Review

The Current Immune Function of Hepatic Dendritic Cells

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While only a small percentage of the liver as dendritic cells, they play a major role in the regulation of liver immunity. Four major types of dendritic cell subsets include myeloid CD8α$^-$B220$^-$, lymphoid CD8α$^+$B220$^-$, plasmacytoid CD8α$^-$B220$^+$, and natural killer dendritic cell with CD8α$^-$B220$^-$NK1.1$^+$ phenotype. Although these subsets have slightly different characteristics, they are all poor naïve T cell stimulators. In exchange for their reduced capacity for allostimulation, hepatic DCs are equipped with an enhanced ability to secrete cytokines in response to TLR stimulation. In addition, they have increased level of phagocytosis. Both of these traits suggest hepatic DC as part of the innate immune system. With such a high rate of exposure to the dietary and commensal antigens, it is important for the hepatic DCs to have an enhanced innate response while maintaining a tolerogenic state to avoid chronic inflammation. Only upon secondary infectivity does the hepatic DC activate memory T cells for rapid eradication of recurring pathogen. On the other hand, overly tolerogenic characteristics of hepatic DC may be responsible for the increase prevalence of autoimmunity or liver malignancies. *Cellular & Molecular Immunology*. 2007;4(5):321-328.

Key Words: hepatic dendritic cell, immune tolerance, autoimmunity

Introduction

Dendritic cells (DCs) are recognized as the most potent antigen presenting cells (APCs) of the immune system, and are also responsible for characterizing the pathogenicity of the invading antigen (1). Through constitutive phagocytosis, immature DCs are able to survey the periphery for foreign antigens. Any antigens that are captured in the presence of danger signals, such as TLR ligands, will activate the DC to cease phagocytosis and upregulate adhesion molecules and chemokine receptors necessary for their migration to the draining lymph node (1). Following naïve T cell activation based on the recognition of MHC peptide complex presentation by the DC, it is up to the T cells to carry out the remainder of the immune response. On the other hand, it is even more important for the DCs to remain inactive upon the capture of non-pathogenic antigens as they are typically present at a higher abundance, especially the mucosal DCs that reside in the immediate barrier between our body and the outside environment. The same characteristics can also be found in DCs that reside in the liver.

Due to the amount of harmless dietary and commensal antigens that travel *via* the portal vein into the liver parenchyma, immune tolerance is crucial to prevent constant immune activation and chronic inflammation of the liver and the intestinal tract. The liver also plays a key role in oral tolerance. By creating a mesenterico-caval shunt that directly allows the mesenteric vein to flow into the inferior vena cava, antigen specific oral tolerance has been eliminated (2). In general, antigens introduced into the portal circulation are tolerated in comparison with the same antigen injected into the systemic circulation (3).

One of the best examples of immune tolerance in the liver is the phenomenal acceptance rate allogenic liver transplant (4). Many of the cellular mechanisms responsible for the success in liver transplantation have been recently elucidated. In particular, liver derived DC progenitors and hepatic regulatory T cells have been shown to prolong allograft survival (5, 6). Further investigation of these two cellular components is not only the key to the continual success we've experienced in allogenic liver transplantation, but also other organ transplants as well.

As the hepatic DCs are intrinsically swayed towards immune tolerance, one may question their ability to provide sufficient immune protection during opportunistic intestinal infection. Similar to epithelium associated DCs, hepatic DC plays an important role in fighting off malignancies and infections with its enhanced innate responses (7, 8). Their immediate response through surface receptors, increase level

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Received Jul 31, 2007. Accepted Aug 26, 2007.

of phagocytosis, and NK cell activation offers a first line immune response to contain and alleviate pathogenic insults. With the appropriate signals, hepatic DC can also be activated for the induction of T cell activation, chemokine and cytokine mediated immune responses (9).

Antigen presenting cells in the liver

There are 3 major types of APCs in the liver distinguished by their location, specific antigen responsiveness, T cell activation abilities, and cytokine secretion profile.

Liver sinusoidal endothelial cells

Dietary and commensal antigens entering from the intestinal tract through the portal tract will flow into the sinusoidal lumen and encounter the liver sinusoidal endothelial cells (LSECs). These LSECs act as a fenestrated filter for antigen within the portal circulation prior to entering the liver parenchyma. They are characterized by high level expression of ICAM-1 and VCAM-1 to recruit leukocytes for the purpose of immune surveillance (10, 11).

Kupffer cells

Kupffer cells (KCs) are the resident macrophages of the liver portal circulation. As they patrol the portal areas, they can freely transcytose the LSEC to eliminate pathogens in the space of disse, lymph of the liver. Through phagocytosis and the secretion of cytokines and chemokines, KCs can efficiently contain and eliminate invading pathogens (11). In particular, KCs can secrete IL-12 in response to bacterial or tumor antigens which can activate NK cells and natural T cells (12). KCs in a normal mouse liver have also been found to express CD86, an important T cell co-stimulating molecule in APC (13).

Hepatic DCs

Hepatic DCs are usually found in the portal triad and the central veins. Although all three major APCs can efficiently capture antigens and process those for MHC class II (MHC II) presentation. However, only the LSECs and KCs exhibit a mature immune state as they express co-stimulatory molecules and constitutively secrete IL-1 and IFN-γ (14). Hepatic DCs on the other hand can migrate through the LSECs and into the space of disse and travel toward the celiac lymph nodes while maintaining an immature state (14, 15).

Other APCs

In additional to the classical APCs described above, hepatocytes and biliary epithelium can also become APCs under the right microenvironment (16-18). In contrast to normal livers, hepatocytes from patients with clinical hepatitis have been found to express MHC II. Human intraheptic biliary epithelium cells (HIBECs) can express MHC II after stimulation with IFN-γ and TNF-α. However, they fail to express co-stimulatory molecules necessary for T cell activation. By addition of anti-CD28 to the co-culture of activated HIBEC and allogenic $CD4^+$ T cells, IFN-γ secretion and lymphoproliferation were detected *in vivo*. The ability of these atypical APCs to play a pathogenic role is currently under investigations; in the mean time we will direct our attention to the most potent APCs of all, the hepatic DCs.

Table 1. Hepatic DC Subsets ($CD19^-$, $CD3^-$, $CD11c^+$) in the C57BL/6 liver (19)

Subset	Phenotype	% of Total
Lymphoid	$CD8\alpha^+$, $B220^-$, $CD11b^-$, $DX5^-$	18
Myeloid	$CD8\alpha^-$, $B220^-$, $CD11b^+$, $DX5^-$	30
Plasmacytoid	$CD8\alpha^-$, $B220^+$, $CD11b^-$, $DX5^-$	19
Mixed Lymphoid + Myeloid	$CD8\alpha^-$, $B220^-$, $CD11b^-$, $DX5^-$	17
NKDC	$CD8\alpha^-$, $B220^+$, $CD11b^{lo}$, $DX5^+$	16

Hepatic DC subtypes

In the normal mice, hepatic $CD11c^+$ non parenchymal cell (NPC) population contains NK cells, B cells and T cells (19). After selecting against $DX5^+$, $CD19^+$ and $CD3^+$ surface markers, the 3 major subtypes of murine hepatic DC ($CD19^-$, $CD11c^+$) are lymphoid ($CD8\alpha^+$, $B220^-$, $CD11b^-$), myeloid ($CD8\alpha^-$, $B220^-$, $CD11b^+$) lineage, and plasmacytoid ($B220^+$, $CD11b^-$) (20, 21). Both the myeloid and lymphoid hepatic DCs are also refered to as conventional DCs (8). These conventional DCs are mainly located at the periportal fields and central veins, while the plasmacytoid DCs are located within the liver parenchyma (19). An additional hepatic DC with $B220^-CD11b^-$ phenotype has been characterized to contain a mixture of myeloid and lymphoid characteristics (22). Table 1 lists all the identified subtypes including a recently discovered hepatic DC subset called natural killer dendritic cell (NKDC). These DCs are an intermediate in the development of normal DCs (23). NKDCs are exclusively found in the $B220^-$, $CD11c^{int}$ DC subset and carry all the NK surface markers ($CD69^+2B4^+DX5^+$) as well (19, 24). Upon stimulation by IL-12 alone or in combination with IL-18, NKDC can secrete IFN-γ, lyse target cells and activate naïve T cells (24, 25).

While the NKDC subset makes up only 16% of the total $CD11c^+$ cells in a B6 mouse liver, the predominant form of hepatic DC is the $B220^-CD11c^{int}$ population (19). In contrast, splenic DC is predominated by the $B220^-CD11c^{hi}$. High CD11c expression usually corresponds to high CD80, CD86, CD40 expression and high levels of MHC II, making them very potent naïve T cell activators. On the other hand, not only does hepatic DC have low expression of co-stimulatory molecules thus rendering them poor T cell activator, they make up a very small population of the liver.

Hepatic DC enrichment

With only less than 1% of the NPC population as hepatic

DCs, isolating sufficient amount of hepatic DC is a timely and costly task. Several methods using cytokine stimulation have been developed to increase the total hepatic DC population *in vitro* and *in vivo*.

GM-CSF

Similar to the typical enrichment process of bone-marrow derived DCs, granulocyte macrophage-cell stimulating factor (GM-CSF) could induce hepatic DC progenitors ($CD11c^{lo}$ MHC II^{lo}) from NPC *in vitro*. In addition, GM-CSF could also cause them to mature to $CD11c^{hi}$MHC II^{hi} hepatic DCs (26). The same effect can be seen *in vivo*. By using transgenic mice that over expresses GM-CSF, not only was there a massive expansion in the immature hepatic DC population, but there was also a large increase in the number of hepatic DC progenitors (27).

Fms-like tyrosine kinase 3 ligand (Flt3L) injections

Another method for hepatic DC enrichment is the intravenous injection of Flt3L into a mouse. This method will dramatically increase the number of hepatic NPCs and DCs. As immature hepatic DCs are rapidly differentiated from hepatic DC progenitors, there is a proportional increase in both myeloid and lymphoid hepatic DC subsets (28). When used in combination with GM-CSF, total hepatic DC population can be increased up to 15% (29).

IL-3 and anti-CD40L derived hepatic DCs

One additional type of DC-like cell has been derived from the mouse liver using IL-3 and CD40L mAb stimulation. These hepatic DCs are able to regulate T cell activation and apoptosis (30). These DC-like cells contain surface markers such as DEC-205^{high}, $CD11c^{-}$, $B220^{+}$, and $CD19^{-}$ after IL-3 and CD40L stimulation. Although immunoglobulin (Ig) rearrangement has been detected in these DCs, they lack surface Ig expression. They are morphologically distinct from all myeloid and lymphoid DC progenitors. Although its existence *in vivo* is under investigation, this can possibly be another intermediate in the development of DCs.

Hepatic DC population dynamics

The hepatic portal circulation involves antigens entering from the portal triad and exiting through the central vein as shown in Figure 1. As soon as antigens are captured by hepatic DCs at the sinusoidal area of portal tract, the hepatic DC would transcytose into the space of disse and migrates toward the regional lymph nodes. Using an intravenous injection of particulate matter, Mastuno et al. were able to observe particulate-laden hepatic DCs in the celiac lymph nodes or in the spleen (9). This was consistent with splenic DC maturation, as they down-regulated their phagocytic activity and increased their chemokine receptors targeting the regional lymph node.

Chemokine and chemokine receptors on hepatic DC

Timely expression of chemokines and their receptors is the key in hepatic DC migration in the liver.

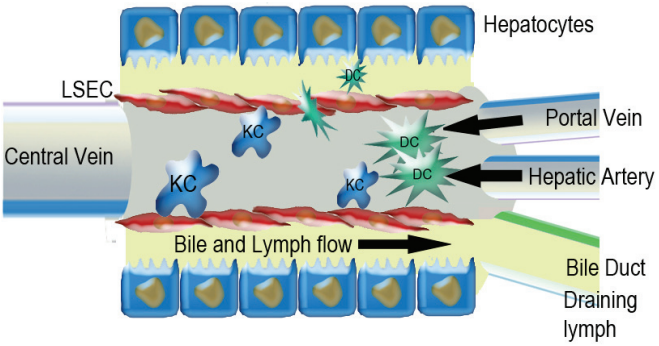

Figure 1. Hepatic portal lymphatic circulation diagram.

The trafficking pattern of murine hepatic DC subtypes has been extensively studied. Immature hepatic DCs isolated from Flt3L treated mice have expressed moderate levels of mRNA for CCR1, CCR5, and CCR7. Very low levels of mRNA were detected for CCR6 and very high levels for CCR2. CCR1, CCR2 and CCR5 are chemokine receptor responsible for migration of immature DC to areas of inflammation (31, 32). The ligands for CCR1 are CCL5/RANTES and CCL3/MIP-1α while CCR2 responds to MCP (1-4). Conflicting evidences have been presented for the migration response towards CCL3/MIP-1α (31, 32). These differences could be attributed to the method of isolation and preparation of hepatic DCs. However, upon maturation by overnight culture with GM-CSF, all subtypes of hepatic DCs (lymphoid, myeloid, and plasmacytoid) upregulated mRNA expression of CCR7 (31). The upregulation of CCR7 will allow the hepatic DCs to migrate towards the CCL19 and CCL21 secreted from the regional lymph nodes.

The hepatic DC migration pattern can also be up-regulated by environmental stimulus. Chronic exposure of hepatic DC to ethanol increases its ability to migrate towards the regional lymph nodes (33). The same effect cannot be seen in splenic DCs.

Chemokine secretion by the hepatic DCs is important in the recruitment of T cells and the formation of the immune synapse. Both immature and mature liver derived DCs secrete CCL3/MIP-1α, CXCL1, CCL2/MCP-1 and in particular, a strong expression of CCL5/RANTES. Upon LPS stimulation, is noted to further enhance CCL3/MIP-1α secretion (32). The production of CCL3/MIP-1α can recruit T cells expressing CCR5 in the liver (34). In addition, CCL20/MIP-3α is the most commonly expressed chemokine in the liver. Its corresponding chemokine receptor, CCR6, can also be found on intrahepatic T cells. Incubation of activated hepatic DCs with apoptotic cells induces DCs secretion of CCL20/MIP-3α to recruit activated T cells (34, 35). By secreting the appropriate chemokines, hepatic DCs can gain access to circulated T cells. However, the result of their interaction largely depends on the type of molecular interaction within the immune synapse and the arsenal of

cytokines within the liver microenvironment.

APCs and immune tolerance

KCs and LSECs

KCs and LSECs are both capable of capturing and processing antigens. Even with constitutive expression of CD86 on their surface, they are unable to induce T cell differentiation towards Th1 *in vivo* and poorly initiate the inflammatory responses in the liver (36). There are several mechanisms by which they may down-regulate immune reactivity. Under the stimulation of LPS, these APCs will respond by secreting IL-10, transforming growth factor-β (TGF-β) and prostanoids to promote immune tolerance (11). Other than secreting regulatory cytokines, LPS stimulated LSECs and KCs have been demonstrated to induce apoptosis in non-specific T-cell hybridomas (37, 38). In another report, LSECs are able to prime T cells to secrete IL-4 and IL-10 (36). Even though LSECs and KCs are able to exert immune regulation on multiple levels, hepatic DCs remain to be the main initiator of immune tolerance in the liver.

Hepatic DCs

Since DCs are the most efficient APCs, they can readily tip the balance between an active immune response and immune tolerance (39). In comparison to BMDCs or splenic DCs, hepatic DCs are comparably less immunogenic. Although conflicting data have been shown in different reports about the expression level of maturation markers for freshly isolated liver hepatic DCs, co-culturing these hepatic DCs with allogenic T cells resulted in minimal IFN-γ production and T cell proliferation (40). GM-CSF derived hepatic DCs have been shown to increase T cell secretion of IL-10 in a mixed lymphocyte reaction. The effects of these hepatic DCs *in vivo* also resulted in the induction of tolerance. Transfer of these hepatic DCs into allogenic mice resulted in IL-10 and IL-4 secretion by mononuclear cells while transfer of BMDCs resulted in IFN-γ production (41). In addition, hepatic DCs can suppress immune reaction through the promotion of T cell apoptosis. Even though all immature hepatic DCs express surface FasL, the lymphoid $CD8\alpha^+$ hepatic DCs can induce higher level of allogenic T cell apoptosis in comparison to the myeloid $CD8\alpha^-$ population (42). One possible explanation for the immuno-suppressive behavior of hepatic DCs could be the liver micro-environment.

Hepatic microenvironment promotes tolerance

Several reports have indicated that the hepatic micro-environment plays a role in retarding the maturation process for hepatic DCs (15, 43). Resident cells such as the LSECs, KCs, and lipocytes are all capable of secreting IL-10 and TGF-β. In response to the increase in local TGF-β concentration, hepatocytes will secrete IL-10 to further promote a tolerogenic microenvironment (44). Exposure of DCs to high levels of IL-10 and TGF-β have been shown to reduce co-stimulatory molecule expression leading to the development of regulatory DCs (45).

As most DC populations associated with mucosal sites are in general tolerogenic, it is no surprise that hepatic DCs fall under the same category (46, 47). In regards to primary T cell response, it is clear that hepatic DCs tend to prime naïve T cells into Th2, Th0 or T-regulatory phenotype. Only with further activation signals, can the hepatic DCs acquire co-stimulatory signals needed to generate IFN-γ secreting Th1 cells.

DC and immunogenic response

Priming naïve T cells

In order to activate hepatic DCs to prime naïve T cells, a combination of specific extracellular matrix protein and antigens are known to overcome the tolerogenic nature of hepatic DCs. GM-CSF derived hepatic DCs in the presence of collagen type I stimulation (48), which is also the dominant type of collagen found in the liver parenchyma, is able to obtain the maturation markers necessary for priming naïve T cells. However, the effect and importance of collagen type I on hepatic DC maturation *in vivo* is questionable and is currently under investigation.

Antigen specific hepatic DC activation

GM-CSF derived hepatic DCs are characterized with $CD11c^{lo}$, $CD44^+$, $CD24^+$, MHC II^{lo} and $CD86^{lo}$, and high phagocytic abilities (8, 30). The same culture protocol applied towards splenocytes yielded immature DCs in an activated state with high expression of MHC II and CD86 and limited ability to under phagocytosis. The treatment of these hepatic DCs with IFN-γ and TNF-α failed to induce hepatic DCs maturation and allogenic T cell activation (40). Instead, pulsing hepatic DC progenitors with hepatitis B surface antigen (HBsAg) or keyhole limpet haemocyanin (KLH) for 48 hours results in the upregulation of MHC II and CD86 to expression levels similar to the splenocyte derived DCs (40). Co-culturing of these activated hepatic DCs with allogenic memory T cells induces IL-12 and IFN-γ, respectively. The same antigens, HBsAg or KLH pulsed into LSECs and KCs resulted in high level of IL-10 secretion instead. In the case where both $B220^-$ (myeloid and lymphoid) and $B220^+$ (plasmacytoid) hepatic DCs are pulsed with OVA, only the $B220^-$ DCs and not the $B220^+$ hepatic DCs were able to induce T cell to secrete IFN-γ and IL-2 (19). These results suggest that myeloid and lymphoid hepatic DCs are the main initiators of immunity within the liver (36, 49, 50). Although most T cell activation occurs within the lymph nodes, evidence of T cell proliferation can also be detected in the portal tract associated lymphoid tissue (PALT).

Portal tract associated lymphoid tissue

After DCs process the captured antigens, they can either migrate to the draining lymph nodes, remain in the site of infection (granuloma), or associate with neighboring B or T cells to form a PALT (51). PALTs are very similar to the

classical lymphoid follicles (51). PALT is defined by Yoneyama et al. as the area near the portal triad where hepatic DCs interact with immunoreactive B or T cells. Formation of these PALTs may allow the hepatic DC to interact with corresponding T cells without entering the regional lymph node. The center of the PALT is composed of B cell follicles populated by antigen loaded follicular DCs. In between these B cell follicles are the $CD4^+$ T cells. As the vascular endothelium of the PALT is able to secrete CCL21, cells with CCR7, such as mature DCs and naïve T cells, are readily recruited to this area (52). Surrounding the B and T cells are the macrophages. Formation of PALT is suggestive of liver inflammation as patients with primary sclerosing cholangitis (PSC) have multiple PALT formation within their portal area (53, 54).

Innate response from hepatic DCs

As the link between innate and adaptive response, DCs carry a robust set of receptors against a variety of common pathogens. Recent discoveries in the functional coupling of these surface receptors have confirmed that hepatic DCs are quite different from the splenic DCs.

TLRs on hepatic DCs

Hepatic DCs from the C57BL/6 mice injected with Flt3L has increased surface expression levels of TLR2 and TLR4 in comparison to splenic DCs (8, 55). Culturing of these hepatic DCs with a panel of TLR ligands induces secretion of TNF-α and IL-6 (55). The only TLR ligand that failed to elicit a response is flagella. Surprisingly, CpG stimulation induced a very strong inflammatory cytokine response but a decrease level of T cell activation (8). Evidence of decrease innate response can also be seen in hepatic DCs isolated from Flt3L injected mice. There was a 2 to 5 fold decrease in TLR4 mRNA levels in the hepatic DCs in comparison to splenic DCs. This reduction in mRNA is consistent with the decrease ability of hepatic DCs to stimulate allogenic T cell response under low levels of LPS (10 ng/ml) stimulation. Even with a concentration of LPS at 1 μg/ml, the hepatic DCs only moderately increase their potency in activating T cells, but still remain to be less potent than the splenic DCs. Under low level of LPS stimulation, hepatic DCs co-cultured with T cells exhibited a dramatic decrease in both IFN-γ and IL-4 secretion. In contrast, increasing LPS concentration only leads to a dominating IL-4 production. The adoptive transfer of LPS stimulated hepatic DCs leads to a Th2 cytokine profile in the allogeneic recipient (55).

Hepatic DC and NKT cell activation

CD1d are MHC-like molecules important in the presentation of glycolipids. Since hepatic DCs express CD1d on their surface, α-Galactosylceramide (α-GalCer) can be readily presented to NKT cells in the liver (19). These activated hepatic DCs are potent activators of NKT cells *in vitro* or *in vivo* (56). Activation of NKT cells will result in high levels of IFN-γ and IL-12 production. The same effect could be seen in the CMS4 murine tumor model. Injection of α-GalCer pulsed DC resulted in NKT cells activation and suppressed tumor activity (57).

Table 2. Hepatic diseases associated with DCs

Disease	Role of DCs in disease
Hepatitis	Decrease T-cell allostimlatory ability in both HBV and HCV (61, 63)
Murine Cytomegalovirus	Reduce production of IFN-I in hepatic DCs in comparison to splenic DCs (19)
Hepatocellular Carcinoma	Reduced number of total DCs (64) and reduced T-cell stimulatory capacity (65)
Primary Biliary Cirrhosis	Increase secretion of nitric oxide and decrease allostimulatory activity (68)
Bile Duct Ligation	Increase total DCs and increase allostimulatory activity (69)

Hepatic DCs and their role in liver diseases

With increasing recognition of the DC's ability to balance immunity and tolerance, our understanding of their roles in autoimmunity, carcinogenicity and immune deficiencies becomes increasingly important. Table 2 lists the deficiencies in DC that are associated with hepatic diseases. Therapies involving the modulation of DCs to promote tumor antigen responsiveness and tolerance toward allergens have already begun (58, 59).

Hepatitis viral infection

In both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, there are evidence of DC abnormalities. In a murine model for chronic HBV carriers, DCs had decreased allostimulatory capabilities (60). The loss of T cell stimulatory reaction can also be seen in GM-CSF and IL-4 cultured DCs that were isolated from the peripheral blood of patients with chronic HBV infection (61). In patients with HCV, peripheral blood DCs failed to respond to TNF-α stimulation, decrease secretion of bioactive IL-12/p70, and also have decreased allostimulatory capabilities (62, 63). HCV infection is also associated with increase production of CCL3/MIP-1α by T cells, fibroblasts, and KCs residing near the portal areas (34). In response, DCs and T cells with CCR2 will be recruited to the area of infection.

Murine cytomegalovirus

Plasmacytoid hepatic DCs either infected with murine cytomegalovirus (MCMV) or incubated with CpG can produce type I IFN (IFN-I). However, $B220^+$ splenic DCs underwent the same treatment resulted in 3-6 fold increase in the amount of IFN-I release (19). This loss of IFN-I product may provide a window of opportunity for the MCMV to successfully infect hepatic tissues.

Hepatocellular carcinoma (HCC)

The elimination of tumors relies on the DCs to effectively capture, process, and present tumor antigens. A decrease in total abundance or activity of DCs can be devastating tumor surveillance. In patients with HCC, the total number of DCs in the peripheral blood is reduced (64). Culture of DCs with hepatoma cell line caused IL-10 release and a decreased stimulatory capacity in the DCs (65). Injection of Flt3L in a HCC mouse model increased total number of DCs and reduced the onset of HCC (66).

Autoimmune diseases

Primary biliary cirrhosis is an autoimmune disease marked by increased number of DCs in its portal tracts (67). Not only do these DCs have an increase secretion of nitric oxide, but they also have decreased ability for allostimulatory capabilities (68).

Bile duct ligation

In the murine model for bile duct ligation (BDL), total myeloid $CD8\alpha^-$ hepatic DCs increased from 20% to 80% of total DC population and their absolute number was increased by more than 15 fold. These $CD8\alpha^-$ hepatic DCs were characterized by increase antigen uptake *in vivo*, high IL-6 secretion in response to LPS, and increase T cell stimulatory activity (69).

Summary

One of the reasons by which the liver has been recognized as the least immunogenic of transplanted organs is due to the tolerogenic properties of the hepatic DCs. Upon migration of these hepatic DCs into the recipient lymph nodes, they will cause T cell anergy or tolerance in alloreactive T cells (5, 15). The removal of donor leukocytes in rat liver transplantation caused organ rejection (70), while the replacement of these leukocytes prevented organ rejection (71). One possible explanation is the theory of microchimerism by Starzl et al. states that the donor and recipient DCs are able to cause alloreactive T cell apoptosis in the recipient and donor tissues, respectively (72-74). A second mechanism that could possibly lead to immune tolerance is the exhaustive deletion of recipient leukocytes due to the early activation caused by a large dose of donor leukocytes (75). Regardless which mechanisms is correct, hepatic DCs play a key role in minimizing liver transplantation rejection. In the cases of liver diseases, treatments to increase the activation state of hepatic DCs might relieve disease progression. In most diseases, reduce DC reactivity and severely reduce total DC are detected. The enhancement of hepatic DCs functionality and population size can be the key in the prevention and treatment for many liver diseases.

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