment, tissue or organism comprising all proteins that are encoded in the genome and represents the next step in the study of biological systems [37,38]. Studying the genome/proteome in AILD will shed light on common and distinct pathological pathways leading to AILD.

As with translation of many genomic discoveries, translating this work into direct health benefits will require interaction among a wide array of biomedical disciplines, including genomics, molecular biology, clinical medicine, pharmacology and bioinformatics.

Shared genetic basis of different autoimmune diseases

An emerging theme in the genetics of complex disorders is the considerable overlap of genetic susceptibility factors between related diseases. The recent PSC iCHIP study [8] has revealed strong positive correlation of 44 non-HLA loci identified in GWAS of seven clinically associated autoimmune disorders, including ulcerative colitis (UC), Crohn's disease (CD), T1DM, coeliac disease (CeD), psoriasis, rheumatoid arthritis (RA) and sarcoidosis, suggesting close similarity in the genetic architecture of PSC and each of these conditions. Of these loci, 11 achieved genome-wide significance and 33 loci achieved suggestive significance ($p < 5 \times 10^{-5}$) in the standard test of association. Functional network analysis showed that candidate genes at pleiotropic loci were related in terms of their function, highlighting common pathways involved in the pathogenesis of PSC and clinically associated disorders. These observations suggest there might be distinct mechanisms by which autoimmunity occurs, each mechanism predisposing to a particular phenotype or set of phenotypes. This might also suggest that there might be unique immunologic pathways that we have to focus on for therapeutic intervention (Fig. 2).

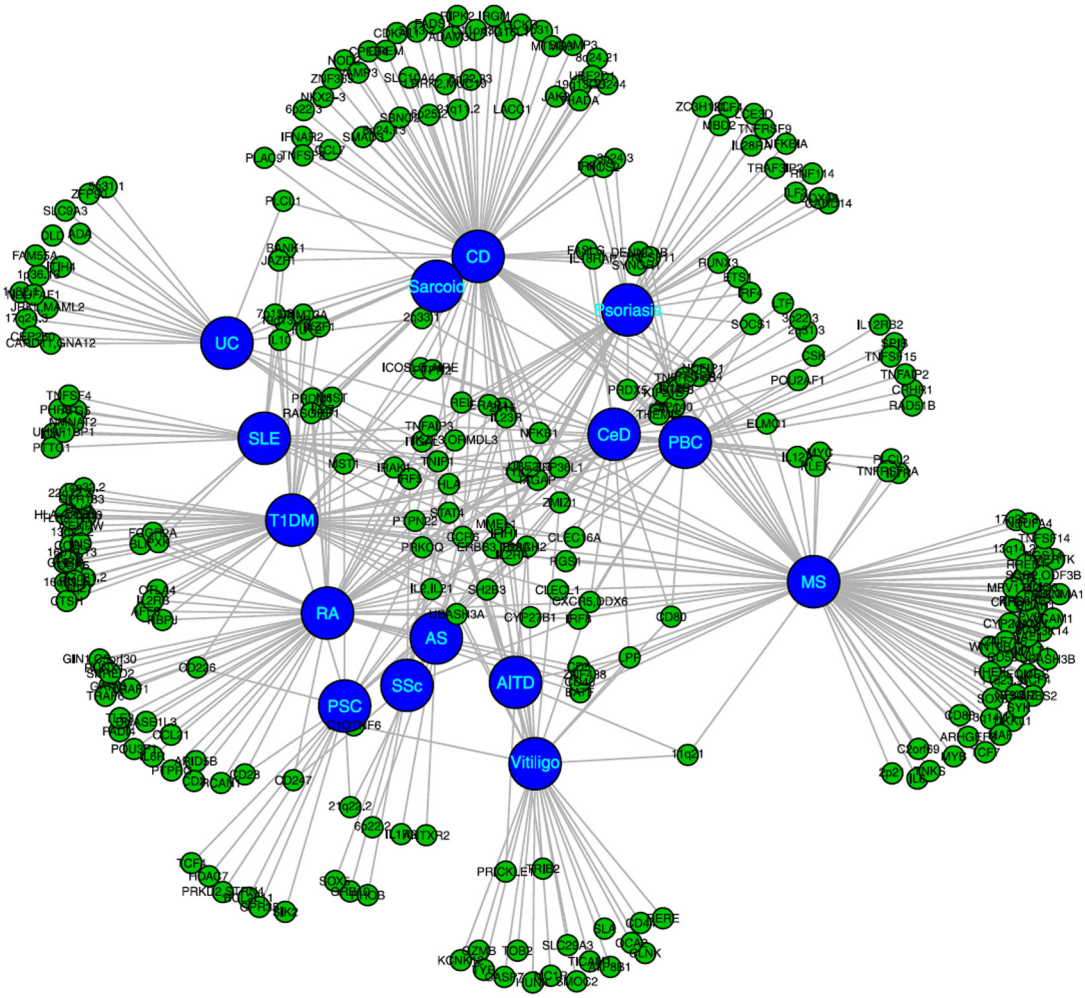

Fig. 2. Network map showing complexity of shared genetic effects. Some shared risk loci are involved in the pathogenesis of several autoimmune disorders. These loci are clustered in the centre of the figure. Other shared risk loci are associated with only two conditions. Numerous risk loci are associated with a single disorder. It is plausible that the central loci associated with numerous conditions are those involved in autoimmunity in general, whereas risk loci specific to a given disease determine the particular phenotype. AITD, autoimmune thyroid disease; AS, ankylosing spondylitis; CeD, coeliac disease; CD, Crohn's disease; PSC, primary sclerosing cholangitis; MS, multiple sclerosis; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; SLE, Systemic lupus erythematosus; SS, systemic sclerosis; T1DM, type 1 diabetes mellitus; UC, ulcerative colitis. Reproduced from [156]. With permission from the Editor in Chief Prof. Eric M. Gershwin.

An alternative interpretation is that the pervasive sharing of risk variants of genes across a wide range of autoimmune diseases implies that the common variants identified through GWAS are not particularly helpful in explaining the organ-specific manifestation of a given autoimmune trait. The most likely explanation for the ambiguity of the genetic findings is that phenotypes might be the result of gene-gene interaction (epistasis) or gene-environment interaction. From this perspective, the study of the 'exposome', which represents the environmental factors which we are exposed to in a lifetime, represents a cutting-edge tool in the study of autoimmunity [39]; the study of the exposome needs to address exogenous factors, such as tobacco smoke, diet, drugs, occupational exposures, environmental pollutants, ultraviolet radiation, heavy metal, and endogenous factors related to the environment, including by-products of inflammation, lipid peroxidation and oxidative stress [40]. Some of these components may act as nucleophiles or electrophiles, and as such, would be capable of DNA and protein modification [41]. Recent studies in T2DM have shown that the exposome can indeed be measured and characterized using environmental-wide association studies (EWAS), where epidemiological data are comprehensively interpreted in a manner similar to GWAS [42]. Growing interest in the field of autoimmune diseases is in the exploration of the 'infectome', which is the part of the exposome referring to the collection of an individual's infectious exposures, which are associated with the disease. An autoimmune disease can be induced or triggered by infectious agents. In many cases, it is not a single infection but rather the 'burden of infections' from childhood that is responsible for the induction of autoimmunity. In contrast, the hygiene hypothesis underlines the protective role played by infections [39]. Further hints regarding infective factors potentially involved in the development of or protection against autoimmunity can be provided by the study of the 'microbiome', defined as the community of commensal, symbiotic, and pathogenic microorganisms that share our body space. For example, in the case of PBC, it may be

Table 1. Transplant activity and survival for autoimmune liver diseases in two different eras (1988–2001 and 2000–2009) in Europe. The number of LT for AIH and PSC has remained stable over the time while the number of LT for PBC, despite the rise in the prevalence of the disease, has declined.

Disease	From Jan 1988 to Dec 2001								From Jan 2000 to Dec 2009					
	No. patients	%	Survival						No. patients	%	Survival			
			1 yr		5 yr		10 yr				1 yr		5 yr	
			Patient	Graft	Patient	Graft	Patient	Graft			Patient	Graft	Patient	Graft
Autoimmune hepatitis	991	3	81	76	72	65	65	58	1069	2	88	84	80	72
Primary biliary cirrhosis	2959	8	83	79	77	71	69	64	1929	4	90	85	83	78
Primary sclerosing cholangitis	1731	4	83	78	75	65	66	54	2170	5	90	83	82	72

European Liver Transplant Registry report [45,145].

pertinent to understand the normal microbiome of the urinary bladder and vagina, as infections in these sites have been associated with PBC [43].

Studying the role of the different aspects of the exposome in the development of autoimmune diseases could complement classical immunological research tools and GWAS. Several factors suggest that PBC may represent an ideal model disease for the investigation of the role of the exposome: its relatively high prevalence compared to other immunologic diseases; the well-known evidence in support of a combination of genetic, environmental, and infectious factors involved in the pathogenesis of the disease; the variability of its natural history, which suggests the presence of high-risk and low-risk patients; the association with other autoimmune diseases; and the lack of need of immunosuppression, which might impair the immunological assessment of the 'infectome' (the infective component of the exposome). More recently, there is indicative evidence that in addition to genetics, other complementary mechanisms are involved in the pathogenesis of autoimmunity, in particular, epigenetics – defined as stable and heritable patterns of gene expression caused by mechanisms other than changes in the underlying DNA sequence. Epigenetic mechanisms primarily consist of DNA methylation, histone modifications and small non-coding RNA transcripts. Epigenetic marks can be affected by age and other environmental triggers, and can therefore provide a plausible link between environmental factors and the onset and development of autoimmune liver disease [44].

Below, we review the basis of the autoimmune response toward the graft in patients with and without previous autoimmune disease and examine the current evidence on mechanisms that lead to the autoimmunity and their link to transplant rejection.

Liver transplantation for autoimmune liver disease

AIH, PBC, and PSC represent three major indications for liver transplantation (LT) in Western countries [45]. Paradoxically, the rise in the documented prevalence of PBC [46] contrasts with the fall in the transplant rate (Table 1). Reasons for this decline are not clear but may relate to a changing pattern of disease, increased rates of diagnosis, more effective treatment or other causes. The proportion LTs for AIH and PSC has remained stable (2% and 4%, respectively); in some areas, such as in the Scandinavian countries, which have a relatively low prevalence of hepatitis C and alcoholic liver disease (ALD), PSC is the leading indication accounting for 16% of the LT [47]. LT in AILD is indicated when liver failure occurs with complications similar to those for end-stage liver disease caused by other aetiologies. An unacceptable quality of life because of severe, treatment-resistant pruritus or severe hepatic encephalopathy may also merit consideration for transplantation. Fatigue in PBC and other cholestatic liver diseases is often severe and disabling. Cross-sectional studies have shown no evidence of improved fatigue after LT [48,49]. We have recently shown, in a single-centre, prospective, longitudinal cohort that fatigue improves after LT. However, 44% of the 31 patients had moderate to severe fatigue at two years after LT. Whether this improvement is enough to justify organ allocation in patient with fatigue alone, without liver failure, remains still an open issue [50].

Recurrent cholangitis related to dominant strictures or intrahepatic strictures not amenable to dilatation and stenting in PSC rarely represent indication for LT. Cholangiocarcinoma (CCA) may complicate PSC, with a 10-year incidence of 7–9% [51]. Risk factors for CCA include advanced disease (elevated bilirubin, variceal bleeding), proctocolectomy, chronic ulcerative colitis with colorectal cancer or dysplasia, long history of inflammatory bowel disease, and polymorphisms of the NKG2D gene [52–54]. Historically, the presence of such a tumour contra-indicates LT because of the high rate of recurrence. However, studies from the Mayo Clinic suggest that in highly selected cases, aggressive treatment with chemo- and radiotherapy may allow some patients to have a good outcome (54). Hepatocellular carcinoma (HCC) occurs in patients with AILD with cirrhosis, with a variable incidence (AIH: 1.9% per year [55]; PBC 4% – 12.3 at 10 years [56–58]; PSC: 2% per year [59,60]) and represents an indication for LT. The prioritization of these patients for LT is the same as for other liver diseases associated with HCC.

Outcomes after LT for AILD are generally excellent (Table 1). Specific post-transplant issues in patients transplanted for AILD are recurrence of the original disease and a higher rate of rejection, which may both impact on survival. Furthermore, PSC transplant recipients with concomitant IBD are more likely to develop colon cancer, with a cumulative incidence at 10 years after LT of 8.2% [61]. Routine surveillance colonoscopy is therefore usually recommended.

Recurrence of autoimmune liver disease after liver transplantation

Autoimmune liver disease might be expected not to recur after LT as the grafts should be protected from such injury from the outset by levels of immunosuppression that prevents allograft rejection. However, AIH, PBC, and PSC recur in many recipients and recurrence may be more aggressive than the original disease (Table 2).

Recurrent AIH (rAIH) is reported in about 23% and is diagnosed at a median interval of 26 months, but recurrence after more than 10 years after transplant and in those taking 17.5–20 mg of prednisolone per day, has been reported. rAIH may be seen with normal liver tests so the use of protocol biopsy may identify those with clinically silent recurrence [62]. Histological features of rAIH include a mononuclear infiltrate of lymphocytes and plasma cells extending from portal tracts to lobular parenchyma and an absence of features of acute rejection such as endothelialitis and ductulitis. There is some evidence that corticosteroid withdrawal does not precipitate rAIH [63], although recurrence is often responsive to an introduction of, or an increase in the dose of corticosteroids.

The diagnosis of recurrent PBC (rPBC) is made on histological criteria since liver tests are nonspecific and AMA persist irrespective of evidence of graft histology. The reported prevalence rate of rPBC ranges from 0% to 35%. The reported incidence rate is 21–37% at 10 years and 43% at 15 years [62]. The median time to rPBC ranges between 3 and 5.5 years. The reported recurrence frequency rate increases with time and varies in part because of different diagnostic criteria as well as different policies for protocol biopsies, since recurrence may be present with normal liver tests. Because of the beneficial effect of UDCA in slowing the progression of PBC in the native liver, this is commonly offered to those with evidence of rPBC. However, the assessment of drug efficacy is challenging as many patients have normal or near normal liver tests at diagnosis; the current data, which are limited, suggest that UDCA does not seem to influence patient and graft survival [64].

PSC has been shown to recur between 10% and 27%, with a mean interval between LT and onset of 6 months to 5 years [62]. Recurrent PSC (rPSC) needs to be distinguished from secondary sclerosing cholangitis. There are several causes of secondary sclerosing cholangitis, including hepatic artery thrombosis, ischemic and ischemia/reperfusion injury, infection with CMV or HIV, ABO incompatibility and rejection; the diagnosis is made on showing multiple non-anastomotic strictures with no other risk factors. There is no established medical therapy for rPSC. UDCA may be of benefit in those with coexisting UC, as some suggest it reduces the risk of colon cancer [65]. Interventional cholangiographic treatment of biliary strictures should be considered when dominant strictures are present; however, such approaches are rarely feasible since most strictures are multiple and most recipients have a Roux loop (since the disease affects both the intra- and extra-hepatic bile ducts). Therefore, *magnetic resonance imaging* (MRI) is often used to diagnose or exclude rPBC although *percutaneous transhepatic cholangiography* (*PTC*) allows both diagnostic and, in some cases, therapeutic intervention. Recent series report the successful use of single and double balloon enteroscopy in patients with roux loop [66,67].

Immunosuppressive strategies to reduce the risk of recurrence of AILD are difficult to be evaluated since majority of studies are retrospective and detailed information, including changes in immunosuppression and disease stage where the change of medication took place, are missing.

Graft loss due to recurrent disease is not a major issue in PBC, but it is in AIH and PSC (percentage of graft lost due to recurrent disease: 1.3% in PBC; 6.2% in AIH; and 8.4% in PSC) [68]; the rate of graft loss from rAIH may be falling because of increasing long-term use of corticosteroids in these patients.

LT provides a unique setting to help understand the pathophysiology of autoimmune liver diseases. Using protocol follow-up and liver biopsies to pinpoint the onset of disease, it might be possible to elucidate the innate and adaptive immune processes active at the earliest stage of disease. In practical terms, this is not easily achieved since the majority of centres have discontinued the practice of protocol liver biopsies in allograft recipients other than HCV.

Risk factors for recurrent AILD

Assessment of risk factors for recurrence of AILD requires not only comparison between patients with and without recurrence (which is problematic because some patients without recurrence at the time of analysis will subsequently develop recurrence) but also a consistent approach to the diagnostic criteria, and in the use of protocol biopsies.

AIH: The pathogenesis of recurrent AIH is unclear; recent data suggest that recipient memory T cells might be driving the auto-immune process, which means that auto-antigenic peptides are being recognized on mismatched donor HLA class 1 and 2 molecules in the graft [69]. rAIH can occur on the background of immunosuppression that is adequate to prevent rejection [70]. This might be interpreted as meaning that such levels of immunosuppression inhibit auto-antigen specific T regs leading to subsequent inflammation and hepatocyte injury [71]. Risk factors for recurrence of AIH after OLT have been assessed in several studies, but most remain unvalidated and controversial. Donor and recipient matching for HLA-DR3 or DR4 is a controversial risk factor [62,72,73]. The analysis of HLA matching from the National Institute of Health (NIH) Liver Transplantation Database showed that HLA-DR locus mismatching was a significant risk factor for recurrence of AIH [74]. A recent study reports that elevated IgG before LT and moderate to severe inflammation in the explant are associated with an increased risk of recurrent autoimmune hepatitis. These findings suggest that recurrence of autoimmune hepatitis may reflect incomplete suppression of disease activity prior to LT [75].

PBC: Several studies have shown that tacrolimus-based immunosuppression is associated with an increased risk of recurrence of PBC, with a reduced time to recurrence compared with ciclosporin [76,77]. Whether tacrolimus is truly associated with recurrence or represents a surrogate of another time-dependent variable is unknown. The role of genetic factors has not been investigated thoroughly. The human leukocyte antigen (HLA) profile and HLA donor-recipient mismatch have controversial association in rPBC [78–82]. We have recently identified the association between rPBC and a non-HLA locus (*rs62270414*) in position 3q25, which hosts the *IL12A* gene. We found an additive effect between this SNP and the choice of calcineurin inhibitor at one year with the risk of rPBC; this is greatest with a combination of tacrolimus at one year and rs62270414 genotype AG or GG, and least with a combination of ciclosporin at 1-year and rs62270414 genotype AA [77]. Although these findings are preliminary and require confirmation, they are intriguing in that they suggest mechanisms causing PBC in the allograft and native liver might be similar.

PSC: An intriguing risk factor well documented for rPSC is the link with IBD. Specifically, the absence of inflammation in the intestine, either due to absence of concurrent IBD or colectomy before or during LT has a protective effect against rPSC [83]; this is in keeping with the hypothesis of aberrant homing of mucosal lymphocytes to the liver in the development of PSC [84]. However these findings were not consistent in all studies. rPSC has also been associated with acute cellular rejection (ACR), particularly steroid resistant ACR [85–87]. It is currently unknown whether rPSC results from a response to an immunogenic

Table 2. Published series of recurrent autoimmune liver disease after liver transplantation.

Disease	Authors	Time period	Cohort size	Recurrence rate (%)	Median time to recurrence (mo)	Risk factors
AIH	Prados E *et al.,* [146]	1984-1996	27	33	30	Type I (*vs.* type II) AIH
	Milkiewicz P *et al.,* [73]	1982-1998	47	28	29	Donor DR3^{-}/Recipient DR3^{+}
	Ratziu V *et al.,* [147]	1985-1992	25	20	24	n.d.
	Reich DJ *et al.,* [148]	1988-1995	32	25	15	n.d.
	Gonzales-Koch A *et al.,* [149]	1985-1998	41	17	52	Recipient HLA DR3/DR4
	Montano-Loza AJ., [75]	1989-2008	46	24	30	Presence of moderate to severe inflammation and high IgG levels before LT
PBC	Neuberger J *et al.,* [76]	1982-2002	485	23	62 (Tac) 123 (CyA)	Tac-based IMS
	Abu-Elmagd *et al.,* [150]	1982-1996	421	11	66	Younger age; CIT
	Charatcharoenwitthaya P *et al.,* [79]	1985-2002	164	34	42	Tac-based IMS
	Sanchez EQ *et al.,* [151]	1985-1999	169	11	58 (CyA ± Aza) 60 (CyA ± MMF) 24 (Tac ± MMF)	Tac-based IMS; donor alleles A1, B57, B58, DR44, DR57,and DR58; recipient allele B48
	Manousou P *et al.,* [82]	1988-2008	138	26	74 (Aza) 31 (never on Aza)	n.d.
	Jacob DA *et al.,* [152]	1989-2006	115	14	61	n.d.
	Carbone M *et al.,* [77]	1983-2009	248	42	62	Tac-based IMS and genotype AG or GG at rs62270414
PSC	Goss JA *et al.,* [153]	1984-1996	127	8.6	n.d.	n.d.
	Jeyarajah DR *et al.,* [154]	1985-1995	100	18	21 (mean)	ACR
	Graziadei I *et al.,* [155]	1985-1996	150	20	14 (cholangiography) 46 (histology)	n.d.
	Vera A *et al.,* [78]	1986-2000	152	37	36	Male sex, intact colon before LT
	Campsen J *et al.,* [86]	1988-2006	130	17	n.d.	CCA prior to LT (RR 3.77)
	Alabraba E *et al.,* [83]	1986-2006	230	23.5	55	Time and type of colectomy; ECD graft

ACR, acute cellular rejection; AIH, autoimmune hepatitis; Aza, Azathioprine; CCA, cholangiocarcinoma; CyA, Ciclosporin; CIT, cold ischemic time; ECD, extended criteria donor; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IMS, immunosuppression; LT, liver transplantation; MMF, Mycophenolate Mofetil; n.d., not determined; Pred, prednisolone; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; Tac, tacrolimus.

damaged biliary system due to ACR, or common factors predispose to both ACR and recurrent disease. Genetic factors that have been associated with biliary strictures after LT include metalloproteinase-2 genotype [88] and CCR5-Δ32 [89].

A recent series of 114 PSC living donor LT (LDLT) from Japan [90] has shown that grafts from first-degree-relatives, especially parents, carried the greatest risk of rPSC. A partial explanation may be that first-degree relatives and siblings have a prevalence of PSC about 100-fold that of nonrelatives [91]. The incidence of recurrence in recipients with grafts from related donors other than parents as well as nonrelated donors was similar to those reported for deceased donors LT [87]. Another possible mechanism contributing to the effect of first-degree-related donors might be linked to the effect of a shared genetic disposition in a blood-related recipient and donor pair including the HLA system.

Rejection after liver transplantation in autoimmune liver disease

The reported incidence of ACR after LT generally shows a large variation between different centres and time periods (Table 3), and this is partially related to evolving immunosuppressive strategies, different policy on protocol biopsies and to a lesser extent, discrepancies in the diagnostic criteria for rejection. There are relatively few published studies with specific focus on the incidence of rejection after LT according to underlying disease, and there are no studies focused on characterizing histopathological differences in the inflammatory infiltrates of ACR in different liver disease. Based on available data, and the variation in reporting rejection rates, it is hard to state with certainty that patients transplanted for autoimmune condition carry a higher risk of acute cellular rejection (ACR) compared to other patient groups.

However, there is some evidence that patients transplanted for AILD are more likely to experience ACR compared to those transplanted for non-autoimmune liver disease. It is of interest that indications for which there is no evidence of immune involvement in the pathogenesis of the original liver disease, such as alcoholic hepatitis and fulminant hepatic failure from paracetamol overdose, are associated with the lowest incidence of ACR [92,93].

AIH: A few series reported that patients transplanted for AIH were more likely to develop both early acute rejection and late acute rejection (LAR, acute rejection after 90 days post LT) [94–98]. One study showed a higher incidence of ACR requiring T cell depleting antibodies, such as OKT3 treatment, in the first 12 months post-OLT [98]. However a higher rate of ACR does not seem to affect the graft survival. We have recently shown

Table 3. Published series of acute and chronic rejection in autoimmune liver disease.

Disease	Authors	Time period	Cohort size	Rejection rate (%)	Type of rejection	Risk factors
AIH	Farges O *et al.,* [93]	1984-1992	17	17	Chronic	n.d.
	Molmenti EP *et al.,* [97]	1984-1998	55	20	Acute	n.d.
	Wiesner RH *et al.,* [96]	1990-1994	45	60	Acute	n.d.
	Milkiewicz P *et al.,* [98]	1982-1998	77	15.6 (2% in the control group - ALD)	Chronic	Younger age and histological features of moderate or severe ACR
	Vogel A *et al.,* [94]	1987-1999	28	82 (50% in the control group - Wilson's and glycogen storage disease)	Acute	n.d.
				14 (8% in the control group)	Chronic	
	Thurairajah PH *et al.,* [92]	2000-2010	46	9 (6% in the control group-HCV)	Late Acute	n.d.
PBC	Farges O *et al.,* [93]	1984-1992	66	1.5	Acute	Lack of use of anti-CMV polyclonal immunoglobulins
				4.5	Chronic	n.d.
	Milkiewicz P *et al.,* [98]	1982-1998	386	8.2	Chronic	n.d.
	Seiler CA *et al.,* [95]	1983-1998	22	68	Acute	n.d.
	Thurairajah PH *et al.,* [92]	2000-2010	165	16 (6% in the control group-HCV)	Late acute	
PSC	McEntee G *et al.,* [157]	1985-1988	44	100	Acute	n.d.
	Shaked A *et al.,* [158]	1991	36	17	Acute	n.d.
	Farges O *et al.,* [93]	1984-1992	23	52	Acute	n.d.
	Narumi S *et al.,* [104]	1988-1993	33	57	Acute	IBD
	Miki C *et al.,* [105]	1982-1994	55	67	Acute	IBD
	Wiesner RH *et al.,* [96]	1990-1994	126	46	Acute	n.d.
	Jeyarajah DR *et al.,* [154]	1985-1995	115	39	Chronic	Younger age
	Graziadei I *et al.,* [155]	1985-1996	150	69 (59% in the control group)	Acute	IBD
				8 (4.4% in the control group)	Chronic	
	Milkiewicz P *et al.,* [98]	1982-1998	136	7	Chronic	n.d.
	Bathgate AJ *et al.,* [159]	1992-1998	16	63	Acute	n.d.
	Brandsaeter B *et al.,* [160]	1984-2003	49	71 (51% in the control group)	Acute	n.d.
	Thurairajah PH *et al.,* [92]	2000-2010	87	14 (6% in the control group-HCV)	Late acute	n.d.

ACR, acute cellular rejection; ALD, alcoholic liver disease; CMV, cytomegalovirus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; n.d., not determined.

in the Birmingham cohort (period 2000–2010) that the risk of developing LAR was not increased in those transplanted for AIH. This might be explained by the policy of long-term steroid treatment in patients transplanted for AIH introduced in Birmingham after 2000 [92]. Unfortunately, patients transplanted for AIH have been shown to have a higher frequency of chronic ductopenic rejection (CR) or 'ductopenia', which affects more than 50% of portal tracts and an obliterative arteriopathy affecting large- and medium-sized arteries, which occur generally after the first year post-LT [93,98]. Data from an older cohort in Birmingham (period 1982–1998) showed that patients transplanted for AIH, who developed CR were younger than other AIH patients at LT and more often had histological features of moderate to severe acute rejection on early post-LT biopsies [98]. Risk factors for CR in AIH have not been reported in other series. The impact of improvements in immunosuppression on the risk of CR remains uncertain.

PBC: There are reports showing patients transplanted for PBC suffer more frequently from ACR [98,95,98–101]. We recently reported that PBC recipients have one of the highest risks of LAR, with an odds ratio of 2.1, compared to those with hepatitis C that had the lowest risk of LAR. A pre-LT diagnosis of PBC and a young recipient age were the only independent predictors of LAR in the Cox logistic regression model. In this study, graft survival was worse in those with LAR, but we have not specifically assessed the outcome of those transplanted for PBC [92].

PSC: Many older series have reported a higher incidence of ACR in patients transplanted for PSC [100,102]. Again, the number of ACR episodes had no impact on patient or graft survival but such an effect may be masked by relatively small numbers and the heterogeneity of patients. In our recent Birmingham cohort those transplanted for PSC had one of the highest risks of LAR with an OR of 1.8 [92]. There are conflicting data about whether the presence of IBD has an adverse impact on the risk of rejection of PSC after the transplantation. Some groups have reported a higher incidence of ACR in PSC patients with ulcerative colitis (UC) compared with PSC patients without UC [96,103–105]. These data were not confirmed in other cohorts [106].

The reason why patients with AILD might have an increased frequency of rejection is not clear. There are recent data from the lung transplantation field suggesting that pre-existing immune response to self-antigens might augment the risk of developing alloimmune response to mismatched donor antigens [107–109].

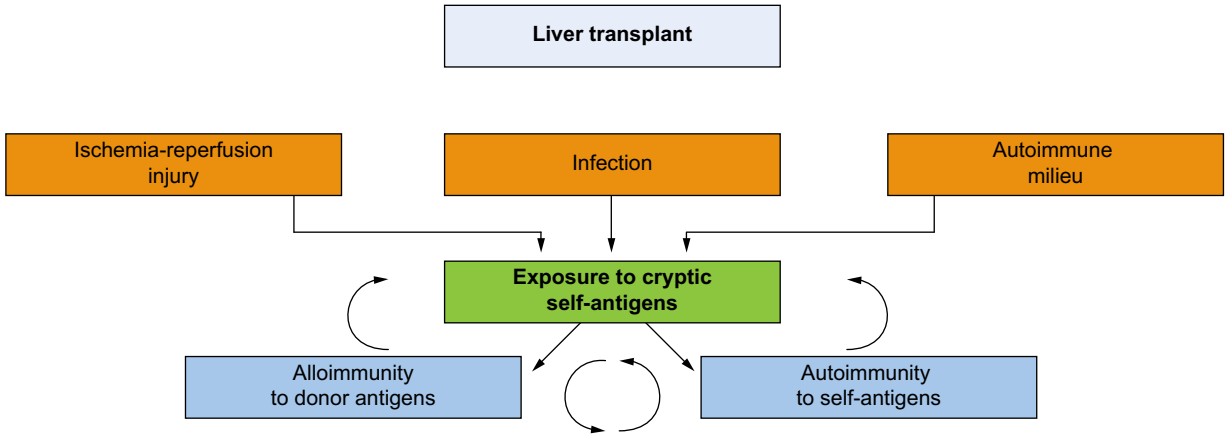

Fig. 3. Hypothetical link between autoimmunity and alloimmunity mechanisms after liver transplantation for autoimmune liver disease.

NK cells may be important because of their ability to recognize allogeneic MHC antigens and their potent cytolytic activity; they have emerged as a focus of interest in the transplant field as they might participate in the immune response in both acute and chronic rejection of solid organ allografts [110]. They possess a variety of inhibitory and activating receptors, such as the KIRs, which recognize MHC class I molecules and kill target cells that display reduced levels of MHC class I antigens. There is evidence that KIR interaction with donor HLA-C ligands leads to a differential degree of NK cell inhibition and this might influence the development and degree of CR, subsequent fibrosis and outcome of the allograft [111]. However, the effect of NK epitope mismatching on ACR after LT is uncertain. Modulation of KIR and donor HLA (particularly HLA-C) interactions might represent an important novel approach to promote long-term graft and patient survival after organ transplantation. This is of interest since particular combinations of KIRs and HLA class I ligands that reduce NK cell inhibition have been shown to increase the susceptibility to autoimmune diseases in general [112]; specifically, particular genetic variants of ligands for NK cell receptors might increase the risk of PSC [113]. Consistent with this, an increase in NK cells in the liver in PSC, compared with other liver diseases has been described [114]. NK cells have been called into question in PBC, since they have been shown to be involved in the destruction of cholangiocytes, and NK-T cells are partly responsible for the exacerbation of disease in PBC [115–117]. Furthermore, a marked suppression of anti-mitochondrial autoantibodies (AMA) and cytokine production from autoreactive T cells has been shown in a murine model of PBC following in-vivo depletion of NK and NK-T cells [118]. These data overall imply a major role for NK cells effector mechanisms in the pathogenesis of AILD. These might represent some of the effectors of a 'crosstalk' between alloimmune response and autoimmune response after organ transplant that perpetuate each other, and could in part explain why those transplanted for AILD are more likely to experience rejection (Fig. 3).

While early ACR does not seem to impact on long-term outcome, CR is much more closely associated with graft failure. It was previously assumed that mainly alloimmune responses contribute to the pathogenesis of CR. However, more recent findings, particularly in the field of lung transplantation, demonstrate that autoimmunity to tissue-restricted self-antigens may contribute to the immunopathogenesis of CR following transplantation [109]. Some authors have therefore proposed that the autoimmune component should be recognized in the pathogenesis of CR and be considered in developing new strategies for preventing and/or treating CR following transplantation.

De novo autoimmune hepatitis after liver transplantation

A clinical entity sharing the biochemical, immunological, and histological characteristics of AIH, called *de novo* AIH (dn-AIH), has been well described in adults and children undergoing LT for a range of diseases unrelated to autoimmunity [119] (Table 4). The clinical manifestations of dn-AIH are similar to those of recurrent AIH including a prominent plasma cell infiltrate with interface

Table 4. Published series of *de novo* autoimmune hepatitis.

Authors	Time period	Cohort size	Median age of recipient at transplant (yr)	Frequency (%)	Median time to dn-AIH (mo)
Kerkar N *et al.,* [161]	1991-1996	180	8.3	4	24
Gupta P *et al.,* [162]	1995-2000	115	2.2	5	102
Miyagawa-Hayashino A *et al.,* [125]	1990-2002	633	10	2.1	37
Venick RS *et al.,* [126]	1984-2003	619	3.6 (mean)	6.6	84 (mean)
Eguchi S *et al.,* [163]	1997-2007	72	45	5.6	18 (mean)
Cho JM *et al.,* [164]	1994-2007	149	12.4*	2.7	78
Hernandez HM *et al.,* [165]	1990-1999	155	3.5	2.5	61

*Age at presentation; age at transplant not reported in the original paper.
AIH, autoimmune hepatitis.

hepatitis, hypergammaglobulinaemia, increased serum IgG levels, and autoantibodies. Dn-AIH has also been diagnosed in the absence of autoantibodies [120] and in some patients without increased serum IgG levels or autoantibodies [121]. Such variations in diagnoses makes assessment of the literature challenging. Dn-AIH generally presents after one year post-LT and usually responds well to increased immunosuppression, but some cases progress to cirrhosis or graft failure [122]. As in recurrent autoimmune hepatitis, the HLA status of the recipient [123], the duration after LT [124], and the number of rejection episodes [125,126] have been proposed as contributing factors, but none of these has been consistently recognized as predictive of its occurrence. However, weaning from corticosteroid therapy does not seem to be a trigger.

The immune response in dn-AIH may be directed against alloantigens, neo-antigens, or self-antigens. An alloantigen in dnAIH has been identified in the glutathione-S-transferase T1 (GSTT1), which is an alloantigen present in some individuals and that generates alloantibodies in those who lack it [127]. The gene that encodes GSTT1 is absent in 20% of the white population, and GSTT1 donor/recipient genotype mismatch has been suggested as a necessary condition for the appearance of autoantibodies and *de novo* AIH [127]. However, dn-AIH has also been described in the absence of a GSTT1 mismatch [128]. There is evidence that the choice of calcineurin inhibitor may influence the development of *de novo* AIH mediated by anti-GSTT1 antibodies, with patients treated with tacrolimus having a lower occurrence [129]. These observations support the concept that dn-AIH may represent an alloimmune response (i.e., a form of rejection), in which immune-mediated injury is directed towards hepatocytes rather than bile ducts or vascular endothelium; and GSTT1 might represent not the only alloantigen that can trigger an autoimmune response. Further support for an alloimmune mechanism in dn-AIH is the strong correlation with previous rejection history and steroid dependence [130].

Alternatively, the inflammatory response within the donor liver may also unmask neo-antigens and intensify the co-stimulatory signals that activate lymphocytes [131–133].

Some argue that the immune response in de-AIH may be directed against self-antigens. It has been shown that bronchial administration of anti-MHC class I antibodies in the native lungs of HLA-mismatched mice induced bronchiolar scarring, a manifestation of chronic allograft rejection in the lung; this is accompanied by up-regulation of IL17 and *de novo* antibody formation to the self-antigens, such as K-a 1-tubulin, and collagen V, also seen in chronic human lung rejection [134]. Authors have hypothesised that chronic alloimmune injury may release protected self-antigens, which elicit autoantibody formation, and that the cycle may be perpetuated by ongoing IL17 signaling, a known facilitator of alloimmunity and autoimmunity. Further supporting the autoimmune hypothesis is the presence of a plasma cell inflammatory infiltrates, hallmark of autoimmune injury, and the fact that anti-MHC class I antibodies fail to induce bronchiolar scarring in B cell deficient mice [135].

Some experts argue that rejection and dn-AIH are part of the same spectrum [136]; rejection during the early stage post-transplant is driven by an MHC-restricted and epitope specific process; the resultant graft damage may lead to T cell responses to other graft antigens and breaks tolerance to self-antigens leading to dn-AIH.

An autoimmune-like hepatitis has also been described in LT recipients treated with PegIFN and RBV for recurrent hepatitis C, with no history of AILD [137].

Histological findings are an essential element in the differential diagnosis between dn-AIH, ACR, LAR, and CR. The higher proportion of plasma cells and the severity of the interface activity (more typical in AIH) and the prevalence of bile duct damage (characteristic of rejection) are currently used as markers, albeit imprecise ones. However, no accurate limit for the percentage of plasma cells has been established, and none of these criteria have been tested prospectively for reproducibility, predictive value, or an association with serological evidence of autoimmunity. The time interval between disease occurrence and LT is another important diagnostic clue [138]. Diagnostic difficulties arise when ACR, CR or AIH develop at uncharacteristic intervals after LT [139,140] or when histological manifestations of graft dysfunction are atypical [141,142] or inexplicable [138,143,144]. Future studies aimed at investigating the role of autoantibody and the antigenic specificity of the liver-infiltrating lymphocytes in patients with autoimmune disorder after LT are therefore warranted.

Key Points

- GWAS and iCHIP-association studies in PBC and PSC have improved our knowledge of the genetic architecture of these diseases, highlighting specific pathogenetic pathways in both innate and acquired immune response. Studying gene-gene interaction, gene-environment interaction and epigenetic mechanisms is the best way forward to clarify what is still poorly understood in the pathogenesis of AILD
- There is a remarkable overlap of genetic susceptibility factors between different autoimmune conditions. This suggests distinct mechanisms, by which autoimmunity occurs, each mechanism predisposing to a particular phenotype or set of phenotypes. It follows that there might be unique immunologic pathways that we have to focus on for therapeutic intervention
- Outcomes after liver transplantation for AILD are generally favourable. The original autoimmune disease recurs in a considerable number of recipients. Currently, graft loss due to recurrent disease represents a major issue only in PSC. However, prevention of recurrent PSC is limited by the lack of a clear understanding of the disease in the native liver
- Patients transplanted for AILD seem to have a higher risk of acute rejection. A crosstalk between alloimmune response and autoimmune response after liver transplantation that perpetuate each other might, in part, explain this. It is recognized, however, that acute rejection does not affect long-term survival. Of more concern is the evidence of an increased risk of chronic ductopenic rejection, which is a major cause of graft loss. An autoimmune component should be recognized also in the pathogenesis of chronic rejection
- *De novo* autoimmune hepatitis (dn-AIH) after LT is a well described entity in patients undergoing LT for a range of diseases unrelated to autoimmunity, particularly in the pediatric setting. It is not entirely clear whether the immune response is directed against allo-antigens, neo-antigens, or self-antigens

Conclusions

AILD remains a good indication for LT with excellent patient and graft outcomes. Recurrence of the original disease, particularly of PSC, represents a significant cause of graft loss after LT. Preventive or therapeutic strategies are limited by the lack of a full understanding of the disease pathogenesis in the native liver. LT provides a unique setting to help understand the pathophysiology of AILD. However, variations in clinical practice and the use of protocol liver biopsies means that the understanding of the severity and risk factors for recurrent disease and evaluation of therapeutic interventions is, at best, limited.

A higher risk of both acute cellular and ductopenic rejection is a further challenge in patients transplanted for autoimmune conditions. Early ACR does not impact negatively on long-term outcome and may promote tolerance, while CR is a rare but important cause of late graft dysfunction and graft loss. Immunological factors responsible for the original liver disease may be active post-transplant and potentially act as a predisposing condition for acute and chronic rejection.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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