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Autoimmune Liver Disease Post-Liver Transplantation: A Summary and Proposed Areas for Future Research

Catherine Edmunds, PhD[1] and Udeme D. Ekong, MD, MPH[1,2]

Abstract: Autoimmune liver diseases (AILD) are rare diseases with a reported prevalence of less than 50 per 100 000 population. As the research landscape and our understanding of AILDs and liver transplantation evolves, there remain areas of unmet needs. One of these areas of unmet needs is prevention of disease recurrence after liver transplantation. Disease recurrence is not an insignificant event because allograft loss with the need for retransplantation can occur. Patients transplanted for AILD are more likely to experience acute rejection compared to those transplanted for non-AILD, and the reason(s) behind this observation is unclear. Tasks for the future include a better understanding of the pathogenesis of AILD, definition of the precise pathogenetic mechanisms of recurrent AILD, and development of strategies that can identify recipients at risk for disease recurrence. Importantly, the role of crosstalk between alloimmune responses and autoimmune responses in AILD is an important area that needs further study.

This article reviews the relevant literature of de novo autoimmune hepatitis, recurrent autoimmune hepatitis, recurrent primary sclerosing cholangitis, and recurrent primary biliary cirrhosis in terms of the clinical entity, the scientific advancements, and future scientific goals to enhance our understanding of these diseases.

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Advances in liver transplantation have resulted in improved survival and better outcomes for most patients with liver disease. However, with these advances and longevity of liver allografts come late graft dysfunction, which is often difficult to diagnose and represents a significant medical management issue. Important causes of late graft dysfunction include de novo autoimmune hepatitis (DAIH) (also described in the literature as plasma cell hepatitis and post-transplant allograft hepatitis) and recurrent autoimmune liver disease (AILD). De novo autoimmune hepatitis was first described in 1998 as a form of late allograft dysfunction that did not result from a recognized cause and is not associated with patients who developed autoimmune hepatitis (AIH) as their primary cause of liver disease.[1] It has strong overlapping features with AIH and is seen in 4% to 7% of pediatric and adult liver transplanted patients, mostly pediatric liver transplant recipients.[2-6] Autoimmune liver diseases are rare diseases with a reported prevalence of less than 50 per 100 000 population; and despite advances in the understanding and treatment of AILD, there still remain areas of unmet needs.

MATERIALS AND METHODS

A comprehensive literature search using PUBMED/MEDLINE was conducted to identify articles in peer-reviewed publications that reported on DAIH, recurrent primary sclerosing cholangitis (rPSC), recurrent AIH (rAIH), and recurrent primary biliary cirrhosis (rPBC). The search was performed on November 1, 2014, for peer-reviewed articles published between 1998 through 2014, and used the following search strategy: AIH, PSC, primary biliary cirrhosis, recurrent PSC, rPBC, recurrent AIH, DAIH, liver transplantation, and acute and chronic rejection. The definition of AIH used was as previously described: elevated aminotransferases in the setting of antinuclear antibody (ANA) or antismooth muscle antibody (ASMA) and anti-liver kidney

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[1] *Section of Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Yale University School of Medicine, New Haven, CT.*

[2] *Yale New Haven Transplantation Center, New Haven, CT.*

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Correspondence: Udeme D. Ekong, MD, MPH, Section of Pediatric Gastroenterology and Hepatology, 333 Cedar Street, LMP 4093, PO Box 208064, New Haven, CT 06520. (udeme.ekong@yale.edu).

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microsomal antibody (LKMA) of 1:40 or greater, positive soluble liver antigen, serum IgG greater than upper limit of normal, liver histology compatible with AIH, absence of viral hepatitis, and Wilson disease; a score of 6 in the above considered as probable AIH, a score of 7 or greater considered as definite AIH[7,8] (of note in children, ANA/SMA $\geq$ 1:20 and anti-LKM $\geq$ 1:10 considered as positive).

The definition of DAIH was as previously described: a liver transplant recipient without a history of AILD presenting with unknown etiology of late graft dysfunction. The late graft dysfunction is characterized by elevated aminotransferases typically occurring longer than 2 years after transplant, graft dysfunction not due to any of the following causes: acute and chronic rejection, hepatitis B and C infection, Epstein Barr virus and cytomegalovirus infections, vascular problems, biliary complication, drug toxicity, sepsis, recurrence of primary disease, or posttransplant lymphoproliferative disease; elevated serum immunoglobulin G, positive autoantibody titers: ANA, ASMA, anti-LKM; characteristic biopsy findings of dense lymphocytic portal-tract infiltrate with plasma cells, and interface hepatitis).[9,10] Results of the search were then narrowed down to articles and case reports that described new onset AIH, de novo immune hepatitis or plasma cell hepatitis after liver transplantation. A total of 25 peer-reviewed articles reporting DAIH were included in the final review. This overview is therefore limited to DAIH and does not include other causes of allograft dysfunction, such as chronic hepatitis and interface hepatitis that do not fulfill all the criteria for a diagnosis of DAIH.

For recurrent AILD, the definition of rPSC was based on the Mayo Clinic criteria proposed by Graziadei et al,[11] which requires: a confirmed diagnosis of PSC before liver transplantation; cholangiograms showing nonanastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary tree with beading and irregularity occurring longer than 90 days after transplantation; or a liver biopsy showing fibrous cholangitis and/or fibro obliterative lesions with or without ductopenia, biliary fibrosis, or biliary cirrhosis, exclusion of hepatic artery thrombosis/stenosis, ductopenic rejections, donor-recipient ABO blood type incompatibility, anastomotic structuring alone, and nonanastomotic strictures before day 90 after liver transplantation.

The definition of rPBC was as previously described[12]: liver transplantation for confirmed diagnosis of PBC, persistence of serum antimitochondrial antibody, compatible histopathology (portal inflammation, lymphocytic inflammatory infiltrates, lymphocytic cholangitis, epithelioid granulomas), exclusion of differential diagnostic considerations included (hepatitis C infection with lymphocytic cholangitis, drug-induced liver injury, acute cellular rejection, chronic ductopenic rejection, biliary obstruction, graft-versus-host disease). Two of the above 4 are considered as probable diagnosis; 3 of above 4 are considered as definite diagnosis.

Etiology of DAIH

The etiology of DAIH is unclear; however, it is associated with several risk factors, including the number of acute rejection episodes, steroid dependence,[9] human lymphocyte antigen DR3 (HLA DR3) phenotype,[13] and treatment with pegylated interferon for recurrent hepatitis C in patients who have achieved hepatitis C virus-RNA clearance.[14,15] Sex and age of the organ donor have been implicated; organs from older women have been reported as being associated with increased likelihood of developing DAIH.[16] Though sex and age as risk factors have not been consistently reported by all centers.[9] Interestingly, chronic hepatitis E infection has been described in pediatric liver transplant recipients with persistently elevated serum aminotransferase levels and histological features of portal inflammation and interface hepatitis of unclear etiology; importantly, none of these patients were reported in the publication to fulfill the diagnostic criteria for DAIH[17]; thus, it is unclear if chronic hepatitis E is a risk factor for the development of DAIH.

Pathogenesis of DAIH

One proposed mechanism of the alloimmune response seen in DAIH is related to donor/recipient mismatching across glutathione-S-transferase theta 1 (GSTT1).[18-20] Twenty percent of white and 11% to 58% of other ethnic groups possess a genetic deletion at the GSTT1 locus that results in lack of expression of GSTT1, which is a known drug-metabolizing enzyme.[21] Lack of expression of GSTT1 by a recipient who receives a graft from a GSTT1 expressing donor is thought to result in immune sensitization of the recipient with resultant development of humoral responses to allograft cells expressing GST. Aguilera et al[19] described 6 liver transplant recipients with a recipient/donor combination –/+ for $GSTT1^{-}/GSTT1^{+}$ with circulating antibodies to GST, all of whom developed DAIH. The GSTT1 mismatching is also an example of how genetic polymorphism may contribute to the pathogenesis of immune-mediated disease and suggests a role for atypical antibody-mediated rejection in the pathogenesis of DAIH.[22]

Support for the role of donor-specific antibody in the pathogenesis of DAIH comes from reports of positive complement component 4d (C4d) staining in livers of patients with DAIH and donor-specific antibody against GSTT1 (anti-GSTT1).[23] The C4d is one of the split products generated during complement activation of the classic and alternative pathways. As it is one of the split products that covalently binds to the surface of cells, specific staining patterns have been useful in identifying patients with antibody-mediated rejection in renal transplantation.[24-26] In contrast to the well-established pattern of C4d deposition in renal allografts with antibody-mediated rejection, the pattern of C4d deposition is variable in liver allografts, and there is yet to be a consensus on the relevance of specific staining patterns. Moreover, as the liver is a primary site for the production of local complement factors, staining with C4d may occur in the setting of alternative pathway activation as well. Nonetheless, it does deserve further study especially as it relates to donor-specific antibodies.[23]

Proposed arguments against DAIH and rejection being the same entity include the absence of bile duct involvement in DAIH, and the degree of plasma cell infiltration and severity of interface hepatitis.[10] Additionally, treatment of DAIH differs from classic antirejection regimens. For instance, calcineurin inhibitor dose is typically increased to achieve a higher blood level in acute rejection, whereas a reduction in the calcineurin inhibitor dose has been suggested in DAIH.[27,28] Furthermore, established antirejection therapies seem to be ineffective in DAIH patients.[27,28] One of the important concepts that has arisen from assessing if DAIH and acute rejection are similar entities is the concept of epitope spreading,

which occurs in many immune responses.[29,30] Although a narrow range of antigens may initiate early native immune responses, it is recognized that the ensuing tissue damage results in the exposure of additional epitopes (autoantigens) that continue to drive immune response. Thus, an interesting concept is that initial rejection episodes against the graft may elicit tissue damage exposing neoantigens that perpetuate ongoing cellular and humoral responses. It could be of interest to examine whether collateral damage exposes "neo" self-epitopes when donor cells migrate from the graft and are attacked in the periphery potentially illustrating a mechanism via which transplantation could trigger autoimmunity. Finally, perhaps the question to be addressed is if DAIH is indeed a form of rejection whether the target in this form of rejection is the hepatocyte (not the bile duct), similar to what is seen in AIH.

The immune response in DAIH has also been proposed to be a consequence of reactivity to neoantigens with self-sensitization occurring through molecular mimicry; so short peptide sequences from toxic or infectious agents that resemble self-antigens sensitize cells causing aberrant misrecognition of self-antigens as foreign. Molecules that can contribute to such an effect have been labeled the exposome. Some individuals may be genetically predisposed to reactivity of this kind.[31]

Autoantibodies

Autoantibodies in DAIH are an important diagnostic tool.[10] A key question in understanding the pathogenesis of DAIH is the role played by these autoantibodies and their correlation with disease progression. The hypothesis that they function as a marker for disease[32] was supported by Avitzur et al[33] who showed that positive autoantibodies in children after liver transplantation denoted a higher risk for the development of DAIH over time. Likewise, others have shown that persistence of high titers of ASMA and/or ANA in patients with AIH is associated with disease activity.[34] Alternatively, there is a report of patients transplanted for Wilson disease who develop anti–LKM-1 autoantibodies but show no progression to DAIH; however, it is not known how long these patients were followed up, or whether they may have developed DAIH since publication of the initial observation.[35]

A recent identification of molecular targets of autoantibodies may be helpful in determining whether autoantibodies are in the causal pathway of DAIH. Huguet et al[36] used proteomic tools to identify antigens recognized by the atypical LKMA. The proteomic technique consisted of 2-dimensional gel electrophoresis followed by 2-dimensional immunoblotting and subsequent ion trap mass spectrometry. Using sera from 8 patients with DAIH (including 2 with anti-LKMAs), the group identified several 25 kDa peptides, including the carbonic anhydrase isoform III, and β 1 subunit of the proteasome. In addition, they identified molecular targets of the GST families, that is, θ, α, μ, and π. As acknowledged by the authors, these potential targets of anti-LKMAs must be confirmed using monoclonal antibodies or recombinant proteins. They could then potentially be used to aid in evaluating posttransplant allograft dysfunction.

Of interest is the finding that Con A induction of DAIH in an acute rejection rat liver transplant model (Dark Agouti to Lewis) results in the induction of antinuclear antibodies against histone H1 and high mobility group box 1 with prolonged survival.[37] Con A administration generates a "bystander hepatitis" not AIH. Additionally, Con A is a lectin that interacts with diverse receptors containing mannose carbohydrates. It is a nonspecific activator of immune cells, preferentially activating innate immune cells in the liver producing a transient acute hepatitis. It is therefore not surprising that ANA appears after such injury. Antinuclear antibodies are also probably the less specific autoantibody in patients with AIH. The relevance of Con A in human DAIH is yet to be established.

Clinical and Laboratory Manifestations

Characteristic of DAIH is a histological picture of interface hepatitis and multilobular collapse associated with increased IgG levels and positive autoantibodies, in the setting of elevated serum aminotransferases.[1] As the name implies, cases share immunological, biochemical, and histological features with AIH.[38,39] A pattern of centrilobular necroinflammatory activity with plasma cell infiltration has also been described.[39] Perhaps contributing to the variable terminology used to describe this condition in the literature is the fact that heterogeneity of IgG and autoantibody levels has been described with some centers reporting DAIH patients with low IgG levels and absent autoantibodies.[32] As alluded previously, the role of autoantibodies in DAIH is of interest; particularly, their physiological importance in terms of active involvement in the pathology of DAIH is yet to be determined. Interestingly, IgG 4–positive cases of DAIH have been identified[40] which responds to azathioprine and prednisone, with normalization of alanine aminotransferase levels.[41] It is worth noting that autoantibodies are frequently present without signs of graft dysfunction, particularly in the pediatric population,[32,33,42] and liver biopsy is therefore required to determine the nature of any damage present.[6]

Features of DAIH are summarized in Table 1.

Recurrence of AILD After Liver Transplantation

Autoimmune hepatitis, PSC, and primary biliary cirrhosis recur after liver transplantation[43-53,55-59,61-68]; disease recurrence is however not an insignificant event because allograft loss with the need for retransplantation can occur. There is therefore opportunity for risk stratification/development of strategies that can identify recipients at risk for disease recurrence. A summary of AILD that recur after liver transplantation is presented in Table 1.

Primary sclerosing cholangitis is reported to recur in 10% to 37% of transplanted recipients, a mean of 6 months to 5 years after liver transplantation. It has been hypothesized that enterohepatic lymphocyte recirculation explains the link between PSC and inflammatory bowel disease; so effector T cells generated in lymphoid tissues in the gut during active inflammatory bowel disease persist as long-lived memory cells that recirculate through the liver and can trigger hepatic inflammation under the right conditions, even in the absence of active gut inflammation.[69] Interestingly, colectomy before or during liver transplantation has been reported to have a protective effect against rPSC[53]; however, this protective effect is not consistently reported.[52,54,66,70-73]

Acute cellular rejection and steroid-resistant acute cellular rejection has been associated with rPSC,[52,66,73] and explanations postulated for this association include injury of the

TABLE 1.

Summary of (i) autoimmune liver diseases known to recur after liver transplantation and (ii) de novo autoimmune hepatitis

	rAIH	rPSC	rPBC	DAIH
Recurrence rate (%)	17 – 33[43-48]	10 – 37[49-54]	11 – 42[55-59]	n/a
Clinical manifestations	Normal LFTs, elevated LFTs, hypergammaglobulinemia, lymphoplasmacytic portal infiltrate, central perivenulitis, foci of confluent/ bridging necrosis, interface hepatitis, absence of endothelialitis and ductulitis.	Cholestasis, multiple non-anastomotic strictures with no other risk factor, ductopenia, ductular reaction. Exclude other causes of biliary tract disease such as ischemic cholangiopathy, hepatic artery thrombosis, CMV, HIV, ABO incompatibility, chronic rejection.	Most cases mild/asymptomatic disease, frequently diagnosed on protocol biopsies, lymphocytic or granulomatous cholangitis, focal mononuclear portal inflammation, ductopenia seen in progressive disease. Exclude chronic rejection, biliary obstruction, GVHD, DILI.	Elevated LFTs, pretransplant diagnosis non-immune mediated, positive autoantibodies (ANA, antismooth muscle antibodies, anti-LKMAs), hypergammaglobulinemia, lymphoplasmacytic portal infiltrate, central perivenulitis may be seen, absence of endothelialitis and ductulitis.
Risk factors/contributing factors	HLA-DRB1*0301 or DRB1*0401 in recipient, recipient memory T cells, incomplete suppression of disease activity pretransplant.	Acute rejection, steroid resistant rejection, CCR5-Δ32 mutation, MMP-2 polymorphisms, HLA-DRB1*08, 1st degree related donors.	Tacrolimus based IS, IL-12A locus.	Recipient HLA, duration post transplant, number of rejection episodes.
Graft loss risk	Risk of graft loss[60] HR 4.1 (95% CI, 1.3-12.6). 6.2%	Risk of graft loss[60] HR 6.0 (95% CI, 2.5-14.2). 8.4%	Risk of graft loss[57] HR 0.97 (95% CI, 0.41-2.31) 1.3%[60]	Some cases can progress to cirrhosis and graft failure[31]
Unmet needs	Predicting posttransplant recurrence, identification of high-risk recipients.	Predicting posttransplant recurrence, identification of high-risk recipients.	Predicting posttransplant recurrence, identification of high-risk recipients.	Disease pathogenesis remains unknown, not entirely clear whether immune response directed against allo-antigens, neo-antigens or self-antigens.
Treatment	Often responsive to introduction of, or an increase in dose of corticosteroids.	No established medical therapy. UDCA—coexisting UC. Interventional cholangiographic treatment—dominant strictures. Antibiotics—bacterial cholangitis.	UDCA use associated with biochemical improvement; however, its role in delaying histologic progression remains unknown.	Responds to corticosteroids and Azathioprine (or MMF), concomitant with reduction of the calcineurin inhibitor dose. Difficult to treat patients respond to sirolimus[27]

LFT, liver function test; CMV, cytomegalovirus; UDCA, ursodeoxycholic acid; UC, ulcerative colitis; MMF, mycophenolate; GVHD, graft-versus-host disease; DILI, drug-induced liver injury; MMP-2, matrix metalloproteinases 2.

biliary epithelium from acute cellular rejection increasing autoimmune epitopes with resultant immune-mediated ductal damage,[50] or common factors predisposing to both acute cellular rejection and rPSC, such as a defective mechanism for immune autoregulation.[66]

Support for the role of the immune system in the development of rPSC is seen in the work reported by op den Dries et al[74] where the combination of a loss of function mutation in the CC chemokine receptor 5 (CCR5)-Δ32 with a pretransplant diagnosis of PSC was associated with a significantly higher incidence of nonanastomotic strictures after transplantation. The CCR5 is thought to play a critical role in chemotaxis of regulatory T (Treg) cells to the site of injury.[75-77] The CCR5 deficiency is accompanied by an increase of tissue levels of its ligand, CCL5, thus promoting enhanced influx of T cells into tissues by binding to an alternative receptor, CCR1.[78-81]

Other genetic factors, such as matrix metalloproteinases 2 gene promoter polymorphisms of donor and recipient, together with a pretransplant diagnosis of PSC, are reported to be a risk factor for the development of nonanastomotic strictures after liver transplantation.[82] Similarly, some major histocompatibility complex (MHC-II) haplotypes are thought to influence the natural history of PSC after liver transplantation, for example, liver allografts from HLA DR52-positive donors are reported to protect against rPSC,[50] and the presence of HLA-DRB1*08 is associated with an increased risk of rPSC.[66] Finally, first degree–related donors is associated with more than 3 times the risk of rPSC.[83]

Autoimmune hepatitis is reported to recur in 17% to 33% of transplanted recipients. Recurrence can be indolent and detected only by surveillance laboratory testing and liver biopsy assessments.[47,84,85] Risk factors implicated in recurrence include the susceptibility alleles HLA-DRB1*0301 or DRB1*0401 in the transplant recipient,[47] HLA-DR locus mismatching,[86] incomplete suppression of disease activity before transplantation, suggesting correlation between proinflammatory mechanisms before transplantation and rAIH.[48] It has been suggested that recipient memory T cells play a role in the pathogenesis of rAIH as they recognize conserved autoantigenic peptides expressed by mismatched donor HLA in the allograft, thereby mediating rAIH.[12] Regulatory T cell dysfunction is implicated in the pathogenesis of AIH by some groups,[87] as such, it has been speculated that immunosuppression used after transplantation may contribute to rAIH by inhibition of autoantigen-specific Treg cells. Inadequate maintenance immunosuppression, especially discontinuation of steroid therapy, has been reported to play a role in disease recurrence,[44] indeed optimization of immunosuppression has been reported to successfully treat histological recurrence.[88] Conversely, rAIH has also been reported in the background of immunosuppression that is adequate to prevent rejection.[89]

In primary biliary cirrhosis, up to 30% of patients show features suggestive of recurrence within 5 years of transplantation.[90,91] The reported incidence rate is 21% to 37% at 10 years and 43% at 15 years.[85] The reported recurrence frequency rate increases with time in part due to different diagnostic criteria and different center policies for protocol biopsies. A big challenge in the diagnosis of rPBC is that recurrence may be present with normal or clinically insignificant elevations of liver tests.[56,92-94] Retrospective data suggest an association with tacrolimus-based primary immunosuppression.[90] With regard to genetic risk factors, the role of HLA donor-recipient mismatch in rPBC remains controversial.[56-58,61] Recently, an association between rPBC and the IL12A locus was reported, suggesting that risk loci for PBC in the native liver might influence the risk of rPBC after liver transplantation, and mechanisms causing PBC in the allograft might be similar to those causing PBC in the native liver.[59] The IL-12 signaling results in T_H1 polarization of naive T cells; the authors therefore speculate that the mechanism for rPBC may involve either an inappropriate and sustained T_H1 response or inefficient T_H1 responses to appropriate stimuli as a result of variation in IL-12 signaling.

Proposed Areas for Future Study in DAIH

Fukami et al[95] elegantly studied the role an alloimmune response plays in inducing autoimmunity using a murine model of obliterative airway disease. They sought to test whether antibodies developed after transplantation to mismatched donor MHC induces autoimmunity. Anti-MHC class 1 antibodies or control antibodies were administered intrabronchially into native lungs of mice. Animals receiving anti-MHC class 1 but not control antibodies developed a lesion similar to chronic rejection seen after human lung transplantation. Lungs of mice receiving anti-MHC class 1 antibody induced IL-17 as well as de novo antibodies to self-antigens, collagen V, and K α tubulin 1. The IL-17 neutralization resulted in reduction of autoantibody and lesions induced by anti-MHC class 1 antibodies. Their results suggest that antibodies to donor MHC can induce autoimmunity mediated by IL-17.

Interestingly, immunohistochemistry of the de novo liver showed IL-6 positivity within portal tracts as well as IL-17A positivity though to a lesser degree than IL-6 (Figure 1B-C). The IL-6 together with IL-1β and transforming growth factor β is needed to drive naive T cells toward differentiation to the T_H17 program.[96,97] Taken together, this may suggest a potential role for IL-17 in the perpetuation of chronic inflammation in DAIH.

Another interesting observation is the role Treg cells may play in DAIH. The Treg cells are a subset of T helper cells expressing the canonical marker, forkhead box P3 transcription factor (FoxP3); that negatively regulates the immune response and plays a critical role in maintaining peripheral self-tolerance.[98] Their dysfunction has been postulated to play a role in the pathogenesis of several autoimmune disorders.[99-103] Similar to some reports in systemic lupus erythematosus,[104-107] rheumatoid arthritis,[108] and AIH,[109] decreased Treg numbers and frequency in peripheral blood have been previously reported in pediatric liver transplant recipients with DAIH[110]; Of note, decreased Treg numbers and frequency in AIH has not been observed by all groups.[111-113] This may be due to lack of a well-defined specific Treg marker in humans and heterogeneity in phenotypes.

A link between epigenetics and various autoimmune diseases has been reported[114] DNA methylation is an epigenetic phenomenon: methylation of CpG islands in promoter regions regulates gene transcription and methylation of CpGs leads to gene repression by inhibiting binding to transcription factors. The methylation status of the Treg-specific demethylation region of the FoxP3 noncoding sequence has been shown to regulate expression of the transcription factor, FoxP3; and the demethylation status of CpG islands of FoxP3 is thought to correlate with full suppressive activity

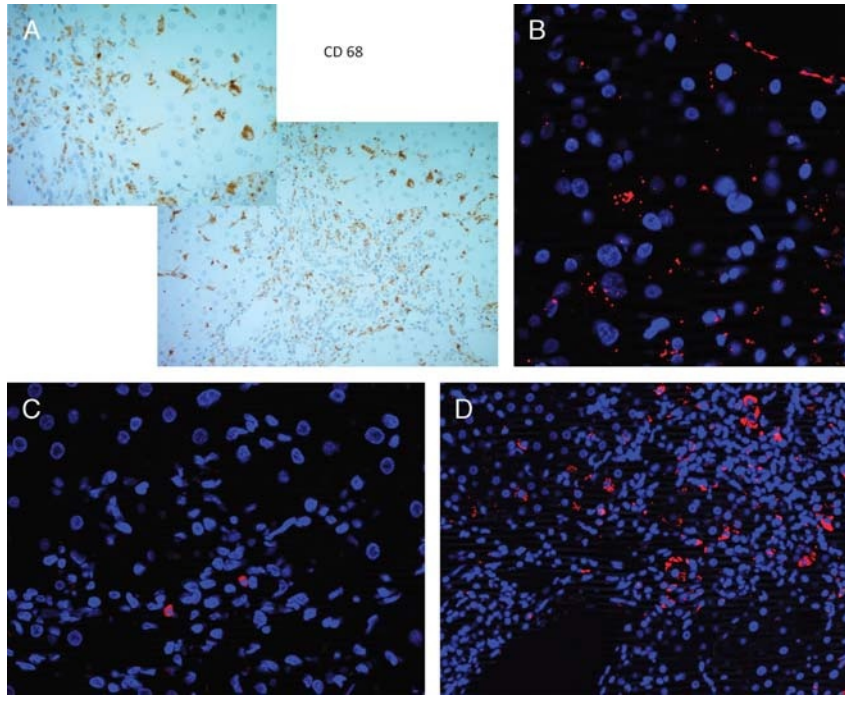

FIGURE 1. Immunohistochemical staining of paraffin-embedded liver sections from DAIH patients. Immunofluorescence staining of cytokines associated with the T_h17 program. Formalin-fixed, paraffin-embedded 4-μ-thick sections from liver biopsies of patients with DAIH were stained for expression of CD 68- and 7-μ-thick sections were stained for expression of IL-6, IL-1β, and IL-17A. A, 200× (insert, 400×) magnification: portal tract with nearby lobule showing numerous CD 68-positive cells. B, 40× magnification shows a cluster of IL-6–positive cells within the portal tract (4',6-diamidino-2-phenylindole [DAPI], blue; IL-6, orange). C, 40× magnification shows very few IL-1β–positive cells present within the portal tract (DAPI, blue, IL-1β, orange). D, 20× magnification shows several IL-17A–positive cells present within the portal tract (DAPI, blue; IL-17A, orange).

of Treg cells.[115-117] A proposed area for future study would therefore be investigation of the role epigenetics might play in the pathogenesis of DAIH by examining, for instance, DNA methylation of Treg-specific demethylation region of the FoxP3 noncoding sequence of de novo Treg cells. This would also clarify whether Treg cell dysfunction contributes to the pathogenesis of DAIH.

The above concepts warrant further study; as such, we propose a model (Figure 2) to guide future research into the pathogenesis of DAIH. The model we propose supposes that graft injury may be initiated by acute rejection. The resulting graft injury reveals previously unseen epitopes. The IL-17 would contribute to the inflammatory milieu and lead to the production of antibodies by B cells. The absence of

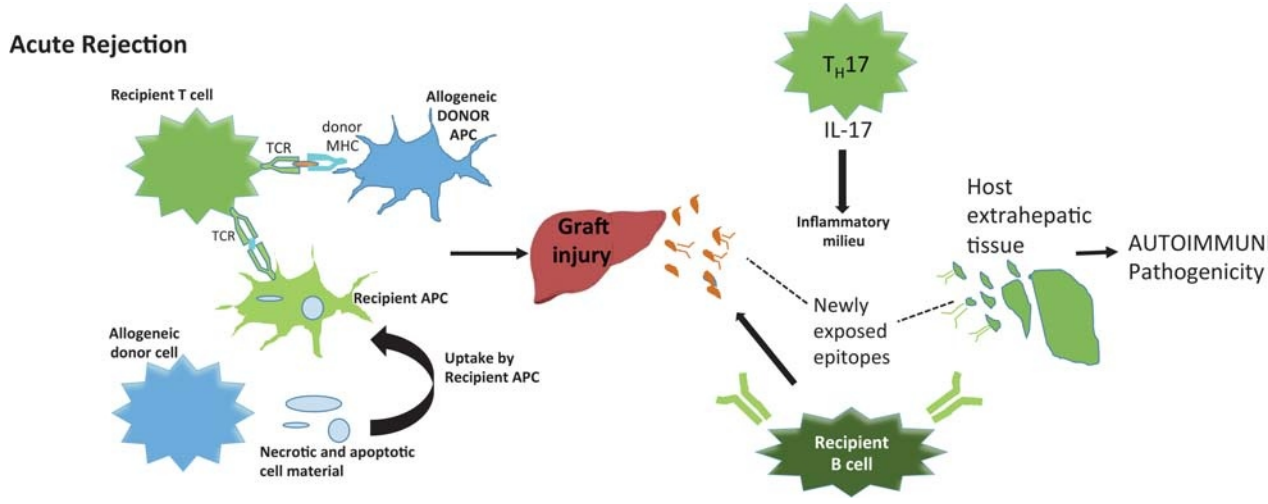

FIGURE 2. Proposed model for future research into pathogenesis of DAIH. Acute rejection episodes may prime the immune system to mount a self-directed response. Acute rejection is initiated by the large number of recipient T cells that recognize donor alloantigens encoded by MHC.[125,126] Alloantigen presentation may be via direct pathway or indirect pathway.[127] Graft injury reveals previously unseen epitopes. IL-17 would contribute to an inflammatory milieu and lead to the production of antibodies by B cells. In the absence of other negative regulatory mechanisms, this possibly contributes to the development of autoimmunity.

negative regulatory mechanisms possibly contributes to the development of autoimmunity.

Proposed Areas for Future Study in Recurrent AILDs

A common theme with AILD is evidence that suggests that patients transplanted for AILD are more likely to experience acute rejection compared to those transplanted for non-AILD. The reason(s) behind this observation are unclear; and how this likelihood to develop rejection may be related to disease recurrence is unknown. Data from the lung transplant field has provided new insights demonstrating that alloimmunity can induce immune responses to self-antigens (autoimmunity) and also a crosstalk between alloimmune and autoimmune responses contribute to the immunopathogenesis of chronic rejection.[95] In this context, collagen V is expressed ubiquitously in the lungs and incorporated within collagen I fibrils, making it immunologically protected. Exposure of CoIV to the immune system (after epithelial and endothelial injury from any cause) results in T cell–specific responses to CoIV in a rat model of lung transplantation. Transfer of these CoIV-specific T cells to other transplanted rats (including isografts) results in the development of chronic rejection.[118,119] CoIV-specific immune responses have similarly been demonstrated in human lung transplant recipients with chronic rejection[120-122]; additionally, there is an emerging role of IL-17–mediated immune responses to self-antigens in the pathogenesis of chronic rejection.

In total, these observations suggest that inflammation due to alloimmune responses after transplantation can lead to the development of de novo immune responses against self-antigens. On the flip side, preexisting immune responses to self-antigens can augment the development of alloimmune responses to mismatched donor antigens and both can lead to chronic rejection.[123] This lends support for "crosstalk" between alloimmune and autoimmune responses that perpetuate one another, leading to chronic rejection.

Important mediators in the pathogenesis of chronic rejection after transplantation are cellular immune responses to self-antigens. Over the past few years, an emerging role for IL-17 has been observed.[95] Although CD4 T_h17 cells are a common source of IL-17, NK cells, neutrophils, and γδ-T cells are other sources of IL-17 and may play a potential role in chronic rejection. Indeed, NK cells have emerged as a focus of interest in the transplant field because it is thought they play a role in the immune response in acute and chronic rejection.[124]

An unmet need in AILD is prevention of disease recurrence after liver transplantation. At present, there is no systematic approach to reduce the risk of disease recurrence, and experience from long-term follow-up studies suggests that graft loss from disease recurrence is not an insignificant problem.[60] How the increased likelihood to develop rejection may be related to disease recurrence is unknown. Current hypotheses suggest a crosstalk between inflammatory responses by autoimmune and alloimmune mechanisms may lead to chronic rejection. A proposed link between autoimmune and alloimmune mechanisms after liver transplantation for AILD is suggested. Future studies should investigate if in patients with preexisting immune responses to self-antigens, who undergo liver transplantation, de novo donor-specific antibodies, and antibodies to self-antigens precede the development of rejection and disease recurrence; this may support their use as biomarkers after liver transplantation. Strategies targeted toward prevention, such as the use of antibody depleting regimens, can then be studied. Also, neutralization of IL-17 may represent an important aspect of future therapeutics in preventing recurrent AILD and should be studied. Other opportunities for prevention of disease recurrence after transplantation include identification of high-risk recipients using well-powered genetic and translational studies.

CONCLUSIONS

As the emphasis has shifted from ensuring immediate survival and managing early postoperative complications, the need to address long-term outcomes and the factors that influence these outcomes is urgent. Research into understanding the factors driving late allograft dysfunction could potentially open up new therapeutic options, leading to continued improvement in long-term patient and graft survival and quality of life.

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