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Review

Liver-associated immune abnormalities☆

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ABSTRACT

In recent years, the cross talk between the liver and the immune system is being uncovered, in part by studying liver involvement in primary immune deficiencies (PID) and in part by investigating the alterations of the immune system following orthotopic liver transplantation (OLT). Here we review some of the reciprocal interactions between the liver and the immune system. Patients with PID, particularly those involving inherited defects in T and B cells or innate immunity are prone to infections and inflammatory responses that often involve the liver. Omenn's syndrome, familial hemophagocytic lymphohistiocytosis, AIRE, FOXP3 and CD25 deficiencies, common variable immunodeficiency, CD40 ligand deficiency, chronic granulomatous disease and autoimmune lymphoproliferative syndrome are some of the notable PID associated with typical hepatobiliary abnormalities. Knowledge gained from studying these PID together with laboratory and histological evaluations can assist in managing PID-associated liver dysfunction. The liver itself also has important effects on the immune system, as evident from the growing experience with patients surviving OLT. Up to 40% of pediatric patients who receive OLT suffer from post transplantation allergy, autoimmunity, and immune-mediated disorders (PTAA). PTAA is more common after liver and heart transplantations than kidney transplantations. Potential contributing factors for the increased frequency of PTAA after OLT include the age of the patients, the prolonged use of tacrolimus and the reduced regulatory immune function with a shift towards a TH2 immune response. Better understanding of the mechanisms leading to the development of PTAA after OLT will also improve the management of these conditions.

The liver is one of the largest internal organs and receives the equivalent of the whole blood volume every 3–4 min. Eighty percent of the blood flowing into the liver is from the portal system, carrying bacterial antigens, food allergens, apoptotic cells and debris, thereby placing the liver at the center of many potential immune responses. Yet, these immune stimulants rarely elicit a response. Moreover, various pathogens, such as Hepatitis C virus can remain for many years in the liver without triggering a robust immune response [1]. In recent years, the cross talk between the liver and the immune system is being uncovered, in part by studying liver involvement in primary immune deficiencies (PID) and in part by investigating the alterations of the immune system following orthotopic liver transplantation (OLT). Here we review some of the reciprocal interactions between the liver and the immune system.

1. Liver abnormalities associated with primary immune deficiencies

PID is a rapidly growing group of > 350 conditions, characterized by increased susceptibility to infections, autoimmunity and auto-inflammation as well as tumor and malignancy development [2]. Classification of these conditions has been traditionally based on the defective arm of the immune system that is predominantly involved. Most common are defects in T and B cells, innate immunity (including neutrophils and complement) or combinations of these. For many of these diseases, gene alterations are already known, while others are actively being pursued. Some of the notable PID associated with liver abnormalities will be detailed below.

Recognizing that PID is the cause of the liver dysfunction,

Abbreviations: AIRE, Autoimmune regulator; FA, Food allergies; HLH, Hemophagocytic lymphohistiocytosis; HT, heart transplantation; KT, kidney transplantation; PID, primary immunodeficiency; PTAA, Post transplantation allergy, autoimmunity, and immune-mediated disorders; OLT, Orthotopic liver transplantation; SCID, severe combined immune deficiency

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particularly if accompanied by other infectious or autoimmune manifestations, may also alter patient's management. For example, appreciation that non-remitting autoimmune hepatitis is due to profound inherited T cell defect will often lead to pursuing allogeneic rather than autologous hematopoietic stem cell transplantation [3,4].

1.1. Predominantly T cell abnormalities

1. Omenn's syndrome: Defects that severely compromise the generation and function of thymocytes and T cells cause a condition known as severe combined immune deficiency (SCID). Patients typically suffer from increased susceptibility to infections that may also affect the liver. In addition, 10–20% of patients with SCID develop an inflammatory reaction known as Omenn's syndrome that is characterized by erythroderma and desquamation of the skin, alopecia, diarrhea and colitis, hepatosplenomegaly and lymphadenopathy [5]. Laboratory evaluations often reveal hematological cytopenias, elevated IgE and eosinophila. Many patients with Omenn's syndrome also suffer from hepatitis. In contrast to typical SCID where T cells are lacking, patients suffering from Omenn's syndrome may have normal or even increased CD4+ and CD8+ T cells, attributed to few T cells that escaped selection in the thymus [6] and expand in the periphery. The rogue T cells then attack normal tissues, including the skin, gastrointestinal tract and liver, resembling acute graft-versus-host disease. Liver biopsies in patients with Omenn's syndrome have shown diffuse microvesicular steatosis, Kupffer's cells hyperplasia, necrotic hepatocytes and destruction of bile ducts accompanied by a lymphoid cells infiltrates in the portal area and biliary ducts [7]. While commonly associated with inherited defects in recombination activating genes 1 and 2, mutations in many other genes have been shown to cause Omenn's syndrome [8–10]. Steroids and calcineurin inhibitors (such as cyclosporine A) are often needed to control the inflammatory response until the definitive management of the SCID, allogeneic hematopoietic stem cell transplantation.
2. Familial hemophagocytic lymphohistiocytosis: Primary familial Hemophagocytic lymphohistiocytosis (HLH) is caused by genetic defects leading to failure of cytotoxic T cells and natural killer cells to terminate immune activation, which might be triggered by infections such as EBV or evolve spontaneously [11]. Patients typically suffer from prolonged fever, hematological cytopenia, hemophagocytosis in the bone marrow or other lymphatic tissue, splenomegaly and neurological abnormalities. Laboratory evaluations reveal markedly elevated ferritin and triglycerides, low levels of fibrinogen as well as hepatitis. The “cytokine storm” characteristic of HLH can be associated with increase in IL18, soluble IL2, serum CD163 and others [12]. The liver is commonly involved in familial HLH. Liver biopsy often shows infiltrating histiocytes and lymphocytes, and in many cases hemophagocytosis might be evident. Infrequently the damage to hepatocytes affected by HLH can lead to liver failure [13]. Liver transplantation in cases of secondary HLH can be used as a therapeutic modality despite the risk of disease recurrence in the immediate post-transplantation period [14]. Defects in many genes important for the function of T and NK cells have been shown to cause familial HLH. For example, mutations in the SH2D1A gene, which encodes the signal transducing protein SLAM-associated protein, result in a condition known as X-linked lymphoproliferative type 1 or Duncan disease. Affected males suffer from impaired production of antibodies, autoimmunity and increased frequency of malignancy. Additionally, patients have increased susceptibility to EBV disease that can also lead to rapid liver failure.
3. MHC class II deficiencies: Inherited defects in genes encoding several transcription factors involved in generating MHC class II proteins, such as CIITA, RFX5, RFXAP and RFXANK can cause recurrent severe infections, failure to thrive, diarrhea and autoimmune cytopenia. Infrequently, autoimmunity against the liver and biliary tract have been noted [15]. Although CD4+ T cells are usually reduced, total lymphocyte number is often normal.
4. AIRE deficiency: Autoimmune regulator (AIRE) is important for expression of tissue specific antigens by medullary thymic epithelial cells. Defects in AIRE cause Autoimmune Polyendocrine Syndrome type-1, which is also known as polyendocrinopathy-candidiasis-ectodermal dystrophy. Impaired AIRE function prevents the normal negative central selection of auto-reactive thymocytes, although the expression of AIRE in lymph nodes suggests that peripheral selection of T cells might also be affected. Patients suffer from diverse autoimmune manifestations, including primary hypoparathyroidism, autoimmune adrenal insufficiency, insulin dependent diabetes mellitus, hematologic cytopenia and gonadal failure [16]. Autoimmune hepatitis at variable severity has been reported in 8–16% of patients, ranging from asymptomatic autoantibody detection with spontaneous regression to fulminant liver failure. Liver-Kidney microsomal autoantibodies, particularly against cytochrome P450 1A2 or 2A6 have frequently been found, however their diagnostic and prognostic significance for liver disease remain to be determined [17]. Liver biopsies performed in few patients have shown low-grade chronic active autoimmune hepatitis [18]. In addition, patients often suffer from chronic, difficult to treat mucocutaneous candidiasis and ectodermal dystrophy. Aire-deficient mice have also been shown to suffer from defective central tolerance leading to polyendocrine abnormalities and autoimmune hepatitis with autoantibodies to liver antigens.
5. STAT1 defects: Bi-allelic mutations in the STAT1 gene have been associated with susceptibility to mycobacteria, while single allele mutations cause increased susceptibility to infections and diverse autoimmune manifestations. Patients with single allele mutations, often characterized in vitro as gain-of-function, can present with mucocutaneous candidiasis. Among 274 patients with STAT1 gain-of-function mutations, 6 patients were reported to develop autoimmune hepatitis before adulthood [19]. Few patients have also been reported to develop cholangitis [20]
6. FOXP3 deficiency: Inherited hemizygous mutations in FOXP3 cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, characterized by abnormal generation and function of CD4 + CD25 + FOXP3+ regulatory T cells, important for maintaining peripheral tolerance [21]. Regulatory T cells can suppress immune responses indirectly through action on antigen presenting cells or directly on other lymphocytes by cell-cell contact or secretion of cytokines, including TGF-βa-10 and IL-35 [22,23]. Affected male patients suffer from multi-organ autoimmunity that can present at infancy with insulin-dependent diabetes mellitus, hypothyroidism, eczema, severe enteropathy, glomerulonephritis and cytopenia. In a recent multicenter study, 18 of 96 patients with IPEX syndrome had autoimmune hepatitis [24]. IPEX syndrome is associated with a broad spectrum of autoantibodies, however these antibodies do not correlate with patients' clinical or laboratory findings [25]. Interestingly, a patient with IPEX syndrome was reported with high titer IgA anti-mitochondrial antibodies, typically associated with primary biliary cirrhosis, however the patient did not suffer at the time of this report from liver disease [25].
7. CD25 deficiency: Inherited defect in CD25, the alpha chain of the IL2 receptor, was the first immunodeficiency and autoimmunity condition where a molecular diagnosed was identified [26]. CD25 deficiency leads to marked susceptibility to infections such as CMV, reflecting the profound T cell dysfunction. In addition, a CD25-deficient patient was described with lymphocytic infiltration and liver dysfunction, reminiscent of primary biliary cirrhosis [26]. The patient also had elevated serum antibody to PDC-E2 [27].
8. SP110 deficiency: Autosomal recessive defects in the SP110, a central interferon-induced nuclear protein that also regulates nuclear factor-κB function, cause venoocclusive disease with

immunodeficiency. Initially described among infants of Lebanese origin, this condition is now recognized across the world as causing T and B cells dysfunction. While T cell numbers can be normal or reduced, memory T cells and IgG are markedly decreased [28]. Most patients develop hepatic lobular vascular occlusion and hepatic fibrosis manifesting as hepatomegaly and/or hepatic failure.

9. IgG4 related disease: The pathogenesis of IgG4 related disease is not clear, yet there are accumulating data suggesting a central role for T cells in disease development [29]. Moreover, while 60–70% of patients have elevated IgG4, the current consensus is that IgG4 is not a cause for the disease. Characteristic features of this increasingly recognized condition include tumor-like swelling of involved organs, a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, and fibrosis that has a characteristic "storiform" pattern. Typical organs involved include the salivary and lacrimal glands, the lungs, the retroperitoneum and the aorta. Many patients suffer from autoimmune pancreatitis. Sclerosing cholangitis and cholangiocarcinoma have been reported among few patients with IgG4 related disease [30]. Serum IgG4≧1.25 upper limit of normal was recently shown to distinguish patients with IgG4-associated sclerosing cholangitis from those with other disease aetiologies [31].

1.2. Predominantly B cell abnormalities

1. Common variable immunodeficiency: Common variable immunodeficiency is a heterogeneous group of immune defects characterized by reduced immunoglobulin levels and impaired production of antibodies [32]. Intensive genetic studies are gradually revealing the diverse aetiologies for common variable immunodeficiency, although in many patients the exact cause is still unknown. > 1/3 of patients suffer from autoimmunity that might be the presenting feature, involving multiple organs, including the liver. Some patients might also develop progressive nodular regenerative hyperplasia [33] or liver cirrhosis [34]. Few patients have even required OLT that seem to carry a worse outcome in comparison to other OLT recipients [35].
2. CD40 ligand deficiency: CD40 ligand, or CD154, is expressed primarily on T cells and has a central role in activating B cells and immunoglobulin class switch recombination. Inherited defects in CD40 ligand cause an X-linked disease characterized by elevated (or preserved) levels of IgM with low IgG, IgA and IgE, a condition known as hyper-IgM syndrome [36]. Patients suffer from increased susceptibility to infections and autoimmunity, including hepatitis. In addition, there is a high frequency of sclerosing cholangitis, often in association with *Cryptosporidium* infection [37]. Hepatocellular carcinoma and cholangiocarcinoma have also been reported among patients with HyperIgM syndrome.
3. CD40 deficiency: Patients affected by CD40 deficiency suffer from similar susceptibility to infections and autoimmunity as with CD40 ligand defects. CD40 deficiency is an autosomal recessive disorder affecting both genders [36].
4. IL21 Receptor deficiency: IL21 receptor deficiency was recently described in few patients with a phenotype resembling CD40 ligand deficiency and elevated IgE [38]. The patients suffered from early onset of recurrent infections, chronic cholangitis as well as biliary and hepatic cirrhosis associated with Cryptosporidium infection.

1.3. Innate immunity defects

1. Shwachman–Diamond syndrome: Shwachman–Diamond syndrome is characterized by neutropenia, severe exocrine pancreatic insufficiency, metaphyseal dysplasia and bone marrow failure or myelodysplastic syndrome. Additionally, patients commonly develop liver abnormalities. Hepatomegaly is found in roughly 15% of patients, and 50%–75% of patients will have serum liver enzymes 2–3 times above the normal levels [39]. Few patients suffered severe pan-lobular fatty changes with peri-portal and portal inflammatory infiltration and bridging fibrosis, as well as micro-vesicular and macro-vesicular steatosis. Defects in several genes including SDBS [40], EFL1 [41], DNAJC21 [42] have been shown to cause Shwachman–Diamond syndrome.
2. Chronic granulomatous disease: Chronic granulomatous disease is attributed to impaired formation of reactive oxygen compounds by immune cells, such as neutrophils and macrophages. This is caused by X-linked or autosomal recessive mutations in genes important for the NADPH oxidase complex. Patients can present at any age with infections due to catalase expressing pathogens, extensive non-infectious granulomas or autoimmunity including inflammatory bowel disease-like condition. Liver abnormalities are frequently identified. In a cohort of 194 patients with chronic granulomatous disease, liver enzymes were elevated in 73%, with persistent elevations of alkaline phosphatase in 25% [43]. Liver biopsies frequently reveal granulomata and lobular hepatitis. In a large study, liver abscesses and hepatomegaly were each seen in one-third of cases.

1.4. Defects in death domains

1.4.1. Autoimmune lymphoproliferative syndrome

Autoimmune lympho-proliferative syndrome is caused by inherited or somatic defects in genes coding for molecules involved in the FAS-caspases apoptosis-inducing pathway. Patients typically present at early age with persistent non-malignant lymphoproliferation and intermittent autoimmunity involving primarily hematopoietic cells. Later in life there is increased frequency of lymphoma. Additional laboratory features include increased T cells characterized as CD3+ TCRalpha +beta+ CD4-CD8- ("double negative"), serum vitamin B12, IgG, IL10 and Fas ligand. Fas-mediated in vitro apoptosis assay may also be defective. In a recent study 5% of patients with ALPS suffered from acute seronegative autoimmune hepatitis [44] that in some led to liver fibrosis

2. Immune abnormalities associated with liver transplantation

OLT are performed at an increasing frequency and for diverse aetiologies in pediatric and adult patients. In recent years, advances in patients and donor selection and preparation, better surgical techniques, monitoring, as well as availability of safer and effective immune modulatory techniques have contributed to improved short and long-term survival of patients after OLT. A multicenter study by the North-American SPLIT group (Studies of pediatric Liver Transplantation) revealed an 84.8% survival 5 years after pediatric OLT [45], while the 10 year survival is > 80% [46]. The increased long-term survival after OLT has also led to emphasis on improving quality of life for patients, including better understanding and management of post-transplantation immune abnormalities [47,48].

In 1997, a male recipient of a liver-kidney transplant, harvested from a young donor who died from peanut-induced anaphylaxis, developed de novo peanut allergy 3 months after the transplant. He was also found to have peanut-specific IgE and increased basophil degranulation upon ex vivo exposure to peanuts [49]. A female patient who had received a kidney and pancreas transplant from the same donor did not develop clinical or laboratory evidence of peanut allergy. In subsequent years, there were additional reports of patients who exhibited passive transfer of peanut allergies after OLT, often when the donor had died from anaphylaxis [50,51]. In some of the patients, the allergic reactions subsided [52]. However, the increasing numbers of atopic manifestations following OLT suggested that the phenomena might also be associated with the transplant itself. Nowak-Wegrzyn et al. described 6 infants who developed food allergies (FA) up to 1 year after OLT, where none of the donors were known to have FA, although 3 suffered from asthma and or allergic rhinitis [53]. Similarly, Levy

et al. reviewed a 20-years single center experience and identified 4 children with de novo FA among 65 patients (6%) who received liver or liver-kidney transplants [54]. In contrast, none of 265 kidney transplant (KT) recipients in the same center developed FA. A study from Vienna, Austria of 19 children who received OLT, found 5 with laboratory evidence for FA, yet only 2 (10%) with allergic symptoms, emphasizing the importance of thorough evaluations before establishing the diagnosis of allergies [55]. Another large retrospective study found that 8.5% of 352 pediatric OLT recipients developed FA and/or eosinophilic gastrointestinal disease [56]. Chart reviews and follow-up questioners in 176 pediatric OLT recipients at Baylor University, Texas, identified 14.2% with allergic diseases, including 40% with FA, 56% with atopic skin disease, while asthma, allergic rhinitis or both were found in 66% of patients [57]. Even higher frequencies of FA following OLT have recently been described. In Ghent, Belgium, 13 of 49 patients (26%) developed FA [58], while in Tokyo, Japan, 42 of 206 (20.4%) patients < 36 months of age developed IgE and non-IgE mediated FA [59]. Similar frequency (21.4%) was also reported in a prospective study from Ankara, Turkey, although only 28 patients received OLT [60].

Autoimmune manifestations have also been reported at higher frequencies after OLT than in general populations. A single center retrospective study identified 5 patients among 158 liver recipients (3%) who developed autoimmune cytopenia [61]. Similarly, among the 256 OLT recipients 8 (3%) cases of new-onset immune-mediated thrombocytopenic purpura were identified [62]. Moreover, autoimmune cytopenia developed in 6 of 141 OLT (4%) at Boston Children's Hospital versus only 4 of 340 (1.2%) of kidney transplant recipients at the same center [63].

Several causes for the immune abnormalities found after OLT have been proposed (Table 1). Many have attributed the immune abnormalities to ongoing exposure to tacrolimus, a calcineurin inhibitor commonly used after transplantation. This hypothesis was supported in part by clinical improvement of the autoimmune cytopenia when an alternative immune suppressant was used [63]. However, in many other conditions, including KT, tacrolimus was not associated with such a high frequency of immune abnormalities suggesting additional mechanisms beyond tacrolimus use. Also, Boyle et al. reported that following split OLT into 2 recipients, only one patient developed FA, while both were treated with tacrolimus [64]. Another potential mechanism for immune abnormalities after OLT is the unique immune milieu of patients with reduced regulatory immune function and a shift towards a TH2 response. Although the number of regulatory T cells in the blood of patients with FA following OLT is not different than those who did not develop FA, peripheral blood mononuclear cells from those with FA demonstrated higher IL5 secretion and low IL10 secretion [65].

To further characterize the immune abnormalities following OLT, we recently studied patients who received OLT between the years 2000 and 2012 at the Hospital for Sick Children, Toronto, Ontario, a provincial referral center for such procedures [66]. This cross-sectional analysis also included patients who received KT and heart transplantations (HT) during the same period thereby mitigating potential bias related to practice changes, to advances in infections and to graft rejection surveillance or management. The inclusion of KT also enabled comparison of the effects of tacrolimus, which was used for transplant recipients of both procedures as well as a "negative control" group given the multiple reports of low frequency of allergies in KT recipients. HT provided a group of children who are typically transplanted at an early age similar to OLT, as well as a "positive control" group, given the high frequency of immune abnormalities following HT. Patients were excluded if they had immune abnormalities prior to transplantation, had a follow-up period after transplantation that was shorter than 6 months or incomplete data. Altogether, 266 patients were included in the study (Table 2). As expected, KT was performed at a significantly older age than OLT or HT. Post transplantation allergy, autoimmunity, and immune-mediated disorders (PTAA) developed in 40% of patients who received OLT and HT compared to only 4% after KT (Table 2). The PTAA included FA, eosinophilic esophagitis/gastroenteritis, atopic dermatitis, rhinitis, asthma, autoimmune cytopenia, vasculitis, inflammatory bowel disease and alopecia (Table 2). PTAA developed within 2 years of transplant in the majority of patients. Multivariate logistic regression analysis identified positive family history of allergies, young age at transplantation, eosinophilia, and positive post-transplantation Epstein–Barr virus as independent risk factors for the development of PTAA. In contrast, length of post-transplantation steroid treatment, presence and frequency of acute rejections, organ type (living donor versus cadaveric), donor/recipient blood types and compatibility, and non-EBV infections were not associated with risk for PTAA. The effects of tacrolimus could not be evaluated as > 90% of the patients received this medication. The study further emphasized the impact of young age on the development of allergies and FA particularly after OLT, an intriguing finding, as it has often hypothesized that tolerance is greater at early age.

Additional studies are currently underway to decipher the immunological mechanisms disrupted by OLT, thereby providing better understanding of the role of the liver in immunity and improving the care of patients with PID or those undergoing OLT.

Table 1
Proposed risk factors for immune abnormalities after liver transplantation.

Donor preexisting allergies or immune abnormalities
Age of the recipient at time of transplantation
Preexisting recipient allergies
Recipient's family history of allergies
Chronic infection (such as EBV) in the recipient
Use of tacrolimus
Reduced number or function of regulatory T cells
Eosinophilia post-transplant

Table 2
Characteristics of post-transplantation allergy, autoimmunity, and immune-mediated disorders.

	Liver	Kidney	Heart
Number of patients transplanted	111	103	52
Median age of transplant, years	1.7	1.2	10.8
Prevalence (%) of males	57	54	71
Prevalence (%) of patients with PTAA	40.5	39.8	3.8
Prevalence (%) of allergy	38.7	38.8	3.8
Prevalence (%) of Asthma	9	15.5	1.9
Prevalence (%) of Food allergies	15.3	4.9	0
Prevalence (%) of autoimmunity	4.5	9.7	0
Prevalence (%) of hematological cytopenia	1.8	4.9	0
Prevalence (%) of inflammatory bowel disease	0.9	4.9	0
Prevalence (%) of vasculitis	0.9	1	0
Prevalence (%) of PTAA within 2 years of transplant	89	71	100

3. Summary

In conclusion, knowledge gained from studying PID can assist in managing associated liver dysfunction, while better understanding of the mechanisms leading to the development of PTAA after OLT will improve the management of these transplanted patients. Together these conditions help decipher the important cross talk between the liver and the immune system.

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