Published in final edited form as:

Liver Transpl. 2018 January ; 24(1): 89–97. doi:10.1002/lt.24873.

Environmental peer pressure: CD4⁺ T cell help in tolerance and transplantation

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Abstract

The liver participates in a multitude of metabolic functions that are critical for sustaining human life. Despite constant encounters with antigenic-rich intestinal blood, oxidative stress and metabolic intermediates, there is no appreciable immune response. Interestingly, patients undergoing orthotopic liver transplantation benefit from a high rate of graft acceptance in comparison to other solid organ transplant recipients. In fact, co-transplantation of a donor liver in tandem with a rejection-prone graft increases the likelihood of graft acceptance. A variety of players may account for this phenomenon including the interaction of intrahepatic antigen presenting cells with CD4⁺ T cells and the preferential induction of Foxp3 expression on CD4⁺ T cells following injurious stimuli. Ineffective insult management can cause chronic liver disease, which manifests systemically as: antibody mediated disorders, ineffective antiviral and antibacterial immunity, and gastrointestinal disorders. These sequelae share the requirement of CD4⁺ T cell help to coordinate aberrant immune responses. In this review, we will focus on CD4⁺ T cell help due to the shared requirements in hepatic tolerance and coordination of extrahepatic immune responses. Overall, intrahepatic deviations from steady state can have deleterious systemic immune outcomes, and highlight the liver's remarkable capacity to maintain a balance between tolerance and inflammatory response while simultaneously being inundated with a panoply of antigenic stimuli.

Introduction

Anatomic location can have a crucial influence on T cell subset differentiation and function (1, 2). The specialized functions of the liver create a unique microenvironment in which T cells are exposed to different environmental stimuli in comparison to other peripheral lymphoid organs. The liver is a vital site of non-redundant metabolic functions required for sustaining life. As such, it is equipped to manage a certain degree of inflammation such that normal metabolic functions may continue uninterrupted. This unique property reputes the liver as a “tolerogenic site” due to constant encounters with a wide array of self-antigens, food antigens, gut commensals, oxidative stress, and metabolites without any appreciable immunological consequences or tissue damage (3–13). This is due to a complex

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The authors have no conflicts of interest to disclose.

collaboration of liver antigen-presenting cells (APCs), lymphoid cells, and non-parenchymal cells at steady state.

The liver is comprised of distinct tissue-resident lymphoid and non-lymphoid cells that do not appear in peripheral counterparts (8, 14). In both humans and mice, the liver lymphoid compartment is enriched in non-conventional immune cell subsets including natural killer (NK) cells, and TCR $\gamma\delta$ + T cells (4, 8). The collective actions of these lymphocytes critically contribute to early immune responses to pathogens, anti-tumor responses and maintenance of liver homeostasis. Interactions of intrahepatic CD4+ T cells and liver-resident APCs such as dendritic cells, Kupffer cells (KCs) and liver sinusoidal endothelial cells (LSECs) help facilitate tolerance. In comparison to peripheral counterparts, intrahepatic APCs maintain an immature phenotype and preferentially produce tolerogenic cytokines, such as IL-10, following the encounter of antigens (6, 12, 15, 16). The interaction of intrahepatic APCs and T cells has been implicated as a mechanism of maintaining peripheral tolerance to self-antigens, food antigens, and allografts (13, 17–19). Conversely, the poor immunogenicity of the liver microenvironment is associated with permissiveness to chronic hepatotropic infections and weak anti-tumor responses (6, 8, 11). Due to the composition of the liver lymphoid and non-lymphoid compartments and the multitude of metabolic and immunologic functions in which they participate, the cells in the liver form a distinct microenvironment. Thus, the events within the intrahepatic milieu could potentially hold the key to treating a variety of immunological disorders and management of graft acceptance.

The overall tolerogenic nature of the liver is exemplified in the context of solid organ transplantation. For example, early studies of liver transplantation in pigs revealed spontaneous tolerance of the engrafted liver (20). In fact, donor matched liver transplantation in tandem with a rejection-prone graft, such as the kidney, can halt rejection episodes (21). As a result, many patients do not require overly aggressive immunosuppressive regimens following orthotopic liver transplantation (22–24). Liver-graft rejection episodes are largely T cell mediated (5, 25–27) and there have been substantial efforts in understanding how the intrahepatic T cell immune responses can facilitate tolerance to allografts. Although pre-transplant indicators of graft acceptance rates are not well defined, there is evidence that immune responses within the liver may contribute to systemic tolerance of foreign antigens—including allografts (28, 29). Moreover, perturbations within the liver microenvironment, such as chronic fibrosis, can manifest extrahepatically as inflammatory and autoimmune disorders, largely T mediated phenomena (3, 12, 30–32). Here, we will review the influence of the liver microenvironment particularly on CD4+ T cell subset help and associated alterations during liver disease and how it can contribute to breaks in tolerance. Overall, a better understanding of the role of the intrahepatic microenvironment in transplant outcomes will inform clinical decisions surrounding transplantation.

I. Extrahepatic manifestations of liver injury and influence on clinical decisions surrounding transplant

Despite different mechanisms of eliciting liver damage, nearly all liver insults converge at hepatic stellate cell (HSC) activation, which initiates fibrosis (33). When provoked, HSCs

become activated and secrete collagen, extracellular matrix proteins, profibrotic cytokines, chemokines and retinoic acid to begin the tissue repair process. Once the insult is resolved, this process reverses as scar tissue is replaced by healthy tissue (34). This process, fibrosis reversible liver scarring, initiates the liver wound healing process and functions to siphon the insult away from healthy tissue (33, 34).

The increased instance of CD4+Foxp3+ T cells in the fibrotic liver (35) co-exists with aberrant B cell activation that is often accompanied by systemic antibody mediated autoimmunity during chronic liver disease (3, 30, 36, 37). While these CD4+Foxp3+ T cells are capable of CD8+ T cell suppression, our own studies have defined a novel fibrosis-induced CD4+ Foxp3+ T cell sub-population that promotes Ig-mediated extrahepatic symptoms of liver disease through CD40L expression (38)(**outlined in** Figure 1). In addition, during liver injury, activated hepatocytes produce complement proteins, which are key mediators of liver repair (39–41). Consequently, studies in human PBMCs have found that stimulation through CD46, the complement receptor, in the presence of professional APCs (i.e. monocytes and dendritic cells) and inflammatory cytokines can also induce Foxp3 expression on CD4+ T cells (42, 43). These so-called complement-Tregs (“cTreg”) can also suppress CD8+ T cell responses (43), while stimulating antibody production from B cells via CD40L expression (42). This may represent a pathway in which existing liver injury in end-stage kidney disease may predispose the recipient to antibody-mediated rejection episodes. Interestingly, emerging clinical evidence suggests that targeting the complement pathway with eculizumab, a monoclonal antibody against C5, attenuates acute antibody-mediated rejection episodes in the setting of transplantation (44).

The risk of antibody-mediated rejection can be significantly reduced when kidney transplant recipients are simultaneously transplanted with a liver allograft from the same donor (45–47). Early studies in rodent models suggest that liver-resident populations, such as Kupffer cells, contribute to absorption and subsequent clearance of alloreactive antibodies (48, 49). In the clinic, simultaneous liver-kidney (SLK) transplants are performed in patients that experience renal non-recovery during chronic liver disease (46, 50). SLK transplant rates have increased since the implementation of the model of end-stage liver disease (MELD) scoring system (46). The MELD criteria emphasize serum indicators of kidney function such as creatinine (51, 52), as indicators of SLK transplant candidacy (**outlined in** Figure 2). However, these criteria do not decouple kidney disease as a co-morbidity of liver disease. In fact, some patients experience near complete renal recovery once liver disease is addressed with liver transplant alone (52–54). While MELD criteria and assessment of kidney function in liver transplant candidates may be a point of disconnect among centers, there are clear benefits of SLK in patients with high levels of donor-specific antibodies prior to transplantation (55).

ESLD-related destruction of the intrahepatic microarchitecture, hemodynamic alterations and loss of detoxification functions have been attributed to kidney disorders associated with ESLD (56). Thus, any renal recovery following hepatic transplantation alone may simply be the outcome of successful engraftment and regained liver function (Reviewed in (56)). In addition to physiologic perturbations, the intrahepatic milieu fundamentally changes in such a way that implicates aberrant immune responses such as constitutive antibody

production (38, 57). Accordingly, ESLD-related increases in serum antibody content and immune complexes can potentially accumulate and cause kidney damage (27, 44). In either case, liver transplantation could conceivably reconstitute kidney function in ESLD patients as well as alleviate aberrant immune responses.

II. Intrahepatic immune responses govern peripheral tolerance to food and alloantigens

Hepatic CD4⁺ T cells receive different cues than the peripheral CD4⁺ T cells due to their interaction with liver-resident APCs and other non-parenchymal cells within the liver. Because the liver shares an estimated 70% of its blood supply with the gut via portal venous blood, the microenvironment is continually bathed in microbial products, metabolites and food antigens (13). The liver has been implicated as a key anatomic site of maintaining peripheral tolerance via direct and indirect modulation of T cell responses (11, 58). For instance, intrahepatic CD4⁺ T cell help may be a determinant in responses to innocuous antigens, such as food versus allergy inducing stimuli. Early studies have demonstrated that the liver participates in tolerance to food antigens (17, 59–61). For example, these experiments have found that diverting portal venous blood flow could ameliorate oral tolerance of ingested ovalbumin in naïve mice (61). This suggests that the context in which antigen is presented in the periphery versus intrahepatic presentation can differentially influence the quality and magnitude of the immune response. Thus, mechanisms of eliciting oral tolerance may be intrinsic to the liver.

Interestingly, clinical reports indicate that liver allograft donor-derived food allergies can be transferred to recipients (62, 63). Clinical management of these new post-transplantation allergies employs T cell based immunosuppressive strategies (63). Studies in rodent models suggest that inducible regulatory T cells, iTregs, play an important role in the outcome responses to innocuous food antigens (18, 19). iTreg generation is a consequence of intrahepatic presentation of antigen to CD4⁺ T cells and is regarded as a mechanism of dampening the intrahepatic inflammation (5, 9, 12, 64, 65). Combined, these studies highlight a putative role of intrahepatic presentation of food antigens to CD4⁺ T cells as a tolerance mechanism that has yet to be explored.

III. Intrahepatic CD4⁺ T cell priming

It is not clear what determines the outcome of hepatic tolerance. However, there is considerable evidence that liver-resident APCs and non-parenchymal cells participate in graft acceptance (29, 66). Mixed lymphocyte reactions (MLRs) of LSECs presenting allo-antigens to CD8⁺ T cells demonstrate an underappreciated role of LSECs tolerizing anti-graft immunity even in complete MHC mismatch (67–69). Furthermore, HSCs undergoing activation as a result of inflammatory events (70) promote increased regulatory T cells via *all-trans* retinoic acid; this population can suppress immune-mediated injury to the graft (65, 71). Another study by Morita and colleagues (72) suggested that regardless of which mechanisms are at play, tolerance of hepatic allografts requires IFN γ , a cytokine commonly associated with rejection. Using IFN γ $-/-$ mice, they found that the IFN γ pathway in hepatic non-parenchymal cells is critical for suppressing rejection responses. Upon sensing

inflammation, IFN γ -signaling on hepatic non-parenchymal cells led to increased PD-1 expression and other key mediators of apoptotic death of infiltrating CD8 $^{+}$ T cells (72). Although seemingly counter-intuitive compared to peripheral compartments, these data suggest that episodes of acute inflammation trigger immunomodulatory pathways aimed at limiting immune mediated injury and allowing preservation of organ function. Altogether, these studies suggest that liver-intrinsic mechanisms contribute to the unusually high rate of graft acceptance.

Liver- resident DCs can critically influence CD4 $^{+}$ T cell helper functions following antigen recognition and hence contribute to the net “tolerogenic” environment. Typically, upon recognition of microbial stimuli through toll-like receptors (TLRs), DCs become activated, mature and gain the capacity to uptake antigens and initiate the immune response. While peripheral DCs are anatomically sequestered from constant stimulation, this is not the case in the liver (73–75). Due to the variety of microbial products contained in the portal venous blood flow, intrahepatic dendritic cells (DCs) have reduced TLR4 expression in comparison to their splenic counterparts (76). This is advantageous in the context of maintaining the tolerogenic nature of the liver microenvironment since reduced TLR4 expression means that liver-resident DCs do not mature in response to normal levels of endogenous endotoxin (76). The immunologic consequences of CD4 $^{+}$ T cell priming by intrahepatic DCs preferentially result in an IL-10 and IL-4 mediated response to specifically induce “regulatory” and “Th2”-like phenotypes (76, 77). Splenic DCs on the other hand promote a more inflammatory response characterized by Th1 type cytokine production and increased proliferative capacity (76). In addition to DCs, liver resident macrophages, KCs, have been implicated in dampening CD4 $^{+}$ T cell responses to cognate antigen. At steady state, KC stimulation of CD4 $^{+}$ T cells also results in a decreased activation state in comparison to splenic DCs (78). Interestingly, co-cultures of CD4 $^{+}$ T cells initially activated by splenic DCs could be suppressed by addition of KCs via prostaglandin secretion (78). These cells may function as an additional mechanism in which ongoing inflammation is more effectively managed within the liver.

LSECs are liver resident scavengers that take up systemic and/or circulating antigens and present them to intrahepatic lymphocytes (79). During steady state, LSEC-primed transgenic CD4 $^{+}$ T cells are less activated than those primed with cognate antigen by splenic DCs (11, 16, 80). The *in vivo* significance of this finding was investigated using the ovalbumin mediated autoimmune hepatitis adoptive transfer model (81). OT-II CD4 $^{+}$ T cells and OT-I CD8 $^{+}$ T cells carry a transgenic TCR specific for different ovalbumin peptides. Co-transfer of LSEC-primed OT-II CD4 $^{+}$ T helper cells along with OT-I CD8 $^{+}$ T cells (implicated in liver injury in this model), was sufficient to suppress the ongoing immune response and attenuate liver injury (81).

While mechanisms that limit intrahepatic immune reactions occur at steady state, episodes of inflammation can result in enhanced immunogenic properties of liver APCs. Mouse models of both chemically-induced and dietary insufficiency-mediated liver injury have demonstrated that KCs in particular lose expression of PD-L1, a tolerogenic mediator that exerts its function through interactions with PD-1 to suppress the T cell response (12, 82) while gaining expression of the immunogenic CD80 molecule (83). As a result, these KCs

were able to stimulate immune-mediated liver injury through immunogenic priming of transgenic CD4⁺ T cell help (83). This work is one of the first demonstrations of *in vivo* consequences of enhanced immunogenicity acquired by KCs during liver injury. Aside from KCs, LSECs acquire immunogenicity that is postulated to be the result of the inflammatory environment within which they reside (16). Instead of promoting an anergic and/or regulatory CD4⁺ T cell phenotype, fibrotic liver LSECs gain capacity to stimulate CD4⁺ T cell proliferation and activation (16). Thus, fibrosis promotes an inflammatory shift in the liver microenvironment that fosters immunogenic alterations in liver-resident APC populations, both phenotypically and functionally. More study is required to better understand how the newly acquired stimulatory capacity of liver APCs governs immune-mediated injury and such understanding would benefit both angles of liver fibrosis and transplantation.

Organ injury is inevitable during organ procurement from the donor; this is usually the result of ischemia and reperfusion associated with transplantation. Ischemia Reperfusion Injury (IRI) is caused by the absence of blood flow (ischemia, anoxia) and subsequent reintroduction of blood in the tissue (reperfusion, reoxidation); even brief periods of IRI are an unavoidable consequence transplanting any organ from a donor into a recipient. Aside from transplantation, IRI occurs during other physiologic events such as myocardial infarction, stroke and other vascular blockages (84). Surprisingly, IRI-like injuries can occur, as during chronic liver disease, due to destruction of hepatic architecture associated with liver fibrosis. During steady state, the hepatic architecture permits relatively diffuse blood flow due to the fenestrated endothelial layer (73, 75, 85). Disruption of hepatic blood flow results in glycogen consumption and consequent ATP depletion (86), thereby perpetuating metabolic disturbance, accumulation of reactive oxygen species (ROS) and inflammation (87). Together, IRI drives hepatic parenchymal cell death and subsequent alteration of intrahepatic architecture.

Perhaps the transient nature of lymphocyte interactions within the intrahepatic milieu contributes to the management of immune responses. Patients can experience increased portal blood pressure due to destruction of the hepatic architecture, which can limit blood flow (73, 75, 85). As a result, interaction of infiltrating and resident populations can be prolonged and contribute to the exacerbation of inflammation or to the expansion of antigen-specific cell populations that would not otherwise become activated (88–90). Thus, deviation from homeostatic architecture during liver fibrosis or IRI-associated tissue destruction may prolong interaction of intrahepatic CD4⁺ T cells with APCs. These interactions can facilitate immunogenic priming of CD4⁺ T cell help as opposed to promoting a “regulatory” T cell function; this may play a role in immune-mediated graft injury (91).

Overall, much of the work aimed at elucidating antigen presentation to CD4⁺ T cells in the liver employs transgenic T cells derived from the spleens of donor animals. The disparate outcomes following exposure to antigen in the presence of liver versus splenic DCs or KCs and LSECs highlights the critical role of organ resident populations on the outcome of a primary immune response. Under normal conditions, a lack of a Th1-like response to cognate antigen is clearly beneficial for the liver in terms of limiting inflammation; however, this also makes the liver vulnerable to pathogens and permissive to tumor growth (reviewed

in (6, 8)). While the implications of liver inflammation and its effects on CD4⁺ T cell priming are just starting to be elucidated, further studies defining liver-specific immune alterations in CD4⁺ T cell helper function will inform novel strategies to manage chronic liver disease and graft acceptance.

IV. Concluding remarks

CD4⁺ T cell fate and effector functions are dictated by integration of environmental cues and co-stimulatory properties of APCs. The inflammatory and autoimmune manifestations (3, 12, 30–32) of liver disease suggest that the physiologic microenvironment critically contributes to systemic tolerance; perturbations can have deleterious consequences. Alterations in the liver microenvironment during fibrosis can facilitate activation of typically hypo-responsive liver-resident APCs; resulting in enhanced T cell priming (16, 83). Considering the detrimental inflammatory outcomes, activation of intrahepatic APCs seems to reinvigorate or access populations of T cells that have been partitioned to the liver. Harnessing intrahepatic APC activation has important therapeutic potential for vaccination strategies against chronic hepatotropic infections and cancers that have evaded the immune system. While this may be a long way off, modulation of the liver microenvironment has the potential to tap into CD4⁺ T cells that would have otherwise been anatomically sequestered and non-responsive. A clear understanding of the intrahepatic factors and outcomes of CD4⁺ T cell mediated adaptive immune responses could elicit novel therapeutics for liver diseases as well as autoimmune syndromes and cancers.

Due to the therapeutic effects of Treg transfer therapy strategies in experimental model systems (5, 18, 19, 92) and more recently, clinical transplant settings (93), it is reasonable to consider these approaches in controlling inflammatory extrahepatic symptoms of liver disease (94). In principle, the transfer of Tregs can serve to limit immune-mediated injury to the inflamed liver. However, it is important to consider that the composition of the fibrotic liver microenvironment is permissive to pathogenic fate decisions (42, 43, 95–97). As a result, Treg transfer therapies for liver diseases may indeed exacerbate the extrahepatic sequelae rather than curtail it. More investigation is necessary to predict the outcome of this approach.

The systemic consequences of liver diseases, suggest a greater role for the liver in modulating peripheral homeostasis as well as an interconnection of the liver and other anatomic compartments. For example, the entire body's blood supply passes through the liver around 360 times per day (98)—the liver sequesters antigen rich intestinal blood components from circulation (13). These scavenger functions of the liver may contribute to successful outcomes of SLK in patients with high levels of donor-specific antibodies (46). Therefore, it is plausible that the liver can be influenced by inflammation from other peripheral compartments, such as the gastrointestinal tract, or by consequences of peripheral IRI and vice versa. This is an active and exciting avenue and more likely these pathway connections will be elucidated soon as the field expands.

In summary, the liver is unlike any other anatomic compartment. It is responsible for metabolic functions, protein production, detoxification, regulation, and serves as a site of

immunologic education. Although the liver has evolved to manage a certain degree of deviation, surpassing the “point of no return” has detrimental effects on immunologic tolerance as well as general health. These extrahepatic manifestations of disease implicate the underappreciated role of the liver as a rheostat for immunologic harmony.

Acknowledgments

We thank Drs. Manoj Thapa, Eduardo Salinas, Young-Jin Seo, Jaclyn Espinosa and Luca Micci for fruitful scientific discussions and Amelie Grakoui for manuscript editing. We also would like to thank our support by NIH grants R01AI070101, R01AI124680, and R01AI126890 to A.G., and ORIP/OD P51OD011132 (formerly NCRR P51RR000165) to the Yerkes National Primate Research Center. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Figure 1. The fibrotic liver microenvironment promotes aberrant CD4+ T cell functions

The liver has the unique ability to repair itself upon injury. This serves the purpose of liver wound healing as well as maintenance of metabolic functions without an appreciable immune response. This is due, in part, to the interactions of intrahepatic CD4+ T cells and liver-resident APCs. Steady-state CD4+ Foxp3+ T cells are induced by HSC derived *all-trans* retinoic acid, or by recognition of cognate antigen presented by intrahepatic APCs. The resulting “regulatory” T cells suppress immune mediated injury by CD8+ T cells and B cell functions (**left**). If liver insult is not adequately resolved, the fibrotic liver microenvironment promotes a population of CD4+ Foxp3+ T cells that retain the ability to suppress CD8+ T cells. A sub-population stimulates B cells through CD40L expression. This seems to critically participate to the extra-hepatic antibody mediated disorders and poor CTL responses associated with chronic liver diseases (**right**).

Figure 2. Renal dysfunction due to End-Stage Liver Disease (ESLD)-related immune aberrations Typically, the destruction of the intrahepatic microarchitecture, hemodynamic alterations and loss of detoxification functions have been attributed to kidney disorders associated with ESLD (56). The MELD criterion uses kidney function as a clinical decision making tool for SLK versus liver transplant alone (**top**). In some cases, liver transplant alone can rescue kidney functions (references (52–54)) and thereby reducing the need for SLK (**bottom**). This suggests that immune responses within the liver may affect the kidney and perhaps other peripheral organ functions.